Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): II. Externalizing superspectrum

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The Hierarchical Taxonomy of Psychopathology (HiTOP) is an empirical effort to address limitations of traditional mental disorder diagnoses. These include arbitrary boundaries between disorder and normality, disorder co-occurrence in the modal case, heterogeneity of presentation within disorders, and instability of diagnosis within patients. This paper reviews the evidence on the validity and utility of the disinhibited externalizing and antagonistic externalizing spectra of HiTOP, which together constitute a broad externalizing superspectrum. These spectra are composed of elements subsumed within a variety of mental disorders described in recent DSM nosologies, including most notably substance use disorders and "Cluster B" personality disorders. The externalizing superspectrum ranges from normative levels of impulse control and self-assertion, to maladaptive disinhibition and antagonism, to extensive polysubstance involvement and personality psychopathology. A rich literature supports the validity of the externalizing superspectrum, and the disinhibited and antagonistic spectra. This evidence encompasses common genetic influences, environmental risk factors, childhood antecedents, cognitive abnormalities, neural alterations, and treatment response. The structure of these validators mirrors the structure of the phenotypic externalizing superspectrum, with some correlates more specific to disinhibited or antagonistic spectra, and others relevant to the entire externalizing superspectrum, underlining the hierarchical structure of the domain. Compared with traditional diagnostic categories, the externalizing superspectrum conceptualization shows improved utility, reliability, explanatory capacity, and clinical applicability. The externalizing superspectrum is one aspect of the general approach to psychopathology offered by HiTOP and can make diagnostic classification more useful in both research and the clinic.

Key words: HiTOP, externalizing, disinhibition, antagonism, antisocial personality disorder, Cluster B personality disorders, substance use disorders, clinical utility

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The Hierarchical Taxonomy of Psychopathology (HiTOP) consortium aims to integrate research on the empirical organization of psychopathology, with the goal of delineating a comprehensive descriptive system[1-3]. Taxonomies in frequent use (e.g., the DSM) have notable limitations, such as arbitrary boundaries between psychopathology and normality, diagnostic instability, heterogeneity within disorders, disorder co-occurrence in the modal case, and inability to conceptualize subthreshold cases. The HiTOP approach mitigates such problems by: a) defining psychopathology in terms of continua ranging from normative to maladaptive; b) delineating continua based on observed covariation among signs, symptoms and syndromes, and c) arranging continua in a hierarchy, ranging from more narrow and specific (e.g., clusters of symptoms) to more broad and general (e.g., spectra of inter-related diagnostic phenomena).

An approach based on continua or dimensions of human individual differences resolves issues of arbitrary thresholds and diagnostic instability. Thresholds indicating specific clinical options can be described based on evidence, and test-retest reliability of dimensional psychopathology constructs is notably greater than that of arbitrary diagnostic categories[4-7]. No patients are excluded from the system (i.e., individuals with subthreshold or atypical symptoms are all characterized on a set of dimensions), providing a boon to case conceptualization. The HiTOP approach also reduces diagnostic heterogeneity by grouping empirically related symptoms together and arraying them along distinguishable dimensions[8-11]. Comorbidity is rendered understandable, because related conditions form elements in psychologically coherent spectrums.

The working HiTOP system currently includes six broad spectrums: internalizing, somatoform, disinhibited externalizing, antagonistic externalizing, thought disorder, and detachment[1-3]. These spectrums reflect continuous individual differences in a given domain across the entire population. Broad spectrums, in turn, are combined into larger groupings or superspectra: emotional dysfunction (internalizing and somatoform), externalizing (disinhibited and antagonistic), and psychosis (thought disorder and detachment)[12-16]. Above these superspectra, the HiTOP approach also recognizes a general psychopathology factor[17,18].

The working HiTOP system was created by reviewing a con-

siderable body of research, but external validity and utility have been less well documented, because previous reviews of these topics had limited scope. With this in mind, the Utility Workgroup of the HiTOP consortium assembled teams of experts to comprehensively review evidence on the validity and utility of the working HiTOP model. Expert reviews were organized according to the three superspectra. The present paper is the second in this series (the first focused on psychosis[19] and the third will examine emotional dysfunction) and focuses on the externalizing superspectrum.

The externalizing superspectrum encompasses two spectra: disinhibited externalizing and antagonistic externalizing. The disinhibited externalizing spectrum includes tendencies to act on impulse, without consideration for potential consequences. Empirically, disinhibition tends to be accompanied by societally prohibited behaviors that align psychologically with the core of the construct, for example, the use of psychoactive substances to excess[20] and with minimal regard for future consequences. The antagonistic externalizing spectrum includes tendencies to navigate interpersonal situations using antipathy and conflict, and to hurt other people intentionally[21], with little regard for their rights and feelings.

These spectra encompass both maladaptive traits and more time-limited symptoms, with the distinction pertaining to the timescale of the phenomena[22]. For example, a series of specific disinhibited behaviors (e.g., a brief period encompassing impulsive purchases and other decisions that reflect immediate reward more than longer-term consequences) could be driven by a specific life crisis, rather than being generally characteristic of a person. If such behaviors persist across time and circumstances, they become additionally indicative of a disinhibitory trait. Similarly, a specific hostile interaction is an antagonistic phenomenon, while frequent and recurrent hostile interactions are indicative of an antagonistic trait. As described at length throughout this review, disinhibited and antagonistic behaviors tend to co-occur at notably greater than chance levels, illustrating the phenotypic coherence of the broad externalizing superspectrum[23].

The goal of this paper is to review the extensive evidence documenting the structural coherence and content of the externalizing superspectrum and the disinhibited and antagonistic spectra, and the utility and validity of these diagnostic constructs.

STRUCTURAL EVIDENCE

Composition of major dimensions

The externalizing superspectrum has long emerged in research on the structure of mental disorders and of maladaptive personality traits. Indeed, studies have revealed that externalizing psychopathology is separate from other superspectra, including internalizing psychopathology in youth[24-30] and both internalizing and thought disorder/psychosis in adults[31-34]. Across these bodies of research, clinical diagnoses or dimensional symptom counts of antisocial personality disorder (PD), attention-deficit/hyperactivity disorder (ADHD), alcohol, cannabis, nicotine, and other substance use disorders (SUDs), and intermittent explosive disorder in adulthood, as well as conduct disorder (CD) and oppositional defiant disorder (ODD) in childhood, clearly reflect a distinct and overarching externalizing superspectrum, as summarized in Table 1 and pictured in Figure 1.

The extant evidence further supports parsing the externalizing superspectrum down into disinhibited and antagonistic externalizing spectra[1]. This bifurcation is more clearly evident in maladaptive trait research and in the adult rather than the child psychopathology literature, and these major domains can be observed in the psychiatric diagnosis literature as well.

As summarized in Table 1, three main observations are evident from this literature. First, the majority of studies identify antisocial PD as an indicator of both disinhibition and antagonism, which supports this disorder as a non-specific and core indicator of the general externalizing superspectrum. In fact, the criteria for antisocial PD are quite evenly spread across both disinhibited and antagonistic features. Second, alcohol and other SUDs are specific to the disinhibited externalizing spectrum. Third, some DSM PDs (i.e., paranoid, narcissistic and histrionic) appear relatively specific to the antagonistic externalizing spectrum. These findings are also generally consistent with Krueger et al's multifaceted model of the externalizing spectrum[15], which considers general externalizing together with more specific liability factors for callous-aggression (the unique component of antagonism) and substance misuse (the unique component of disinhibited externalizing).

One condition deserving specific consideration is borderline PD, as its relevance to general externalizing, as well as its specificity to antagonism vs. disinhibition, appears dependent on other indicators included in the structural model. In studies in which internalizing psychopathology is also prominently featured, borderline PD tends to load robustly with internalizing and less consistently with externalizing[39,46,48,52]; moreover, when dimensional traits are considered in addition to psychiatric diagnoses, this PD loads distinctly on internalizing[64]. In other words, the preponderance of research evidence indicates that borderline PD does load with the internalizing spectrum, while its association with externalizing (and even specific placement within antagonism vs. disinhibition)[65,66] is less clear. At this point, borderline PD is therefore best considered an indicator of both internalizing and, to a lesser degree, the general externalizing superspectrum, likely with different components of the disorder being related to these two spectra. As such, borderline PD is only provisionally included in the externalizing superspectrum, as noted in Figure 1.

It is further noteworthy that, while clearly representing antagonistic externalizing in the context of the broader externalizing superspectrum, paranoid and histrionic PD have other influences as well, given their multifaceted nature. For instance, paranoid PD may appear more strongly linked to the psychosis superspectrum when disorders of this type are clearly represented in the set of structural indicators[13,32,65]. Histrionic PD also has direct links (in the negative direction) to the detachment spectrum[64], which is also supported in the general personality literature[67,68].

Finally, although the externalizing superspectrum is well rep-

Table 1 Structural evidence on the externalizing superspectrum and the disinhibited and antagonistic spectra

	Sample size	Sample type	ASPD	AUD	Other SUD	IED	CD	ODD	ADHD	NPD	PPD	HPD	BPD
Externalizing superspectrum													
Dunedin Multidisciplinary Health and Development Study (Caspi et al[31], Krueger et al[35])	1,037	Community/longitudinal	+	+	+		+						
Early Developmental Stages of Psychopathology (Beesdo-Baum et al[36], Wittchen et al[37])	3,021	Community/longitudinal	+	+	+								
NESARC waves 1 and/or 2 (Carragher et al[38], Eaton et al[39], Keyes et al[32], Lahey et al[40])	43,093 & 34,653	Community/adults	+	+	+				+		–		–
Tennessee Twin Study (Lahey et al[27], Waldman et al[41])	4,050	Community/children & adolescents					+	+	+				
WMH Surveys (de Jonge et al[42], Kessler et al[43])	21,229	Community/ longitudinal		+	+	+	+	+	+				
Blanco et al[24]	9,244	Community/adolescents		+	+		+	+	+				
Castellanos-Ryan et al[25]	2,232	Community/adolescents		+	+		+	+	+				
Conway et al[44]	25,002	University/adults		+	+				+				
Cox et al[45]	5,877	Community/adults	+	+	+								
Forbush & Watson[46]	16,423	Community/adults	+	+	+	+	+		+				+
Forbush et al[47]	1,434	Community/longitudinal	+	+	+		+						
Gomez et al[26]	2,099	Outpatient/youth					+	+	+				
James & Taylor[48]	1,197	Community/adults	+	+	+								–
Krueger[49]	8,098	Community/adults	+	+	+								
Krueger et al[50]	1,048	Community/adolescents		+	+		+						
Martel et al[28]	2,512	Community/children					+	+	+				
Martel et al[28]	8,012	Community/adults		+	+		+	+	+				
Miller et al[51]	1,325	Veterans/adults	+	+	+								
Miller et al[52]	214	Veterans/adults	+		–		+						+
Olino et al[29]	541	Community/children						+	+				
Tuvblad et al[53]	1,219	Community/children					+	+	+				
Verona et al[33]	4,745	Community/adults	+	+	+								
Verona et al[30]	223	Mixed/youth		–	–		+	+	+				
Young et al[54]	668	Community/adolescents			+		+		+				
Total positive			11/11	16/17	17/19	2/2	15/15	10/10	14/14	0/0	0/1	0/0	2/4

Table 1 Structural evidence on the externalizing superspectrum and the disinhibited and antagonistic spectra (*continued*)

	Sample size	Sample type	ASPD	AUD	Other SUD	IED	CD	ODD	ADHD	NPD	PPD	HPD	BPD
Disinhibited spectrum													
MIDAS (Forbes et al[13], Kotov et al[55])	2,900	Outpatients/adults	+	+	+		+			–	–	–	–
Norwegian Institute of Public Health Twin Panel (Kendler et al[56], Røysamb et al[57])	2,794	Community/adults	+	+	+		+			–	–	–	+
Conway & Brown[58]	4,928	Outpatients/adults		+	+								
Conway et al[59]	815	Community/longitudinal		+	+								
Farmer et al[60]	816	Community/longitudinal	+	+	+		+						
Kim & Eaton[61]	43,093	Community/adults	+	+	+								
Slade & Watson[62]	10,641	Community/adults		+	+								
Vollebergh et al[63]	7,076	Community/adults		+	+								
Wright & Simms[64]	628	Outpatients/adults	+	+	+					–	–	–	–
Wright et al[34]	8,841	Community/adults		+	+								
Total positive			5/5	10/10	10/10		3/3			0/3	0/3	0/3	1/3
Antagonistic spectrum													
MIDAS (Forbes et al[13], Kotov et al[55])	2,900	Outpatients/adults	+	–	–		+			+	+	+	+
Norwegian Institute of Public Health Twin Panel (Kendler et al[56], Røysamb et al[57])	2,794	Community/adults	–	–	–		–			+	+	+	+
Farmer et al[60]	816	Community/longitudinal	–	–	–		–	+	+				
Kim & Eaton[61]	43,093	Community/adults	+	–	–								
Wright & Simms[64]	628	Outpatients/adults	–	–	–					+	+	+	–
Total positive			2/5	0/5	0/5		1/3	1/1	1/1	3/3	3/3	3/3	2/3

+: indicator included in analysis with meaningful loading (.30 or larger), –: indicator included in analysis but did not load meaningfully. ASPD – antisocial personality disorder, AUD – alcohol use disorder, SUD – substance use disorder, IED – intermittent explosive disorder, CD – conduct disorder, ODD – oppositional defiant disorder, ADHD – attention-deficit/hyperactivity disorder, NPD – narcissistic personality disorder, PPD – paranoid personality disorder, HPD – histrionic personality disorder, BPD – borderline personality disorder, NESARC – National Epidemiologic Survey on Alcohol and Related Conditions, WMH – World Mental Health, MIDAS – Methods to Improve Diagnostic Assessment and Services.

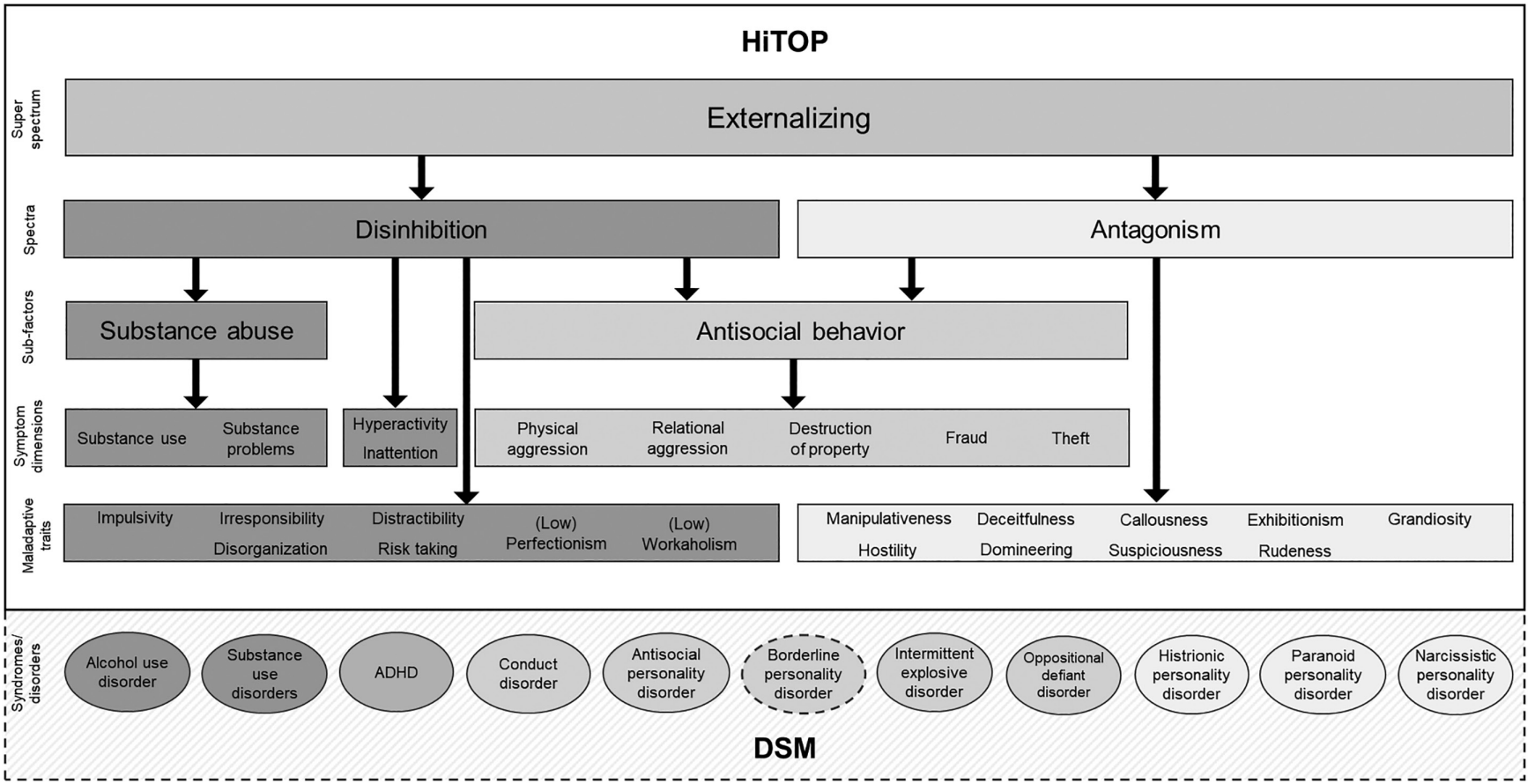

Figure 1 Conceptual model of the externalizing superspectrum. Dashed lines represent provisional inclusion. Specifically, the dashed line surrounding borderline personality disorder represents that this disorder falls under two superspectra (externalizing and internalizing). The dashed line surrounding the diagnoses section indicates that these categorical diagnoses do not belong to the model; they are meant to represent how a dimensional model encapsulates DSM diagnoses. HiTOP – Hierarchical Taxonomy Of Psychopathology, ADHD – attention-deficit/hyperactivity disorder.

resented in the youth psychopathology literature, evidence for bifurcation of disinhibition and antagonism prior to adulthood is less clear (see Table 1), likely owing to the lack of clearly defined indicators for making this separation. In contrast with the adult literature, there are no diagnoses or explicit symptom measures of callous-unemotional traits, narcissism, or paranoia/suspiciousness included in structural modeling studies with children/adolescents, making it virtually impossible for these factors to emerge in the youth literature. Additionally, in young children, substance use is likely to be uncommon. Furthermore, links between personality traits and disorders are less well established in the youth (especially child) literature[69], making an analysis from this perspective less straightforward. Further research is definitely needed to obtain a clearer picture of psychiatric representations of antagonism in youth, especially beyond what are typically referred to as callous-unemotional traits[70].

Role of personality traits

The hierarchical structure of the externalizing superspectrum closely parallels the organization of normal-range personality traits[1,71]. The general externalizing dimension is broadly linked to individual differences in the higher-order trait factor of constraint vs. disconstraint[72], which emerges in three-factor models of normal and abnormal personality[72-75]. When additional factors are extracted, this broad constraint vs. disconstraint dimension divides into two more specific components: agreeableness vs. antagonism, and conscientiousness vs. disinhibition[73,75,76]. These two subdimensions, in turn, form the basis for distinguishing antagonistic from disinhibited forms of externalizing.

Antagonistic externalizing has been linked to a variety of specific maladaptive traits that reflect problematic relations with others. It should be noted that some of these traits also show lesser associations with other forms of psychopathology[1,77-83]. The traits that have been most strongly and consistently associated with the antagonistic externalizing spectrum include manipulativeness (i.e., exploiting and taking advantage of others), deceitfulness (i.e., lying and cheating in pursuit of one's goals), callousness (i.e., being cold-hearted and lacking empathy), exhibitionism (i.e., engaging in attention-seeking behaviors), grandiosity (i.e., being arrogant and feeling entitled to special treatment from others), aggression (i.e., engaging in hostile and even violent behavior), rudeness (i.e., being blunt, tactless, and interpersonally insensitive), domineering (i.e., the proneness to be forceful and controlling in relationships), and suspiciousness (i.e., questioning the honesty, fidelity, and motives of others).

Disinhibited externalizing has also been linked to multiple maladaptive traits reflecting disorganization, poor impulse control, and a lack of concern regarding the consequences of one's behavior[1,77,78,80-83]. The specific traits that have been most strongly and consistently associated with the disinhibited externalizing spectrum include impulsivity (i.e., acting spontaneously on the spur of the moment without concern for consequences), irresponsibility (i.e., being undependable and failing to fulfill obligations), distractibility (i.e., problems in attention and difficulties in focusing on tasks), risk taking (i.e., being reckless and engaging in potentially dangerous activities), (low) perfectionism (i.e., having low standards for the completion of work), and (low) workaholism (i.e., being more interested in having fun than in work-related activities).

These trait correlates, in turn, help to explain the specific types of personality-related pathology that are subsumed within each spectrum, including both adult[1,67,84,85] and youth disorders[86-93]. As can be seen in Figure 1, the antagonistic externalizing spectrum subsumes narcissistic, paranoid and histrionic PDs. Disinhibited externalizing includes ADHD, alcohol use disorder, and SUDs. Disorders such as conduct disorder, antisocial PD, intermittent explosive disorder, ODD, and borderline PD contain trait characteristics related to both spectra (e.g., impulsivity and anger/aggression).

VALIDITY EVIDENCE

Behavior genetic evidence

Evidence for a genetically coherent externalizing superspectrum has emerged most strongly from twin studies of constituent disorders and related personality traits in both youth and late adolescent/adult samples.

Specifically, in youth samples, twin studies have shown high heritabilities (h^2) and moderate levels of non-shared environmental influences, but non-significant shared environmental influences, for ADHD (h^2=~60-80%)[94] and ODD (h^2=~30-70%)[93], as well as for psychopathic traits (such as callous-unemotionality and narcissism)[95]. These studies have also found moderate heritability (h^2=~50%), shared environmental influences, and non-shared environmental influences for CD[96], and moderate heritability for various forms of youth antisocial behavior, including rule breaking and aggression[97], with its various forms such as reactive, proactive and relational aggression[96,98,99].

Most importantly, behavior genetic studies have provided evidence for the coherence of the externalizing superspectrum by showing high levels of genetic overlap across ADHD, ODD and CD[41,100,101], such that the largest contributor to the overlap among these disorders or the covariation among their symptom dimensions is represented by common genetic influences. This is also borne out by studies that have directly estimated the magnitude of genetic influences on an externalizing factor, and have found it to be highly heritable[41,102].

Evidence for the genetic basis of the externalizing superspectrum in youth also includes studies that have demonstrated common genetic influences between these disorders and personality traits such as behavioral disinhibition, neuroticism, and low prosociality[54,103,104].

Twin studies in late adolescent/adult samples provide considerable evidence for the validity of the externalizing superspectrum[54,103,104]. This evidence comes from studies of PDs, SUDs, and their symptom dimensions and related traits (e.g., antisocial behavior).

The "Cluster B" PDs, when examined individually, exhibit moderate to large heritability estimates[105]. The covariance among these disorders can be accounted for by a genetic common factor, with a second genetic factor accounting for variance in antisocial and borderline PDs[106]. Antisocial PD has also been included as an observed indicator in a highly heritable externalizing factor[50,103]. Relatedly, Kendler et al[66] reported evidence for a genetically coherent "Axis I" externalizing factor encompassing antisocial PD as well as CD, alcohol abuse/dependence, and drug abuse/dependence. These authors also found a genetically coherent "Axis II" externalizing factor encompassing dependent, histrionic, narcissistic, obsessive-compulsive, paranoid and borderline PDs, along with eating disorders.

The DSM-5 includes an alternative dimensional model of PDs as opposed to the criteria of the categorical diagnostic model. Most relevant to externalizing are the higher-order domains of antagonism and disinhibition, which are moderately heritable[107,108]. In a joint exploratory factor analysis including the DSM-5 alternative trait model domains, PD symptoms and normal personality domains, three genetic factors emerged: a PD/neuroticism factor, an antagonism/antisocial factor, and a factor reflecting schizoid/detachment[109].

Twin/family studies compellingly demonstrate that SUDs are genetically influenced, with ~50% of the variance in alcohol use disorders[110], 50-60% in problematic cannabis use[111], ~40-80% in cocaine use disorders[105,112,113], 20-50% in opioid dependence[105,112], and ~60% in nicotine dependence[114] being due to genetic influences. Critically, twin studies indicate that genetic influences are largely shared across SUDs[115]. Further, related psychiatric and behavioral manifestations, such as childhood conduct problems, adult antisocial behavior, behavioral undercontrol and impulsivity[116], also load on this shared genetic factor, which is highly heritable (~80%)[50,54]. A general liability towards externalizing explains the majority of genetic influences for alcohol and other SUDs, including 74-80% of the genetic influences on alcohol use disorders and 62-74% of those on other SUDs; it also accounts for 33-37% of the genetic influences on nicotine dependence.

Molecular genetic evidence

Molecular genetic research also supports an appreciable contribution of genes to individual disorders and traits within the externalizing superspectrum.

Candidate gene studies of ADHD have provided some suggestive evidence of association for genes within the dopamine and serotonin neurotransmitter systems, including the dopamine transporter and D4 and D5 receptor genes (*DAT1*, *DRD4* and *DRD5*), the serotonin transporter and receptor 1 genes (*5HTT* and *HTR1B*), and the synaptosomal-associated protein 25 gene (*SNAP-25*)[117].

Genome-wide association studies (GWAS) of various childhood disorders, such as ADHD[118], CD[119], and ODD or CD within the context of ADHD[120], have found evidence for several genome-wide significant associations and polygenic influences, each with a small effect size, that contribute to the risk for these disorders. In addition, moderate genetic correlations have been found between ADHD and other disorders, such as depression and anorexia nervosa; related traits, such as neuroticism and subjective well-being (negative); and important life outcomes, including ever having smoked, the number of cigarettes smoked per day, and intelligence and educational attainment (both negative)[120].

Interestingly, ADHD was not genetically correlated with antisocial behavior in another study, likely due to the relatively small sample size and the heterogeneity of measures of antisocial behavior[121]. In contrast, ODD or CD in the context of ADHD was highly genetically correlated with aggression and antisocial behavior, and its polygenic risk score was more predictive of cognitive functioning, educational outcomes, and having children at a younger age than that for ADHD without ODD or CD[120]. Nonetheless, the maximum variance explained by the polygenic risk score in these outcomes was quite low (0.36%).

In adolescent and adult samples, GWAS of externalizing PDs are still in their infancy, with only borderline and antisocial PDs being investigated to date, using relatively small samples. One molecular genetic study indicated that borderline PD is heritable[122], but did not test for its genetic association with any other form of externalizing psychopathology. Current GWAS evidence indicates that antisocial behavior is heritable and significantly genetically correlated with CD and neuroticism, but not with schizophrenia, bipolar disorder or ADHD[121]. Furthermore, a study found high genetic correlations of antisocial behavior with lifetime cannabis use and cigarette smoking, but not with alcohol consumption[123], while another study did not find an association between polygenic risk scores for antisocial PD and either tobacco or alcohol use[124]. A GWAS of antisocial PD[125] reported the most associated gene (*ABCB1*) to be one involved in immune function and associated with various forms of substance abuse. These studies have also found that many common genetic variants, each with a small effect size, contribute to risk for antisocial behavior. Finally, a large GWAS of normal personality traits did not find that agreeableness has genetic correlations with any externalizing disorders or other forms of psychopathology[126].

The majority of GWAS on substance use have focused on alcohol-related phenotypes, including alcohol dependence[127], alcohol use disorder[128], number of alcoholic drinks per week[129], and maximum alcohol intake. Studies of these phenotypes have employed moderately to extremely large sample sizes, thus being well-powered. One finding which robustly emerged from these GWAS is that genetic influences on alcohol consumption are only moderately correlated with those on alcohol use disorders[130]. Cannabis related GWAS are beginning to reach adequate power[131-133], but still require even larger samples. GWAS on cocaine dependence[134,135] and opioid dependence[136-138] are currently underpowered. It is important to note that, even in large cohorts, polygenic risk scores continue to predict only small proportions of the variance in independent samples (e.g., the polygenic risk score from a GWAS involving ~1 million participants explained only about 2.5% of the variance in alcohol consumption).

Newer multivariate methods such as genomic structural equation modeling (genomic SEM)[139,140] can be used to model the underlying factor structure of genetic correlations from a set of phenotypes of interest using GWAS summary statistics. These methods enable researchers to move beyond a single disorder or behavior in gene identification efforts, and instead focus on identifying genes contributing to the underlying latent factor(s). Genomic SEM is currently being applied in the international Externalizing Consortium, which analyzed genome-wide data on seven phenotypes related to the externalizing superspectrum from ~1.5 million people and identified nearly 600 significant genetic loci associated with a general liability to externalizing[141]. A polygenic risk score derived from this dataset predicted up to 10% of the variance in general externalizing scores in independent samples, and emerged as significant in both within-sibling and between-sibling comparisons. These analyses suggest that focusing gene identification efforts on general externalizing liability, rather than on individual externalizing disorders/behaviors, is a fruitful approach to advancing knowledge of genes contributing to this psychopathological domain.

Environmental risk factors

Decades of observational research have identified a wide range of environmental risk factors for externalizing problems, spanning a variety of social domains. Meta-analyses document that abuse, neglect, hostile parenting, neighborhood violence, and affiliation with deviant peers all exhibit significant associations with diverse externalizing phenomena[142-144]. Longitudinal research in the community confirms that these effects can endure through adolescence and beyond[145].

Effects of toxic environments are not only robust, but also diffuse. That is, prominent etiological events appear to engender risk for a variety of externalizing mental health conditions and maladaptive personality traits[146]. Indeed, there are essentially no known unique environmental risk factors for any substance use or behavioral disorder.

This observation prompted research on how environmental pathogens relate to composites of externalizing phenotypes. In an epidemiologic sample, various forms of childhood maltreatment predicted individual differences on a latent externalizing dimension constructed from substance use and antisocial behavior disorders[147]. This effect was replicated in a number of cohort studies[148,149]. Across studies, the severity of social stress predicted variation in the broad externalizing factor, but not unique components of the specific observed externalizing conditions. This pattern is evident in research on other risk factors that focus on externalizing outcomes which transcend traditional disorder boundaries. Peer victimization, discrimination experiences, and other chronically stressful conditions such as romantic conflict and unemployment, all predicted standing on a latent externalizing spectrum in separate community samples[150,151].

The connection between externalizing problems and environmental stressors over time is almost certainly bidirectional. Research in community samples shows that variation in a latent externalizing factor predicts future rates of both acute life events (e.g., arrest) and ongoing strains (e.g., marital discord)[152,153]. These stressful conditions, in turn, presumably set the stage for continued externalizing behavior. This type of person-environment fit implies a vicious cycle of stress exposure and worsening externalizing problems, akin to the transactional peer selection and socialization effects on externalizing risk in adolescence[145].

As a whole, longitudinal research has revealed strong connections between a wide range of environmental exposures and the externalizing superspectrum. Much less is known about whether certain environments predispose selectively to disinhibited vs. antagonistic spectra (or any other more homogeneous components) within the superspectrum. The available data at this time suggest that environmental risk is largely non-specific. More research using genetically informative designs is needed to verify the etiologic roles of putative environmental risk factors by controlling for passive gene-environment correlation (e.g., parents creating a home environment that is influenced by their heritable characteristics)[154].

Cognitive and emotional processing abnormalities

Generally speaking, the externalizing superspectrum model helps to organize the literature on cognitive deficits, as reflected in Figure 1. In particular, there is overwhelming evidence that cognitive impairment is prominent in disinhibited forms of externalizing.

Evidence of impaired executive functioning is most substantial for antisocial PD[155-159] and CD[160,161], followed by disinhibitory traits[162-166]. Additionally, deficits in sustained attention, inhibitory control, and sluggish cognitive tempo are associated with ADHD[162,167-172]. There is evidence of cognitive deficits in children with ODD, albeit less abundant[173,174], which might be partly explained by high comorbidity with both ADHD and CD[175,176]. There is even less evidence of cognitive deficits related to intermittent explosive disorder, which is mostly characterized by impairments in social cognition and emotion regulation[177-180]. Impairments in executive functions are extensively reported in individuals with drug and alcohol dependence[181-188].

Under the antagonistic externalizing spectrum, the evidence of cognitive deficits is strong for borderline PD[189,190], whereas findings concerning narcissistic, histrionic and paranoid PDs are mostly derived from symptom, descriptive and trait checklists[191,192].

Antisocial traits are linked with deficits in the ability to regulate emotions and diminished responsiveness to distress in others[193-196]. ODD is associated with deficits in empathy, and impaired emotion regulation has been reported in both ODD and intermittent explosive disorder[180,197,198]. There is evidence for emotion dysregulation impairments also in substance dependent individuals[199-201].

Impaired facial affect recognition and emotional regulation

deficits are observed in individuals with borderline PD[202,203]. The evidence concerning narcissistic and paranoid PDs (respectively, difficulties in emotional empathy and regulation[204], and hypervigilance and stress reactivity[205]) has come from symptom, descriptive and trait checklists, rather than behavioral task performance.

Neurophysiological indicators

The best-established neurophysiological indicator of broad externalizing is reduced amplitude of the visual P300 (P3) event-related potential (ERP)[206], a positive-going ERP that occurs in relation to rare or otherwise salient visual events within an ongoing stimulus series.

Originally thought to be indicative of proneness to alcohol problems[207], subsequent research showed reduced P3 to be related to various other externalizing conditions as well[208]. Ultimately, it became clear that P3 operates as an indicator of the highly heritable liability for externalizing problems in general[209,210]. Like broad externalizing, P3 amplitude is appreciably heritable, and its association with this superspectrum factor reflects additive genetic influences in common between the two[211,212].

Other evidence points to a genetically-based association between broad externalizing and performance on executive control tasks[213], and overlap is evident in the relations of P3 amplitude and executive task performance with broad externalizing[166,214]. The implication is that reduced P3 reflects a weakness in cognitive control capacity that is associated with heritable risk for externalizing problems in general[215,216], highlighting P3 as a marker of the broad externalizing factor at the superspectrum level of HiTOP.

Another less well-established candidate indicator of broad externalizing is reduced amplitude of the error-related negativity (ERN), a negative-going ERP that is evident following errors in a speeded reaction time task, and is theorized to reflect performance monitoring and error detection processes. Reduced ERN was initially reported for individuals high in impulsive traits[217,218], and later for individuals high in broad externalizing[219]. Further research is needed, though, to evaluate the specificity of the relationship of reduced ERN to broad externalizing, and the neural systems basis of this relationship. In addition, research is needed on the etiologic basis of the association between ERN and externalizing problems, given the limited work of this kind to date[220].

Studies that have specifically assessed antagonistic externalizing tendencies along with broad externalizing have shown reduced P3 and ERN in relation to the latter, but not to antagonism-specific variance[221,222]. By contrast, high antagonistic externalizing is reliably associated with reduced brain reactivity to fearful face stimuli. Multiple studies have reported reduced amygdala activation to fearful faces in children/adolescents exhibiting antagonistic externalizing tendencies (sometimes termed "callous unemotionality")[223,224] along with conduct problems, compared to children lacking in antagonistic externalizing. Importantly, this effect has been found to be specific to antagonistic externalizing (callous-unemotionality) by contrasting groups of children matched for externalizing problems but differing in levels of callous-unemotionality[210]. Consistent with this, two studies[225,226] reported reduced early-ERP responses to fearful faces in adults scoring high on a measure of antagonistic externalizing (termed "callousness"); broad externalizing was also assessed in these studies, and effects were shown to be attributable to callousness-specific variance. This impaired responsiveness to fearful faces may reflect general emotional insensitivity among those high on antagonistic externalizing, or perhaps a more specific deficit in the capacity for empathy or affiliative capacity among these individuals[227].

Interpretation of the research literature on neurophysiological indicators of problems situated specifically within the disinhibited externalizing spectrum of HiTOP – in particular, substance use problems – is hampered by a failure to differentiate between specific factors versus broad externalizing liability[228], neglect of the distinction between liability indicators and symptom or "scar" indicators[229], and the substance-specific nature of particular indicators[230]. For example, while there is considerable evidence for a distinct role of reward system dysfunction in substance addictions, it remains unclear at this time whether addiction proneness entails heightened or diminished sensitivity to naturally occurring rewards[231-233], due to limitations of existing research. To address these limitations, longitudinal studies are needed that differentiate between neural measures of premorbid liability to externalizing problems in general, as opposed to measures indicative of addiction liability more specifically, or active symptoms or persisting consequences of substance addiction[229].

Neuroimaging

As with other psychiatric domains, the neuroimaging literature on externalizing has been dominated by case-control studies of individual disorders, but these are now complemented by growing research taking the transdiagnostic dimensional approach. This work is identifying alterations in a number of circuits involved in social-emotional processing, aversive learning, emotional regulation, and cognitive control, with varying levels of specificity between antagonism and disinhibition domains, as well as narrower lower-order constructs that contribute to these domains. We highlight some of the key circuits as a demonstration of the compatibility of neuroimaging data with the HiTOP model of externalizing.

Among the most frequent findings is the observation of reduced amygdala volume, which has been seen in case-control studies or disorder-specific symptom measures of psychopathy and antisocial personality[234], conduct and oppositional problems[174], borderline personality[235,236], aggression and violence[237], risk for substance use problems[238,239], and ADHD[240]. While amygdala volume reductions correlate with broad measures of externalizing traits[241,242], they appear most pronounced for callous-unemotional and antagonistic traits[174,243] as opposed to disinhibition features.

Given the importance of the amygdala in social-emotional

processing, emotional responses to aversive stimuli, and aversive learning[244], such findings fit with psychological and psychophysiological models emphasizing social-emotional and fear learning deficits as core features in the etiology of antagonistic spectrum problems[245-247]. This having been said, reduced amygdala volume has also been reported for other diagnostic constructs (e.g., post-traumatic stress disorder)[245-247], such that the specificity of this association would benefit from further study.

Reductions in amygdala volume are paralleled by changes in task-related activity in disorders with high antagonism characteristics, as repeatedly demonstrated in functional magnetic resonance studies of individuals with antisocial-psychopathic and borderline personality traits[248,249]. Again, the associations appear to most robustly reflect antagonism/callous-unemotionality rather than disinhibition. For instance, lower task-relevant activations are seen in the bilateral amygdala among individuals with ODD/CD as compared to ADHD in a number of tasks[174], and studies using dimensional measures of symptom severity have repeatedly observed reductions in the amygdala response to social-emotional stimuli in relation to callous-unemotional traits[210,223,250].

The amygdala is just one part of a limbic/paralimbic network that has been implicated in different aspects of externalizing[251,252]. Neuroimaging studies of psychopathy especially emphasize the orbitofrontal/ventromedial prefrontal cortical (OFC/VMPFC) region[253], that shares strong structural and functional connectivity with the amygdala[254]. Such an involvement is consistent with the key role of this region in social cognition, including empathy and moral reasoning[255,256], and has helped form the basis of one of the most prominent neural models of psychopathy[253]. Critically, portions of this region have long been associated with the ability to inhibit behavior, with lesions often causing both antisocial behavior and problems with impulsivity and disinhibition[257]. It is thus notable that phenotypic associations with structural and functional features in these circuits extend beyond antagonism or callous-unemotional traits. Both human and animal models demonstrate the importance of the OFC/VMPFC region to both substance use history and the risk for developing substance use[258-260] as well as behavioral addictions[261].

Despite indications of overlap that point to involvement beyond antagonism or disinhibition domains, important differences emerge between ventromedial and ventrolateral prefrontal regions, which appear generally consistent with the core cognitive and emotional functions of these regions. Problems with social antagonistic factors are more prominently reflected in ventromedial regions, while alterations in ventrolateral regions (lateral orbital/inferior frontal) are more related to cognitive control (including response inhibition) and executive functions[262]. For instance, deficits in cognitive control show significant associations with task-related inferior frontal gyrus engagement in both substance dependence and ADHD[263,264].

The dorsal anterior cingulate cortex has been of particular interest in relation to externalizing due to its role in both attention and error monitoring. Alterations in both structure and function have been reported for this area in relation to various externalizing conditions, including ADHD[263,265,266], psychopathy and violent behavior[252], disruptive behavior[267], substance dependence[260,268,269], and behavioral addictions[261]. These findings are of particular interest given the importance of this region in the generation of the ERN[219], providing convergent evidence for a core role of this area in cognitive control deficits in externalizing problems as a whole (i.e., at the superspectrum level of the HiTOP system).

In considering the involvement of cortical areas in externalizing psychopathology, it should be noted that some neural correlates may extend quite broadly, even if particular areas play more focal roles in the expression of specific forms of externalizing. For example, the largest meta-analysis to date of findings for ADHD[265] reported evidence not only for lower surface area in frontal, cingulate and temporal cortical regions, but also lower average effect across the whole cortical area, with the severity of this overall deficit declining from childhood to adolescence and eliminated by adulthood. It will be increasingly important to consider how phenotypic expressions of externalizing are related to, and change with, processes of brain maturation[270,271].

The basal ganglia have been a further focus of interest in the externalizing literature. In particular, dysfunction in mesolimbic and nigrostriatal systems has been repeatedly implicated in reward-motivational processes relevant to risk for and development of addictions[272-274], and also ADHD[265,275,276]. Differences in the functioning of these systems have been linked to altered processes of reward valuation, discounting behavior and impulsivity that characterize externalizing problems[264,277-279]. Even with respect to antagonistic behaviors, individual differences in the functioning of mesolimbic circuits may dramatically affect the manner in which antagonistic actions are expressed – for example, in the sort of impulsive-antisocial actions that emerge in these conditions.

In one of the few studies to examine neuroimaging activation in relation to an externalizing factor, while controlling for scores on a general psychopathology factor, fronto-parietal network hypoactivation during a working memory task was related to increased scores on a "behavioral disturbance" factor, primarily comprising ADHD and CD symptoms[280]. These findings are complemented by recent work reporting relations for the same behavioral disturbance factor with enhanced connectivity within the fronto-parietal control network, but decreased connectivity within the default mode network[281]. Other dimensional measures of externalizing have similarly been associated with network dysfunction in many of the same regions identified in the foregoing summary of findings[282,283]. Consideration of neural networks and their features, as opposed to individual brain regions, almost certainly will prove essential to characterizing the role of neural systems and processes in externalizing problems.

Other biomarkers

Aberrant patterns of DNA methylation have been linked to externalizing psychopathology, including addiction[284,285] and antisocial behaviors[286-288]. Epigenetic findings also indicate common

downstream biological processes in ODD and ADHD, including dysregulation of long-term neuronal synaptic plasticity[289]. DNA methylation is thought to represent a molecular pathway through which environmental exposures become translated into phenotypic variation, conferring increased susceptibility to externalizing disorders[290,291]. Accordingly, one study identified an epigenetic risk score to broad (tobacco, cannabis and alcohol) substance abuse liability, which mediated the prospective association between prenatal maternal tobacco smoking and adolescent substance use[292].

An inflammation-related epigenetic risk score at birth was associated with higher externalizing problems across childhood and adolescence[293]. Elevated levels of pro-inflammatory markers (e.g., cytokines, C-reactive protein) in peripheral tissues such as blood have also been reported in externalizing psychopathology[294-296], including ADHD[297-299], antisocial PD[300], and substance abuse[300-303], although the overall evidence in this respect is mixed.

Meta-analytic evidence supports lower cortisol levels in patients with ADHD[304]. In general, reduced cortisol is also associated with persistent aggression and other antisocial and disinhibited behaviors in children and adults[305-307]. Moreover, blunted cortisol response to stress has been associated with relapse in patients with addiction[308]. Thus, lower cortisol may reflect an impairment in the ability to regulate stress responses that underpins chronic externalizing psychopathology, as well as other forms of psychopathology more broadly[309].

Low platelet monoamine oxidase B (MAO-B) enzyme activity, which is a proxy of low central serotonergic functions, has been consistently shown to correlate with impulsive, aggressive and antisocial personality traits and behaviors, including ADHD[304], alcohol-related problems, and smoking[310]. The role of MAO-B in externalizing disorders is thought to be independent of the effects of tobacco smoking on the enzyme[311]. Moreover, there is evidence for low cerebrospinal fluid serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) levels characterizing alcohol abuse and antisocial behavior, including disinhibited forms of aggression[312,313], although this effect remains debated[314]. Thus, serotonin hypofunction may be a shared biological mechanism underlying disinhibited and antagonistic psychopathology.

Overall, research evidence suggests that conditions within the disinhibited and antagonistic externalizing spectra share common biological signatures. However, conclusions have been constrained by methodological limitations of the existing studies, including small sample sizes, focus on a single disorder, and paucity of longitudinal designs, which are particularly relevant for disentangling biological markers of risk vs. consequences of substance use and/or medication.

Temperamental antecedents

Continuity in the traits that underlie the externalizing superspectrum, beginning in early childhood through adolescence and adulthood, has been documented by research[74,315-319].

For example, disinhibition is captured by low effortful control in early childhood[315,316], which has been shown to be a robust predictor of subsequent externalizing behaviors[320,321]. This literature is paralleled by evidence that low agreeableness and conscientiousness (captured together in low effortful control) together predict externalizing behaviors later in childhood and adolescence[315,320]. Negative affectivity has also been found to consistently predict externalizing[320,321], but with low specificity, as it tends to act as a broadband risk for subsequent psychopathology[31,322].

A similar pattern of low effortful control and high negative affectivity has been found to prospectively predict antisocial behavior indicators, including CD, ADHD, ODD and antisocial PD[13,321,323-327]. By contrast, limited evidence exists for intermittent explosive disorder[328]. A large prospective study (N=4,983) in Australia found that high negative affectivity, low effortful control, and high surgency (extraversion) at age 4-5 each uniquely predicted the development of ADHD and CD symptoms to age 12-13[329]. Similarly, a study of two birth cohorts from Norway (N=797) found that high negative affectivity and high surgency predicted increases in ODD symptoms from age 4 to 6[326]. Although not included in traditional models of temperament, callous-unemotional traits in childhood and adolescence (i.e., low empathy, lack of remorse, and insensitivity to distress of others) also robustly and prospectively predict risk for severe antisocial and related behaviors[224,330].

There is little evidence regarding the childhood antecedents of adult PDs included in the antagonistic spectrum of the HiTOP model (e.g., histrionic, narcissistic and paranoid PD)[317], while some research has found that negative affectivity[316,331] and low effortful control[331,332] predict borderline PD, mirroring the findings for other externalizing disorders. Finally, SUDs, reflecting disinhibited externalizing in the HiTOP model, are consistently related to low effortful control[333,334], as well as high negative affectivity[334], with some evidence also pointing to an association with surgency/extraversion (e.g., for cannabis use)[335].

Overall, the combination of negative affectivity with low effortful control represents a consistent constellation of temperamental traits that acts as an antecedent to the externalizing superspectrum. Disinhibited and antagonistic spectra do not tend to show differential associations with childhood temperament, although there is some evidence that callous unemotionality represents an additional risk factor for severe antisocial behavior.

Illness course

Several authors have described a trajectory of externalizing behaviors that begins with hyperactivity and impulsivity in preschool-age children, followed by delinquency in middle school, and SUDs and antisocial personality in late adolescence and emerging adulthood[336-338]. This pattern of progression of externalizing behaviors suggests a shared etiology, and has led to the suggestion that the so-called "co-occurrence" among individual DSM externalizing disorders is largely artifactual, stemming from the split of a unitary construct into multiple diagnoses.

The validity of the externalizing superspectrum is also supported by the high stability over time of externalizing behaviors[339,340], from middle childhood through late adolescence[340]. Olson et al[341] measured externalizing outcomes throughout the school-age period and at age 17 using a multi-informant approach. They found that children at risk for externalizing problems later in childhood and at age 17 were perceived as "difficult" and resistant to control as toddlers. Parental perceptions about child behaviors predicted externalizing behavior as early as at 13 months and remained persistent predictors throughout late adolescence.

Antagonistic and disinhibited spectra have not shown substantial evidence of differential patterns of developmental trajectories.

Treatment response

Numerous treatments have proven effective for a broad array of externalizing disorders in children and adolescents, including behavioral/psychosocial[342-344], systems- or school-based[345-347], and psychopharmacological interventions[348-351], while only few treatments have been successfully used for externalizing in adults (for instance, motivational interviewing has long been used to treat SUDs, and treatment effects have been found to last up to two years, with 75% of participants gaining some type of improvement[352]).

A meta-analysis of 36 randomized, between-subjects comparison studies of psychosocial treatment efficacy for externalizing problems in children less than 8 years of age[353] found that general externalizing symptoms showed the largest treatment response, followed by opposition/non-compliance. Impulsivity/hyperactivity showed the weakest response (although the effect size was still within the "medium" range). These findings suggest that a dimensional approach designed to treat specific components of externalizing may have greater clinical utility than applying individual treatments to individual disorders.

In support of a dimensional approach, Epstein et al[354] carried out a meta-analysis of 28 studies of psychosocial interventions for childhood externalizing problems. Using random effect variances, they found that dimensional externalizing severity scores accounted for significant additional variance in predicting treatment outcomes.

Furthermore, there appears to be utility for assessing the full range of the externalizing superspectrum in randomized clinical trials designed to treat externalizing psychopathology. For example, in the meta-analysis by Battagliese et al[355], the authors stated that they could not examine effects of cognitive-behavior therapy on certain diagnostic subgroups because no studies measured ADHD symptoms in children with a diagnosis of ODD and only two studies included children affected by CD. Given the high rates of diagnostic co-occurrence within the externalizing spectrum, assessing and treating the full range of externalizing problems for an individual client may be a parsimonious and effective approach to designing future interventions.

Summary of validity evidence

The validity evidence reviewed herein is summarized in Table 2. This table shows a substantial coherence within the disinhibited and antagonistic spectra, as well as an overlap between them. This supports the validity of a hierarchical conceptualization, involving an overarching externalizing superspectrum with two distinguishable spectra. As shown in the column "Summary of specificity", most validators (sixteen) are evident for the broad externalizing superspectrum, with some (eight) evident for disinhibition and one for antagonism.

Notably, cells that are blank in the table indicate a lack of evidence, not the absence of an effect. These may therefore be fruitful areas for future inquiry. Generally speaking, large sample designs where all elements of the externalizing superspectrum are well characterized, along with multiple validators, can improve inferences by helping to address questions of generality and specificity.

Many validators considered here may not be specific to externalizing. For example, pro-inflammatory biomarkers were characterized as also related to the psychosis superspectrum of HiTOP in our previous paper in this series[19]. These and other factors (e.g., childhood adversity) are likely broadly relevant to psychopathology risk, and not specific to externalizing risk.

Generally speaking, these validity findings dovetail well with the structural perspective on psychopathology taken in the HiTOP consortium. In contemplating the validity of psychopathological concepts, it is no longer sufficient to focus on putative diagnostic categories in isolation. Rather, broad characterization of psychopathological phenomena, along with assessment of specific validators in large samples, can deepen our understanding by revealing the interplay between the structural organization of psychopathology and multiple putative causes and correlates.

UTILITY EVIDENCE

Reliability

Some of the largest studies on the reliability of the diagnosis of mental disorders have come from field trials of the official classification systems, the DSM and ICD. Results of the DSM-5 field trials documented moderate/good reliability for alcohol use disorder (test-retest kappa coefficient of 0.40) and questionable reliability for antisocial PD (kappa=0.21)[356]. These estimates are lower than those observed in field trials of DSM-IV, largely due to the fact that "usual clinical interview approaches"[356] were utilized in the DSM-5 field trials instead of highly structured diagnostic interviews as in the DSM-IV field trials[357]. Nevertheless, complementary analysis of DSM-5 cross-cutting dimensional measures of externalizing-related constructs (confined to alcohol, tobacco and illicit drug use) demonstrated higher reliability compared to their categorical counterparts[358].

Direct comparisons of continuous and categorical measures of psychopathology are rare. In a comprehensive review, Markon

Table 2 Validators of the disinhibited and antagonistic spectra

	Both spectra						Disinhibited spectrum				Antagonistic spectrum				Summary of specificity
	ASPD	CD	ODD	IED	BPD	Traits	AUD	SUD	ADHD	Traits	NPD	HPD	PPD	Traits	
Genetics															
Family/twin	++	+	+		++	+	+	+++	+	++	++	++		+	B
Polygenic risk		+	+						+						B
GWAS	+	+	+		+		+++	+	+	++					D
Environment															
Neighborhood risk factors						++		++							B
Peer interactions						++		++							B
Childhood maltreatment	+++	+++	+++	+++	+++	+++		+++							B
Cognition/Neurobiology															
Cognitive deficits	+++	+++	+	–	++	+++	+++	+++	+++	+++	–	–	–		B
Emotional processing abnormalities	+++	+++	++	+	+++	+++		++	+++	+	+	+	+		B
Reduced amygdala volume	++	+	+		++	+		++	+					+++	B
Involvement of OFC/VMPFC						++		+++							B
Task-related inferior frontal gyrus engagement								++	++						D
Aberrations in dorsal anterior cingulate				+				++	+++					+	B
Reward system dysfunction								+++							D
Dysfunction in mesolimbic and nigrostriatal systems								+++	+++	++					D
Reduced amygdala activation to fearful faces		++												+++	A
Blunted P300							++	++							B
Blunted error-related negativity										++					D
Biomarkers															
DNA methylation						+				+					B
Elevated pro-inflammatory markers	+							+	+						D
Low cortisol						+		+	+						D
Low MAO-B						+	+		+	+					D
Antecedents/Course															
Low effortful control	++	++	+		++	+++		+++	++	+++				++	B
High negative affectivity	+	+	++		++	+++		+	++						B
Extraversion/surgency		+	+					+	+						B
Treatment															
Response to psychosocial interventions						+				+				+	B

+: some evidence for effect, ++: some replications, +++: repeatedly replicated finding, –: some evidence for reverse effect, – –: some replications for reverse effect, – – –: repeatedly replicated reverse effect, A – linked to antagonism, D – linked to disinhibition, B – linked to both, ASPD – antisocial personality disorder, CD – conduct disorder, ODD – oppositional defiant disorder, IED – intermittent explosive disorder, BPD – borderline personality disorder, AUD – alcohol use disorder, SUD – substance use disorder, ADHD – attention-deficit/hyperactivity disorder, NPD – narcissistic personality disorder, HPD – histrionic personality disorder, PPD – paranoid personality disorder, GWAS – genome-wide association studies, OFC/VMPFC – orbitofrontal/ventromedial prefrontal cortex, MAO-B – monoamine oxidase B.

et al[4] found that continuous measures of psychopathology were generally more reliable than discrete measures across all psychopathology domains, and that the overall meta-analytic reliability estimate for the externalizing domain was 0.77.

A growing body of research has examined the reliability of PDs and personality dimensions that fall within the externalizing spectrum. Using the Personality Inventory for DSM-5 (PID-5)[359], a questionnaire specifically developed to operationalize the DSM-5 dimensional trait model for PDs, a high internal reliability of the disinhibition (McDonald's omega = 0.80) and antagonism (omega = 0.83) domains was documented[360].

In a study of the stability of PID-5 domains over a one-year period, the externalizing domains of the PID-5 were relatively stable across a one-year period in individuals diagnosed with PDs[361]. In a study examining both personality traits and PDs, high levels of stability over a two-week period (referred to as dependability by the authors) were reported in PID-5 domains of antagonism (0.86) and disinhibition (0.86)[362]. In addition, the authors provided evidence of clear advantages of dimensional over categorical ratings for PDs traditionally linked to the externalizing domain (e.g., antisocial PD).

Explanatory and prognostic power

Using data from two waves of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study, a large general population longitudinal investigation, Kim and Eaton[61] demonstrated that an externalizing dimension at Wave 1 predicted Wave 2 mental disorder diagnoses more strongly than individual diagnoses.

Externalizing dimensions have also outperformed diagnoses when explaining variance in suicidality, psychotic-like experiences and internalizing-type disorders[363]. Furthermore, the externalizing dimension has been shown to mediate the relations of constructs such as childhood maltreatment with diagnosed externalizing-type mental disorders (e.g., SUDs)[147]. Similar general vs. disorder-specific findings are evident when examining constructs such as perceived racial discrimination[151], stress responsivity[59], and transmission of externalizing disorders from parents to offspring.

Collectively, this research points to the superiority of the HiTOP conceptualization of externalizing psychopathology in predicting a wide range of disorder validators.

Clinical utility

The utility of integrating the HiTOP model into clinical practice has been recently addressed[364]. Conway et al[44] demonstrated that the HiTOP structure generalizes well to patterns of comorbidity among diagnoses assigned by health practitioners in everyday practice. They further demonstrated that categorical diagnoses did not offer additional incremental validity when predicting suicidality and self-injury, over and above the identified HiTOP dimensions.

Research on the clinical utility of dimensional versus categorical conceptualizations of externalizing largely comes from the PD field, and draws heavily from studies that examine practitioner ratings of utility. Using case vignettes as well as data obtained from actual patients, these studies evaluate the clinical utility of dimensional and categorical frameworks across various dimensions of utility (e.g., ease of use, utility in communicating with other health professionals, usefulness in formulating a therapeutic intervention, and usefulness in treatment planning). Recently, Bornstein and Natoli[365] summarized this literature and found that dimensional models of PD are rated more positively than categorical models with respect to most areas of clinical utility.

MEASUREMENT

The Externalizing Spectrum Inventory (ESI) is one of the most well-validated instruments to measure individual facets and global levels of the externalizing superspectrum. The ESI was developed using a bottom-up process to target 23 unidimensional facets of externalizing and capture the hierarchical structure of broad externalizing (or disinhibition) along with specific factors associated with callousness/aggression and substance abuse[15].

Independent validation studies have demonstrated that the broad factors of the ESI possess concurrent validity against the Multidimensional Personality Questionnaire (MPQ)[366], measures of integrity, and a range of DSM-IV symptoms of externalizing disorders, personality traits, psychopathy, and symptoms of substance dependence[219,367,368].

Recent efforts have focused on improving the clinical utility of the ESI via the development of data-driven brief forms and adaptive scales. Patrick et al[16] constructed brief forms of the 23 facets with a total of 160 items (down from 415 items), ranging from 3 to 11 items per facet, which maintained high internal consistency, replicated the structure of the full ESI, and demonstrated similar validity in relation to the MPQ. Additional independent validation has confirmed the favorable psychometric properties of the brief form[369]. More recently, Sunderland et al[370] have demonstrated the feasibility of computerized adaptive versions of the ESI, producing similar scores as the full ESI with acceptable levels of reliability using very few items tailored to each respondent.

Omnibus clinical personality inventories are also available to assess the externalizing spectrum. Primary examples include the Minnesota Multiphasic Personality Inventory-2-Restructured form (MMPI-2-RF)[371] and the Personality Assessment Inventory (PAI)[372]. Specifically, the MMPI-2-RF captures behavioral/externalizing dysfunction at the higher order level, which comprises pervasive dysfunction with under-controlled or acting-out behaviors, as well as specific facet measurement (juvenile conduct problems, substance abuse, aggression, and anger proneness), all of which have been shown to directly map onto the same externalizing spectrum model as HiTOP and the ESI[373-376].

The MMPI-2-RF Personality Psychopathology Five (PSY-5-RF) scales also have trait-level measures of higher-order antagonism

(aggressiveness) and disinhibition (disconstraint). Furthermore, factor analytic research with the PAI scales has typically revealed three- or four-factor structures, with factors resembling disinhibition and antagonism usually emerging[373].

There are also several personality measures that map onto, and therefore operationalize, the externalizing superspectrum via dimensional personality traits, including the PID-5[359], the NEO Personality Inventory 3 (NEO-PI-3)[377], and the Comprehensive Assessment of Traits Relevant to Personality Disorder (CAT-PD)[378]. The PID-5 explicitly measures the antagonism and disinhibition trait domains that emerge from a broader externalizing superspectrum[379]. Similarly, a conjoint analysis of several dimensional personality trait inventories – the PID-5, CAT-PD and NEO-PI-3 – has provided evidence of a five-factor solution that bore strong resemblance to the HiTOP model and included factors for antagonism and disinhibition that converged onto a single externalizing dimension in hierarchical analysis[83].

In child and adolescent populations, a number of measures have been used extensively to assess externalizing and disinhibited behaviors, such as the Child Behavior Checklist (CBCL)[380], the Strengths and Difficulties Questionnaire (SDQ)[381], and the Diagnostic Interview Schedule for Children (DISC)[382], with factor analysis consistently identifying strong coherence between these measures and the broader HiTOP structure[383-385].

Finally, there are numerous scales designed to measure specific facets of externalizing and disinhibited behavior, such as substance use, impulsiveness, and aggression[386-388].

IMPLICATIONS

The HiTOP approach aims to advance our understanding of the natural organization of externalizing psychopathology in at least three major ways.

First, externalizing psychopathology encompasses two spectra, disinhibition and antagonism. These spectra show both similarities and differences, consistent with the fundamentally clarifying idea of disinhibitory and antagonistic aspects of a broader and more general externalizing superspectrum. Nevertheless, to characterize a patient fully, a profile across major psychopathology spectra needs to be considered, as detailed in previous HiTOP publications[1,19,364].

Second, the HiTOP approach underscores a growing consensus that clinically significant externalizing problems lie on a continuum with normative functioning and maladaptive traits. Developmentally earlier expressions of disinhibitory and antagonistic traits often precede the onset of serious sequalae (e.g., behaviors that are grounds for arrest). In this way, the HiTOP approach melds dimensional and developmental perspectives on psychopathology, as parts of a more integrated approach to understanding both development and broad population-level variation in socially consequential externalizing tendencies.

Third, the HiTOP approach addresses heterogeneity within externalizing problems by explicating specific trait and symptom dimensions that constitute broader spectra. Figure 1 provides an evidence-based guide to constituent narrow-band elements of externalizing. Nevertheless, continued research on the nature of specific sub-elements of externalizing psychopathology would be welcome, as the field pivots toward basing nosology on evidence, as opposed to diagnosis by tradition and putative authority[15,374].

FUTURE DIRECTIONS

The proposed HiTOP model of the externalizing superspectrum is based on extensive evidence. Nevertheless, intriguing possibilities exist to explore the discrete vs. continuous nature of psychopathology based on data. The HiTOP model is meant to include all empirical psychopathological entities, whether dimensional or categorical in nature. Only dimensions have been established empirically to date. Setting aside the complex political issues implied by this situation (e.g., the way authoritative nosologies tend to recognize committee-derived categories as opposed to empirically-derived dimensions), quantitative techniques can adjudicate between more continuous and more discrete accounts of the structure of psychopathology. Further research along these lines can help to continue to place psychiatric nosology on firmer empirical footing[3,19].

Systematic research can also provide a means for linking psychopathological variation with intervention implications in a principled manner. Rather than imposing arbitrary diagnostic thresholds, diagnostic algorithms can link clinical presentations with optimal intervention strategies. Practically speaking, clinical decisions rarely focus on "to treat or not to treat". Rather, an ordinal set of interventions varying in intensity is typically deployed in response to a corresponding level of clinical need. For example, externalizing problems frequently present as SUDs, because substance dependence creates an acute clinical need. Substance use intervention can range from medically responsible outpatient detoxification, to partial hospitalization, to inpatient services. This rough ordinal scale of intervention is typically tethered to clinical need (e.g., medical complications may require close observation to resolve, and a corresponding inpatient stay). Ultimately, these sorts of treatment options can be tethered to intensity of presentation in a principled way, relying on the types of evidence reviewed herein.

CONCLUSIONS

The HiTOP approach to clinical diagnosis provides an empirically based and hierarchical conceptualization of externalizing disorders that was derived from evidence. The validity evidence reviewed herein is extensive, and the utility of the approach was also reviewed and is readily apparent. Assessment instruments for externalizing constructs already exist, and the HiTOP approach can therefore be readily implemented.

Further research will be beneficial, but the HiTOP model is ready for use by scientists and clinicians interested in basing

their approaches on evidence as opposed to putative authority. The HiTOP approach addresses problems of heterogeneity, comorbidity and low reliability, thereby providing valid and reliable descriptions of patients to drive both discovery and intervention.

APPENDIX

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