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Linking RDoC and HiTOP: A new interface for advancing psychiatric nosology and neuroscience

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Abstract

The Research Domain Criteria (RDoC) and the Hierarchical Taxonomy of Psychopathology (HiTOP) represent major dimensional frameworks proposing two alternative approaches to accelerate progress in the way psychopathology is studied, classified, and treated. RDoC is a research framework rooted in neuroscience aiming to further the understanding of transdiagnostic biobehavioral systems underlying psychopathology and ultimately inform future classifications. HiTOP is a dimensional classification system, derived from the observed covariation among symptoms of psychopathology and maladaptive traits, which seeks to provide more informative research and treatment targets (i.e., dimensional constructs and clinical assessments) than traditional diagnostic categories. This article argues that the complementary strengths of RDoC and HiTOP can be leveraged in order to achieve their respective goals. RDoC's biobehavioral framework may help elucidate the underpinnings of the clinical dimensions included in HiTOP, whereas HiTOP may provide psychometrically robust clinical targets for RDoC-informed research. We present a comprehensive mapping between dimensions included in RDoC (constructs and subconstructs) and HiTOP (spectra and subfactors) based on narrative review of the empirical literature. The resulting RDoC-HiTOP interface sheds light on the biobehavioral correlates of clinical dimensions and provides a broad set of dimensional clinical targets for etiological and neuroscientific research. We conclude with future directions and practical recommendations for using this interface to advance clinical neuroscience and psychiatric nosology. Ultimately, we

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Contributors

Michelini, Kotov, Latzman and DeYoung conceived this work. Michelini, Palumbo, Latzman and Kotov reviewed the literature. Michelini wrote a first draft of most sections. All authors contributed to the manuscript and approved the final version.

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Conflict of Interest

All authors report no conflict of interest.

envision that this RDoC-HiTOP interface has the potential to inform the development of a unified, dimensional, and biobehaviorally-grounded psychiatric nosology.

1. Introduction

Accurately classifying mental disorders and elucidating their etiologies remain among the greatest challenges of modern clinical psychology and psychiatry. Ongoing efforts seek to refine psychiatric nosology, but rates of misdiagnosis remain high (Regier et al., 2013) and available categorical classification systems, including the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 2013) and the International Classification of Diseases (ICD) (WHO, 1992), carry limited clinical utility for prognosis and treatment (Conway et al., 2019). With regard to etiology, we lack a complete understanding of the causes of any mental disorder, despite considerable efforts in elucidating their genetic (Waszczuk et al., 2020) and neural (Thompson et al., 2020) bases.

These two issues (i.e., diagnostic classification and etiology) are strongly interdependent. On the one hand, developing a refined taxonomy of clinical problems requires a better understanding of the antecedents and processes that lead to different forms psychopathology in order to develop better treatments. On the other hand, progress in understanding the etiology of mental illnesses is hindered by common misdiagnosis and limited validity of diagnoses based on traditional nosologies. Integrating advances in empirical research on diagnostic classification and etiology has the potential to accelerate progress in these fields (Latzman et al., 2020; Waszczuk et al., 2020).

This article proposes an interface to advance these two fronts by leveraging two major initiatives that are using dimensional approaches to promote a radical change in the way mental illness is studied and classified: the Research Domain Criteria (RDoC) framework by the National Institute of Mental Health (NIMH) (Cuthbert & Insel, 2013; Kozak & Cuthbert, 2016) and the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2017; Kotov et al., 2021; Krueger et al., 2018). We start with an overview of the challenges of psychiatric nosologies and the solutions offered by RDoC and HiTOP, highlighting the complementary nature of these frameworks and providing rationale for an interface that bridges between them. We then present a comprehensive map of the interface linking between RDoC constructs and HiTOP spectra based on narrative review of the empirical literature. We conclude with examples of integrative research linking biobehavioral systems with dimensions of psychopathology, and with recommendations for implementing this approach in future studies with the goal to promote progress in elucidating the causes of psychopathology and improving future classifications.

2. Dimensional classifications of psychopathology

Extensive evidence points to major limitation of categorical classifications that make them a poor guide for research and clinical practice, as explained in detail elsewhere (Cuthbert & Insel, 2013; Kotov et al., 2017). First, categorical diagnoses do not adequately reflect the extensive evidence that forms of psychopathology and their underlying processes are continuous in nature (Cuthbert & Insel, 2013; Markon & Krueger, 2005). The imposition of

artificial categories can lead to low diagnostic reliability (Markon et al., 2011), diagnostic instability (due to symptoms presenting just above or below the clinical cut-off), and failure to recognize subthreshold presentations that can be associated with poor functional outcomes and increased risk for more severe psychopathology (Shankman et al., 2009). Second, traditional diagnoses are based on subjective reports or observations of symptoms and do not consider underlying etiological and pathophysiological mechanisms that largely cut across diagnostic boundaries, although this information may be important for selecting effective treatments (Bzdok & Meyer-Lindenberg, 2018). Third, traditional classifications focus on individual diagnoses and ignore widespread comorbidity and developmental continuity between disorders (Caspi et al., 2020), which can substantially undermine prediction of illness course and correct treatment decisions (McIntyre et al., 2012). Fourth, DSM and ICD do not provide tools to consider the extensive heterogeneity within each diagnosis, which makes individuals with the same diagnosis greatly differ from one another and can produce variable treatment response (Fried, 2017). Fifth, overlap in symptoms across different diagnostic categories (e.g., distractibility, anhedonia) can make differential diagnosis especially difficult and contributes to misdiagnosis (Asherson et al., 2014).

Although DSM-5 and ICD-11 are making progress in addressing some of these limitations (Clark et al., 2017), they remain largely categorical. Two major dimensional frameworks, RDoC and HiTOP, have emerged in the last decade to address the limitations of categorical classifications with two different strategies.

2.1 What is RDoC?

The RDoC framework was developed by the National Institute of Mental Health in 2009 to guide research on the neurobiological bases of psychopathology organized around biobehavioral dimensions, and ultimately inform efforts to refine psychiatric classifications (Cuthbert & Insel, 2013; Insel et al., 2010). The approach proposed by RDoC mainly addresses the first (dimensional nature of psychopathology), second (lack of consideration of underlying underpinnings), and fourth (within-disorder heterogeneity) aforementioned limitations of categorical systems. RDoC tackles these limitations by encouraging research on fundamental dimensional biobehavioral systems (e.g., cognition, social processes) cutting across traditional boundaries, as well as on their associations with behavioral manifestations, rather than diagnostic categories, in heterogeneous clinical populations (Cuthbert & Insel, 2013; Kozak & Cuthbert, 2016). A more explicit consideration of the dimensional and heterogeneous nature of psychopathology and its underpinnings is expected to elucidate the processes underlying mental health problems and, in turn, inform their future classification (Cuthbert & Insel, 2013).

The RDoC framework is operationalized in the RDoC matrix (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix.shtml) (Figure 1A). The matrix columns represent eight *units of analysis* (genes, molecules, cells, circuits, physiology, behavior, paradigms, and self-reports), and the rows represent *constructs* and *subconstructs*, representing functional dimensions characterized by specific elements within each units of analysis. Constructs are grouped into six higher-level domains: Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social

Processes, Arousal/Regulatory Systems, and Sensorimotor Systems. Domains, constructs/subconstructs, and units of analysis were defined based on consensus of experts from relevant fields who reviewed the scientific knowledge about major systems relevant to typical and atypical human behavior (Clark et al., 2017; Kozak & Cuthbert, 2016).

2.2 What is HiTOP?

HiTOP is a system developed by a consortium of scientists studying psychiatric nosology (Kotov et al., 2018; Kotov et al., 2017) that proposes a hierarchical dimensional classification of mental health problems. The HiTOP model was constructed based on extensive research using factor analysis and latent class analysis with the goal of organizing psychopathology according to the natural covariance structure of signs, symptoms, maladaptive behaviors and traits, following a long-established quantitative approach to nosology (Achenbach, 1966; Kotov et al., 2017). A major motivation of HiTOP is to reorganize and reconceptualize clinical classification in order to improve clinical practice and inform treatment and prevention, as discussed in detail elsewhere (Mullins-Sweatt et al., 2020; Ruggero et al., 2019; https://hitop.unt.edu/clinical-tools).

HiTOP's approach primarily aims to address the first (dimensional nature of psychopathology), third (widespread comorbidity), fourth (within-disorder heterogeneity) and fifth (symptom overlap) aforementioned limitations of current categorical systems. The model seeks to resolve these issues by delineating broader dimensions that explain psychiatric comorbidity as well as specific dimensions that accommodate within-disorder heterogeneity and symptom overlap between different conditions (Kotov et al., 2020; Kotov et al., 2017; Krueger et al., 2018). The hierarchical organization of HiTOP describes psychopathology at different levels of breadth and specificity (Figure 1B): components are specific dimensions of symptoms and maladaptive behavior (e.g., dysphoria, suicidal ideation); highly correlated components form broader dimensional syndromes (e.g., depression); closely related syndromes define subfactors (e.g., distress); and related subfactors form spectra (e.g., internalizing). More general dimensions also have been described, such as the general factor of psychopathology or p-factor (Caspi & Moffitt, 2018; Lahey et al., 2012). Six spectra have been included in HiTOP so far: Internalizing, Disinhibited Externalizing, Antagonistic Externalizing, Thought Disorder, Detachment, and Somatoform. Seven subfactors have been identified within these spectra (Kotov et al., 2017). Of note, traditional diagnostic categories are not part of HiTOP, as the model seeks to include and reorganize symptoms that constitute these diagnoses.

The model currently incorporates the most common forms of psychopathology, as well as a number of rare conditions (Figure 1B). Conditions that have not been examined in rigorous quantitative research of this type (e.g., most neurodevelopmental problems) are not yet in the system, but are the focus of ongoing efforts (Michelini et al., 2019). The dimensions in the models have been validated with regard to etiology (e.g., genetic and neural underpinnings), predictive validity, and utility for clinical practice (Conway et al., 2019; Kotov et al., 2017; Ruggero et al., 2019; Waszczuk et al., 2020). Although etiological or biological parameters are currently not included, it is expected that empirically-derived and reliable dimensions will have more coherent etiology than traditional categories, thereby producing stronger and

more specific profiles of risk factors, biomarkers, and outcomes, as described in detail elsewhere (Kotov et al., 2020; Krueger et al., in press; Watson et al., in press).

2.3 Similarities and differences between RDoC and HiTOP?

Before describing how RDoC and HiTOP are interconnected, we note key similarities and differences between the two approaches. RDoC and HiTOP share core features:

1. *Intent to move away from diagnostic categories*: Both frameworks recognize the aforementioned limitations of diagnostic categories and emphasize the need for a dimensional approach to psychiatry.
2. *Work-in-progress approach*: Both frameworks are designed to evolve with new evidence, as overseen respectively by the National Advisory Mental Health Council Workgroup on Changes to the RDoC Matrix and the HiTOP Revisions Workgroup. For example, the RDoC Sensorimotor Systems domain involved in control and execution of motor behaviors was added in January 2019 (NIMH, 2019).

Notable differences, however, also exist:

1. *Delineation of dimensions*: RDoC domains and constructs were rationally defined based on consensus of experts regarding biobehavioral systems relevant to mental health. HiTOP dimensions reflect a replicated empirical structure of psychopathology based on covariation among signs, symptoms, diagnoses, and maladaptive behaviors.
2. *Content and units of analysis*: RDoC spans from genes to brain to behavior, placing particular emphasis on neurobiology (e.g., circuits), whereas HiTOP focuses on signs, symptoms, diagnoses, and maladaptive behaviors.
3. *Current gaps and limitations*: The RDoC matrix includes, alongside units of analyses relevant to studying to neural and physiological correlates, units called *behavior* and *self-report*, but at present these units do not intend to include the majority of signs, symptoms, and behaviors requiring clinical attention (e.g., suicidality, hazardous alcohol use) (Kozak & Cuthbert, 2016; Patrick & Hajcak, 2016). Furthermore, many self-report, behavioral, and task exemplars included in RDoC have inadequate or unclear psychometric properties and were not developed to operationalize RDoC constructs as RDoC defines them (Patrick & Hajcak, 2016; Watson et al., 2017). Consequently, RDoC is currently designed as a research framework for translational and clinically-relevant research, but has limited application in clinical practice (Clark et al., 2017; Kozak & Cuthbert, 2016). In contrast, HiTOP dimensions are based on descriptions of clinical phenomena, assessed with clinical interviews, observer-reports, and self-reports (Kotov et al., 2017), but do not take into account their underlying underpinnings. As such, the system remains agnostic with regard to the etiology of psychopathology, even though clarifying the underpinnings of clinical problems included in HiTOP is important for aiding diagnostic and treatment decisions.

3. A new interface linking RDoC and HiTOP

The complementary nature and strengths of RDoC and HiTOP can be leveraged to advance understanding of psychopathology and inform clinical practice (Latzman et al., 2020). Since RDoC currently lacks direct clinical applicability, HiTOP may aid RDoC-informed research by providing psychometrically robust clinical targets. Additionally, since HiTOP does not consider the etiology of psychopathology, RDoC provides a solid transdiagnostic framework for elucidating the underpinnings of the clinical problems in HiTOP beyond what is possible using current diagnoses. The specific aim of the present narrative literature review is to delineate an interface between the two systems. The interface supported by our narrative review can help build a "common language" between RDOC and HiTOP, provoke novel hypotheses for future studies, and encourage future systematic reviews or meta-analyses focused on specific connections. Ultimately, bridging between RDoC and HiTOP may accelerate etiological and translational neuroscience research and inform future clinically-useful classifications that explicitly include psychopathological underpinnings. This will facilitate development of novel treatments targeting mechanisms and with potential effects on a broader range of conditions subsumed by more general dimensions, which are expected to be more efficient for treating commonly co-occurring problems (Barlow et al., 2017; Bzdok & Meyer-Lindenberg, 2018).

Given the broad literature covered by our review, a systematic review of the myriad possible connections between RDoC and HiTOP dimensions was unfeasible and beyond the scope of our article, in line with previous narrative reviews on RDoC and DSM diagnoses (Koudys et al., 2019; Lebowitz et al., 2018). Rather, we present connections between RDoC and HiTOP by reviewing available empirical articles or reviews that focused on markers of these two frameworks, helping us outline an interface between them. We delineated links between RDoC and HiTOP at the most specific level possible: subconstructs or constructs for RDoC and spectra or subfactors for HiTOP (as research on associations of more specific HiTOP elements with RDoC is very limited). With regard to RDoC, we focused on studies investigating elements from the self-reports, paradigms, behaviors, physiology, or circuits RDoC units of analysis, included in the matrix as of April 2020 (other units have not been sufficiently studied together with HiTOP dimensions). These elements of the RDoC matrix were used as exemplars of markers of specific constructs/subconstructs and to distinguish between different constructs/subconstructs within the same domain (e.g., Acute Threat vs. Potential Threat). In the instance of RDoC constructs/subconstructs including elements that are common across several RDoC constructs and domains (mostly from circuits and physiology units of analysis, e.g., amygdala, hypothalamic–pituitary–adrenal axis), we focused on other units of analyses (e.g., behavior and self-report) that could allow us to draw more specific associations. To operationalize HiTOP dimensions, we focused on psychopathology constructs conformant with latent dimensions included in the HiTOP system (i.e., derived through latent variable modeling) or measured by scales capturing symptom or trait dimensions included in HiTOP (Kotov et al., 2017). We further considered empirical studies or reviews focused on multiple categorical disorders that fall under one or more spectra (e.g., studies of various internalizing and/or psychotic disorders). Studies including cases of one disorder and controls were considered if they examined continuous

associations between RDoC and HiTOP markers, but not if they only reported case-control comparisons, as the latter provide limited information about RDoC and HiTOP dimensions.

Some caveats to the literature review should be considered. First, although HiTOP includes most forms of psychopathology, it does not yet cover some conditions, such as autism and learning, motor, or intellectual difficulties, which are therefore not reviewed here. Second, HiTOP provisionally includes a Somatoform spectrum, but this dimension is relatively understudied, especially with regard to its behavioral-neural correlates, and thus not included in our review. Third, since the psychopathological correlates of the RDoC Sensorimotor domain have been rarely investigated to date, it was not possible to identify associations with HiTOP dimensions.

4. Literature review

Our review identified numerous HiTOP correlates of each RDoC construct/subconstruct.

4.1 Negative Valence Systems (Supplementary Figure 1)

Negative Valence Systems include five constructs involved in response to aversive situations.

4.1.1 Acute Threat (Fear)—Markers of RDoC Acute Threat show robust associations with several forms of psychopathology (i.e., panic disorder, agoraphobia, social phobia, specific phobias, obsessive-compulsive disorder) included in HiTOP Fear, a subfactor of the Internalizing spectrum. Several psychophysiological markers, including increased skin conductance and heart rate in the context of defensive reactivity (e.g., exposure to an acute threat), have been related to panic attacks and agoraphobia (Hamm et al., 2016). One study further found that a latent acute-threat factor—defined by self-rated trait fearfulness and physiological reactions potentiated by aversive pictures—was strongly associated with fear disorders, especially phobias (Yancey et al., 2016). At the neural level, some studies have found stronger associations of hyperactivation of the fear circuit (amygdala, insula, anterior cingulate and prefrontal cortex) with fear disorders (e.g., panic disorder and phobias) than with distress disorders (e.g., generalized anxiety disorder and posttraumatic stress disorder) (Brühl et al., 2014; Duval et al., 2015). Alterations in behavioral markers of RDoC Acute Threat, such as increased avoidance of an acute threat (‘flight’ response) and freezing, are also common markers of fear disorders (Blanchard et al., 2011; Corr & Cooper, 2016). Among paradigms, the CO_2 challenge has been shown to capture individual differences in panic symptoms (Battaglia et al., 2014; Rapee et al., 1992). Finally, the association between RDoC Acute Threat and HiTOP Fear is supported by evidence showing that the four dimensions of feared stimuli included in the Fear Survey Schedule (a self-report marker of RDoC Acute Threat) are consistent with the forms of psychopathology included in the Fear subfactor (Beck et al., 1998).

Of note, the association between RDoC Acute Threat and HiTOP Fear appears less supported by studies using fear conditioning paradigms. Multiple anxiety disorders (falling under both Fear and Distress within HiTOP) are associated with increased fear responses only to stimuli associated with safety (i.e., CS−), as opposed to actual danger (i.e., CS+), suggesting that these conditions may not be associated with responses to immediate threat

(Duits et al., 2015). It may be argued, however, that fear conditioning paradigms measure processes related to fear acquisition and learning, rather than acute response to threat. Research examining multiple markers of RDoC Acute Threat is needed to clarify the potential sources of these inconsistencies.

4.1.2 Potential Threat (Anxiety)—Substantial evidence indicates an association between RDoC Potential Threat and HiTOP Fear. Enhanced startle potentiation to uncertain threat has been consistently associated with fear disorders (e.g., social anxiety disorder, specific phobia) (Gorka et al., 2017; Yancey et al., 2015). In a study of adults with various internalizing conditions, startle potentiation to uncertain threat was more strongly associated with fear disorders than distress disorders (e.g., generalized anxiety disorder, major depression) (Gorka, Lieberman, Shankman, & Phan, 2017).). Neuroimaging evidence further suggests common neural bases during processing of threatening stimuli (exaggerated anterior insula reactivity during unpredictable threat and brainstem reactivity during predictable threat) across individuals with internalizing conditions, although brainstem activity during unpredictable threat correlated significantly with a fear dimension, but not with a distress/misery dimension (Radoman et al., 2019). Further, self-report markers of RDoC Potential Threat, such as the Fear of Negative Evaluation scale and the Behavioral Inhibition System scale, show associations with conditions included in HiTOP Fear (Carleton et al., 2011; Corr & Cooper, 2016).

Other studies suggest a differential association of RDoC Potential Threat with the HiTOP Fear and Distress subfactors. Potentiated startle responses may be blunted at high levels of the HiTOP Distress subfactor (McTeague & Lang, 2012; Vaidyanathan et al., 2012; Yancey et al., 2015). An RDoC-informed study showed that a distress/negative affectivity factor was negatively associated with defensive physiological reactivity (startle and heart rate reactivity during fear imagery) (Lang et al., 2016). Similarly, a recent meta-analysis found induced anxiety (e.g., adaptive response to unpredictable threats) and specific phobia, social phobia, and panic disorder (i.e., fear disorders) share similar patterns of hyperactivation in insula, cingulate and prefrontal regions (Chavanne & Robinson, 2021). Conversely, little convergence was found between the underpinnings of induced anxiety and those of PTSD and GAD (i.e., distress disorders), with the latter disorder showing deactivation in insula and cingulate cortex. These findings using physiological and neural markers appear in contrast with evidence on self-report markers of RDoC Potential Threat (anxiety sensitivity and intolerance to uncertainty) suggesting a positive relationship with HiTOP Distress. A meta-analysis on anxiety sensitivity found positively associations with both distress and fear factors derived from associations among internalizing disorders (Naragon-Gainey, 2010). Increased intolerance to uncertainly has also been related with both distress and fear psychopathology (Carleton et al., 2012; Correa et al., 2019), although some evidence suggests a stronger positive relationship with depressive symptoms (Sexton et al., 2003), which is subsumed under HiTOP Distress. Further research is needed to clarify whether different markers of RDoC Potential Threat show differential associations with HiTOP Distress and show more specific associations with certain aspects of HiTOP Internalizing.

4.1.3 Sustained Threat—RDoC Sustained Threat appears robustly linked with HiTOP Distress, as individuals with high sustained threat show high levels of distress symptoms, especially depression and posttraumatic stress (Pryce et al., 2011; Spinhoven et al., 2016). At the neural level, altered neurocircuitry of sustained threat (e.g., amygdala reactivity) has been associates with depression (Henje Blom et al., 2016; Ross et al., 2017). Further, distress psychopathology has been linked with RDoC behavioral markers (e.g., punishment sensitivity, helpless behavior, anxious arousal, and attention bias) (Gentes et al., 2015; Gibb et al., 2016; Harnett, Loxton, & Jackson, 2013; Pryce et al., 2011; Torrubia, Ávilab, Moltób, & Caseras, 2001) and self-report markers (Childhood Trauma Questionnaire) (Spinhoven et al., 2016) of Sustained Threat.

4.1.4 Loss—RDoC Loss also appears robustly linked with HiTOP Distress. This association is supported by studies of the behavioral manifestations of Loss, such as shame, guilt, sadness, worry, hopelessness, and rumination, with show clear links with distress symptoms, especially depression (Grierson et al., 2016; Mazzer et al., 2019; Robinaugh & McNally, 2010; Watson et al., 2012; Watson et al., 2017). This link to HiTOP Distress is also supported by markers in the circuits unit of analysis, such as habit system and reward circuit, which are key to Positive Valence Systems. This evidence is thus discussed more in detailed in section 4.2.

4.1.5 Frustrative Non-Reward—RDoC Frustrative Non-Reward has few markers that apply to humans. Research on behavioral and self-report markers (e.g., Questionnaire of Daily Frustrations) indicate positive associations with depression (Baars et al., 2011) and aggression (Baars et al., 2011; Geniole et al., 2017; Smeets et al., 2017). These studies suggest emerging links of RDoC Frustrative Non-Reward, respectively, with the HiTOP Distress subfactor of the Internalizing spectrum and the HiTOP Antisocial Behavior subfactor of the Disinhibited and Antagonistic Externalizing spectra.

4.2 Positive Valence Systems (Supplementary Figure 2)

Positive Valence Systems are primarily involved in positive or appetitive motivational contexts and comprises three broad constructs, each with three subconstructs.

4.2.1 Reward Responsiveness—The RDoC Reward Anticipation subconstruct is associated with the HiTOP Disinhibited Externalizing spectrum and its Substance Abuse subfactor. Neuroimaging studies using monetary incentive delay (MID) tasks have revealed atypical functioning and/or functional connectivity between the ventral striatum and prefrontal structures (i.e., anterior and ventromedial prefrontal cortex) in relation to symptoms of impulsivity, inattention, and hyperactivity (Hahn et al., 2009; Plichta & Scheres, 2014; Stark et al., 2011). Further, reduced anticipatory signaling has been observed alongside disruption in mesolimbic-dopaminergic systems in addiction-based psychopathology (Balodis & Potenza, 2015; Luijten et al., 2017; Robinson & Berridge, 2001). This RDoC subconstruct also appears linked to the HiTOP Thought Disorder spectrum, as reduced anticipatory signaling in the ventral striatum is associated with negative symptoms of schizophrenia (Radua et al., 2015) Associations of MID-related dysfunctional anticipatory reward processing (decreased caudate activation, increased

activation in the middle frontal gyrus, anterior cingulate cortex [ACC] and frontal lobe) with depressed mood further suggests an emerging link to the HiTOP Distress subfactor (Dillon et al., 2014; Zhang et al., 2013).

Markers of RDoC Initial Response to Reward demonstrate a robust link to the HiTOP Distress subfactor, based on associations of depressed mood with blunted event-rated potentials (ERPs) and behavior during simple guessing tasks (Baskin-Sommers & Foti, 2015; Foti & Hajcak, 2009; Nelson et al., 2016; Nielson et al., 2021; Weinberg et al., 2015). For example, blunted reward positivity prospectively predicts increases in depressive symptoms (Nelson et al., 2016). Further, depressive symptoms are associated with a decreased responsiveness and failure to alter behavioral responses following reward attainment (Foti & Hajcak, 2009). An additional association between RDoC Initial Response to Reward and the HiTOP Substance Abuse subfactor is supported by evidence that reduced or absent activations in the orbitofrontal cortex (OFC), amygdala, and striatum, as well as sensory processing regions, in response to monetary reward or verbal/visual feedback is related with addiction (Diekhof et al., 2008; Koob & Volkow, 2016; Luijten et al., 2017; Redish et al., 2008; Volkow et al., 2010). Further links can be delineated with the HiTOP Disinhibited Externalizing spectrum, via positive associations between psychophysiological markers of reward sensitivity and disinhibitory traits, inattention and hyperactivity-impulsivity (Carlson et al., 2013; Luman et al., 2005) (although negative associations have also been reported (Babinski et al., 2019; Plichta & Scheres, 2014)), and to the HiTOP Antisocial Behavior subfactor, based on reward-driven antisocial and callous-aggressive tendencies (Byrd et al., 2014; Carlson et al., 2013; Frick & White, 2008).

Finally, since markers of RDoC Reward Satiation have not yet been reliably linked to psychopathology, it was not possible to identify links to HiTOP.

4.2.2 Reward Learning—The RDoC Probabilistic and Reinforcement Learning subconstruct shows an association with the HiTOP Distress subfactor. Using probabilistic reward tasks (e.g., Pizzagalli et al., 2009), blunted reward learning has been observed in distress disorders (major depressive disorder, post-traumatic stress disorder, generalized anxiety disorder), as indicated by poor or inflexible modulation of behavior (Dillon et al., 2014; Halahakoon et al., 2020; Morris et al., 2015) and reduced nucleus accumbens and ACC activity (Baskin-Sommers & Foti, 2015). An additional link to the HiTOP Substance Abuse subfactor is supported by robust associations of neural mechanisms of disrupted reward learning (activity within the prefrontal cortex, dorsal striatum, and basolateral amygdala) (Hyman et al., 2006; Redish et al., 2008; Wassum & Izquierdo, 2015) and distorted Pavlovian conditioning (Baskin-Sommers & Foti, 2015; Bevins & Murray, 2011; MacRae et al., 1987) with addiction. This subconstruct also shows an association, although potentially weaker, with the HiTOP Thought Disorder spectrum, via research demonstrating that abnormal neural responses in reward learning via meso-corticolimbic and meso-striatal function (Radua et al., 2015; Ziauddeen & Murray, 2010), rigid reward learning (Deserno et al., 2013), and impaired reversal learning (Ziauddeen & Murray, 2010) are associated with psychotic symptoms.

RDoC Reward Prediction Error is robustly linked to the HiTOP Substance Abuse subfactor. At the neural level, impaired fronto-striatal connectivity (Park et al., 2010) and increased activity of dopaminergic neurons and projections within the striatum, amygdala, and orbitofrontal cortex (OFC; Keiflin & Janak, 2015; Schultz, 2011; Volkow et al., 2010) have been observed in substance use populations in the context of reward prediction. This association is also supported by increases in sign-tracking behavior (Redish et al., 2008), and self-reported craving (Chase et al., 2011; Serre et al., 2015). An additional link may be delineated with the HiTOP Antisocial Behavior subfactor, as indicated by associations of aberrant dopaminergic functioning and neural circuitry to expectancy violations (e.g., OFC, ACC, amygdala) with disruptive behaviors (Blair et al., 2013; Estrada et al., 2019; Sonuga-Barke et al., 2016). Further, some evidence suggests that reduced activity in the dopaminergic frontal, striatal, and limbic system underlying prediction error are associated with psychotic symptoms, suggesting an emerging link to HiTOP Thought Disorder (Corlett & Fletcher, 2012; Radua et al., 2015).

Finally, the RDoC Habit subconstruct also appears linked to the HiTOP Substance Abuse subfactor, as the development of substance-related habits and compulsive behaviors are robustly associated with increased activity in the dorsal striatum and its dopaminergic projections (Everitt & Robbins, 2005; Newlin & Strubler, 2007; Ostlund & Balleine, 2008; Sjoerds et al., 2013; Yin et al., 2008).

4.2.3 Reward Valuation—The RDoC Reward (probability) subconstruct shows a robust link with the HiTOP Antisocial Behavior subfactor, as externalizing behavior is associated with impaired probability discounting, thereby increasing the likelihood of riskier behavioral choices (Olson et al., 2007; Sparks et al., 2014). An additional link can be drawn to the HiTOP Substance Abuse subfactor via a short-term probability discounting process, though findings are mixed and careful consideration should be given to the distinction between probabilistic discounting versus delay discounting (discussed below) in addiction (Redish et al., 2008; Yi et al., 2010).

The RDoC Delay subconstruct demonstrates robust links to the HiTOP Disinhibited Externalizing spectrum and its Substance Abuse and Antisocial Behavior subfactors, respectively supported by associations of greater delay discounting with impulsivity and inattention (Jackson & MacKillop, 2016; Patros et al., 2016; Pauli-Pott & Becker, 2011), substance use (Bickel & Marsch, 2001; Redish et al., 2008; Reynolds, 2006; Yi et al., 2010), and antisocial behavior (Bobova et al., 2009; Dai et al., 2016; Sparks et al., 2014; Woltering et al., 2016).

Research on markers of the RDoC Effort subconstruct reveals an association with HiTOP Substance Abuse, as indicated by associations of addiction with heightened self-reported drive and rash effort-based decision making (Dawe et al., 2004; Franken, 2002), as well as increased fronto-striatal activity associated with effort calculation and expenditure (Redish et al., 2008; Volkow et al., 2010). Further, self-report and task-based behavioral markers link this RDoC subconstruct to disorders and symptoms pertaining to HiTOP Distress via deficient willingness to exert effort and decreased drive (Culbreth, Moran, & Barch, 2018). Indeed, the Effort-Expenditure for Rewards Task (EEfRT) probes effort-based decision

making which show robust associations to depressive symptoms, particularly anhedonia (Dillon et al., 2014; Treadway et al., 2009). Finally, an additional link can be delineated with HiTOP Thought Disorder via associations of negative symptoms of schizophrenia with impaired effort-based decision making (Green et al., 2015; Reddy et al., 2016) and effort-cost computations (Fervaha et al., 2013).

4.3 Cognitive Systems (Supplementary Figure 3)

Cognitive Systems cover six cognitive constructs and their subconstructs.

4.3.1 Attention—Existing research indicates a robust association between markers of RDoC Attention and the HiTOP Disinhibited Externalizing spectrum. With regard to neural circuitry, an imbalance (i.e., reduced anti-correlation) between task positive network (TPN) and default mode network (DMN) is considered a key correlate of inattentive and hyperactive-impulsive symptoms (Gerrits et al., 2019; Sonuga-Barke & Castellanos, 2007). Further, increased intra-individual variability in response times, thought to reflect attentional lapses and to also arise from TPN-DMN imbalance (Sonuga-Barke & Castellanos, 2007), is robustly associated with inattentive, hyperactive-impulsive, and externalizing symptoms (Agnes Brunnekreef et al., 2007; Bastiaansen et al., 2015; Kuntsi et al., 2014; Michelini et al., 2018). The link between RDoC Attention and the Disinhibited Externalizing spectrum is also support by studies indicating a link to the Substance Abuse subfactor of this spectrum, based on associations between attentional impairments and substance use in cross-sectional (Indlekofer et al., 2009; Thoma et al., 2011) and prospective longitudinal studies (Tapert et al., 2002). Another robust association can be delineated between RDoC Attention and HiTOP Thought Disorder. Neural markers of attentional dysfunction (e.g., ERPs reflecting atypical gating, ventral attention network) have been associated with delusional ideation (Galderisi et al., 2014; Lavigne et al., 2020). Increased attentional lapses, distractibility, and impairments in attentional task performance are also robustly associated with symptoms of schizophrenia (Guastella et al., 2013) and positive schizotypy (Marsh et al., 2017; Mohanty et al., 2008; Siddi et al., 2017). The association of attentional lapses, distractibility with manic symptoms further suggests an emerging association between RDoC Attention and the HiTOP Mania subfactor (Glaus et al., 2018; Pagliaccio et al., 2017), which in HiTOP is provisionally connected to both the Thought Disorder and Internalizing spectra.

Additional evidence indicates that RDoC Attention may be linked with HiTOP Detachment, based on associations of poor performance in sustained attention tasks with negative schizotypy (Moreno-Samaniego et al., 2017; Siddi et al., 2017). Another emerging association, although potentially weaker, is with the HiTOP Distress subfactor, supported by associations of attentional markers (e.g., increased reaction time variability, distractibility) with depression and suicidality (Hsu et al., 2019; Keller et al., 2019; van Deurzen et al., 2012).

4.3.2 Perception—RDoC Perception shows a clear association with HiTOP Thought Disorder. This link is supported, at the neural level, by associations of attenuated auditory and visual ERPs (e.g., reduced mismatch negativity, P50, N1, P2, P3) with symptoms of schizophrenia, positive schizotypy, and high psychosis risk (Earls et al., 2016; Pokorny et

al., 2019; Premkuma et al., 2014). Low performance on a visual integration task (Jittered Orientation Visual Integration task) has also been associated with positive and disorganized schizotypy (Panton et al., 2018). Further, this link is supported by evidence of visual and/or auditory perceptual abnormalities (e.g., hallucinations) in individuals with psychotic disorders and at high psychosis risk (Baumeister et al., 2017; Keane et al., 2018; Lehembre-Shiah et al., 2017; Panton et al., 2016).

Although limited evidence exists to link RDoC Olfactory/Somatosensory/Multimodal Perception with HiTOP, associations between olfactory perceptual deficits and psychotic symptoms suggest an emerging link with HiTOP Thought Disorder (Kamath et al., 2018; Kastner et al., 2013).

4.3.3 Declarative Memory—RDoC Declarative Memory shows robust associations with HiTOP Thought Disorder, based on studies linking behavioral deficits and atypical hippocampal function and circuitry with psychotic disorders and psychosis risk (Cirillo & Seidman, 2003; Ivleva et al., 2012; Seabury & Cannon, 2020; Stone & Hsi, 2011). Negative associations between behavioral markers of episodic memory and depressive symptoms further indicate a potential link with the HiTOP Distress subfactor (Huber et al., 2019; Talarowska et al., 2016).

4.3.4 Language—RDoC Language shows a robust link with HiTOP Thought Disorder, as indicated by associations of alterations in brain circuits underlying verbal fluency, language, and sematic systems (Costafreda et al., 2011; Sumner et al., 2018) and behavioral markers of reduced verbal fluency (Docherty et al., 2011; Krabbendam et al., 2005; Siddi et al., 2017) with psychotic symptoms. Further, associations between low verbal task performance and negative schizotypy (Siddi et al., 2017) suggest an additional tentative link with HiTOP Detachment.

4.3.5 Cognitive Control—The RDoC Goal Selection, Updating, Representation, and Maintenance subconstruct, which shares several elements with the RDoC Attention construct, shows robust associations with the HiTOP Disinhibited Externalizing spectrum. This link is based on associations of self-reported executive functions (e.g., Behavior Rating Inventory of Executive Function) with greater disinhibitory traits (Long et al., 2015; Teivaanmaki et al., 2019) and inattentive and hyperactive-impulsive symptoms (Mahone et al., 2002; Mahone & Hoffman, 2007). This link is also supported for the Substance Abuse subfactor of this HiTOP spectrum, based on associations between difficulties maintaining goal-directed behavior (e.g., indexed by executive control over incentive salience and PFC activity) and addiction (Koob & Volkow, 2016). This RDoC subconstruct further shows robust associations with HiTOP Thought Disorder, based on by studies indicating atypical fronto-thalamo-parietal circuitry across psychotic disorders (Lencer et al., 2019) and reporting associations of impaired goal selection and updating with psychotic disorders (Barch & Sheffield, 2014) and positive schizotypy (Steffens et al., 2018). Additionally, a meta-analysis showing an association, albeit of small size, between updating and negative schizotypy supports a further link with HiTOP Detachment (Steffens et al., 2018).

The RDoC Response Selection and Inhibition/Suppression subconstruct shows a robust link with HiTOP Thought Disorder, based on studies reporting associations of altered neural circuitry (e.g., reduced dorsolateral prefrontal activity) (Bourque et al., 2017; Van Voorhis et al., 2019) and behavioral performance impairments (Ethridge et al., 2014; Huddy et al., 2013; Wright et al., 2014) during response inhibition tasks (e.g., in Go/No-Go and Stroop tasks) with psychotic disorders and psychotic symptoms. Another robust link can be drawn to the HiTOP Disinhibited Externalizing spectrum, as atypical brain activity (e.g., reduced event-related theta power) and behavioral markers (e.g., prepotent inhibition, impulsive errors) of response inhibition have been related to disinhibitory traits, inattention, and hyperactivity-impulsivity (Crosbie et al., 2013; Leshem, 2016; Venables et al., 2018; Weafer et al., 2015). Studies on behavioral and neural markers of response inhibition also indicate an association between RDoC Response Selection and Inhibition/Suppression and the Substance Abuse (Smith et al., 2014; Squeglia et al., 2014; Wong et al., 2006) and the Antisocial Behavior (Agnes Brunnekreef et al., 2007; Castellanos-Ryan et al., 2014; Heritage & Benning, 2013) subfactors of the HiTOP Disinhibited Externalizing spectrum. Additional links, potentially of smaller magnitude, may be delineated with the HiTOP Distress subfactor (Macatee et al., 2018; van Deurzen et al., 2012; Venables et al., 2017) and HiTOP Detachment (Steffens et al., 2018) based, respectively, on associations between impaired behavioral markers of response inhibition with distress symptoms (e.g., distress intolerance, affective problems) and negative schizotypy.

The RDoC Performance Monitoring subconstruct shows a robust link to HiTOP Fear, based on the self-reported Yale–Brown Obsessive Compulsive Scale (Y-BOCS) and associations of higher error-related negativity (ERN) amplitude during performance monitoring tasks (e.g., Flankers) with OCD traits (Meyer & Hajcak, 2019; Riesel et al., 2017; Storch et al., 2017; Weinberg et al., 2016) and social anxiety/shyness (Meyer & Hajcak, 2019; Meyer & Klein, 2018). Another well-supported link is with the HiTOP Disinhibited Externalizing spectrum, via associations of reduced post-error slowing, ERN amplitude, and lower insula and anterior cingulate activity during error processing with measures of disinhibition, impulsivity, and inattention and hyperactivity (Carroll et al., 2015; Hill et al., 2016; Kessel et al., 2016; Meyer & Hajcak, 2019; Michelini et al., 2018; Pasion & Barbosa, 2019; Taylor et al., 2018). A blunted ERN has also been linked to positive symptoms (but not negative symptoms) (Morris et al., 2008), and negative symptoms (but not psychotic or disorganized symptoms) in individuals with psychotic disorders (Foti et al., 2012; Foti et al., 2016). These mixed findings warrant further research and support a potential link with HiTOP Thought Disorder.

4.3.6 Working Memory—We examined associations with the broader RDoC Working Memory construct, rather than its subconstructs, since the elements contained within each subconstruct overlap with one another and it is difficult to distinguish them. Available evidence supports a robust association with the HiTOP Disinhibited Externalizing spectrum, based on associations of neural (e.g., reduced theta power) and behavioral performance markers during working memory and interference control tasks with trait impulsivity and inattentive and hyperactive-impulsive symptoms (Jang et al., 2020; Lenartowicz et al., 2019; Michelini et al., 2018; Polner et al., 2015). Similar associations of behavioral markers with

substance use escalation and externalizing problems further suggest links, respectively, with the Substance Abuse (Khurana et al., 2013; Peeters et al., 2014; Squeglia et al., 2014) and Antisocial Behavior (Agnes Brunnekreef et al., 2007; Huang-Pollock et al., 2017) subfactors of this HiTOP spectrum.

Another robust association can be delineated with HiTOP Thought Disorder. This link is supported by associations between atypical neural activity (e.g., ventrolateral PFC) and psychotic symptoms (Pu et al., 2016; Sabharwal et al., 2016) during working memory tasks. Impaired behavioral performance markers during working memory and interference control tasks (e.g., n-back and Stroop) are also associated with psychotic disorders and positive schizotypy (Ettinger et al., 2018; Gold et al., 2019; Lencz et al., 2003; Sabharwal et al., 2016; Schmidt-Hansen & Honey, 2009; Seidman et al., 2016; Wolf et al., 2015; Xie et al., 2018). Initial evidence that working memory impairments are associated with high negative schizotypy also supports a possible link to the HiTOP Detachment spectrum (Xie et al., 2018).

4.4 Social Processes (Supplementary Figure 4)

Social Processes systems mediate responses to interpersonal settings and includes four constructs.

4.4.1 Affiliation and Attachment—Markers of RDoC Affiliation and Attachment demonstrate associations with several HiTOP spectra and subfactors. A robust link can to drawn to HiTOP Distress, as greater insecurity and impairment measured via behavioral paradigms (e.g., Strange Situation) and self-report is related to greater distress-based symptom severity (Colonnesi et al., 2011; Davila et al., 2005; Lee & Hankin, 2009; Madigan et al., 2013). Stronger parental attachment is associated with reduced amygdala reactivity and fronto-amygdala connectivity patterns associated with lower anxiety (Lebowitz et al., 2018). Greater self-reported attachment insecurity indicates a link to HiTOP Thought Disorder, via greater positive, negative, and affective symptoms (Berry et al., 2008; Gumley et al., 2014; Korver-Nieberg et al., 2014), and to HiTOP Detachment, as evidenced by insecure attachment associated with personality pathology and social impairment (Davila et al., 2005; Fossati et al., 2017; Levy et al., 2015; Lorenzini & Fonagy, 2013; Sinha & Sharan, 2007; West et al., 1994). Further, a robust links to the HiTOP Antagonistic Externalizing spectrum and the Antisocial Behavior subfactor are supported by associations of greater attachment insecurity and poor peer affiliation with antagonistic dispositional traits (Davila et al., 2005; Levy et al., 2015; Lorenzini & Fonagy, 2013; Nakash-Eisikovits et al., 2002; Sinha & Sharan, 2007) and disinhibitory and callous/aggressive psychopathology (Davila et al., 2005; Fearon et al., 2010; Hoeve et al., 2012; Laird et al., 2001; Van Ijzendoorn, 1997).

4.4.2 Social Communication—The RDoC Reception of Facial Communication subconstruct is associated with HiTOP Thought Disorder via significant neural disruptions, particularly under-recruitment of the amygdala, fusiform gyrus, and the ventral temporal–basal ganglia–prefrontal cortex system (Chan et al., 2010; Collin et al., 2013; Delvecchio et al., 2013; Habel et al., 2010), and impaired identification (Barkl et al., 2014; Chan et al., 2010; Collin et al., 2013; Kohler et al., 2010) of facial emotional states. Another robust link

to HiTOP Detachment is supported by impaired facial emotion recognition associated with interpersonal detachment (Abbott & Green, 2013; Germine & Hooker, 2011) and negative schizotypy (Morrison et al., 2013; Rosell et al., 2014; Statucka & Walder, 2017; Williams et al., 2007). The HiTOP Antisocial Behavior subfactor also shows a well-supported link, as antisocial, disruptive, and callous-unemotional traits are associated with reduced ability to recognize facial emotions and amygdala dysfunction (Collin et al., 2013; da Costa et al., 2018; Marsh & Blair, 2008; Marsh et al., 2008). A further link can be delineated with HiTOP Distress via dysfunctional neural activation, impaired facial recognition, and attentional biases in individuals with depressive and anxious psychopathology (Bistricky et al., 2011; Bourke et al., 2010; Demenescu et al., 2010; Kohler et al., 2011). Finally, studies on markers of behavioral recognition paradigms and aberrant neural activation suggest an emerging link to HiTOP Mania (Chen et al., 2011; Delvecchio et al., 2013).

RDoC Production of Facial Communication shows a potential link to HiTOP Thought Disorder, as blunted spontaneous and imitative facial emotional expressiveness are associated with negative psychotic symptoms (Kring, 1999; Mandal et al., 1998). Research also suggests an association with the HiTOP Antisocial Behavior subfactor, as reduced reciprocal facial expressivity and mimicry in response to angry stimuli, assessed via observation (Cole et al., 1994; Eisenberg et al., 2001) and facial EMG (de Wied et al., 2010), have been associated with disruptive behaviors and externalizing tendencies.

With regard to the RDoC Reception of Non-Facial Communication subconstruct, a robust association with the HiTOP Thought Disorder is supported via studies showing that psychotic disorders are associated with impaired comprehension of emotional prosody (Hoekert et al., 2007; Lin et al., 2018), humor, sarcasm, and irony (Edwards et al., 2002; Mitchell & Crow, 2005).

Finally, at the behavioral level, RDoC Production of Non-Facial Communication is linked to HiTOP Thought Disorder as negative symptoms of psychosis are associated with impaired production of affective speech prosody (Hoekert et al., 2007; Mitchell & Crow, 2005).

4.4.3 Perception and Understanding of Self—

The RDoC Agency subconstruct shows a primarily link to HiTOP Thought Disorder, based on studies of self-recognition (i.e., hallucinations., source-monitoring; Brookwell et al., 2013; Waters et al., 2012) and self-awareness (Hur et al., 2014).

The RDoC Self-Knowledge subconstruct is reliably linked to the Distress subfactor of the HiTOP Internalizing spectrum. Longitudinal and meta-analytic studies demonstrate associations of distress disorders, traits or symptoms with self-reported emotional awareness (Rieffe & De Rooij, 2012; Sendzik, Ö Schäfer, et al., 2017) and alexithymia (difficulty in naming and describing one’s emotions) (Leweke et al., 2012; Li et al., 2015). Further, the well-supported relationship of alexithymia (O’Driscoll et al., 2014; van ‘t Wout et al., 2004) and impaired self-monitoring (Farrer & Franck, 2007; Stephan et al., 2009) with psychotic symptoms indicate an additional link to HiTOP Thought Disorder. A further robust link is supported for HiTOP Detachment via self-reported alexithymia (Bach et al., 1994; Vanheule et al., 2007) and poor self-insight (Bach et al., 1994; Lim et al., 2019). Finally, emerging

evidence supports a link between RDoC Self-Knowledge and HiTOP Fear, as individuals with fear psychopathology demonstrate poor emotion knowledge (O'Toole et al., 2013; Sendzik, J, et al., 2017; Summerfeldt et al., 2011).

4.4.4 Perception and Understanding of Others—The few markers of RDoC Animacy Perception suggest a link to Thought Disorder, based on evidence suggesting impaired processing of biological motion (Okruszek & Pilecka, 2017).

A link between RDoC Action Perception and HiTOP Antisocial Behavior is supported by impaired facial mimicry and preference within empathic paradigms, as well as poor directed gaze following (Bedford et al., 2017; de Wied et al., 2010; Wagner et al., 2016). HiTOP Thought Disorder also shows an association with this subconstruct, as evidenced by dysfunctional mirror neuron activity (Mehta et al., 2014; Minichino & Cadenhead, 2016) and action blindness (i.e., inability to identify what actions an agent is executing) (Liepelt et al., 2012).

RDoC Understanding Mental States shows a reliable link to Thought Disorder, as psychotic symptom severity is associated with impaired self-report affective empathy (Bonfils et al., 2016, 2017) and cognitive empathy during theory of mind tasks (Bora et al., 2009; Harrington et al., 2005). An additional robust link to HiTOP Antisocial Behavior is supported by associations of impaired empathic functioning with externalizing, antisocial, and callous-unemotional traits (de Wied et al., 2010; Hawes & Dadds, 2012; Miller & Eisenberg, 1988; Moul et al., 2018). Indeed, such empathic deficits are thought to be at the core of traits or symptoms pertaining to antisocial tendencies (Frick & White, 2008). This construct further shows a well-supported link with HiTOP Detachment, as affective and cognitive empathy partially mediates between negative schizotypy and social functioning (Henry et al., 2008; Wang et al., 2013) and self-reported detachment has been related to impaired social cognition (Fossati et al., 2017). Finally, this subconstruct may be linked to HiTOP Distress via impaired affective and cognitive empathy associated with depressive symptoms (Schreiter et al., 2013; Tone & Tully, 2014; Zahn-Waxler & Van Hulle, 2011), though associations with other distress-related symptoms remain unclear.

4.5 Arousal and Regulatory Systems (Supplementary Figure 5)

Arousal and Regulatory Systems are primarily involved in activating neural systems in response to various contexts and providing homeostatic regulation of energy balance and sleep.

4.5.1 Arousal—The RDoC Arousal construct shows a robust positive association with the HiTOP Distress subfactor, based on associations of measures of increased pupil dilatation during video-clips eliciting internalizing reactions (McCord et al., 2017), psychomotor agitation (Leventhal et al., 2008; Parker et al., 1993), and high cortisol productivity (Kircanski et al., 2017) with distress symptomatology (e.g., hopelessness, demoralization, stress/worry, generalized anxiety). High RDoC Arousal is also linked to HiTOP Fear via studies showing associations between skin conductance and social anxiety (Dieleman et al., 2015; Panayiotou et al., 2017). Another robust link to the HiTOP Disinhibited Externalizing spectrum is supported by evidence that skin conductance during a

low-demand attentional task are related with inattention and hyperactivity/impulsivity (independently from antisocial behaviors) (Du Rietz et al., 2019), consistent with theoretical accounts proposing hypo-arousal as a core underpinning of these symptoms (Hegerl & Hensch, 2014; Sergeant, 2005). Reduced arousal in individuals with psychopathic traits, indexed by low cortisol productivity, stress reactivity, and skin conductance levels (Lorber, 2004; Shirtcliff et al., 2009), further indicate an association with the HiTOP Antagonistic Externalizing spectrum. The Antisocial Behavior subfactor at the intersection of the HiTOP Disinhibited and Antagonistic spectra also shows robust associations, as indicated by links of low skin conductance with conduct problems (Lorber, 2004), and of low pupil dilation during video-clips eliciting externalizing reactions with antisocial behavior and aggression (McCord et al., 2017). Finally, evidence of enhanced behavioral activation and hypo-arousal during mania suggests a potential link of RDoC Arousal with HiTOP Mania (Geissler et al., 2014; Hegerl & Hensch, 2014).

4.5.2 Circadian Rhythms—The RDoC Circadian Rhythms construct comprises elements such as morningness/eveningness, which refers to when people have their peak arousal levels. Since eveningness is linked to most forms of psychopathology (Fabbian et al., 2016; Gau et al., 2007; Hsu et al., 2012; Lemoine et al., 2013; Li et al., 2018; Schlarb et al., 2014), we suggest a tentative link to the general factor of psychopathology, or p-factor, which warrants further research.

4.5.3 Sleep-Wakefulness—The RDoC Sleep-Wakefulness construct shows a robust link with the HiTOP Distress subfactor, based on associations of insomnia and low sleep quality with depression and anxiety (Baglioni et al., 2011; Goldman-Mellor et al., 2014; Gregory et al., 2011; Madrid-Valero et al., 2019; Sawyer et al., 2015). A more tentative link can be identified with the HiTOP Disinhibited Externalizing spectrum, its Substance Abuse subfactor, and the Antisocial Behavior Subfactor, as lower sleep quality is associated with inattentive and hyperactive-impulsive symptoms (Gregory et al., 2017), substance abuse (Pieters et al., 2015), and externalizing problems (Denis et al., 2017). Notably, the latter study did not find any association with callous-unemotional traits, suggesting the association is specific to the HiTOP Disinhibited Externalizing spectrum, rather than shared across HiTOP Externalizing spectra (Denis et al., 2017). Finally, dysregulated wakefulness during manic episodes suggest an additional, tentative link to the HiTOP Mania subfactor (Hegerl et al., 2010; Robillard et al., 2016).

5. RDoC-HiTOP interface summary and general discussion

In the previous section, we have delineated an interface between RDoC and HiTOP frameworks by identifying connections between their dimensions based on available literature. Our review indicates a large number of associations of between RDoC constructs/subconstructs and HiTOP spectra/subfactors, which are of varying strength and documented by a varying number of studies. More associations are expected to emerge in future research informed by this interface. Figure 2 illustrates the most robust and consistent connections on the level of RDoC domains and HiTOP spectra. Multiple explanations exist for this large number of associations. First, the domains included in RDoC were designed to be transdiagnostic and capture major biobehavioral systems relevant to multiple forms of

psychopathology (Kozak & Cuthbert, 2016), thus associations of varying strength and direction are expected among most RDoC and HiTOP dimensions. Second, the substantial correlations among psychopathology dimensions likely contributes to widespread associations with RDoC, consistent with high psychiatric comorbidity and limited specificity of biomarkers (Caspi et al., 2020). Third, there is evidence of etiological heterogeneity underlying psychopathology, with multiple etiological pathways contributing to similar clinical manifestations in different individuals (Kendler, 2019). Fourth, the biobehavioral correlates of a given HiTOP dimension may change across development (e.g., some associations may be more prominent in children than adults) (Tseng et al., 2019), thus studies of different developmental periods may suggest different links.

Nevertheless, some connections stood out because of their consistent effects across multiple constructs within each RDoC domain (Figure 2). RDoC Negative Valence Systems were robustly and positively linked to the HiTOP Internalizing spectrum, in line with a vast literature linking negative affectivity with internalizing psychopathology (Chorpita & Barlow, 1998; Clark & Watson, 1991; Hur et al., 2019). RDoC Arousal and Regulatory Systems was also linked to HiTOP Internalizing, but with positive associations with Arousal and negative with Sleep/Wakefulness, consistent with the association between poor sleep and hyperarousal (Kalmbach et al., 2018). RDoC Social Processes were negatively associated with HiTOP Thought Disorder, Detachment, and Antagonistic Externalizing spectra, in line with the prominent role of social functioning in the forms of psychopathology that they subsume (Green et al., 2019; Widiger et al., 2019). RDoC Cognitive Systems dysfunction was robustly linked to HiTOP Thought Disorder and Disinhibited Externalizing spectra, consistent with multiple theoretical models (Baskin-Sommers & Newman, 2013; Green et al., 2019). RDoC Positive Valence Systems showed strong negative links with HiTOP Disinhibited Externalizing, except for Substance Abuse, which showed some positive associations. These opposite links may suggest that substance use show specific correlates (e.g., enhanced Effort and Habit) that distinguish them from other dimensions of the HiTOP Disinhibited Externalizing spectrum.

Overall, our findings highlight that, although the interplay between biobehavioral and clinical features is complex, a number of core connections can be identified, which may serve as the foundation of a unified nosology that systematically describes both clinical presentation and its etiological underpinnings.

6. Practical recommendations and future directions

In this article we have provided a detailed map (section 4, Supplementary Figures 1–5) as well as an overarching summary (section 5, Figure 2) of an interface between RDoC and HiTOP. We have delineated associations between transdiagnostic biobehavioral systems included in RDoC and various clinical phenomena organized in the HiTOP model, but also highlighted more tentative associations where additional research is needed. The identified connections between RDoC and HiTOP dimensions can guide design of applied studies seeking to elucidate the underpinnings of clinical problems using RDoC domains or to validate HiTOP dimensions using etiological and neuroscientific approaches. On the one hand, latent HiTOP dimensions (i.e., obtained through factor analytic approaches) and

assessments recommended by HiTOP (lists for research and clinical applications, respectively, are available in Kotov et al., 2017 and at https://hitop.unt.edu/clinical-tools/hitop-friendly-measures) provide more psychometrically-robust clinical targets than diagnostic categories for RDoC-informed studies. HiTOP-conformant measures may also supplement RDoC's self-report and behavior markers, since the former are more clearly tied to clinical phenomena. On the other hand, RDoC provides a detailed framework to establish the validity of HiTOP dimensions with respect to coherent associations with core biobehavioral and neural dimensions across multiple units of analysis. This will promote a better understanding of the underpinnings of HiTOP dimensions and inform modifications of the model. Together, future efforts using this interface hold promise for promoting future dimensional classifications informed by the taxonomy of clinical problems and by their etiological underpinnings.

A number of links that seem likely for theoretical and empirical reasons were indicated as emerging or tentative to provoke further research, or not included because of a lack of strong studies investigating RDoC and HiTOP markers. For example, we expect HiTOP Detachment to show a negative association with RDoC Positive Valence Systems. Considerable research indicates that Detachment is equivalent to the low pole of the extraversion dimension in normal personality (Suzuki et al., 2015), which is associated with variation in the dopaminergic reward system that is central to Positive Valence Systems (Smillie et al., 2019). Further, emerging evidence suggests that negative symptoms of schizophrenia (currently under Thought Disorder), which have also been linked to deficits in reward processing (Reddy et al., 2016), should instead be located under Detachment (Cicero et al., 2019). Detachment thus likely reflects low sensitivity to reward, suggesting a link to Positive Valence Systems.

An important future direction will be to establish the specificity of the associations delineated in this interface, since most of the studies reviewed examined only a limited set of measures consistent with RDoC and HiTOP dimensions. Assessing multiple HiTOP spectra in any given study would allow researchers to test the specificity of the hypothesized associations with clinical features (i.e., discriminant validity) by showing that an RDoC construct is more strongly associated with one HiTOP spectrum than another. Even within a given spectrum, there may be differential associations of RDoC constructs with different subfactors and specific symptom dimensions. For example, the associations identified between RDoC Positive Valence Systems constructs and HiTOP Distress are based on studies on depressive symptoms, but links to other forms of Distress (e.g., generalized anxiety) are currently less researched. Future research is needed to clarify whether the link of RDoC Positive Valence Systems with HiTOP Distress extends also to other forms of internalizing psychopathology or is specific to depressive symptoms. Specific associations may be identified with assessments that capture several levels of the HiTOP hierarchy, for example through total scale and subscale scores of broad assessments. Similarly, assessing multiple RDoC domains will be essential to identify the relative contribution of core biobehavioral systems to each HiTOP dimension and elucidate their underpinnings.

The evidence supporting this interface comes from studies on community samples, heterogeneous clinical samples, or clinical samples recruited based on a clinical diagnosis

but providing dimensional ratings. Stronger associations between RDoC and HiTOP dimensions may be expected from clinical samples due to greater variability in the clinical range (Sackett & Yang, 2000). Moving forward, as recommended by both RDoC and HiTOP, studies leveraging this interface should focus on demographically diverse population-based samples or samples from mixed patient populations. Researchers may wish to take steps to oversample participants in the range of high risk on the dimensions of interest. These designs are preferable to case-control design, in which the differences between cases and controls on the dimensions of interest are confounded by many extraneous factors (Preacher et al., 2005). Researchers working with existing data can operationalize HiTOP dimensions through latent variable modeling, which is optimal for studying dimensional constructs, but requires large samples. For most applications, samples of at least 300 participants are needed. In smaller samples, dimensional measures based on self- or other-reports consistent with HiTOP, or dimensional scores of symptom severity from clinical interviews, can be used as observed variables, but binary diagnoses should be avoided.

One good example of research that can be done at the interface of HiTOP and RDoC is a study of the IMAGEN sample (N=1700) that investigated neural and cognitive correlates of externalizing problems (Castellanos-Ryan et al., 2014). Using two diagnostic variables (ADHD and conduct disorder) and various self- and parent-reported symptoms and behaviors, such as age at drinking onset, this study reports a latent variable model incorporating three factors resampling the HiTOP Disinhibited Externalizing spectrum and its Substance Abuse and Antisocial Behavior subfactors. Two paradigms listed in the RDoC matrix (under Cognitive and Positive Valence Systems) were administered during fMRI, enabling analysis of associations of the externalizing factors with behavioral and neural variation in response inhibition and reward processing. Results showed similar effects for some biobehavioral variables across the three externalizing factors, but differential effects for others. For example, increased delay discounting was associated with all three factors, but increased OFC activation during reward anticipation was associated only with the substance abuse factor. This study highlights that diagnostic categories can potentially be incorporated into a HiTOP-conformant analysis if there are enough variables to allow diagnoses to be used as indicators of latent variables. Other notable examples are studies using the Philadelphia Neurodevelopmental Cohort (Kaczkurkin et al., 2019) and the Adolescent Brain Cognitive Development study (Karcher et al., 2020).

7. Conclusions

The dimensional approach to clinical research endorsed by both RDoC and HiTOP is the most promising way forward. It requires larger samples and different sampling designs than those with which many clinical researchers are familiar, but the payoff will be more effective scientific research, illuminating the etiology and clinical manifestations of psychopathology. The RDoC-HiTOP interface delineated in this article provides a synergistic approach that brings these dimensional frameworks together, integrates efforts made on both etiological and nosological fronts, and offers a guide for future research. Ultimately, we envision that this interface will contribute to the development of a unified, dimensional, and biobehaviorally-grounded psychiatric nosology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- This article provides a narrative review outlining an interface connecting RDoC and HiTOP dimensions
- RDoC provides a solid transdiagnostic framework for elucidating the underpinnings of HiTOP dimensions
- HiTOP may aid RDoC-informed research by providing psychometrically robust clinical targets
- Leveraging the complementary strengths of RDoC and HiTOP may help advance clinical neuroscience and psychopathology research
- This interface may facilitate the development of future biobehaviorally-grounded classifications of psychopathology

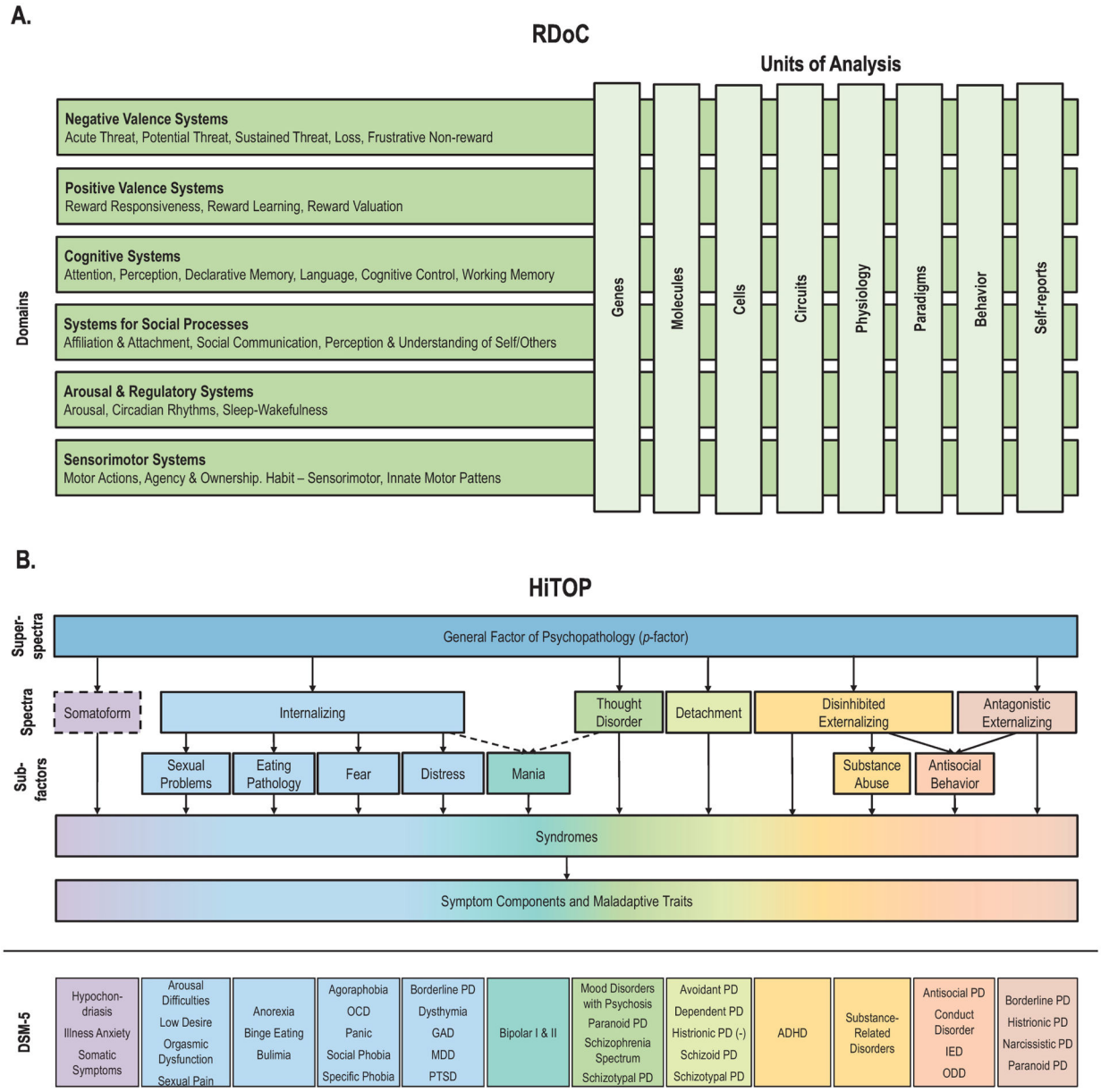

Figure 1.

Research Domain Criteria (RDoC) and Hierarchical Taxonomy of Psychopathology (HiTOP).

Notes: A. The RDoC matrix includes six domains (rows) and their respective constructs (some of which also include subconstructs, not shown here), which can be characterized on the basis of eight units of analysis (columns). B. HiTOP dimensions span from super-spectra (broader and more general) to symptoms components and maladaptive traits (narrower and more specific). Dashed lines indicate provisional elements requiring more study. DSM diagnoses are not part of the HiTOP model and are only included here to allow mapping of their symptoms and signs onto HiTOP. DSM diagnoses mapping onto more than one HiTOP spectrum or subfactor are listed in multiple places. (−) indicates negative association between histrionic personality and the Detachment spectrum.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; GAD, generalized anxiety disorder; IED, intermittent explosive disorder; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; ODD, oppositional defiant disorder; PD, personality disorder; PTSD, posttraumatic stress disorder.

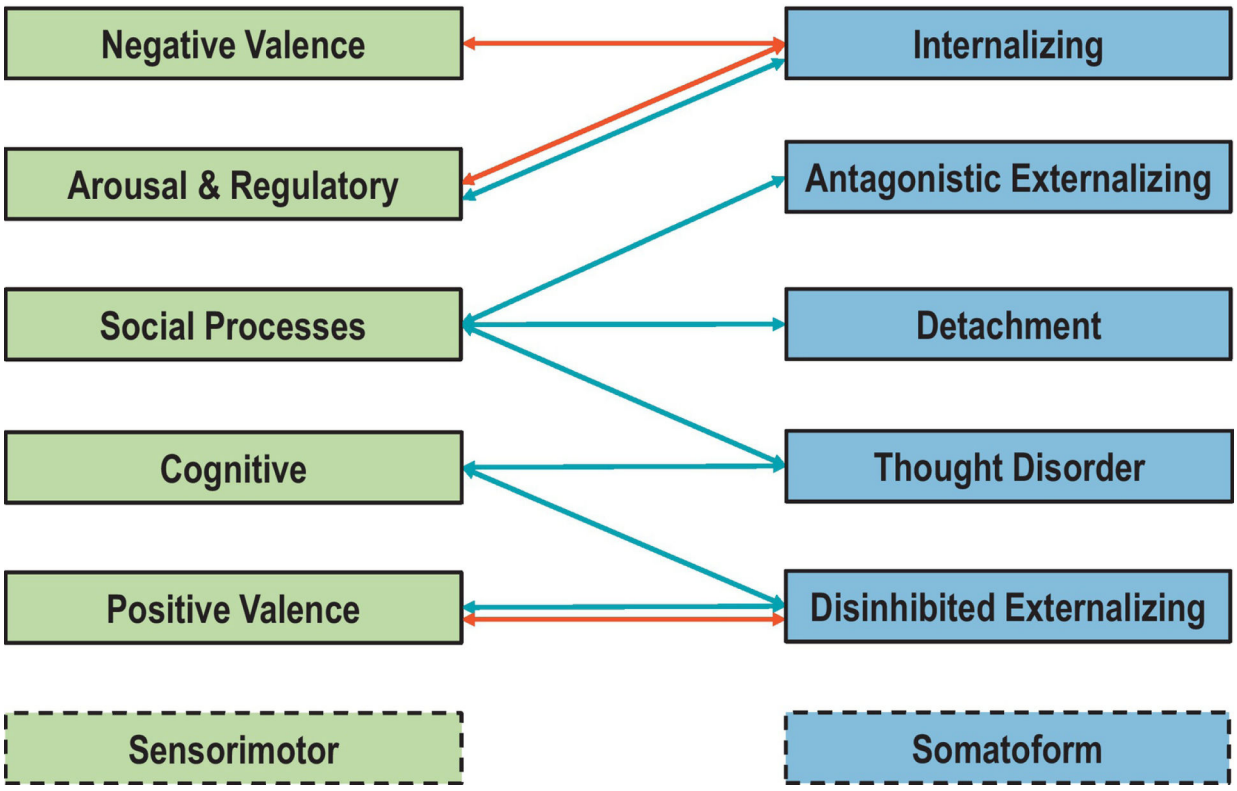

Figure 2.

Overview of top associations between the Research Domain Criteria (RDoC) and the Hierarchical Taxonomy of Psychopathology (HiTOP).

Notes: Arrows show the most consistent associations between RDoC domains and HiTOP spectra (i.e., those depicting robust associations between more than one third of RDoC constructs within a domain with a HiTOP spectrum or its subfactors). Full details of associations between RDoC constructs/subconstructs and HiTOP spectra/subfactors are given in text and Supplementary Figures. Red = positive association; Blue = negative association. Associations that differed in sign across RDoC constructs within the domain are depicted with double arrows.