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Interfacing neural constructs with the Hierarchical Taxonomy of Psychopathology: 'Why' and 'how'

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ABSTRACT

The Hierarchical Taxonomy of Psychopathology (HiTOP) represents a crucial step forward in the empirical refinement of psychiatric nosology. Although grounded in factor analyses of clinical symptoms and affiliated traits, HiTOP encourages research using measures of other types, including neural-system variables, to clarify coherent processes contributing to the hierarchical structure of psychopathology. However, systematic strategies for interfacing HiTOP dimensions with neural-system variables have not been put forth. We discuss reasons for considering neurobiological systems in relation to HiTOP (i.e. 'why') and propose alternative strategies that might be used to develop an interface between HiTOP and neurobiology (i.e. 'how'). In particular, we highlight potential advantages and limitations of establishing this interface through reference to (i) HiTOP dimensions themselves, or conventional personality trait models linked to HiTOP; (ii) alternative trait constructs designed to link conventional personality models and neurobiological measures; and (iii) mechanistic models of neurobiological processes relevant to HiTOP constructs, derived from computational modelling. We discuss the importance of establishing an interface between HiTOP and neurobiology to develop a more comprehensive, mechanistic understanding of psychopathology and to guide the refinement of the HiTOP model. Such efforts have the potential to guide the development and provision of effective, individualized psychological treatment.

The Hierarchical Taxonomy of Psychopathology (HiTOP[1,2]) was recently proposed as a nosological framework for addressing serious weaknesses in the traditional categorical classification of psychological disorders, as represented in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM[3]). A central goal of HiTOP is to clarify points of intersection and distinctiveness among different forms of psychopathology to overcome issues of within-disorder heterogeneity and pervasive co-morbidity across disorders as currently defined in the fifth edition of the DSM (DSM-5[3]). As an alternative to DSM's consensus-based categorical nosology, the HiTOP system provides an integrative, dimensional, and empirically based system for organizing psychiatric symptomatology. More specifically, it draws on findings from factor-analytic investigations of clinical-experiential data (i.e. symptom reports collected using diagnostic interview and/or questionnaire protocols) to organize clinical

symptoms in terms of a multi-level hierarchy that accounts for their specificity through lower-order symptom/component dimensions and their overlap through higher-order spectra.

As such, HiTOP provides a valuable framework for ongoing and continually evolving research. The various aspects of the model require continuing validation, as Kotov et al.[1] point out, using 'validators' from multiple measurement modalities—including genetic risk factors and neural substrates—to corroborate its structure (p. 9). This approach is similar to a recent multi-modal assessment effort undertaken by the APA's Diagnostic Spectra Study Group to identify clusters of psychopathology based on risk factors and clinical presentation (resulting in neurocognitive, neurodevelopmental, psychotic, emotional, and externalizing clusters[4]). Nonetheless, given the HiTOP model's explicit initial focus on clinical symptoms, as well as the clear value of traditional psychological approaches for understanding psychopathology, HiTOP-aligned researchers from the fields of clinical and personality psychology may question the importance of also considering neurobiological measures in the process of validating and refining the model. This article is intended to assuage these concerns, some of which are noted later, by presenting arguments for 'why' investigating the interface between clinical-experiential HiTOP dimensions and neural-system constructs is essential and by discussing some possibilities as to 'how' best to pursue this goal.

'Why': Arguments in favour of interfacing neural constructs with HiTOP

Given that HiTOP's goal is to establish a quantitative-empirical taxonomy for mental illness, one might ask why clinical-experiential measures are not sufficient as an evidence base. Indeed, the HiTOP model's basis in decades of empirical psychological research reflects the immense value of traditional psychological approaches for understanding and organizing the nosology of mental illness. We (along with others[5,6]) maintain that building on clinical-experiential findings using multiple approaches—including cognitive-affective, interpersonal and cultural perspectives—is essential to a full and maximally useful understanding of psychopathology. While a comprehensive discussion of diverse theories of psychopathology is beyond the scope of the current paper, our more modest aim is to make a case for the importance of systematic efforts to link HiTOP research dimensions to clinical neuroscience concepts and data, and to other clinical-psychological findings more broadly. In what follows, we argue that research on the interface between HiTOP and neuroscience—as one example of a complementary field to clinical psychology—can be of substantial value in terms of (i) promoting a more comprehensive, aetiologically oriented understanding of psychological disorders, with clear clinical utility, and (ii) providing unique avenues for validating and refining the HiTOP model.

A more comprehensive understanding of psychopathology

One major argument for considering the interface between HiTOP and neural-system constructs is that this endeavour will promote a more comprehensive understanding of psychopathology. Prominent scholars in the field have argued over the past several decades that a full picture of psychological phenomena depends on systematic analysis in terms of various levels[7,8] or units of analysis,[5,9] from genomic variation through observable behaviour patterns. Research of this kind is needed to provide a detailed characterization of the nomological net[10]—the network of linkages among hypothetical constructs and measures designed to quantify them—of various forms of psychopathology, by integrating knowledge from multiple measurement modalities.[11]

Traditionally, clinical-psychological research has focused on experiential measures, such as report-based questionnaires and clinical

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interviews, to quantify clinical symptomatology and affiliated personality traits. Efforts of this kind form the basis of much of what we know about normal and abnormal behaviour, including the categorical system for psychopathology embodied in the DSM and the quantitative nosology represented in the HiTOP model, and are clearly a critical component of clinical-psychological science. Nonetheless, the biological, psychological, and sociocultural factors that influence psychopathology are interdependent, and research limited to a single approach—for example, questionnaire-based measurement—makes for slow and limited progress in understanding psychological phenomena.[7] For example, fear is a defining feature of most anxiety disorders, and descriptions of the experience of normal and pathological fear gleaned from clinical interviews and symptom questionnaires form the backbone of the Fear spectrum in the HiTOP model. In tandem with these clinical-experiential data, studies on the neurophysiological signatures of fear have been pivotal to our scientific understanding of this basic emotion and its pathological expressions. Further, the refinement and augmentation of exposure therapy, the front-line evidence-based treatment for phobic disorders, can and has unquestionably benefited from research on the neural substrates of fear and extinction learning.[12–14] Approaching psychological phenomena from the standpoint of multiple units of analysis can help to move the field of clinical psychology forward.

Mechanisms of psychopathology. A particular benefit of considering biological aspects of psychological constructs is the potential to elucidate mechanisms of psychopathology. As Kotov et al.[1] argued in the initial HiTOP article, biological measures can '*clarify the nature* of [HiTOP's] quantitative dimensions' (p. 459; emphasis added). The HiTOP framework represents an important step toward organizing observed clinical phenomena empirically and hierarchically (i.e. with different nested levels of complexity); a neuroscientific analysis can provide a means for clarifying *why*, in biological-process terms, symptom dimensions in the HiTOP framework covary to differing degrees. In turn, fuller understanding of biological mechanisms contributing to the structure of psychopathology can help to guide research on targets for and approaches to treatment, in tandem with psychological and sociocultural insights. In many ways, HiTOP represents an ideal framework for research of this type, given its empirically derived dimensional approach. Indeed, the reliability issues inherent in a categorical nosology[1] restrict associations with variables from other levels of analysis, including neurobiological measures. Continuous dimensions of psychopathology boast greater reliability that allows for more substantial correlations with variables of interest, including neurobiology,[15,16] and this feature of the HiTOP model will facilitate continuing mechanistic research.

In some cases, a single clinical phenotype captured in the HiTOP framework based on clinical-experiential measures may well reflect contributions from multiple distinct biological mechanisms, akin to the developmental psychology concept of equifinality. For example, aggression can reflect a failure to exert top-down control over behavioural impulses, *and/or* deficits in affective processing.[17,18] Greater knowledge of the neurobiological processes contributing to an individual's distinct clinical presentation would facilitate the provision of tailored treatment. For example, the development and refinement of psychopharmacological treatments, as well as the prescription of one medication over another for an individual patient, has often occurred more through serendipity or trial and error than through the application of an empirically based understanding of neurobiological mechanisms of action (refer to Baumeister et al.[19] for examples). In contrast, an example of the successful application of this principle comes from the literature on callous-unemotional traits, which characterize a particularly treatment-resistant subset of youths exhibiting conduct problems. Children with callous-unemotional traits show a distinct pattern of physiological hypoarousal to emotional stimuli,

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and knowledge of the neurobiological correlates of callous-unemotionality has led to the development of specialized treatment programmes designed to enhance affective responsiveness through emotional skills training.[20] This innovation provides an illustration of how research on biological factors contributing to the empirical structure of psychopathology can help to enhance the development and provision of individualized treatments.

Common vs. unique factors. Multiple empirical approaches, including neuroscientific ones, are especially critical to the advancement of a hierarchical understanding of psychopathology, as multi-modal research can help to clarify factors that contribute to common vs. unique elements of variance in clinical symptomatology. For example, while inhibitory control deficits—as indexed by reduced electrocortical response and poorer behavioural performance—contribute broadly to the Disinhibited-Externalizing spectrum,[21] individual differences in neural sensitivity to reward may contribute uniquely to the emergence of substance use problems, a subfactor of this spectrum.[22] As an extension of the previously noted points regarding psychopharmacology, neurobiological research in the context of the HiTOP model could help to elucidate the impact of particular medications on systems pertinent to broad spectra of psychopathology vs. processes more specific to a given subfactor. Similarly, research on the neural mechanisms of psychopathology could clarify why some clinical treatments appear generally effective (e.g. the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders[23]), whereas others act more specifically (e.g. prolonged exposure for post-traumatic stress disorder[24]). As of yet, these mechanisms of action and their hierarchical organization are unclear.

Latent risk vs. manifest expression. Several risk factors for psychopathology, particularly in the personality literature, have been identified through report-based research, aiding in the early identification of individuals likely to develop manifest psychological disturbance. Neuroscientific research can complement and supplement these efforts by identifying biomarkers of risk for later psychopathology that predate the full or even partial expression of the disorder. For example, the brain's executive attention network has been linked to report-based and behavioural measures of temperament factors such as weak executive control and deficient affective-behavioural regulation in children, which comprise important risk factors for psychopathology.[25,26] Further, computerized training may help to mitigate weaknesses in executive attention network function, reducing risk for later psychopathology.[27,28] The identification of other biological risk factors can help to refine the development of effective methods for preventing, curtailing, and remediating mental health problems.

Validation of the HiTOP model

Another major argument for working to establish an interface between the HiTOP model and non-report-based measures, such as neural responses, pertains to continuing validation of the model. HiTOP represents the culmination of extensive factor-analytic research focusing on psychopathology symptom data. Given its exclusive reliance on report-based and interview-based data thus far, neurobiological variables and other non-experiential measures have naturally been reserved as criterion variables in examinations of the model's construct validity. If HiTOP dimensions showed clear and predictable relations to neurobiology, for example, the model would appear to be developing in a valid way.

One empirical illustration of this point comes from the literature on startle response and the Internalizing spectrum.[29] 'Phobic' disorders (i.e. symptomatology situated within HiTOP's Fear subfactor) are associated with enhanced startle-blink reactivity in the context of unpleasant picture viewing (i.e. enhanced aversive startle

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potentiation). However, disorders within the Distress subfactor of HiTOP are associated with enhanced baseline startle reactivity (i.e. at rest or during viewing of non-emotional pictures[29]) and reduced rather than enhanced aversive startle potentiation.[30,31] These contrasting reactivity patterns are thought to reflect the specificity of fear symptomatology to a phasic threat-response system involving the central nucleus of the amygdala (believed to mediate aversive startle potentiation) and of distress pathology to a tonic negative arousal system involving the bed nucleus of the stria terminalis (known to be associated with enhanced baseline startle). That the Fear and Distress subfactors of HiTOP, which were derived from factor analyses of clinical-experiential data, correspond with physiological indicators of these differentiable neural systems provides further evidence for the validity of this distinction. This perspective is congruent with Tellegen's[32] assertion that when traits can be linked to psychobiological systems, 'these constructs begin to acquire *surplus meaning* which leads to explanations and testable hypotheses about additional phenomena' (p. 14, emphasis added). This 'surplus meaning' can then provide insights into relevant processes and mechanisms.[32] The use of neurobiological measures as criterion variables increases our confidence in the validity of a construct and allows for delineation of its empirical–nomological network.[11]

Conversely, such validation studies could elucidate the potential role of method variance in the existing HiTOP model. The exclusive use of clinical-experiential data in the model's development could have led to the delineation of some dimensions that appear psychologically meaningful from these measurement approaches but that are multidimensional and complex from the standpoint of processes and mechanisms. One potential example of this concept is the Distress subfactor of the HiTOP model, which includes symptoms of depression and worry currently conceptualized in DSM-5 as major depressive disorder and generalized anxiety disorder, respectively. Although these symptoms frequently co-occur and are represented in a single subfactor within HiTOP, evidence exists to suggest that they are associated in opposing directions with an electrocortical measure of emotional processing, the late positive potential.[33] Research of this type may reflect avenues of differentiation within components of the HiTOP model and can help to guide its refinement at lower-order levels. Another example of the use of physiological measures to understand the structure of psychopathology pertains to the psychosis spectrum. Kotov et al.[34] utilized two electrocortical indices of performance monitoring —the error-related negativity and error positivity —as 'neural validators' to guide data-driven decision making about the factor structure of psychotic symptoms. These examples illustrate how research directed at linking HiTOP dimensions to non-report-based types of data, including neurophysiological measures, can help to advance the empirical evolution of the model, in line with the stated goals of the HiTOP consortium.[1]

In sum, research investigating the interface between HiTOP dimensions and non-report-based measures, such as neurophysiological indicators, would serve the dual purposes of more fully explicating the nomological net of psychopathology-relevant constructs—including providing mechanistic explanations of clinical symptomatology, with important implications for the treatment of mental illness—and facilitating the validation and refinement of HiTOP. Next, we consider possible approaches to exploring this interface.

'How': Methods of interfacing neural constructs with HiTOP

Different methodological approaches could be used to interface the HiTOP framework with neurobiological-system concepts and measures. In what follows, we consider three approaches—direct-mapping, alternative trait, and computational models—and discuss their advantages and limitations, with reference to existing studies that have used these techniques. While highlighting these specific approaches as important alternatives to

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be evaluated, we acknowledge that other viable approaches may well exist, that analytic decisions need to be tailored to the particular research questions of interest,[35] and that particular approaches may be more appropriate for some goals relative to others.

Direct mapping to HiTOP symptom dimensions and conventional personality trait models

The most intuitive and direct method for investigating the interface between HiTOP and neural-system variables is to measure symptom dimensions represented in HiTOP and attempt to identify their neurobiological correlates. Indeed, a number of correlational studies have reported relations for measures of HiTOP-related dimensions with indices of brain structure and function, as well as polygenic risk scores.[36] Examples of studies that have examined associations of HiTOP spectra and/or subfactors with event-related potential, diffusion tensor imaging, and structural or functional magnetic resonance imaging measures are provided in Table 1. This direct-mapping approach is intuitively appealing in that the identification of clear and consistent neurobiological correlates would provide an external validation of the factor structure of HiTOP. Additionally, such findings might provide insights into the mechanisms of these symptom dimensions, with implications for early identification and intervention, as described earlier.

Further, given that personality can provide a general framework for psychopathology,[37–39] a related approach is to work toward interfacing psychopathology-related trait constructs from traditional models of personality with indicators of neural-system functions. Such research might involve systematically investigating the neural correlates of particular traits from well-known models such as the five-factor model (FFM[40]). A salient advantage of this strategy is that the HiTOP framework was developed in part with reference to this widely studied model of personality.[1] Thus, traits of the FFM and related models are directly represented in HiTOP (e.g. trait neuroticism is linked to the Internalizing spectrum[1]), and any demonstrated linkages for personality with neurobiology would serve to reinforce and validate the existing HiTOP structure. Additionally, many personality traits from traditional models, such as the FFM trait of neuroticism, are viewed as relatively stable predispositions toward particular forms of psychopathology, suggesting that these traits could serve as a bridge between biology and psychopathology. Research confirming these relations would advance scientific understanding of psychopathology by expanding its nomological net and would allow for the assessment and treatment of trait dispositions and biomarkers prior to the full expression of psychopathology, as represented in the HiTOP symptom dimensions.[41]

However, there are notable limitations to approaches seeking to link HiTOP symptom dimensions or related personality traits directly to neurobiology. One is that reported relations of symptom dimensions and traditional personality traits with neurobiological variables have been inconsistent. This is understandable, in part, owing to the aforementioned issue of method variance: Relationships between only partially related constructs assessed using sharply different methods (e.g. self-report or interview vs. neurophysiology) can be expected to correlate only modestly.[42] As a result, effect sizes are often relatively small (Table 1), and small-*N* studies may be underpowered to detect them, contributing to inconsistent findings. Nonetheless, the small magnitude of cross-method associations does not imply that they are unimportant or discourage continuing research on the interface between HiTOP and neurobiology. Instead, as outlined earlier, these effects are of critical importance in the explication of the wider nomological net of psychopathology[43] and in the continuing validation of the HiTOP model. Larger sample sizes and more sophisticated statistical modelling methods, as outlined in subsequent sections, may be necessary to better clarify how neurobiological variables relate to report-based trait or symptom measures.

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Table 1: Example studies linking HiTOP-related dimensions to structural and functional neural measures (MRI/fMRI, EEG/ERP and DTI)

Spectra	Relevant traits	Neurobiological correlates (Pearson's *r*)	Key citations
Internalizing (Int.)	Negative affectivity	Increased LPP (emotion–neutral; partial $r = 0.26$); reduced limbic GMV ($rs = -0.13$ to -0.22)	Rozalski & Benning[44]; Snyder et al.[45]
Thought disorder (Tht.)	Psychoticism	Reduced LPP (emotion–neutral; partial $r = -0.26$); reduced Pe for apathy/asociality symptoms (partial $r = -0.30$); reduced activation of dlPFC ($r = -0.12$)	Kotov et al.[34]; Rozalski & Benning[44]; Shanmugan et al.[46]
Disinhibited externalizing (DE)	Disinhibition	Reduced P3 ($r = -0.17$ to -0.25); reduced ERN ($r = 0.29$) and theta power to errors ($r = -0.24$); reduced activation in fronto-parietal cortex, thalamus, cerebellum ($rs = -0.11$ to -0.15)	Hall et al.[47]; Patrick et al.[48]; Patrick et al.[49]; Shanmugan et al.[46]; Venables et al.[21]
Antagonistic externalizing (AE)	Callous-aggression; antagonism	Reduced P2 and N170 ERPs to fearful faces ($rs = -0.15$ to -0.21 and 0.15 to 0.22, respectively); increased thickness of left caudal MFG (partial $r = 0.09$)	Brislin & Patrick[50]; Brislin et al.[51]; Hyatt et al.[52]
Detachment (Det.)*	—	—	—
Subfactors**	**Relevant traits**	**Neurobiological correlates (Pearson's *r*)**	**Key citations**
Sexual problems (Int. Spectrum)	Impulsivity; compulsivity	Reduced superior frontal mean diffusivity for sexual compulsivity symptoms ($r = -0.64$); reduced P3 (sexual–neutral) with lower sexual desire ($r = 0.33$)	Miner et al.[53]; Steele et al.[54]
Eating pathology (Int. Spectrum)	Impulsivity; compulsivity; reward sensitivity	Increased VPP to same-gender bodies ($rs = 0.33$ to 0.44)	Groves et al.[55]
Fear (Int. Spectrum)	High threat sensitivity	Increased global GMV***; increased startle response (threat–neutral; $r = 0.31$)	Behester et al.[56]; Vaidyanathan et al.[57]
Distress (Int. Spectrum)	Low reward sensitivity	Increased executive network activation ($rs = 0.11$ to 0.15); reduced RewP ($r = -0.20$) and ventral striatum activity ($rs = -0.07$ to -0.08); increased amygdala volume	Bowyer et al.[58]; Holmes et al.[59]; Shackman et al.[60]; Shanmugan et al.[46]; Stringaris et al.[61]

(*Continues*)

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Table 1: (continued)

Subfactors**	Relevant traits	Neurobiological correlates (Pearson's *r*)	Key citations
		(*r* = 0.14); reduced mPFC thickness (*r* = −0.09)	
Mania (Int./Tht. Spectra)	High reward sensitivity; high approach motivation	Increased left frontal activity (fMRI *r* = 0.28, EEG *r*s = 0.26 to 0.30)	Bebko et al.[62]; Harmon-Jones et al.[63]
Substance abuse (DE Spectrum)	Low reward sensitivity	Reduced RewP (*r* = −0.21)	Joyner et al.[22]
Antisocial behaviour (DE/AE Spectra)	—	Reduced surface area and grey matter volume of left cuneus (partial *r* = −0.08)	Hyatt et al.[52]

Note. HiTOP, Hierarchical Taxonomy of Psychopathology; MRI, magnetic resonance imaging; fMRI, functional MRI; EEG, electroencephalography; ERP, event-related potential; DTI, diffusion tensor imaging; LPP, late positive potential ERP; GMV, grey matter volume; Pe, error positivity ERP; dlPFC, dorsolateral prefrontal cortex; ERN, error-related negativity ERP; MFG, middle frontal gyrus; VPP, vertex positive potential ERP; RewP, reward positivity ERP; mPFC, medial prefrontal cortex.

*We could not identify any studies examining neural correlates of a dimensional measure of detachment.

**Identified traits and neural correlates for subfactors exclude the spectrum-level traits and correlates described earlier.

***r was not reported.

A further issue is that the HiTOP dimensions and traditional models of personality were developed without direct reference to biological variables.[43] For example, the FFM was developed on the basis of natural language (lexical) descriptions of personality.[40] Unsurprisingly given this approach, research to date using functional and structural neuroimaging and electroencephalography has failed to identify consistent neurobiological correlates of most FFM traits.[11,64] However, even putatively psychobiological theories of personality, such as Eysenck's extraversion-neuroticism-psychoticism model and Cloninger's tridimensional model, have often failed to show theory-consistent associations in empirical studies.[65–67] Almost certainly, this reflects the fact that these models were developed through use of self-report and/or other-report data without accompanying reference to biological measures. Although fewer studies have examined neurobiological correlates of HiTOP-related symptom dimensions, a similar pattern may well emerge given the exclusive use of clinical interviews and symptom questionnaires in the development of HiTOP. A small number of consistent neural correlates of symptom dimensions have been identified, including the association between disinhibited-externalizing symptoms and reduced amplitude of P3 brain response,[48] thanks in part to the close ties among constructs of externalizing proneness, trait disinhibition, and executive function.[21,68,69] Other symptom dimensions without as strong a cognitive or affective foundation are less likely to relate in consistent, replicable ways with measures of brain structure and function.

A final concern pertains specifically to efforts to relate HiTOP dimensions to neurobiology. As noted earlier, one of the major reasons to examine biological systems in relation to psychopathology is to better understand risk for and mechanisms of clinical problems. Accordingly, a great deal of psychophysiological research has utilized measures of neural response in youth as prospective indicators of risk for psychopathology. The

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aforementioned association between disinhibited-externalizing symptoms and reduced P3 response[48] is all the more important because P3 response is also reduced in individuals *at risk for* developing externalizing problems.[70] Similarly, other electrocortical responses reflecting reward sensitivity (i.e. gambling-task reward positivity and feedback negativity) and emotional processing (i.e. affective-picture late positive potential) have been established as prospective risk factors for depressive symptomatology.[71–73] Another event-related potential, the error-related negativity, prospectively predicts the onset of anxiety disorders in children.[74] These findings suggest that some neurobiological variables that relate to psychopathology may be best conceptualized as reflecting broad trait-risk indicators, rather than disorder-specific or symptom-specific indicators. As a result, HiTOP symptom dimensions may be less likely to relate in predictable, distinct and robust ways with neurobiological variables; other approaches may be more fruitful. It will be important in future research to directly compare the replicability of neurobiological correlates with symptom dimensions at differing levels of the HiTOP model, as some aspects of the hierarchy—particularly the higher-order levels—may be more dispositional in nature and thus relate more consistently to neurobiology.

Given that research efforts over many years have not yielded dependable neurobiological correlates of traits from traditional personality models—even those purportedly based in neurobiology—and at least some HiTOP symptom dimensions appear likely to follow a similar pattern, methods for conceptualizing and assessing trait and symptom dimensions may need to shift in order to interface more effectively with neurobiology.

Alternative trait models

Recent research has sought to address the previously noted disjunction between personality trait constructs and biological systems variables by operationalizing traits using indicators from different measurement modalities—i.e. self-report, neurobiological, and/or task-behavioural variables.[21,49,75] This multi-modal, neurobehavioural (NB) trait approach provides another potential strategy for linking specific psychological constructs represented in HiTOP to neurobiological systems. In this approach, NB traits are conceptualized as normative individual-difference characteristics that transcend measurement modalities, loosening the construct's ties to any modality in particular. In contrast with traditional personality trait models, NB trait constructs directly incorporate neurobiological data. Thus far, the traits of inhibition–disinhibition[21,49] and threat sensitivity[75] have been operationalized as NB trait factors, using self-report trait scales, electrocortical and peripheral psychophysiological responses, and behavioural performance as indicators. These multi-modal NB factors show strong associations with criterion variables in both clinical symptom and psychophysiological modalities.

For example, Patrick et al.[49] reported on the development of an initial model for the NB trait of inhibition–disinhibition based on work demonstrating that psychometric scale measures of trait disinhibition, known to be predictive of externalizing symptomatology, correlated modestly but robustly with different variants of P3 brain response. They performed a factor analysis using two scale measures and two P3 indicators of disinhibition and found a single-factor solution, which they interpreted as a joint psychological-neural index of trait disinhibition. Scores on this factor correlated robustly with both externalizing symptomatology ($r = 0.65$) and a separate variant of P3 not included in the factor ($r = -0.37$) but were unrelated to internalizing symptomatology, demonstrating discriminant validity. This work illustrates the process of reshaping a psychological construct to represent the interface between personality and neurobiology. Moreover, this NB disinhibition factor, and a counterpart NB threat sensitivity factor reported by Yancey et al.,[75] can readily be tied to dimensions of the HiTOP model:

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disinhibition is akin to the broad Disinhibited-Externalizing dimension of the model, and threat sensitivity corresponds to the Fear subfactor of the Internalizing spectrum.[76,77]

Neurobehavioural traits differ from traits of conventional models of personality in that they are treated as 'open constructs'[10]—i.e. as provisional concepts subject to revision based on data. By contrast, personality traits of the FFM were inferred from correlations among lexical descriptors of personality and are treated as established points of reference ('closed constructs') for studying and elucidating various phenomena of psychological interest (e.g. interpersonal behaviour, educational or job success, and clinical problems). Reliance on psychological traits defined without reference to biology poses a limitation to efforts to identify neurobiological correlates and virtually ensures small and inconsistent associations. In contrast, scale-assessed NB traits are treated as provisional and modifiable on the basis of observed associations—both convergent and discriminant—with non-report-based measures. As stated by Patrick et al.,[49] this approach allows 'psychological conceptions of target constructs to be reshaped by accumulating knowledge of physiological indicators … that cohere with the psychometric index of the target trait' (p. 905). This method is similar to and builds on earlier work by Depue and Lenzenweger,[78] in which a personality trait construct observed in the experiential-report domain was refined through reference to analogous patterns of mammalian behaviour. Empirical research on the neurobiology of animal behaviour was then used to formulate hypotheses about the neurobiology of human personality. As such, the work of Depue and Lenzenweger[78] and Patrick et al.[49] serve as complementary illustrations of an iterative approach to construct definition and refinement directed at interfacing personality with neurobiology.

The NB trait approach has certain distinct advantages that could help to advance a more comprehensive understanding of psychopathology. First, constructs operationalized using neural and report-based measures together appear to capture *risk* for psychopathology, rather than elements of manifest symptomatology. Evidence for this point comes from twin research showing that (i) NB traits are substantially genetically influenced and (ii) these genetic influences account for the covariation between NB traits and clinical symptomatology.[77] Thus, NB traits appear to index biologically based dispositional liabilities for psychopathology, rather than experiential influences per se or transient 'states' that characterize clinical problems. As noted earlier, improved quantification of risk factors can guide improvements in early identification and intervention.

Another salient advantage of the NB trait approach is that it is grounded in basic measurement methods—e.g. scale psychometrics and factor analysis—that are familiar to clinical psychologists, increasing its applicability to clinical contexts. Nonetheless, it is also amenable to advanced psychometric approaches, such as structural equation modelling and item-response theory, that can help to optimize constituent measures and integrate them most effectively to quantify a construct of interest and clarify its nature.[79] Finally, much as they transcend measurement modalities, NB trait constructs transcend particular instruments and tasks. For example, they can be quantified in psychological-scale terms using items from different personality questionnaires, and physiological indicators can be drawn from any well-designed task paradigm with established ties to the trait, reducing reliance on a particular task or self-report measure. As such, these constructs can be operationalized in existing large-scale, multi-modality datasets—including longitudinal, twin, genomic, and/or animal studies—to identify additional non-report (e.g. neural and task-behavioural) indicators and thereby advance understanding of their nomological nets.[16,80]

Neurobehavioural traits also provide an appropriate means for continuing validation of the HiTOP model. In addition to further refining NB traits and delineating their associations with

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HiTOP symptom dimensions, validation research can also be undertaken to build NB trait models for some of the constructs already represented in the HiTOP framework. If a single NB factor cannot be operationalized for a given construct, it may suggest that this aspect of the HiTOP model requires further refinement to reflect its multidimensionality—or, alternatively, that portions of the model have meaning mainly in the psychological-experiential modality of assessment (discussed next). Such research would need to consider that NB traits transcend modalities and particular measures; therefore, modelling efforts should incorporate indicators from multiple psychometrically sound questionnaires and multiple well-designed task paradigms to overcome issues inherent to a given measurement tool.

The NB trait approach is not without limitations. First, as described earlier, NB traits are quantified at the intersection between personality and neurobiology. From the standpoint that dispositional traits can be risk factors for psychopathology,[81] NB traits may be particularly useful for characterizing neurobiological systems relevant to risk for—as opposed to active expression of—psychopathology. This feature constitutes both a strength and a limitation of this approach and perhaps, more broadly, any methodological approach seeking to interface neurobiology with HiTOP. Symptom-based dimensions may capture important elements of clinical problems that are specific to the experiential-report modality,[82] whereas the personality–neurobiology interface may be specific to a set number of points of intersection at particular levels.[78,83] From this perspective, the NB trait approach is unlikely to be suitable for every aspect of the HiTOP model. Additionally, to the extent that NB traits can provide an interface with neurobiology in the interest of developing a more comprehensive understanding of psychopathology, it may not always be clear *where* in the hierarchy a given NB trait can be expected to play a role. Whereas some NB traits may relate to higher-order dimensions of the hierarchy (e.g. trait disinhibition to the Disinhibited-Externalizing spectrum), others may be better conceptualized as interfacing with the maladaptive trait level of the hierarchy. Other units of the HiTOP symptom hierarchy, such as the broad Internalizing dimension, are likely to relate to multiple NB traits—e.g. both threat sensitivity and reward sensitivity[58,75]—with lower-order dimensions relating more directly to a given NB trait—e.g. threat sensitivity to the Fear subfactor. These questions would need to be the focus of continued research.

Computational models

A third method with potential utility for efforts to interface HiTOP with neurobiology is computational modelling, a sophisticated and cutting-edge set of techniques that can be used to characterize and quantify mechanisms within psychological or biological systems. Broadly speaking, computational modelling utilizes computer algorithms and detailed, a priori theoretical models to infer and analyse latent processes and mechanisms that explain manifest behaviour.[84,85]

Computational modelling of behavioural (e.g. reaction time) and/or neural response data has been performed primarily in the field of cognitive psychology over the last 40 years[85] to shed light on human cognition and behaviour, with more recent applications to clinical psychology for the purposes of elucidating cognitive-behavioural processes leading to and maintaining psychopathology. Processes of interest are often drawn from the literature on associative learning and decision making. For example, Hallquist et al.[86] described a mechanistic model of borderline personality disorder that linked behavioural manifestations of latent decision-making processes to neural-system activity (quantified using electrocortical and functional neuroimaging responses) and phenotypic aspects of the disorder. These authors argued that simple correlations between psychological variables (e.g. trait neuroticism) and neural responses have been small and inconsistent because of the substantial theoretical gap between what is measured via these modalities. They advocated for

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computational modelling as a promising technique for bridging these units of analysis through modelling of latent intermediate processes[86] and testing theories of how and why separable processes lead to measurable behaviours, symptoms, and neural responses.[87] Computational modelling has also been used to elucidate the mechanisms of cognitive control deficits in schizophrenia.[88] As an extension of the NB trait approach described earlier, computational modelling could be used to interface clinical-experiential data (as reflected in HiTOP dimensions) with neurobiological responses by modelling latent processes contributing to both.[84]

Another important feature of computational modelling is its applicability to research on individual differences. Estimates can be derived from a given model in the form of 'computational phenotypes'[87] or 'computational multidimensional profiles'[89] that reflect between-subjects variation in the mechanisms of interest. In this way, an individual's performance on a well-designed task could be used to compute an estimate of dysfunction in a particular cognitive process[87] and then linked to a dimension of psychopathology. For example, Sevgi et al.[90] demonstrated that individual computational phenotypes reflecting reliance on social information during a decision-making task were associated with scores on a measure of the autism spectrum. Further, including self-report data in a computational model along with behavioural variables appears to improve its predictive accuracy.[87]

Computational modelling holds particular promise as a technique for interfacing HiTOP dimensions with neurobiology in the pursuit of a more comprehensive understanding of psychopathology. One distinct advantage of this approach is that it overcomes issues inherent in behavioural summary scores (e.g. reaction time or task-performance accuracy), such as task impurity and causal ambiguity, to extract a mechanistic model that identifies separable cognitive processes contributing to behaviour.[89] These mechanisms can then be used as a bridge between clinical symptoms and measured neural correlates, potentially pointing to targets for intervention. An individual's relative 'estimates' for particular mechanisms over others could also facilitate the provision of customized treatment that takes into account an individual's distinct clinical and cognitive presentation. Brazil et al.[91] highlighted the potential of this approach by quantifying the relative use of social vs. reward-based information during appetitive learning and demonstrating differential relations for these two forms of information use with distinct psychopathic personality traits. The authors suggested that treatment approaches should consider an individual's presentation given the demonstrated links between personality and mechanisms of learning from past behaviour.[91]

Another major advantage of computational modelling is that it provides a clear avenue for validation (and/or refinement) of the HiTOP model. To the extent that mechanisms identified through these models correspond in predictable, consistent ways with the spectra, subfactors, and other levels of the HiTOP hierarchy, confidence can be gained in the validity of the framework, as described earlier. If particular HiTOP constructs were revealed to be more complex mechanistically than was evident from analyses of clinical-experiential data, the model could be revised to reflect these empirical findings. Conversely, computational models can reveal points of mechanistic similarity across seemingly distinct forms of psychopathology and thereby contribute to refinement of the HiTOP model and identification of treatment targets. For example, reinforcement learning models have demonstrated common disturbances in dopaminergic and cortico-basal ganglia-thalamocortical circuits across schizophrenia, addictive disorders, and attention-deficit/hyperactivity disorder, despite their lack of apparent coherence in the current HiTOP model.[92] In turn, this finding could inform treatment strategies. Importantly, however, validation efforts must rely on models with a strong theoretical foundation to permit researchers to differentiate between an inappropriately specified computational model and an aspect of the HiTOP model that requires refinement.

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In parallel with the benefits of computational modelling for research on HiTOP, the HiTOP model is especially well suited to clinical applications of computational modelling, given its eschewal of traditional categorical classifications of psychopathology. Conventional dichotomous diagnoses with arbitrary symptom thresholds are known to muddy the waters of mechanistic analyses.[87] The use of more reliable and valid outcome variables, such as HiTOP dimensions, can help to improve the predictive utility of computational models.

Despite these myriad advantages and the natural coupling of computational modelling with the HiTOP framework, some limitations and cautionary points warrant mention. First, computational models are specific to the tasks by which data are collected[86]; moreover, it can be difficult to parse competing mechanisms within a single task.[87] Additionally, test–retest reliability and construct validity have been less systematically investigated in computational phenotyping than in, for example, personality psychology.[87] To overcome these issues, models based on behavioural data often rely on multiple tasks in an attempt to triangulate and isolate a process of interest. In the same way, research using clinical-experiential data must be careful to measure outcomes of interest in different ways (e.g. using clinical interviews, symptom questionnaires, and personality inventories). The use of separate participant samples for exploration and confirmation of computational models will also be essential in this regard. The intentionally strong reliability and validity of the HiTOP model will be a boon to computational modelling efforts.

A final and especially noteworthy issue with the use of computational modelling is that it requires extensive training in computer science and advanced mathematics to be used in a confident, informed way; at this point in time, analytic software for work of this kind is likely to be fairly opaque and inaccessible to most psychology researchers.[87] Collaboration between HiTOP researchers and computational neuroscientists will be essential for the effective application of this promising technique to the quantitative nosology of psychopathology. Recent multidisciplinary initiatives have sought to make computational modelling more accessible to researchers with adequate foundational knowledge of this approach through user-friendly computational software (e.g. the hBayesDM package in R[93]).[1] We anticipate that tools of this nature will increase the widespread use of computational modelling techniques in years to come.

Conclusion

The HiTOP initiative stands to benefit greatly from systematic efforts to connect its clinical dimensions with neurobiological constructs and measures. Understanding how biological processes relate to HiTOP dimensions, which are empirically derived from exclusively psychological-experiential data, can help to facilitate greater understanding of the nature of these dimensions and support efforts to develop targeted treatments. In parallel, examining HiTOP's relations to neurobiology can serve as an important means for validating the model and identifying avenues for refinement.

Here, we have described three potential strategies—by no means exhaustive—for working to interface the HiTOP model with neurobiology, the first involving direct mapping of the neural correlates of symptom dimensions and traditional personality traits, the second focusing on alternative NB traits operationalized using data from different modalities, and the third focusing on use of computational modelling to investigate the mechanisms of psychopathology. These strategies could also be utilized in combination with one another. For example, computational modelling methods could be applied to report-based measures along with known neurophysiological and/or task-behavioural indicators of NB trait

[1]We are grateful to an anonymous reviewer for calling our attention to this R package.

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constructs. Use of differing strategies with complementary strengths is likely to prove particularly effective for validating and refining the HiTOP model as it currently stands, and helping to establish a more comprehensive, integrative, and mechanistic model of the full array of psychopathologies.

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