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Neurobiology and the Hierarchical Taxonomy of Psychopathology: progress toward ontogenetically informed and clinically useful nosology

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The Hierarchical Taxonomy of Psychopathology (HiTOP) is an empirical structural model of psychological symptoms formulated to improve the reliability and validity of clinical assessment. Neurobiology can inform assessments of early risk and intervention strategies, and the HiTOP model has greater potential to interface with neurobiological measures than traditional categorical diagnoses given its enhanced reliability. However, one complication is that observed biological correlates of clinical symptoms can reflect various factors, ranging from dispositional risk to consequences of psychopathology. In this paper, we argue that the HiTOP model provides an optimized framework for conducting research on the biological correlates of psychopathology from an ontogenetic perspective that distinguishes among indicators of liability, current symptoms, and consequences of illness. Through this approach, neurobiological research can contribute more effectively to identifying individuals at high dispositional risk, indexing treatment-related gains, and monitoring the consequences of mental illness, consistent with the aims of the HiTOP framework.

Introduction

The Hierarchical Taxonomy of Psychopathology (HiTOP) was advanced to characterize the empirical structure of psychopathology and overcome the myriad problems inherent in consensus-based nosologies such as the Diagnostic and Statistical Manual of Mental Disorders (DSM). The HiTOP model, which is derived from factor-analytic studies of symptoms, diagnoses, and maladaptive trait data, describes a hierarchy of continuous dimensions accounting for broader spectra and super-spectra as well as narrower, symptom-level manifestations of psychopathology (Figure 1). For example, the Internalizing spectrum encompasses narrower subfactors including Fear and Distress, which, in turn, encompass even more specific clinical phenotypes (e.g., social anxiety, insomnia). One particular strength of
HiTOP’s emphasis on transdiagnostic common factors contrasts with the recent Addictions Neuroclinical Assessment (ANA) framework, which attempts to use neurobiology to address heterogeneity within a single phenomenon (i.e., addiction), failing to consider that many neural indicators of latent liability for psychopathology need to be distinguished from those reflecting symptoms and consequences of clinical illness. The ANA and similar initiatives do not specifically address this critical point, and it remains unclear what aspects of substance addiction are indexed by variables they identify as relevant neural indicators. This muddled picture is likely to impede the development of improved measurement of manifest symptomatology, as represented in the HiTOP framework, provides an unprecedented opportunity to elucidate the ontogeny of mental illness—the developmental-experiential processes that, over time, give rise to psychopathology and its consequences. A deeper, developmentally informed understanding of the mechanisms and processes that contribute to the range of known psychological problems would contribute directly and importantly to prevention and intervention efforts, consistent with calls by psychiatrists for transdiagnostic “staging models” of psychopathology. The goal of the present paper is to describe an ontogenetic framework for continuing research on the emergence, progression, and persistence of psychopathology in the context of the HiTOP framework. In doing so, we argue for the utility of neural systems variables alongside experiential and behavioral descriptions in characterizing these pathways.

Importantly, however, we also highlight distinctions in the role neurobiology is expected to play at different points in the ontogeny of psychopathology. For example, neural indicators of latent liability for psychopathology need to be distinguished from those reflecting symptoms and consequences of clinical illness. The ANA and similar initiatives do not specifically address this critical point, and it remains unclear what aspects of substance addiction are indexed by variables they identify as relevant neural indicators. This muddled picture is likely to impede the development of HiTOP provides a framework for more systematically investigating common and specific etiological processes in psychopathology using neurobiological methods and measures.

Improved measurement of manifest symptomatology, as represented in the HiTOP framework, provides an unprecedented opportunity to elucidate the ontogeny of mental illness—the developmental-experiential processes that, over time, give rise to psychopathology and its consequences. A deeper, developmentally informed understanding of the mechanisms and processes that contribute to the range of known psychological problems would contribute directly and importantly to prevention and intervention efforts, consistent with calls by psychiatrists for transdiagnostic “staging models” of psychopathology. The goal of the present paper is to describe an ontogenetic framework for continuing research on the emergence, progression, and persistence of psychopathology in the context of the HiTOP framework. In doing so, we argue for the utility of neural systems variables alongside experiential and behavioral descriptions in characterizing these pathways.

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effective interventions. Differences among latent liability, current symptomatology, and consequences of psychopathology warrant strong consideration in the search for biological indicators of mental illness.

The HiTOP framework, too, can benefit from a formalized ontogenetic model of psychopathology. The current focus of HiTOP is on the most clinically salient point of this progression—ie, current manifest symptomatology. However, it cannot be assumed—indeed, it seems unlikely—that biological correlates of manifest symptom dimensions represented at various levels of the HiTOP hierarchy will necessarily reflect etiological mechanisms contributing to these dimensions. The HiTOP model is descriptive, providing important information about the empirical structure of psychopathology and points of observed cooccurrence versus distinctiveness of symptoms, with major implications for nosological refinement. Building upon the model as it stands, the ontogenetic synthesis presented here is intended to more clearly explicate the temporal and etiological aspects of psychopathology. From this perspective, a systematic, developmentally oriented program of research is needed to characterize the nature of biological processes that are relevant to various stages in the progression from latent liability to active psychopathology and its consequences.

The basic form of the proposed ontogenetic framework for psychopathology is depicted in Figure 2. Each element of the framework is discussed in further detail below with reference to the running example of substance problems, as well as other syndromes where space allows. Briefly,
The model defines liability factors as premorbid, transdiagnostic individual-difference characteristics conducive to psychopathology. These risk factors are presumed to reflect genetically influenced neural and cognitive processes, as well as early childhood experiences such as maltreatment or fetal alcohol exposure, that create a context for the operation of experiential influences on psychological processes and behavior. The delineation of dispositional characteristics that prospectively predict psychopathology can help to identify individuals in greatest need of preventive efforts and those likely to be most amenable to particular treatments.

Finally, consequences of psychopathology encompass the lasting psychological and neurobiological alterations that are caused by mental illness and persist despite fluctuations in symptom expression. Of particular interest in this ontogenetic model are the structural and functional neural abnormalities caused by episodes of mental illness, consistent with a “scar model.” “Scarring” differs from current symptomatology in that it is maintained regardless of improve-
ment in symptoms. Consequences of psychopathology play an important role in the ontogenetic pathway because they can be used to monitor the progression of a syndrome in terms of persisting effects on the brain and behavior.

**Liability and its neural indicators**

Within the ontogenetic framework, liability factors can be defined as genetically influenced dispositions, susceptible to early environmental modulation, that are associated with risk for psychopathology prior to the onset of illness. The identification of liability factors is a crucial research priority, as they serve as the basis for investigating how distal, heritable dispositions intersect with and contribute to more proximal pathogenic processes to give rise to manifest psychopathology. Further, research on latent liability factors and their manifestations across particular measurement modalities (eg, specific patterns of neural response; Figure 3) can allow for the identification of individuals most likely to exhibit later psychopathology, so they can be prioritized for prevention programs. Knowledge of an individual’s constellation of liability factors could also be used to predict the efficacy of particular intervention approaches and thereby guide treatment planning.

Different strategies can be used to identify indicators of liability and establish their prognostic efficacy (Figure 4). The first and most crucial is to conduct longitudinal studies of young people exhibiting a candidate liability indicator to determine whether it prospectively predicts the emergence of the expected form of psychopathology. For example, longitudinal studies have identified indicators that are informative about the future likelihood of developing substance problems (SPs) and the probable course of such problems. Of note, although initially aimed at specific SPs such as alcohol or cocaine use disorder, numerous studies over the past several decades suggest that the most robust indicators of SP liability reflect risk for externalizing problems more broadly. The implication is that these indicators operate at higher levels of the HiTOP system (ie, the Disinhibited Externalizing spectrum or Externalizing super-spectrum.) Although not visually depicted in the original HiTOP model (Figure 1), the Externalizing super-spectrum is conceptualized as encompassing the Disinhibited Externalizing and Antagonistic Externalizing spectra. HiTOP-aligned research can facilitate efficient discovery of such principles by attending to multiple levels of the hierarchy simultaneously, rather than requiring decades of research on clinical groups segregated by diagnosis to reach the same conclusion.

![Figure 3. Depiction of the relation of liability to its indicators.](image-url)

Here, liability is conceptualized as a latent (unobservable) predisposition to some form of psychopathology (eg, externalizing problems). This latent factor can be operationalized and measured through observable indicators from different modalities, including neural (eg, blunted target-P3 response), behavioral (eg, lower accuracy on an executive function task), and report-based indicators (eg, higher scores on a questionnaire assessing disinhibition). See ref 37 for further discussion of the relations between latent constructs and observable indicators.
One example of a well-established neural indicator of liability for SPs and other externalizing conditions is the target-P3 event-related potential (ERP), a brain response elicited by infrequently occurring task stimuli requiring a response. The P3 is thought to reflect cognitive processing following stimulus events, and it covaries positively with task measures of executive function. Research beginning in the 1980s found blunted amplitude of the target-P3 ERP response to be consistently linked to SPs, with later research extending this finding to individuals with externalizing problems of other types. Blunted target-P3 was also observed in clinically unaffected relatives of individuals with externalizing problems, such as children of parents with SPs, and twin studies revealed a substantial contribution of genetic influences to target-P3 amplitude. Building on these findings, Iacono and colleagues demonstrated that blunted target-P3 in adolescence predicted subsequent development of SPs and other externalizing problems in adulthood. The prospective nature of this association, together with evidence for familial aggregation, suggests that blunted target-P3 response, as a reflection of diminished cognitive processing of task-relevant stimuli, may constitute an indicator of liability for externalizing psychopathology.

Another key approach to evaluating candidate liability indicators is to quantify genetic influences on an indicator variable’s association with psychopathology using multivariate causal modeling in twin studies. A substantial genetic contribution to the observed covariance between a putative liability indicator and an outcome measure of psychopathology implicates the presence of a common genetic predisposition in both. In conjunction with longitudinal research showing that the indicator predates and prospectively predicts symptomatology, twin study analyses demonstrating common genetic influences provide compelling evidence that the variable in question operates as an indicator of liability to that form of psychopathology. As an example, Hicks and colleagues used twin modeling to demonstrate that the association between blunted target-P3 amplitude and externalizing symptomatology was attributable entirely to genetic influences in common between the two. In sum, blunted target-P3 amplitude appears to be evident prior to the onset of externalizing psychopathology and shares heritable variance with externalizing problems. (Of note, target-P3 and other executive function-related liability indicators are unlikely to be innately determined, but rather represent a product of genetic and environmental influences that give rise to a characteristically disinhibited cognitive-motivational style.) These features suggest that blunted target-P3 response can be considered an indicator of liability for externalizing psychopathology.

Given that known liability factors tend to operate in a multifinal manner—increasing risk for a variety of psychopathologies—future research should establish whether liability factors as described here relate mainly to higher-order HiTOP dimensions, or in some cases relate selectively to a more specific form of psychopathology. For example, neuroimaging studies suggest that differentiable structural and functional correlates are observed at general versus more specific levels of the hierarchy, but it is not yet known whether these correlates function as liability indicators. Similar to Barlow’s triple vulnerability model, which posits that increasingly specific liabilities guide the expression of anxiety, transdiagnostic liabilities operating at higher levels of HiTOP (eg, the Externalizing superspectrum) could be supplemented by more specific risk factors to produce particular signs and symptoms at the lower levels (eg, SPs).
Indexing liability using measures from different modalities: the psychoneurometric approach

One promising approach to improving the quantification of liability factors is to combine measures of a liability construct from different response modalities (eg, self- or other report, neural reactivity, task performance; Figure 3) into a multi-method “psychoneurometric” composite. For example, liability for externalizing problems can be operationalized by combining scores on one or more questionnaire measures of disinhibition (ie, assessing tendencies to act in impulsive-irresponsible ways) with one or more variants of P3 brain response. This approach to quantifying externalizing liability is advantageous compared with a purely questionnaire-based measure because twin research demonstrates that a larger portion of the composite’s predictive association with externalizing problems can be attributed to shared genetic variance. The reason is that the variance in common between scale-assessed disinhibition and externalizing problems reflects overlap in terms of environmental as well as genetic influences, whereas the variance in common between P3 brain response and externalizing problems reflects mainly overlapping genetic influences (Figure 5). Prospective-longitudinal research could be undertaken to confirm that dispositional characteristics quantified in this manner predate manifest symptomatology and persist...
through remission and relapse, as would be expected of liability factors (Figure 4).

**The role of the environment**

The progression from latent liability to manifest psychopathology depends importantly on environmental influences. For example, genetic predispositions appear to exert greater influence on SPs among adolescents who associate with alcohol-using peer groups, an example of gene x environment interaction. In other words, the contribution of liability tends to be amplified in a developmental context that is conducive to psychopathological expression. Moreover, an individual’s level of exposure to adverse environments can be predicted by genetic liability factors, a phenomenon known as gene-environment correlation. For example, individuals exhibiting weak inhibitory control—a heritable liability factor—appear more likely to select environments that lead to easier drug access, such as deviant peer groups. Moreover, upon initiating substance use, an individual’s overestimation of their peers’ drug use predicts cognitive and physiological changes associated with a worse trajectory. Overall, the cascading associations between liability and environment promote the emergence of psychopathology.

**Current symptomatology and concomitant neural indicators**

Neural indicators of liability, as described above, predate the emergence of clinical symptoms and are likely to remain stable over the course of the illness. In contrast, as psychopathology first arises and fluctuates in severity over time, other neuropsychological indicators are likely to follow a temporal course that parallels symptom changes. Such concomitant indicators are part and parcel of the psychopathology itself (ie, disease-related dysfunction), as they accompany the presence of and changes in subjective experience and observed behavior patterns. Importantly, HiTOP-aligned symptom dimensions allow for the precise delineation of longitudinal relations between self- or other-rated symptoms and neural features, in ways that traditional diagnostic categories cannot. Small changes in expression of HiTOP dimensions over time, regardless of their proximity to arbitrary DSM diagnostic thresholds, could be linked to modest within-person changes in neural response, whereas studies using diagnostic categories would offer far less precision in identifying such associations. An example of a concomitant process pertaining to SPs is incentive sensitization, wherein stimuli that become associated with substance-related reward over time (eg, a hypodermic needle) acquire potency as motivational cues (ie, become objects of “wanting”) separate from the hedonic impact of the substance itself (“liking,” eg, high of heroin). This process is thought to contribute to the maintenance of SPs and proneness to relapse following cessation of use.

**HiTOP provides an ideal platform for ontogenetic research, given its reliable, clearly organized, and structurally valid symptom dimensions**

Incentive sensitization to psychoactive substances can be considered a concomitant indicator of SPs because it appears to (i) develop alongside SPs; and (ii) vary longitudinally with SP symptom severity. Evidence for these points comes from ERP research demonstrating variability in the neural responses to substance-related cues among individuals with varying severity of SPs, as well as longitudinal changes in these responses within SP-diagnosed individuals who experience recovery. One robust electrocortical indicator of incentive sensitization is the alcohol cue reactivity P3 response (ACR-P3), which is evoked by alcohol-related cues in the context of a larger visual categorization task. The ACR-P3 appears to capture incentive valuation (ie, degree of “wanting”) of alcohol and is greater in heavier-drinking individuals. Other ERP indicators of incentive sensitization appear to covary with the longitudinal course of SPs. For example, in one study of individuals treated for cocaine use disorder, increases from pre- to post-treatment in the late positive potential response to pleasant non-drug-related images were found to be associated with decreased craving of cocaine following treatment.

Taken together, these findings suggest that neural indicators of incentive sensitization may covary with the severity of SPs, both across individuals and within the same subjects over time. Importantly, unlike a liability factor, incentive sensitization cannot occur in substance-naïve individuals, instead developing concomitantly with the emergence
of SPs. One benefit of identifying such indicators is that they can then be utilized as measures of within-subject change in psychopathology, including treatment-related improvements. Incorporating regular assessment of these indicators into treatment could be particularly helpful for syndromes characterized by low insight into one’s own symptoms, such as SPs, as a supplement to report-based measures and behavioral tasks (eg, the drug-choice paradigm, in which subjects decide between viewing substance-related and -unrelated images). Knowledge of concomitant neural indicators could also facilitate the development of novel interventions, such as neurofeedback training, that hold promise for ameliorating certain forms of psychopathology.

Neural indicators that change concomitantly with symptomatology can also shed light on the prospective course of psychopathology, perhaps because of their presumed proximity to an underlying neural mechanism. (Note that it is critical not to conflate observed differences between patient and healthy control groups on some neural measure with discovery of a mechanism underlying that form of psychopathology, given: [i] the abovementioned limitations of diagnostic-group research that HiTOP was designed to address, as well as [ii] the impossibility of making mechanistic inferences from cross-sectional, ontogeny-agnostic studies, particularly when relevant experimental work has not been performed.) For example, once an individual has accumulated experience with alcohol, ACR-P3 amplitude appears to prospectively predict increased engagement in heavy drinking; this association may reflect the mechanistic role of incentive sensitization in the transition from repeated alcohol use to alcohol dependence. Whereas neural indicators of liability are clinically useful for identifying individuals at increased risk for psychopathology prior to symptom onset, concomitant neural indicators may have distinct utility for predicting future course among those already experiencing psychopathology.

Complicating matters further, liability and concomitant processes likely interact, such that mechanisms promoting symptom maintenance and exacerbation are enhanced by dispositional risk factors. One example from the neuroimaging literature is that, as incentive sensitization increases, a growing imbalance between incentive reward and executive control brain networks seems to lead to increasingly compulsive drug-related urges. Although executive control network activation in part reflects externalizing-related liability, its interaction with other brain systems in the context of emerging incentive sensitization promotes further development of substance-related psychopathology. This type of interplay is important to consider in studies seeking to identify neurobiological indicators of psychopathology risk and expression.

Consequences of psychopathology

The final component of this ontogenetic framework consists of the lasting consequences of psychopathology, including neurobiological measures indicative of dysfunction caused by illness. In contrast to the concomitant indicators described above, neural indicators that do not abate with the remission of psychological symptoms are consistent with a “scar” resulting from the experience of mental illness. Some of the most apparent consequences of psychopathology are medical, such as liver failure resulting from chronic alcohol overuse, or esophageal damage following frequent purging behaviors in eating pathology. However, psychopathology can also have lasting impacts on many psychological domains, from cognitive ability and personality to sensorimotor adaptations, and these effects are likely mediated by biological changes. Neural consequences of psychopathology play an important role in the ontogenetic pathway because they can be used to monitor the progression of an illness in terms of lasting effects on the brain, in the same way that medical tests can be used to quantify the progression of liver failure.

As discussed for liability factors, one critical tool for establishing a given neural indicator as a consequence of psychopathology is longitudinal research. In contrast to liability indicators, which must be present prior to the onset of psychopathology and persist over the course of illness, and concomitant neural indicators, which must be present along- side clinical symptoms, scarring becomes apparent only following symptom onset and must persist in the face of changes in clinical presentation. Studies examining such a progression are exceedingly rare, and none to our knowledge have used HiTOP-aligned symptom-dimension designs. In the psychosis field, research has suggested that individuals diagnosed with schizophrenia may experience greater brain tissue loss per year than healthy controls, with inconsistent links between symptom fluctuations and the rate of neural degeneration. However, these
gray matter alterations may also be present in high-risk premorbid individuals, suggesting they are not solely a consequence of the experience of psychosis. The advent of large-scale longitudinal studies that include functional and/or structural neural data will be of enormous utility in the search for indicators of neural scarring, as premorbid brain data will be available for those who go on to develop psychopathology.

In addition to longitudinal studies, co-twin control analyses provide another means for evaluating whether an individual difference characteristic reflects liability for versus consequences of psychopathology. This approach involves comparing twins with differing levels of symptomatology on a characteristic of interest, controlling for genetic and shared environmental influences. Evidence from co-twin control studies suggests that central nervous system hyper-arousal and resultant negative affectivity—as well as alterations in electrocortical dynamics related to response inhibition—occur as consequences of alcohol use, and that alcohol, cannabis, and tobacco use contribute causally to reduced ventral striatum functional connectivity. Each of these indicators is strongly linked to externalizing psychopathology, but they are also implicated in other syndromes; in contrast, as described above, gray matter decrements appear relatively unique to psychosis. It remains to be seen which neural indicators reflect scarring effects at differing levels of specificity within the HiTOP hierarchy.

**Research on other spectra and future directions**

Various report-, performance-, and physiology-based measures have been shown to relate to diverse forms of psychopathology, but it remains unclear whether the constructs assessed by such measures represent stable pre-existing liability factors, correlates of current psychopathology, or lasting consequences of illness. Ongoing work on the ontogeny of mental illness will require comprehensive, multimodal assessment as well as longitudinal studies with genetically informative samples (eg, twins and/or individuals providing genomic data).

The topics discussed here are not unique to SPs, nor to the Externalizing super-spectrum. Neural indicators of liability have been described in relation to numerous other forms of psychopathology. For example, the reward positivity (“RewP”) brain-ERP response shows a consistent negative association with major depression and prospectively predicts increases in depressive symptomatology. Importantly, this brain-response measure appears to index proneness to depression rather than neural dysfunction associated with current depressive symptomatology. Bolstering the case for liability status, reduced RewP response is present in unaffected family members of depressed individuals and is observed even in preschool-aged depressed children. The RewP is also beginning to be examined in relation to other forms of psychopathology involving reward system dysfunction, including SPs. Beyond the RewP, numerous studies demonstrate that neurobiological indicators, including other ERP measures, can be used to index liability for a range of psychopathology, including—but not limited to—SPs. A limitation of work to date is that relatively few studies have utilized dimensional symptom measures, and none to our knowledge have explicitly examined higher-order spectra of psychopathology in relation to ERPs, apart from the externalizing-P3 literature described above. HiTOP provides an optimal platform for testing research questions of this kind. For example, the notion that neural indicators of liability might operate primarily at higher-order levels of the HiTOP model represents an important topic for future investigation.

In contrast to the growing literature on neural indicators of liability, relatively little dimensional work has been undertaken to distinguish these from neurobiological indicators of current symptoms or lasting consequences for any of the HiTOP dimensions. Much more extensive longitudinal and dimensional work is needed to better understand the latter two elements of the ontogenetic pathway, with the goal of predicting the future course of clinical problems and monitoring disease- and treatment-related change using neural measures.

Beyond the individual model elements we have emphasized (liability, current symptomatology, consequences) and our specific focus on neurobiological indicators, the ontogenetic framework proposed here is not unique to the SP literature, nor to explicitly HiTOP-aligned research. It complements and extends existing ontogenetic models of externalizing, bipolar, and thought disorders. For example, McGorry et al proposed a “clinical staging” model of psychosis, mania, and depression wherein signs and symptoms largely overlapped at the earliest stages but became increasingly
distinct during the progression to acute, severe symptomatology. In parallel, our model posits that factors driving symptom expression at early stages should not be studied in isolation (e.g., mania versus control group), but rather in line with a hierarchical understanding of mental illness at the HiTOP spectrum or super-spectrum level. For purposes of early identification and intervention, time is better spent understanding liability processes contributing to the generation of disordered cognitive and behavioral patterns shared across syndromes (i.e., at higher levels of HiTOP), rather than in any subgroup alone. Conversely, symptom expression at the last stage of McGorry’s model is highly differentiated and would likely operate at the symptoms/components level of HiTOP, potentially driving consequences specific to psychotic symptom expression and not mania, or vice versa. Here, neural indicators of current symptomatology and, perhaps, lasting consequences would be expected to show specificity to a particular syndrome. As illustrated by the parallels with McGorry’s model, as well as with models of other forms of psychopathology, the HiTOP framework and this ontogenetic perspective can be applied to myriad psychopathological conditions.

Conclusion

The ontogenetic model we have described provides a framework for organizing existing knowledge and guiding continued research on the etiology, mechanisms, and consequences of mental illness as represented in the HiTOP model. In particular, we have emphasized how neurobiological measures can aid in this endeavor and the ways in which HiTOP provides an ideal platform for ontogenetic research, given its reliable, clearly organized, and structurally valid symptom dimensions. With a greater knowledge of the distinct liability factors, concomitant indicators, and lasting consequences associated with particular symptom dimensions, mental health professionals will be better equipped to identify and intervene with at-risk individuals and monitor the progressive remediation and lasting consequences of their psychopathology.

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