

Integrating NIMH Research Domain Criteria (RDoC) into depression research

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The NIMH Research Domain Criteria (RDoC) initiative grew out of the agency's goal to develop 'new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures' [1]. In this article, we review how depression research can be meaningfully conducted within an RDoC framework, with a particular focus on the Negative Valence Systems construct of Loss. New efforts to understand depression within the context of RDoC must seek an integrative understanding of the disorder across multiple units of analysis from genes to neural circuits to behavior. In addition, the constructs or processes must be understood within the context of specific environmental and developmental influences. Key concepts are discussed, and we end by highlighting research on rumination as a prime example of research that is consistent with RDoC.

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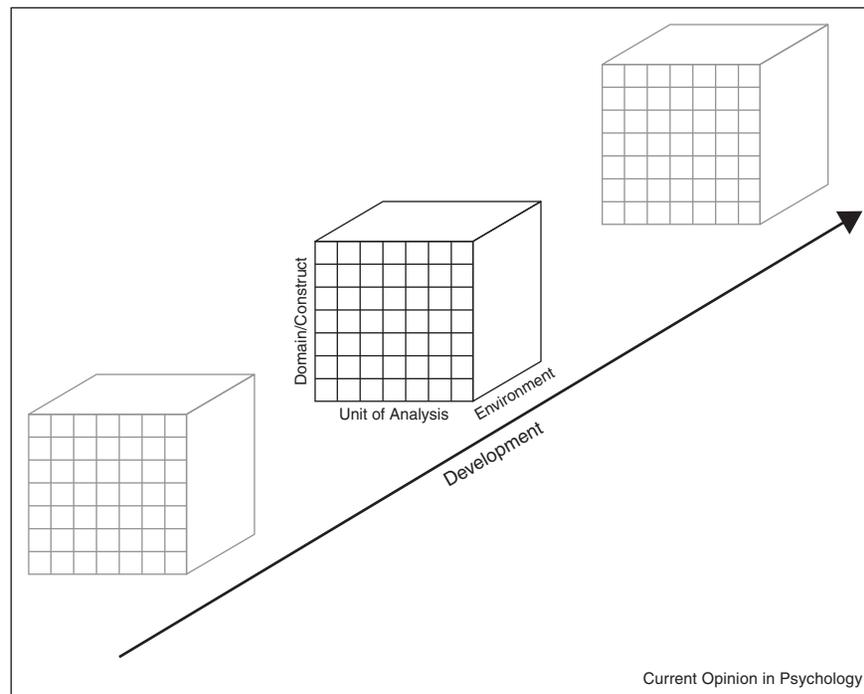
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Strategy 1.4 of the 2008 National Institute of Mental Health (NIMH) Strategic Plan was to 'Develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures' [1]. The Research Domain Criteria (RDoC) initiative grew directly out of this aim, with the explicit goal of linking classification of psychopathology to recent advances in genetics and neuroimaging, which often suggest core features or influences that occur across traditional diagnostic boundaries [2]. Depression, as currently defined, spans two of the RDoC domains: the Loss construct within the Negative Valence Systems domain and various Reward constructs within the Positive Valence Systems domain. This article focuses specifically on the Loss construct (for a RDoC-oriented discussion of reward processing and depression, see Ref. [3]).

Constructs within RDoC are defined across multiple units of analysis, with developmental and environmental/contextual influences seen as additional dimensions within a broader four-dimensional matrix [4,5]. This four-dimensional model is presented in [Figure 1](#). The key departure of this figure from the traditional two-dimensional RDoC matrix (<http://www.nimh.nih.gov/research-priorities/rdoc/research-domain-criteria-matrix.shtml>) is that it explicitly highlights how the traditional axes of domains/constructs and units of analysis must be understood within the context of specific environmental and contextual influences. In addition, the constructs and processes featured in RDoC change over time, both in terms of the development of the individual and the development or progression of the disease. Three developmental windows are highlighted in the figure to emphasize the fact that any current presentation by an individual or disease has a developmental history and a future trajectory that must be taken into account if we are to truly understand the disorder. Therefore, within RDoC, forms of psychopathology are viewed as neurodevelopmental disorders with core disruptions in specific brain circuits that are linked to influences and disruptions across units of analysis ranging from genes and molecules to physiology, behavior, and self-report, which must be understood in terms of specific environmental and contextual influences [2].

The goal of this article is to discuss how to integrate RDoC into depression research, with a particular focus on the measurement of depression. Prior to RDoC, the 'measurement of depression' was easy. One simply administered a standardized self-report or clinician-administered measure of depressive symptoms or the relevant section(s) of a structured clinical interview. With RDoC, however, comes an increasing focus on the heterogeneity not only of depression but also of other disorders. Therefore, the measurement of depression at the symptom level must become more focused, perhaps focusing specifically on affective, cognitive, or somatic symptoms of depression. In contrast, however, measurements within the RDoC Loss construct become much richer, and assessments across each unit of analysis become more salient. Therefore, researchers are given greater flexibility in designing their studies (and seeking NIMH funding) to focus specifically on the processes or mechanisms they want to study rather than always having to link them to DSM diagnoses [5]. In addition, there is an explicit focus on the full range of functioning from normal to abnormal [2] reflecting clear priorities that have formed a

Figure 1



Expanded four-dimensional RDoC matrix.

cornerstone of developmental psychopathology research since its inception [6,7].

The Negative Valence System construct of Loss

Within the current RDoC matrix, every construct is defined across multiple units of analysis. The central feature within this organization is disruptions in a specific (set of) neural circuit(s) (cf. [5]). For the Loss construct (see Figure 2), the key disruptions are within cortico-limbic circuitry (heightened limbic reactivity to affectively salient stimuli, reduced activation in prefrontal areas, and reduced functional connectivity between these regions) as well as increased activity in the default mode network, disruptions that have been highlighted in depression research more generally (for reviews, see Refs. [8–10]). At the genetic level of the Loss construct, the current iteration of the RDoC matrix focuses primarily on genes known to regulate neurotransmission of monoamines including serotonin and dopamine (e.g. 5-HTTLPR, 5-HT receptor genes, *MAOA*, and *COMT*), though these have not been identified in genome-wide association studies (GWAS; e.g. [11]), a point to which we return shortly. The molecular level of the Loss construct highlights the roles of glucocorticoids, sex hormones (estrogen and androgen), oxytocin, vasopressin, and cytokines. At the physiological unit of analysis are peripheral measures of autonomic nervous system (ANS), hypothalamic–pituitary–adrenal (HPA) axis, and neuroimmune dysregulation. To this list, we may add pupil dilation,

which is greater in depressed adults [12] as well as at-risk children [13^{*}] compared to controls following exposure to affectively salient stimuli, and which also predicts remission following cognitive therapy for depression [14]. At the behavioral unit of analysis, Loss is categorized by a heterogeneous list of features, many of which are congruent with current DSM criteria for major depressive disorder (e.g. sadness, anhedonia, guilt, morbid thoughts, psychomotor retardation, deficits in executive function, and disruptions in sleep, appetite, and libido) as well as rumination and biases in attention and memory. Finally, the self-report level of analysis highlights attributional styles and hopelessness.

Loss in the context of environment and development

As noted above and in descriptions of RDoC (e.g. [5]), environmental influences are considered a separate dimension of the RDoC matrix. These influences are arguably more salient to researchers examining depression and the RDoC Loss construct than for any other construct within RDoC. Severe negative life events, particularly those characterized by potential or actual loss of relationships or status, are the strongest individual predictors of depression onset [15]. The relation is bi-directional in that depressed and at-risk individuals also contribute to the generation of additional negative events in their lives, particularly interpersonal events [16,17]. Most major theories of depression, including cognitive and genetic

Figure 2

Negative Valence Systems Construct of Loss							
Units of Analysis							
Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
MAOA; COMT; DAT1; 5HTTR; 5HTRs	Downregulation of Glucocorticoid Receptors; Upregulation of CRH; Estrogens; Androgens; Oxytocin; Vasopressin; Inflammatory Molecules		Sustained Amygdala Reactivity; Decreased DLPFC Recruitment; Decreased vmPFC (incl. rostral cingulate); Increased Insula Activation; Increased Posterior Cingulate Activity; Decreased R Parietal; PVN; Hippocampus; Orbitofrontal Cortex; Habit Systems (Striatum/Caudate/ Accumbens); Increased Default Mode Activity; Dysregulated Reward Circuitry)	ANS, HPA, & Neuroimmune Dysregulation; Prolonged Psychophysiol ogical Reactivity	Rumination; Withdrawal; Worry; Crying; Sadness; Loss- relevant Recall Bias; Shame; Attentional Bias to Negative Valenced Information; Guilt; Morbid Thoughts; Psychomotor Retardation; Anhedonia; Increased Self- focus; Deficits in Executive Function (e.g., Impaired Sustained Attention); Loss of Drive (Sleep; Appetite; Libido); Amotivation	Change in attributional style; Hopelessness	

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Negative Valence Systems construct of Loss.

theories, present vulnerability-stress or diathesis-stress models of risk in which the focus is factors that influence a person's level of depression risk following the occurrence of negative life events. Supporting these models, there is growing evidence that risk for depression following negative life events is greater among individuals exhibiting various forms of cognitive vulnerability including negative attributional/inferential styles, rumination, and biases in attention and memory (for reviews, see Refs. [9,18]). There is also evidence for gene \times environment ($G \times E$) models of risk for depression involving genes associated with serotonergic or HPA axis functioning (for a review, see Ref. [19]), though these studies have largely focused on single candidate genes and there is some question about the replicability of the findings (e.g. [20,21]). Indeed, researchers now recognize that psychiatric disorders such as depression, as well as intermediate phenotypes or endophenotypes associated with depression, are likely impacted by the combined influence of multiple genes operating within specific biological pathways. Given this, researchers have begun to examine aggregate levels of influence across multiple genes and there is a call to scale this up to GWAS \times environment analyses (e.g. [22^{**},23,24]), which

may help to resolve the previous null GWAS findings. In combination, what these studies suggest is that depression-relevant influences across multiple units of analysis cannot be understood without considering the environmental context. To this, we would also add the 'mood context' as we know that various forms of vulnerability to depression may remain latent until 'activated' by a negative mood (cf. [25^{*},26]).

Like environmental influences, development is viewed as an additional dimension to the RDoC matrix. These considerations are also central to depression research. For example, there appear to be developmental shifts in the direction of, firstly, amygdala-prefrontal connectivity [27^{**}], secondly, cortisol reactivity to stress [28], and thirdly, attentional biases and pupillary reactivity to affectively salient stimuli [29–31], as well as genetic influences on neural development (i.e. gene \times development interactions; [32,33^{*}]). There are also developmental increases in the stability of cognitive vulnerabilities to depression [34,35] as well as in the magnitude of cognitive vulnerability \times stress interactions [34,36]. Finally, there is evidence for sensitive periods in which the effects of

environmental stressors may have a stronger impact on the development and functioning of neural and physiological systems [19]. Therefore, researchers examining depression and the RDoC Loss construct must understand how specific processes or influences change across development, both in terms of the development of the individual and development of the disease.

The study of rumination as an example of a multiple-levels-of-analysis approach

Within the Loss construct, perhaps the best example of the multiple-units-of-analysis approach to research advocated by RDoC has been for rumination. Rumination, defined as the tendency to passively contemplate the causes and consequences of one's negative mood, is cross-sectionally correlated with levels of depressive symptoms and predicts prospective changes in depressive symptoms and onset of depressive diagnoses [9,18]. In line with the RDoC aim of identifying mechanisms that may cut across traditional diagnostic boundaries, we should note that rumination predicts prospective changes not only in depression, but also anxiety, alcohol abuse, disordered eating, and self-harm [37].

Rumination has been linked to disruptions in the same neural circuits as those highlighted in the Loss construct, including disruptions in cortico-limbic circuitry (e.g. [38,39,40–42]). At the physiological level, disruptions in this cortico-limbic circuit are tied to levels of heart rate variability (HRV), with higher levels reflecting better physiological capacity for flexible emotion regulation in response to stress [43]. Importantly, higher levels of rumination are associated with lower levels of HRV at rest [44] as well as greater reductions in HRV following a laboratory-based interpersonal stressor [45]. Similarly, both state and trait levels of rumination are positively correlated with higher levels of basal cortisol and cortisol reactivity (for a review, see Ref. [46]). Behaviorally, rumination is significantly associated with other forms of cognitive vulnerability to depression including attention and memory biases (working memory and overgeneral autobiographical memory; for a review, see Ref. [47]).

There are also clear genetic, environmental, and developmental influences on rumination. Rumination is moderately heritable ($h^2 = .20-.41$) and exhibits shared genetic variability with depression [48–50]. Evidence for the impact of specific candidate genes is limited and mixed but there is at least some evidence for the role of a polymorphism in the brain-derived neurotrophic factor (*BDNF*) gene (e.g. [51,52]; but see also Ref. [53]). Rumination is thought to develop during childhood [54], stabilizing into a relatively trait-like influence during adolescence [35]. There is evidence that negative life events and negative family environment contributes to the development of rumination [53,55,56], effects that

may be moderated by variation in genes that influence stress sensitivity [57] and HPA axis reactivity [58].

These findings highlight rumination as a dynamic process that is likely a major driving force in the neurodevelopmental progression of depression. Notably, however, our focus on rumination brings up important considerations that will need to be addressed by investigators seeking to integrate RDoC into depression research. First, women are more likely to ruminate than men [59,60] and are more likely to experience depression, but only once they enter adolescence [59]. However, the role of sex differences are not highlighted anywhere in the current RDoC matrix for any of the domains. Second, although RDoC encourages research examining the full range of functioning and processes that may cut across current diagnostic boundaries, the majority of imaging studies have focused on rumination solely within the context of a current MDD diagnosis (for exceptions, see Refs. [41,42]). Third, future research is needed to determine whether each of the influences identified in this article is a cause, correlate, or consequence of depressive symptoms (or some mixture of these three), which is an essential step toward developing more targeted and effective intervention and prevention programs. Finally, we should note that recent efforts to integrate cognitive, genetic, and neural models of depression risk [8,61,62] are just the types of multiple-levels-of-analysis research that RDoC is trying to promote.

Conclusion

In summary, we are reminded of a quote from Stephen King's *The Dark Tower* series, 'There are other worlds than these' ([63], p. 266). We try to keep these words in mind during our studies so that each time we find ourselves focused on a particular measure at a specific unit of analysis, we remember that this measurement is connected to, and only makes sense in relation to, constructs at other units of analysis both micro and macro and within a specific environmental and developmental context.

Conflict of interest

The authors have no conflicts of interest.

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