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Understanding Suicide Risk within the Research Domain Criteria (RDoC) Framework: Insights, Challenges, and Future Research Considerations

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Abstract

Suicide is a leading cause of death worldwide. Prior research has focused primarily on sociodemographic and psychiatric risk factors with little improvement in the prediction or prevention of suicidal behavior over time. The Research Domain Criteria (RDoC) may be an especially useful framework for advancing research in this area. This paper provides a brief and broad overview of research on suicidal behavior relating to each of the RDoC domains—highlighting the RDoC construct(s) where research has focused, construct(s) where research is lacking, and suggestions for future research directions. We also discuss major challenges for suicide research within the RDoC framework, including the intersection of RDoC domains, interaction of domains with the environment, incorporation of developmental stage, integration of distal and proximal processes, and inclusion of suicide-specific constructs. We conclude by underscoring important considerations for future research aimed at using the RDoC framework to study suicidal behavior and other forms of psychopathology.

Keywords

Research Domain Criteria; suicide; suicide attempt; suicide prevention; risk factors

One human dies by suicide, on average, every 40 seconds (WHO, 2014). Suicide is a leading cause of death worldwide accounting for over 800,000 deaths each year (WHO, 2014). Non-fatal suicidal behaviors (suicide attempts) and thoughts of ending one's life (suicide ideation) are even more common, occurring in 2.7 and 9.2% of the population, respectively (Nock, Borges, Bromet, Cha, et al., 2008). In the U.S. alone, the annual cost of suicidal behaviors (attempts and deaths) is estimated to be \$93.5 billion (Shepard, Gurewich, Lwin, Reed, & Silverman, 2016).

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Author Contributions

C.R.G. and M.K.N. developed the concept for the review. C.R.G., C.B.C., and E.M.K. drafted the paper, and M.K.N. provided critical revisions. All authors approved the final version of the paper for submission.

Over the past five decades, an increasing number of studies have focused on identifying reliable risk factors for suicidal behavior. Unfortunately, this research has not improved our ability to predict (Franklin et al., 2016) or prevent suicide (Zalsman et al., 2016). The gaps in existing research are also highlighted by the limited efficacy of interventions for suicidal individuals (Glenn, Franklin, & Nock, 2015; Tarrier, Taylor, & Gooding, 2008), suggesting the field does not fully understand the mechanisms leading to suicidal behavior.

The stunted progress in predicting and preventing suicide can be attributed to at least three major limitations of extant research (Glenn & Nock, 2014). First, the majority of previous research has focused on the same sociodemographic (e.g., male gender for suicide deaths) and psychiatric (e.g., major depressive disorder) risk factors for suicide—most of which are distal from suicidal behavior, time-invariant (i.e., put an individual at lifetime risk but do not indicate *when* an individual is at heightened risk), and not specific to suicide (i.e., confer risk for psychopathology more broadly). Recent meta-analytic work suggests that these risk factors are poor predictors of future suicide attempts and deaths (Franklin et al., 2016). In addition, the focus on sociodemographic and psychiatric variables has provided little insight into the *psychological processes* that lead individuals down the pathway to suicide and particularly those that may indicate *when* an individual is at short-term risk (Glenn & Nock, 2014).

A second major gap is the limited knowledge of predictors of suicidal behavior among those who think about suicide. This is an important research focus given that only one-third of individuals who think about suicide will ever act on their suicidal thoughts (Nock, Borges, Bromet, Alonso, et al., 2008; Nock, Green, et al., 2013). Moreover, substantial research now indicates that most existing risk factors predict suicide ideation but *not* suicidal behavior (Borges et al., 2010; Bruffaerts, Kessler, Demyttenaere, Bonnewyn, & Nock, 2015; Kessler, Borges, & Walters, 1999; Nock, Borges, & Ono, 2012; Nock, Hwang, et al., 2009; Nock, Hwang, Sampson, & Kessler, 2010). In sum, suicidal thoughts and suicidal behaviors are both important targets for research, but should be examined separately.

A third major limitation is the field's reliance on self-reported measures of suicide risk, which are poor predictors of future suicidal behavior (Busch, Fawcett, & Jacobs, 2003; Qin & Nordentoft, 2005). Self-reports of suicide risk may be limited by individuals' motivation to hide or conceal their suicidal plans or intent (Busch et al., 2003; Qin & Nordentoft, 2005) and generally poor ability to report on the processes underlying their behavior (Nisbett & Wilson, 1977).

Taken together, these findings highlight the great need for research that examines *new* risk factors to predict suicidal *behavior* using *multimethod* approaches. This research is essential to improve understanding of the pathogenesis of suicidal behaviors, to help identify those at heightened risk for suicide, and to suggest potential targets for effective intervention.

Research Domain Criteria

The Research Domain Criteria (RDoC) framework aims to guide a new era of research on psychopathology and may be ideal for addressing the aforementioned gaps in knowledge.

The RDoC initiative was first introduced in 2009, stemming from the National Institute of Mental Health's (NIMH) strategic plan to stimulate research on the pathophysiology of psychiatric illness with the ultimate goal "to develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" (NIMH, 2008). In a dramatic departure from the current categorical classification system employed by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013), RDoC aims to identify transdiagnostic dimensions, spanning from normal to abnormal functioning, that are more fine-grained than the heterogeneous constructs and disorders typically examined in psychopathology research (Insel et al., 2010; Sanislow et al., 2010).

The RDoC framework organizes pathophysiologic mechanisms according to *what* they are and *how* they are measured. Accordingly, it consists of five transdiagnostic domains (*Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Social Processes, Arousal and Regulatory Systems*) that can be examined across seven units of analysis (genes, molecules, cells, circuits, physiology, behavior, self-report). The initially proposed constructs and subconstructs within each overarching domain were selected based on their construct validity and evidence for an underlying neural system or circuit (Cuthbert & Kozak, 2013).

RDoC and Suicide – Insights

There are a number of reasons why the RDoC framework may be particularly useful for understanding suicide risk. First, rather than being specific to any one disorder, suicidal thoughts and behaviors occur among those suffering with a range of psychiatric conditions, including: depressive, bipolar, psychotic, anxiety, substance use, and impulse-control disorders (Borges et al., 2010; Nock, Borges, Bromet, Alonso, et al., 2008). RDoC's emphasis on transdiagnostic dimensions is conducive for the study of this type of behavior. Second, as already noted, the emphasis on diagnostic risk factors has not been useful for improving understanding of the development or prediction of suicidal behavior (Franklin et al., 2016). The identification of transdiagnostic processes is a high priority in suicide research, and RDoC provides a useful starting point for selecting the types of constructs that could help move the field forward. Third, RDoC's emphasis on integrating information across multiple units of analysis is particularly applicable given the known shortcomings of self-report methods for assessing suicide risk (Busch et al., 2003; Qin & Nordentoft, 2005). Taken together, the goals of RDoC are ideal for advancing suicide research by moving beyond diagnostic predictors, identifying specific transdiagnostic psychological processes, and assessing suicide risk factors across multiple units of analysis.

In the sections below and in Table 1, we provide a brief ("birds-eye") view of the extant research on suicidal behavior (suicide attempts and deaths) relating to each of the RDoC domains. It is important to note that this overview is in no way comprehensive or meant to cover all relevant suicide research. For instance, given the scope of our review, we focus on suicidal behaviors, but also recognize the importance of examining risk factors for suicide ideation. The purpose of this review is to begin to examine the suicide literature through the RDoC lens. For each domain, we highlight the RDoC constructs that have been the focus of

prior research (sample references for specific studies within each domain are provided in Table 1), the construct(s) for which research is lacking, and suggest areas for future research in each domain. Given the scope of this overview, we focus on individual mechanisms rather than diagnoses. Of course, there is a substantive body of work around diagnostic and environmental risk factors for suicidal behavior that provides indirect, yet relevant, support for underlying mechanisms related to RDoC. While maintaining a focus on mechanisms, we reference this literature when relevant to a specific RDoC domain and individual construct.

Finally, here we explain our approach for incorporating genetics studies from the suicide literature. Although family studies indicate that suicidal behavior is heritable (Brent, Bridge, Johnson, & Connolly, 1996; C. D. Kim et al., 2005; Tidemalm et al., 2011), the role that specific genes play in familial transmission is less clear (Mirkovic et al., 2016). Given that genetic risk factors (including candidate gene studies and genome-wide association studies [GWAS]) are related to a range of constructs throughout the RDoC matrix, we discuss these studies in a separate section following the individual RDoC domains. However, within the RDoC domains (and primarily in Table 1), we include gene \times environment (G \times E) studies that can be more closely tied to a specific RDoC domain or construct based on the environmental factor examined. Lastly, it is important to note that the environmental variables that may play a role in the pathophysiology of suicidal behavior (e.g., in G \times E studies) might be at least somewhat heritable, particularly controllable or dependent life events, such as a fight with a romantic partner (Plomin, 1994; Plomin & Bergeman, 1991).

Suicide and Negative Valence Systems

The *Negative Valence Systems* domain refers to systems that respond to aversive contexts, including *acute threat*, *potential threat*, *sustained threat*, *loss*, and *frustrative nonreward*. In the suicide literature, this domain has received significant attention, particularly in the areas of *loss* (e.g., a range of negative life events such as interpersonal loss), *sustained threat* (e.g., childhood adversities), and *frustrative nonreward* (e.g., behaviors and traits characterized by aggression; see Table 1). Far less research has focused on *acute threat* (“*fear*”) and *potential threat* (“*anxiety*”) other than examining psychiatric disorders and symptoms related to suicide risk.

In Table 1, we also provide research examples of potential mediators and moderators linking these *Negative Valence* constructs to suicidal behavior. For instance, in terms of potential mediators for the *loss* construct, events such as interpersonal loss may be linked to suicidal behavior to the degree that they increase feelings of loneliness (Zuroff, Fournier, & Moskowitz, 2007) or guilt and humiliation (Hendin, Maltzberger, Lipschitz, Haas, & Kyle, 2001). Moreover, well-researched constructs also have been the focus of *diathesis-stress* (or *vulnerability-stress*) models to understand the pathophysiology of suicidal behavior. In terms of potential moderators, the existing literature tends to focus on either cognitive factors (*cognitive-vulnerability* models) or genetic factors (G \times E models; see discussion of G \times E replication issues in *Suicide and Genetics* section). For instance, potential cognitive diatheses for the *loss* construct include negative attributional style (Kleiman, Riskind, Stange, Hamilton, & Alloy, 2014), perfectionism (Hewitt, Caelian, Chen, & Flett, 2014), and problem solving deficits (Grover et al., 2009).

Future directions—Related to the *loss* construct, more studies are needed that move beyond examinations of the mere presence of these events to mechanistic research that examines *how* these experiences confer risk for suicide and over what period of time. Moreover, there is ample research indicating that childhood adversities and chronic stress (*sustained threat*) confer risk for suicide. Studies assessing more fine-grained mechanistic questions, such as the duration of *sustained threat* necessary to increase suicide risk, are needed. For *frustrative nonreward*, research is needed that teases apart the risk conferred by different types of aggression, as it is currently unknown if these forms of aggression have differential effects on suicide risk. Related to *acute and potential threat*, it is important to consider individuals' fear about death and suicide specifically, beyond trait-level fear. Central to contemporary suicide theories (Joiner, 2005; O'Connor, Platt, & Gordon, 2011) is the notion that acquiring fearlessness about death is an essential step to move an individual from thinking about suicide to acting. Indeed, initial evidence suggests that fearlessness about death may differentiate suicide attempters from suicide ideators (Dhingra, Boduszek, & O'Connor, 2015; Smith, Cukrowicz, Poindexter, Hobson, & Cohen, 2010). Future research is needed to integrate findings implicating both heightened general fear-potentiated startle and *reduced* fear of death/suicide specifically in the pathogenesis of suicidal behavior.

Suicide and Positive Valence Systems

The *Positive Valence Systems* domain refers to processes that respond to rewarding contexts. Although most prior research on diagnostic risk factors lacked the specificity needed to examine constructs within this domain, recent research has focused on particular *Positive Valence* facets that may confer risk for suicide, including *approach motivation* (e.g., reduced willingness to work for a reward, or reward “wanting”), *initial responsiveness to reward attainment* (e.g., reduced responsiveness to expected rewards, or reward “liking”), and *reward learning* (e.g., difficulty flexibly adapting to new information to increase the probability of rewards; see Table 1).

Future directions—Although promising, the more fine-grained research in this area is limited and relatively new. It is still unclear how to integrate literatures that suggest seemingly contradictory influences on constructs within the *Positive Valence* domain. For instance, disorders and traits characterized by both hyperresponsiveness (e.g., substance use and impulse-control disorders; Borges et al., 2010; Nock, Hwang et al., 2010) and hyporesponsiveness to rewards (e.g., anhedonia; Fawcett et al., 1990; Nock & Kazdin, 2002) have been linked to suicidal behavior. Given the fluidity of suicidal crises (Rudd, 2006), some of this discrepancy may be due to studies examining suicidal individuals at different time intervals from their most recent suicide attempt (e.g., attempts could occur weeks to decades prior to the assessment). Future research would benefit from clarifying which fluctuations in the *Positive Valence* domain may be due to suicidal *traits* (having ever engaged in suicidal behavior) and suicidal *states* (acute suicidal crises; see *Future Research Considerations* section). Moreover, it will be important for future studies to integrate knowledge from circuit and behavioral units of analysis with genetic and molecular units of analysis. For instance, although dopamine plays an important role in motivation, salience, and learning, the research evidence linking dopaminergic dysfunction to suicide risk is weak (Mirkovic et al., 2016; Oquendo et al., 2014). Finally, beyond *approach motivation* toward

standardized stimuli (e.g., money), research would benefit from examining how approach toward *suicide-specific* stimuli may underlie the transition from suicidal thinking to suicidal behavior.

Suicide and Cognitive Systems

The *Cognitive Systems* domain captures how people detect, select, and process information, and then use it to guide decisions or actions. The most relevant cognitive deficits underlying suicide risk pertain to *declarative memory* (e.g., overgeneralized autobiographical memory), *working memory*, and select aspects of *cognitive control* categorized by executive attention (e.g., attentional control deficits) and higher-order processes such as decision-making (e.g., making disadvantageous choices), cognitive flexibility (e.g., difficulty adjusting to changing contingencies), and impulsiveness (e.g., difficulty inhibiting behavior; see Table 1). There is also some research linking constructs of *perception* (e.g., auditory hallucinations and pain perception) and *language* (e.g., monotonous and repetitive phrasing) to suicidal behavior. Of note, within this domain in Table 1, we specify behavioral measure names when possible due to inconsistencies in how construct names are paired with the respective behavioral measures and inconsistent findings depending on which behavioral measure is used.

Future directions—*Cognitive Systems* research is varied in both constructs examined and measures used. Future research would benefit from more standard and precise operational definitions of cognitive constructs across suicide studies. As an example of such efforts, attention has recently been captured through the Attentional Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002), a behavioral measure that teases apart executive attention, alerting, and orienting attention. When examined in relation to suicide, Sommerfeldt and colleagues (2016) found that depressed adolescent suicide attempters showed deficits in the ANT alerting index but not on other indices (e.g., orienting attention), nor on other measures of executive attention, relative to depressed adolescent non-attempters. A related direction for future research is to recognize and organize constructs that fall into multiple RDoC domains. For instance, attentional bias toward negatively valenced information or suicide-specific information overlaps across *Cognitive Systems* and *Negative Valence Systems* (see *Challenges* section), and specifically relates to suicide attempts (Becker, Strohbach, & Rinck, 1999; Cha, Najmi, Park, Finn, & Nock, 2010; Gibb, McGeary, & Beevers, 2015). Beyond striving for clearer definitions and structure of constructs, it will be important to extend self-report and behavior-based findings in this area to neural circuits. Executive attention deficits among suicidal individuals has been suggested to implicate dorsal and lateral prefrontal cortex and dorsal cingulate dysfunction (Keilp et al., 2008), but has yet to be neurobiologically tested. This would be a critical step to linking and justifying new findings of the suicide literature across the RDoC matrix.

Suicide and Social Processes

The *Social Processes* are systems responsible for individuals' responses in interpersonal contexts. Social processes related to *affiliation and attachment* have been central to suicide theories for over a century (Durkheim, 1951; Joiner, 2005; O'Connor et al., 2011) and have received the most research in this domain (e.g., loneliness, insecure attachment styles; see Table 1). *Perception and understanding of self* has also been a major area of research within

this domain (e.g., self-esteem, self-criticism, implicit self-identification with death/suicide), whereas research related to *perception and understanding of others* and *social communication* is lacking.

Future directions—Within the *affiliation and attachment* literature (although not limited to this construct), the majority of research has focused on risk with limited research on protective factors (e.g., social support). This is surprising given that these processes have been implicated in the pathogenesis of suicidal behavior for decades and are central to many interventions for suicidal individuals (e.g., attachment-based family therapy (Diamond et al., 2010), dialectical behavior therapy (Linehan, 1993), and interpersonal psychotherapy (Mufson, Moreau, Weissman, & Klerman, 1993). Future research would benefit from identifying other *affiliation and attachment* protective factors, especially those that may be modifiable in treatment. In addition, although we know that social isolation increases with suicide risk (Trout, 1980), we do not yet know the mechanisms of how and why individuals withdraw. Within *perception and understanding of self*, there is promising research using implicit measures of self-identification with death/suicide to predict risk for suicidal behavior (Barnes et al., 2016; Nock, Park, et al., 2010). Given that individuals may be unable or unwilling to report their suicidal plans or intent (Busch et al., 2003; Qin & Nordentoft, 2005), implicit assessments of suicidal thinking (via behavioral tasks, which do not rely on introspection) may overcome limitations of previous self-report research. Although the ability to understand others' mental states is hypothesized to be a core dysfunction, and thus a primary target, in treatments for suicidal individuals (Linehan, 1993; Rossouw & Fonagy, 2012), research focused on the *perception and understanding of others* is lacking (however, see Paradiso, Beadle, Raymont, & Grafman, 2016). Much of the support in *social communication* comes from studies of disorder-specific interpretation biases. There is thus a need for research on possible biases in the production and recognition of facial and non-facial cues related to suicide risk.

Suicide and Arousal and Regulatory Systems

The *Arousal and Regulatory Systems* are responsible for activating context-appropriate neural systems and for regulating homeostasis. In this domain, problems with *sleep-wakefulness* (e.g., insomnia, nightmares, poor sleep quality) have been the most studied construct in relation to suicide risk (see Table 1). Less research has focused specifically on *circadian rhythms* (the endogenously generated biological rhythms of an organism that are tightly linked with the sleep-wake cycle) and on *arousal* (sensitivity of an organism to stimuli in the environment) outside the context of emotional valence.

Future directions—Although there are links between the *Arousal and Regulatory Systems* and risk for suicidal behavior, little mechanistic research has examined *how* disturbances in these systems confer suicide risk (McCall & Black, 2013). Disruptions in sleep-wake cycles and circadian phase have known negative impacts on mood (Boivin et al., 1997) and cognitive functioning (Wright, Lowry, & Lebourgeois, 2012)—both of which have been linked to increased suicide risk (see *Negative Valence* and *Cognitive Systems* sections, respectively). Sleep and suicide also share neurobiological underpinnings that may explain this association, including serotonergic dysfunction (Oquendo et al., 2014; Ursin,

2002) and alterations of the stress-response system (Oquendo et al., 2014; Van Reeth et al., 2000). Future research would also benefit from more fine-grained assessments of sleep disturbance that incorporates objective measurement of sleep quality and quantity using actigraphy (non-invasive monitoring of rest/activity), EEG (brain activity), and polysomnography (gold standard diagnostic tool). Finally, a complete understanding of the risk conferred by dysfunction of these systems will require examining their interactions with both cognitive and affective systems.

Suicide and Genetics

Decades of research have demonstrated that suicidal behavior runs in families (Brent et al., 1996; C. D. Kim et al., 2005; Tidemalm et al., 2011), and at least some portion of this inherited risk is specific to suicidal behavior (Fu et al., 2002). However, it has proven challenging to identify specific genes, or clusters of genes, that confer this risk. The majority of prior research in this area has focused on candidate genes, an a priori approach to examine associations between pre-specified genes of interest (hypothesized based on the role of specific neurotransmitters such as serotonin) and a specific phenotype (e.g., violent suicide attempts). Although the candidate gene approach was initially promising, a range of genes has been examined in relation to suicidal behavior, and across the field of psychiatric genetics more broadly, with little replication (Duncan, Pollastri, & Smoller, 2014). A challenge for most candidate gene studies is small samples, resulting in a large number of false positive findings (Duncan et al., 2014).

Given the lack of replication in prior candidate gene research and the potential for spurious findings, we only note the four candidate genes that have been examined in at least one prior meta-analysis (for a thorough review of all candidate gene research: see Mirkovic et al., 2016). Based on meta-analytic evidence, there is modest support for genetic variants related to serotonergic functioning, including the serotonin transporter gene (5HTTLPR-short allele; Clayden, Zurak, Meyre, Thabane, & Samaan, 2012; Li & He, 2007) and tryptophan hydroxylase 1 gene (TPH1-A allele; Bellivier, Chaste, & Malafosse, 2004; Clayden et al., 2012; Li & He, 2007), as well as for gene encoding brain-derived neurotrophic factor (BDNF-Met allele; Zai et al., 2012) and catechol-O-methyltransferase (COMT-Met allele; Kia-Keating, Glatt, & Tsuang, 2007). However, it is important to note that these findings have been mixed and replication in larger samples with more stringent standards of evidence is needed.

In addition to main effects of candidate genes, a handful of studies have examined how the impact of environmental factors (primarily childhood adversities) on suicide outcomes may be moderated by specific candidate genetic variants (primarily serotonergic genes), or cG×E interaction studies (see examples in Table 1 under *Negative Valence Systems*; Duncan et al., 2014; Mirkovic et al., 2016). Of note, a recent review of 103 cG×E studies in the broader field of psychiatric genetics found that there have been few attempts to replicate previously found interactions and, of those that have been examined, only a small few interactions have replicated (Duncan et al., 2014). Given concerns about false positives, the cG×E research related to suicidal behavior is too limited to make any substantial conclusions

and existing results should be interpreted with caution until interactions have been replicated.

With advances in genetic technology, the field has moved beyond single genetic variant research to examine associations between specific phenotypes and the entire human genome—genome-wide association studies (GWAS). In contrast to candidate gene studies, GWA studies are agnostic to prior research and therefore have the potential to identify novel genetic variants related to suicide risk. In addition, more stringent standards for GWA studies reduce the likelihood of false positives. Eleven GWA studies have been examined in relation to a suicide phenotype, but few significant associations have been found at the stringent GWA significance level and the few that have been found have not replicated (Mirkovic et al., 2016). Despite the null findings, these studies may suggest novel candidate gene targets for future research (e.g., novel genes related to inflammatory response; Galfalvy et al., 2015). Moreover, some of these GWA studies have examined polygenic risk scores—the collective contribution of hundreds of genes in the contribution to suicidal behavior (e.g., Mullins et al., 2014; Sokolowski, Wasserman, & Wasserman, 2016). Though no significant associations have been found yet, the examination of polygenic effects is the type of cutting-edge research needed to identify the complex genetic underpinnings of a multi-determined behavior like suicide (Duncan et al., 2014; Mirkovic et al., 2016).

Another promising research area focuses on epigenetic alterations linked to suicidal behavior (Le-Niculescu et al., 2013; Turecki, Ota, Belangero, Jackowski, & Kaufman, 2014)—most notably expression of the spindle and kinetochore-associated protein 2 (SKA2) gene, which may be important for modulating the hypothalamic pituitary adrenal (HPA) axis (Clive et al., 2016; Guintivano et al., 2014; Kaminsky et al., 2015; Pandey, Rizavi, Zhang, Bhaumik, & Ren, 2016; Sadeh et al., 2016). Epigenetic variation of SKA2 may help explain how early life adversities disrupt stress-response systems to confer risk for later suicidal behavior (Guintivano et al., 2014; Kaminsky et al., 2015). Some have suggested that SKA2 methylation levels may uniquely predict suicidal thoughts and behaviors independent of psychiatric symptomatology, supporting its consideration as a biomarker for suicide risk (Pandey et al., 2016; Sadeh et al., 2016).

RDoC and Suicide – Challenges

In theory, the RDoC framework seems ideal for suicide research. In practice, the implementation of this framework to understand a multi-determined behavior like suicide is complicated. Here we discuss five major challenges to conceptualizing suicide research within the RDoC framework. It is important to note that this list is by no means comprehensive (see also: (Berenbaum, 2013; Bilder, Howe, & Sabb, 2013; Franklin, Jamieson, Glenn, & Nock, 2015; Lilienfeld, 2014; Shankman & Gorka, 2015). Moreover, these challenges do not only impact suicide research, but also are relevant for future efforts to use the RDoC approach to understand psychopathology more broadly.

Constructs at the Intersection of Multiple Domains

Many psychological constructs do not fit neatly within a *single* RDoC domain. A primary cause of this issue is that the framework draws distinctions between potentially overlapping

systems (Shankman & Gorka, 2015). For instance, RDoC separates affective and cognitive systems into distinct domains. Beyond the longstanding debate about whether distinctions can be drawn between cognitive and affective processes (Izard, 1992; Zajonc, 1980), most pathophysiologic constructs of interest involve complex emotion-cognition interactions (Gross & Jazaieri, 2014; Phillips, Ladouceur, & Drevets, 2008). Though the dynamic relationship between domains (and constructs within domains) is recognized by NIMH (Morris, Vaidyanathan, & Cuthbert, 2015), it is currently unclear how to conceptualize processes at the intersection of multiple domains within the RDoC framework.

Consider as an example the construct of impulsive-aggression (behavioral dysregulation including traits of impulsiveness and aggression), which has been proposed as a suicide-specific phenotype (Turecki & Brent, 2016; Turecki, Ernst, Jollant, Labonte, & Mechawar, 2012). Impulsive-aggression falls at the intersection of *Negative Valence (acute threat, sustained threat, frustrative nonreward)*, *Positive Valence (approach motivation)*, and *Cognitive Systems (cognitive control: inhibition-suppression)*. Without clear guidelines regarding how to examine these intersections, it is likely that independent research groups will make different decisions about this approach. As a result, it will be challenging to synthesize research—thereby limiting the utility of this new framework.

Intersections with the Environment

Although not represented in the 2D RDoC matrix, domains, and constructs within domains, not only intersect with each other, but also with different environmental and contextual factors (Insel et al., 2010; Morris & Cuthbert, 2012). For instance, at the construct level, *Loss (Negative Valence domain)*, defined as deprivation of significant social or non-social objects or situations, is intrinsically tied to the environment. Moreover, inherent in diathesis- or vulnerability-stress models for understanding suicide risk (Nock, Deming, et al., 2013; Rudd, 2006; Turecki & Brent, 2016) is the exposure conferred by negative life events experienced both distally (e.g., childhood adversity; Turecki et al., 2012) and proximally (e.g., fight with romantic partner; Bagge, Glenn, & Lee, 2013) from a suicide event. The environment also intersects with units of analysis across constructs. For instance, genetic variants may moderate the role of an environmental event on a suicide outcome (G×E interactions). RDoC emphasizes the mechanistic understanding, or the *impact* rather than just the presence, of these environmental factors (Cuthbert, 2014). The environment may be most accurately depicted as another plane within the RDoC framework (domain × unit of analysis × environment; Woody & Gibb, 2015) with each unit of analysis viewed through an environmental lens (Badcock & Hugdahl, 2014).

Although recognized as important, the actual implementation of this multidimensional space has been accorded short shrift in RDoC discussions. Similar to recommendations for domain intersections, it will be important to specifically outline how environmental factors can be incorporated in the RDoC framework to enhance consistency across research groups. For instance, the field would benefit from assessing the same environmental variables (e.g., specific childhood adversities) using standardized measures to facilitate replications and integration of findings across studies.

Consideration of Developmental Stage

Another important, and complex, dimension to take into account is an individual's developmental stage (Casey, Oliveri, & Insel, 2014; Franklin et al., 2015; Insel et al., 2010; Shankman & Gorka, 2015; Woody & Gibb, 2015). Casey, Oliveri, and Insel (2014) outline three key aspects of neurodevelopment to consider within the RDoC framework: (a) developmental trajectories—atypical interpreted in the context of typical trajectories, (b) sensitive periods for exposure to significant experiences, and (c) complex interaction of systems across development.

A primary goal of RDoC is to “determine the full range of variation, from normal to abnormal, among the fundamental components to improve understanding of what is typical versus pathological” (p. 632; Sanislow et al., 2010). From a developmental psychopathology perspective, abnormal trajectories must be interpreted in the context of normative development (Cicchetti, 1993). Taking an example relevant to our review, suicidal thoughts and behaviors increase drastically during the transition to adolescence—an effect observed cross-nationally (Nock, Borges, Bromet, Cha, et al., 2008; Nock et al., 2012). However, initial understanding of death and suicide in normative samples begins well before the pubertal transition, around ages 5–7 years (Mishara, 1999; Speece & Brent, 1984). This information helps contextualize when knowledge of suicide is typical vs. atypical, as well as indicates that the onset of suicide understanding (childhood) cannot explain the increase in serious suicidal thinking (adolescence). Therefore, the increased suicide risk observed during adolescence needs to be considered in the context of the many normative changes occurring during this developmental stage. For instance, adolescence is typified by significant alterations in neurodevelopment, including rapid increases in the influence of social and emotional cues, while cognitive control develops more gradually, and is flexibly recruited, during this time (Crone & Dahl, 2012; Somerville, Jones, & Casey, 2010; Steinberg, 2005). These neurodevelopmental changes can have both adaptive (e.g., enhanced learning and growth) and maladaptive consequences (e.g., dangerous risk taking). Efforts to enhance understanding of suicide risk across the lifespan (from childhood through older adulthood) must take these normative developmental changes into consideration.

The second neurodevelopmental concept to consider is sensitive periods, or developmental stages when the effects of significant experiences can be particularly deleterious (Casey et al., 2014). Adversities that occur early in life can have a profound impact on neurodevelopment, stress-response systems, and inflammation, and have been linked to a range of negative mental health outcomes including suicide (Heim & Binder, 2012; Turecki & Brent, 2016). Adolescence is a developmental stage characterized by increased sensitivity to the environment, which is ideal for adaptive learning but can be detrimental if/when significant stressors occur (Crone & Dahl, 2012; Steinberg, 2005). For instance, research indicates that a range of childhood adversities confer risk for suicide (see *Negative Valence Systems: sustained threat* in Table 1). Understanding not only which adversities occur, but the timing of these events and the differential developmental consequences based on this timing, will be essential for advancing comprehensive models of suicide risk.

Finally, the third major neurodevelopmental consideration is the interaction between systems across development. Cross-sectional approaches provide a window into dysfunction at one

particular time point. However, “a deficit occurring early in development can give rise to a cascade of more complex deficits as different brain regions mature and interact over time” (p. 351; Casey et al., 2014). To fully understand the trajectory of dynamic systems, research must examine interactions between domains *and* also across developmental periods. The complexity of this research task will require large-scale coordination across multiple research groups (see *Collaboration* section).

In sum, a developmental perspective is essential for understanding risk for psychopathology within the RDoC framework (Casey et al., 2014; Franklin et al., 2015). Although development has been noted as important since the introduction of the RDoC initiative but not included in the original RDoC matrix due to the limits of a 2D representation (Insel et al., 2010; Morris & Cuthbert, 2012), the practical incorporation of developmental stage within the RDoC space is less clear. Development may be most appropriately conceptualized as yet another plane in the matrix whereby a researcher would examine a specific RDoC domain within one or more units of analysis at a particular developmental stage (Badcock & Hugdahl, 2014; Woody & Gibb, 2015). Decisions about where to focus across the developmental plane should be based on development of the individual as well as development of the “disease” (Woody & Gibb, 2015) with the recognition that clinical and nonclinical developmental trajectories may differ (Badcock & Hugdahl, 2014; Franklin et al., 2015).

Here we provide an illustrative example of how one might conduct a developmentally informed study of suicidal behavior within the RDoC framework. First, if we want to isolate a developmental window that may be relevant for both the development of the individual as well as development of suicidal behavior (Woody & Gibb, 2015), adolescence may be a particularly important time period when there are key emotional, social, and biological changes (Crone & Dahl, 2012; Somerville et al., 2010; Steinberg, 2005) coinciding with the onset of suicidal thoughts and behaviors (Nock, Borges, Bromet, Alonso, et al., 2008; Nock et al., 2012). Next, with the benefit of normative developmental data, such as that provided by the Human Connectome Project in Development (HCP-D) in youth ages 5–21 years, researchers could identify key psychological processes (examined at the construct level or at the intersection between multiple constructs) that may be particularly important during this developmental window and that may also be implicated in the pathogenesis of suicidal behavior. For instance, as already noted, adolescence is characterized by accelerated maturation of subcortical regions, such as the striatum and amygdala, which results in adolescents’ greater responsiveness to specific social-emotional and rewarding contexts than during other developmental stages (Crone & Dahl, 2012; Somerville et al., 2010). These neurodevelopmental changes are particularly notable given that specific dysfunctions in reward “wanting,” reward “liking,” and reward learning may confer risk for suicidal behavior (see *Positive Valence Systems* in Table 1). However, most of the construct-specific research related to the *Positive Valence* domain has been conducted in adults, and particularly among older adults (however, see Auerbach et al., 2015). The next step in this line of research is to examine how the specific neurobiological changes during adolescence and related changes in reward processing may increase risk for, and relate to initial onset of, suicidal thinking and behavior during this developmental period. In this way, the RDoC

framework provides a useful lens to extend what we know from basic developmental neuroscience to inform research on developmental psychopathology.

Integration of Distal and Proximal Processes

Diathesis-stress models conceptualize suicide as resulting from the complex interplay between underlying vulnerability (distal) factors and acute (proximal) stressors, which can be examined at both biological and psychological units of analysis (Nock, Deming, et al., 2013; Rudd, 2006; Turecki & Brent, 2016). Unfortunately, the majority of previous suicide research has examined single (primarily distal) predictors in bivariate models, which fail to test these more complex vulnerability-stress interactions. This is particularly problematic as only a handful of significant distal predictors of suicidal behavior (e.g., sociodemographics, psychiatric disorders) have been identified (Franklin et al., 2016). Alarming, the field knows even less about factors that predict risk for suicidal behavior over the *short-term*, such as hours and days (however, see Bagge, Glenn, & Lee, 2013; Bagge, Lee, et al., 2013; Bagge, Littlefield, Conner, Schumacher, & Lee, 2014).

RDoC provides a framework for potentially addressing these limitations. However, within the current system, it is currently unclear how to integrate information about processes that are more distal vs. more proximal to a clinically relevant behavior, such as suicide. Without guidelines for integrating distal and proximal factors, one potential negative consequence is that researchers will pick their preferred construct or dimension—paralleling the single predictor research that predominates the current suicide literature. To ultimately prevent suicide deaths, it will be important for suicide research to clarify how individuals move in and out of acute suicidal states, or “the suicidal mode” (Rudd, 2006), which will require integrating baseline vulnerabilities factors with knowledge of more short-term (proximal) predictors (e.g., see Nock, Deming, et al., 2013; Turecki & Brent, 2016).

Inclusion of Suicide-Specific Constructs

Throughout this review, we have highlighted how the RDoC framework may be useful for identifying transdiagnostic dimensions that increase risk for suicide. However, it is important to note that the majority of the dimensions reviewed are *not* specific to suicidal behavior. For instance, *loss* (*Negative Valence* domain) is related to depressed mood, negative thinking patterns (e.g., rumination), and behavioral disturbance (e.g., withdrawal; Nolen-Hoeksema et al., 1994). Therefore, *loss* may confer risk for suicide to the degree that it relates to these intermediate cognitive, behavioral, and affective patterns. To ultimately improve identification and prediction of short-term risk for suicidal behavior, comprehensive models of suicide risk (Joiner, 2005; Turecki & Brent, 2016; Wenzel & Beck, 2008) must enhance incorporation of both general and *suicide-specific* risk factors. The current RDoC framework makes the examination of suicide-specific risk factors challenging due to restricted inclusion criteria for new constructs and guidelines for construct measurement.

Constructs are included in the matrix to the degree that they can be tied to underlying neural circuits or systems (Cuthbert & Kozak, 2013). Though useful for constraining the heterogeneity of constructs included in the matrix, this guideline highlights a significant criticism of the framework since its inception—potential biological reductionism

(Berenbaum, 2013; Franklin et al., 2015; Lilienfeld, 2014). The prioritization of neural systems is problematic in terms of both reliability (measurement error at these more “objective” units of analysis is overlooked: Hajcak & Patrick, 2015; Lilienfeld, 2014) and validity (psychological/mental states cannot be reduced to physical/brain systems: Barrett, 2012; Miller, 2010). Related to this second point, it is important to note that our concern is with the potential eliminative/explanatory reductionism (i.e., reducing all psychological function to biological causes, thereby making the former obsolete) rather than constitutive reductionism (i.e., suggesting that psychological functions can be linked to an underlying biological cause—a mental process can be linked to a brain process; see Lilienfeld, 2012). We are aware that the developers of the RDoC initiative have responded to criticisms about biological reductionism by suggesting that the “units” of analysis are specifically *not* “levels” of analysis (e.g., Cuthbert & Kozak, 2013; Morris & Cuthbert, 2012). However, the necessity of constructs to be tied to a neural circuit does constrain the specificity of constructs that can be examined and does prioritize this particular unit of analysis for making decisions about additions to the matrix. Although mental events can be tied to the brain (causally linked), they cannot be ontologically reduced, and this translation leads to the loss of important information (Barrett, 2012; Miller, 2010). As a result, it is unclear how to examine psychological constructs central to suicide theories that have not been linked to neural systems, such as unbearable psychological pain or psychache (Shneidman, 1996). Categorization within any single domain fails to accurately describe the intersection of affective and cognitive processes that lead to this aversive mental state.

The second major challenge relates to construct measurement. Currently, the initiative calls for a standardized (i.e., not disorder- or clinical phenomena-specific) set of tasks to be examined in all investigations using RDoC (Morris et al., 2015). While helpful for comparing (dys)function across psychopathologies, standardized tasks prohibit examinations of processing of stimuli *specific* to clinical phenomena. Knowledge of suicide risk has been enhanced by examinations of cognitive and affective processing of *suicide-specific stimuli*. For instance, beyond general difficulties with executive attention (measured by the original Stroop task), recent research has found that suicide attempters demonstrate an attentional bias specific to *suicide* words using a modified Suicide Stroop task (Becker et al., 1999; Cha et al., 2010; Williams & Broadbent, 1986). Another promising area of research indicates that individuals’ implicit self-identification with death/suicide (on an implicit association test) predicts future engagement in suicidal behavior (Barnes et al., 2016; Nock, Park, et al., 2010). Finally, in terms of affective processing, recent research has found that suicide attempters are distinguished from suicide ideators by fearlessness of *death/suicide* (Dhingra et al., 2015; Ribeiro et al., 2014; Smith et al., 2010)—one potential index of acquired capability for suicide (Joiner, 2005; Van Orden et al., 2010). Taken together, this research indicates that examining how suicidal individuals process information specific to suicide may be essential to understand the pathophysiology of suicidal behavior, to help distinguish suicidal behavior from risk for psychopathology more broadly, and ultimately to enhance prediction of suicidal behavior. Moving forward, it will be essential to determine how best to incorporate disorder/outcome specific factors into the RDoC framework.

It is important to note that this issue is separate from, and does not contradict with, the use of common measures to examine suicide-specific constructs across the field (e.g., using the

same self-report measures to assess suicidal thoughts and behaviors, such as those provided in the PhenX toolkit). In fact, using standardized suicide measures (including the same tasks and stimuli) across units of analysis will help move the field forward by facilitating replications and extensions of prior research more efficiently.

RDoC and Suicide – Future Research Considerations

Although RDoC has its challenges and limitations, the framework will likely guide research for decades to come. Below we highlight some important considerations for future research aimed at using the RDoC framework to study suicidal behavior.

Specificity of Suicide Outcomes

A variety of suicide outcomes have been examined in previous research, ranging from broad outcomes (e.g., suicidal vs. nonsuicidal groups) to specific outcomes (e.g., suicide ideation, attempts, and deaths). Studies that use vague and poorly defined outcomes (e.g., “suicidality” and “suicidal” combine suicidal thoughts *and* behaviors; “deliberate self-harm” combines nonsuicidal *and* suicidal self-injury) limit conclusions that can be drawn about risk for suicidal behavior specifically. It is recommended that researchers clearly define their suicide outcomes and avoid using variables that collapse different thoughts and behaviors into a single category. Moreover, given the ultimate goal of preventing suicide deaths, and research indicating that most risk factors for suicidal thoughts do *not* predict behaviors (Borges et al., 2010; Bruffaerts et al., 2015; Kessler et al., 1999; Nock et al., 2012; Nock, Hwang, et al., 2009; Nock, Hwang, et al., 2010), it is recommended that researchers prioritize, and separately examine, the study of suicidal behaviors (suicide attempts and deaths). Finally, given the broad criteria used to define suicide attempts (i.e., self-inflicted injury with any intent to die; Silverman et al., 2007), it will be important for research to further specify common suicide phenotypes of interest. For instance, some researchers have found stronger effects for risk factors among individuals who have made (a) high (vs. low) lethality attempts (Keilp et al., 2001; McGirr, Dombrovski, Butters, Clark, & Szanto, 2012), (b) attempts with high (vs. low) intent to die (Menon, Kattimani, Shrivastava, & Thazath, 2013; Nock & Kazdin, 2002), and (c) multiple (vs. single) attempts (Boisseau et al., 2013; Rudd, Joiner, & Rajab, 1996). These specific attempt categories may be one way to identify more severe suicidal individuals among the large and heterogeneous group of attempters. However, it is important to note that there is not a single, agreed upon definition of “severe” suicide attempts, which makes generalizing across studies challenging. Alternatively, researchers may consider using extremes on an RDoC construct dimension, or suicide-relevant dimension, to identify a more homogenous suicide outcome group. For example, instead of using diagnostic groups, Sanislow et al. (2010) categorized individuals with anxiety based on amygdala responses during fearful stimuli. To categorize more severe suicide attempters, researchers could use thresholds informed by extremes on particular cognitive measures, such as overgeneralized autobiographical memory (Williams & Broadbent, 1986) or attentional bias to suicide (Cha et al., 2010).

Specify Measurement of Suicidal Traits vs. Suicidal States

For decades, prospective suicide research has examined suicidal thoughts and behaviors over large windows of time (e.g., months to years; Franklin et al., 2016). Such work, although useful in many respects, assumes that suicide risk is relatively static, or trait-like, and does not change much in between these long periods of time. A small body of research suggests that this may not be the case. Although some individuals certainly tend to have more suicide ideation than others, even among these high-risk individuals, episodes of suicide ideation tend to fluctuate rapidly. For instance, suicide ideation has been found to fluctuate significantly in the 24 hours leading up to a suicide attempt (Bagge et al., 2014). In another study, nearly 75% of people noted that their typical episode of suicide ideation lasted less than an hour (Nock, Prinstein, & Sterba, 2009). Thus, traditional studies with long time periods between assessments miss this state-like variability in suicide ideation. This issue is also true for the study of suicide risk factors. Indeed, many risk factors are trait-like (e.g., attributional style) and, as already noted, are most relevant when they interact with proximal factors (e.g., life events) that likely vary considerably from day-to-day. Future research within the RDoC framework must consider measurement of trait and state-level suicide risk and how these can be most accurately assessed across units of analysis.

Examine Interactions across Domains

Suicidal behaviors might be thought of as a “perfect storm” between distal and proximal risk factors. The RDoC framework can help identify what these distal and proximal factors are across several domains. As an example, although we know that childhood adversity leads to increased suicide risk, we also know that not everyone who experiences childhood adversity becomes suicidal and those who do may not experience suicidal thoughts or behaviors until many years after the adversity. It may be that factors from other domains explain possible mechanisms of this risk. Turecki et al. (2012) describes pathways between early adversity and suicide risk through dysregulation of the stress-response systems. This dysregulation, which may happen proximal to the adversity but distal to suicide risk, becomes relevant when individuals are exposed to factors from other domains (e.g., loss events) that activate such underlying vulnerabilities and lead to the proximal occurrence of suicidal thoughts and behaviors. Moreover, future research would benefit from focusing on the potential identification of distal factors that indicate specific suicide phenotypes (e.g., individuals who share early life adversity or particular stress-response dysregulation), as well as the proximal factors that activate vulnerabilities associated with these phenotypes.

Identify New Constructs

A critical feature of the RDoC framework is its flexibility and ability to integrate new constructs as informed by research. As an example, prospection or future thinking is a strong candidate for an RDoC construct. While prospection is not currently in the RDoC Matrix, its *dimensionality*, *multiple units of analysis*, and *neural basis* firmly justify its inclusion. Regarding its *dimensionality*, prospection encompasses the full spectrum of variation from normal to abnormal, thereby adhering to a key pillar of RDoC. Regarding its *units of analysis*, the construct of prospection is granular enough so that it can be captured across multiple levels and units of analysis—specifically behavior, (MacLeod et al., 2005), self-

report (Morina, Deepröse, Pusowski, Schmid, & Holmes, 2011), and circuits (i.e., *neural basis*) (Addis, Pan, Vu, Laiser, & Schacter, 2009; Gaesser, Spreng, McLelland, Addis, & Schacter, 2013).

Collaboration

Efforts to “fill in” and expand on the RDoC matrix cannot be done by a single researcher. The transdisciplinary nature of RDoC requires collaboration across experts who can each offer their respective knowledge base (Bilder et al., 2013). Geneticists, neuroscientists, psychiatrists, and psychologists not only have a lot to offer to their respective disciplines, but also to each other and the broader field. Bilder and colleagues (2013) emphasize the importance of building *ontologies* that serve as resources to structure and specify domains of knowledge. Relatedly, we currently are building what will become a publicly searchable database (i.e., ontology) of all extant research examining associations between RDoCian constructs and suicide outcomes (via contract support from NIMH). Through these and other efforts, we aim to accelerate this transdisciplinary effort.

Concluding Comments

Research that aims to understand a complex and multi-determined problem like suicide must move beyond the examination of single sociodemographic and psychiatric risk factors. The RDoC initiative provides a potentially useful, yet challenging, framework to guide transdiagnostic and interdisciplinary research to meet this need. As the field shifts to consider suicide, as well as other important clinical outcomes, from a RDoC perspective, there is a significant need to not only “map out” what is currently known about the associations among RDoC constructs and these clinical outcomes, but to identify and resolve the many challenges that come with embracing and advancing this new perspective. Doing so will not only advance our understanding of suicide and related outcomes, but will help us to better understand the mediators and moderators that lead to these outcomes, and will reveal new treatment targets that may lead to improved prediction and prevention efforts in the years ahead.

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Table 1

Suicide literature related to the Research Domain Criteria (RDoC) matrix.¹

Negative Valence Systems: “primarily responsible for responses to aversive situations or context, such as fear, anxiety, and loss”				
Construct	Definition	Examples	Sample References	Unit of Analysis
Loss	“A state of deprivation of a motivationally significant con-specific, object, or situation. Loss may be social or non-social and may include permanent or sustained loss of shelter, behavioral control, status, loved ones, or relationships. The response to loss may be episodic (e.g., grief) or sustained.”	Interpersonal loss	Bagge, Glenn, & Lee, 2013; Cheng, Chen, Chen, & Jenkins, 2000; Yen et al., 2005	Self-report
		Employment or financial loss	Cheng et al., 2000; Classen & Dunn, 2012	Self-report
		Loss of personal health	Cavanagh, Owens, & Johnstone, 1999; Cheng et al., 2000	Self-report
		<i>Potential Mediators</i>	Sample References	Unit of Analysis
		Loneliness, isolation, decreased belongingness	Zuroff, Fournier, & Moskowitz, 2007 (also see <i>Social Processes</i>)	Self-report
		Guilt and humiliation	Hendin, Maltsberger, Lipschitz, Haas, & Kyle, 2001	Self-report
		<i>Potential Moderators</i>	Sample References	Unit of Analysis
		Negative attributional style	Kleiman, Riskind, Stange, Hamilton, & Alloy, 2014	Self-report
		Perfectionism	Hewitt, Caelian, Chen, & Flett, 2014	Self-report
		Problem solving deficits	Grover et al., 2009	Self-report
Construct	Definition	Examples	Sample References	Unit of Analysis
Sustained threat	“An aversive emotional state caused by prolonged (i.e., weeks to months) exposure to internal and/or external condition(s), state(s), or stimuli that are adaptive to escape or avoid. The exposure may be actual or anticipated; the changes in affect, cognition, physiology, and behavior caused by sustained threat persist in the absence of the threat, and can be differentiated from those changes evoked by acute threat.”	Childhood abuse and neglect	Joiner et al., 2007; Sarchiapone, Carli, Cuomo, & Roy, 2007; Spokas, Wenzel, Stirman, Brown, & Beck, 2009; Ystgaard, Hestetun, Loeb, & Mehlum, 2004	Self-report
		Peer victimization and bullying in youth	Geoffroy et al., 2016; Klomek, Marrocco, Kleinman, Schonfeld, & Gould, 2007	Self-report
		Chronic stress (e.g., interpersonal, occupational)	Baumert et al., 2014; Pettit, Green, Grover, Schatte, & Morgan, 2011	Self-report
		<i>Potential Mediators</i>	Sample References	Unit of Analysis
		Emotion regulation difficulties	Gordon et al., 2015	Self-report
		Hopelessness	Spokas et al., 2009	Self-report
		Engagement in risky behaviors	Dube et al., 2001	Self-report
		Re-victimization	Lee, 2015	Self-report
		Alterations in stress-response system	Turecki & Brent, 2016	Physiology
		<i>Potential Moderators</i>	Sample References	Unit of Analysis
(See potential moderators of <i>loss</i> construct)				

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		Genetic moderators:		
		Serotonin transporter gene (5-HTTLPR)	Roy, Hu, Janal, & Goldman, 2007; Shinozaki et al., 2013	Genes (× environment)
		Serotonin gene HTR2A	Ben-Efraim, Wasserman, Wasserman, & Sokolowski, 2013; Brezo et al., 2010	Genes (× environment)
		Brain-derived neurotrophic factor (BDNF)	Perroud et al., 2008	Genes (× environment)
		Corticotropin-releasing hormone receptor 1 (CRHR1)	Ben-Efraim, Wasserman, Wasserman, & Sokolowski, 2011	Genes (× environment)
Construct	Definition	Examples	Sample References	Unit of Analysis
Frustrative nonreward	“Reactions elicited in response to withdrawal or prevention of reward, i.e., by the inability to obtain positive rewards following repeated or sustained efforts.”	Psychiatric disorders characterized by aggression, anger, and irritability (e.g., impulse-control, substance use, antisocial personality, and intermittent explosive disorders) ²	Evren, Cinar, Evren, & Celik, 2011; Nock, Hwang, Sampson, & Kessler, 2010; Nock et al., 2014;	Self-report
		Trait aggression, anger, irritability	Borges et al., 2010; Hawkins et al., 2014; Swogger, Van Orden, & Conner, 2014	Self-report
		<i>Potential Mediators</i>	Sample References	Unit of Analysis
		Emotion regulation difficulties	Ammerman, Kleiman, Uyeji, Knorr, & McCloskey, 2015	Self-report
		Perceived burdensomeness and lack of belongingness	Hawkins et al., 2014	Self-report
Construct	Definition	Examples	Sample References	Unit of Analysis
Acute and potential threat	Acute threat (“fear”): “Activation of the brain’s defensive motivational system to promote behaviors that protect the organism from perceived danger.” Potential threat (“anxiety”): “Activation of a brain system in which harm may potentially occur but is distant, ambiguous, or low/uncertain in probability, characterized by a pattern of responses such as enhanced risk assessment (vigilance).”	Fear disorders	Borges et al., 2010; Nock, Hwang, et al., 2010	Self-report
		Panic attacks	Yaseen, Chartrand, Mojtabai, Bolton, & Galynker, 2013	Self-report
		Anxiety disorders	Borges et al., 2010; Nock, Borges, Bromet, Alonso, et al., 2008; Nock, Hwang, et al., 2010	Self-report
		Fear-potentiated startle response (but not anxiety-potentiated startle)	Ballard et al., 2014	Physiology
Positive Valence Systems (PVS): “Primarily responsible for responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning”				
Construct nonspecific (i.e., tied to PVS but not to a specific construct with this domain)	<i>(see PVS definition above)</i>	Anhedonia	Fawcett et al., 1990; Nock & Kazdin, 2002	Self-report
		Psychiatric disorders characterized by hyperresponsiveness of the reward system, such as substance use and	Borges et al., 2010; Nock, Hwang, et al., 2010; Vijayakumar, Kumar, & Vijayakumar, 2011;	Self-report

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		impulse-control disorders	Wong, Cheung, Conner, Conwell, & Yip, 2010	
Construct	Definition	Examples	Sample References	Unit of Analysis
Approach motivation	“Involving mechanisms/processes that regulate the direction and maintenance of approach behavior...can be directed toward innate or acquired cues... implicit or explicit goals”	Indifference to reward magnitude (reward valuation)	Liu, Vassileva, Gonzales, & Martin, 2012	Behavior
		Reduced willingness to work for a reward	Auerbach, Millner, Stewart, & Esposito, 2015	Behavior
Initial and sustained responsiveness to rewards	“Mechanisms and processes associated with hedonic responses—as reflected in subjective experiences, behavioral responses, and/or engagement of the neural systems to a positive reinforcer—and culmination of reward seeking.”	Weak paralimbic responsiveness to expected rewards	Dombrovski, Szanto, Clark, Reynolds, & Siegle, 2013	Circuits
Reward learning	“Process by which organisms acquire information about stimuli, actions, and contexts that predict positive outcomes, and by which behavior is modified when a novel reward occurs or outcomes are better than expected.”	Difficulty flexibly adapting to new information to increase probability of rewards:		
		Perseverating on previously rewarding stimuli even when no longer advantageous	Dombrovski et al., 2013	Behavior
		Switching away from newly rewarding stimuli too quickly	Dombrovski et al., 2010	Behavior
Cognitive Systems: “responsible for various cognitive processes” (see Constructs for examples)				
Construct	Definition	Examples	Sample References	Unit of Analysis
Declarative memory	“Acquisition or encoding, storage and consolidation, and retrieval of representations of facts and events.”	Recalling past events in an overgeneralized style with fewer vivid details (e.g., Autobiographical Memory Test)	Arie, Apter, Orbach, Yefet, & Zalsman, 2008; Pollock & Williams, 2001; Williams et al., 1996	Behavior
		Delayed recall	Richard-Devantoy, Berlim, & Jollant, 2015	Behavior
Working memory	“Active maintenance and flexible updating of goal/task relevant information (items, goals, strategies, etc.) in a form that has limited capacity and resists interference.”	Overall working memory deficits (e.g., N-Back Task, Weschler Memory Scale)	Kim, Jayathilake, & Meltzer, 2003; Richard-Devantoy et al., 2015	Behavior
Cognitive control	“System that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context. Additionally, control processes are engaged in the case of novel contexts, where appropriate responses need to be selected from among competing alternatives.”	Executive attention ³ or attention control deficits (e.g., Stroop Task)	Keilp, Gorlyn, Oquendo, Burke, & Mann, 2008; Keilp et al., 2013; Keilp et al., 2001	Behavior
		Making disadvantageous choices (e.g., Iowa Gambling Task)	Jollant et al., 2005; Jollant et al., 2007	Behavior
		Difficulty inhibiting poor responses (e.g., Go/No-Go Test)	Westheide et al., 2008	Behavior
		Decreased activation for disadvantageous choices	Jollant et al., 2010	Circuits

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		in the lateral orbitofrontal and occipital cortices (e.g., Iowa Gambling Task)		
Perception	“Processes that perform computations on sensory data to construct and transform representations of the external environment, acquire information from, and make predictions about, the external world, and guide action.”	Auditory verbal hallucinations	Fujita et al., 2015; Harkavy-Friedman et al., 2003; Nordentoft et al., 2002	Self-report
		Visual acuity	Rim, Lee, Sung, Chung, & Kim, 2015	Behavior
		Chronic pain	Calati, Bakhayi, Artero, Ilgen, & Courtet, 2015; Hooley, Franklin, & Nock, 2014	Self-report
		Higher pain tolerance (e.g., cold pressor task)	Ribeiro et al., 2014	Behavior
Language	“System of shared symbolic representations of the world, the self and abstract concepts that supports thought and communication.”	Speech production patterns, acoustic effects (such as monotonous and repetitive phrasing), and voice quality	Cummins et al., 2015; Silverman & Silverman, 2006	Behavior
Social Processes: “mediate responses to interpersonal settings of various types, including perception and interpretation of others’ actions”				
Construct	Definition	Examples	Sample References	Unit of Analysis
Affiliation and attachment	“Affiliation is engagement in positive social interactions with other individuals. Attachment is selective affiliation as a consequence of the development of a social bond. Affiliation and Attachment are moderated by social information processing (processing of social cues) and social motivation. Affiliation is a behavioral consequence of social motivation and can manifest itself in social approach behaviors.”	Feelings of loneliness and lack of social belonging	Burke, Hamilton, Ammerman, Strange, & Alloy, 2016; Fisher, Overholser, Ridley, Braden, & Rosoff, 2015; Wichstrom, 2000	Self-report
		Perceived burdensomeness	Brown, Dahlen, Mills, Rick, & Biblarz, 1999; Van Orden, Lynam, Hollar, & Joiner, 2006	Self-report
		Avoidant attachment style	Grunebaum et al., 2010	Self-report
		Insecure attachment style	Sheftall, Schoppe-Sullivan, & Bridge, 2014	Self-report
		Family responsibility, including having children at home ⁴	Oquendo et al., 2005; Qin & Mortensen, 2003	Self-report
		School connectedness ⁴	Sampasa-Kanyinga & Hamilton, 2016	Self-report
		Religious affiliation ⁴	Dervic et al., 2004	Self-report
Perception and understanding of self	“The processes and/or representations involved in being aware of, accessing knowledge about, and/or making judgments about the self. These processes and representations can include current cognitive or emotional internal states, traits, and/or abilities, either in isolation or in relationship to others, as well as the mechanisms that support self-awareness, self-monitoring, and self-knowledge.”	Low self-esteem, low self-efficacy, low self-concept	Bolton, Pagura, Enns, Grant, & Sareen, 2010; Lewinsohn, Rohde, Seeley, & Baldwin, 2001; Wichstrom, 2000	Self-report
		High self-consciousness, self-criticism, or self-blame	Bolton et al., 2010; Wiklander et al., 2012; Yen & Siegler, 2003	Self-report
		Implicit self-identification with death/suicide (assessed via the death/suicide Implicit Association Test; d/s IAT)	Barnes et al., 2016; Nock, Park, et al., 2010	Behavior
Perception and understanding of others	“The processes and/or representations involved in being aware of, accessing knowledge about, reasoning about, and/or making judgments about other animate	<i>No examples have been examined in relation to suicidal behaviors</i>		

	entities, including information about cognitive or emotional states, traits or abilities.”			
Social communication	“A dynamic process that includes both receptive and productive aspects used for exchange of socially relevant information. Social communication is essential for the integration and maintenance of the individual in the social environment.”	Increased neural activity to angry faces, potentially indexing sensitivity to signals of anger or social disapproval	Jollant et al., 2008; Pan et al., 2013	Circuits
		Autism spectrum disorders, in which social communication deficits are prominent	Hannon & Taylor, 2013	Self-report
Arousal and Regulatory Systems: “responsible for generating activation of neural systems as appropriate for various contexts, and providing appropriate homeostatic regulation of such systems as energy balance and sleep”				
Construct	Definition	Examples	Sample References	Unit of Analysis
Sleep-wakefulness	“Sleep and wakefulness are endogenous, recurring, behavioral states that reflect coordinated changes in the dynamic functional organization of the brain and that optimize physiology, behavior, and health.”	Psychiatric disorders with core disturbances in sleep, such as mood disorders and posttraumatic stress disorder	Nock, Borges, & Ono, 2012; Nock, Hwang, et al., 2010	Self-report
		Sleep difficulties, including insomnia, hypersomnia, nightmares, and poor sleep quality (e.g., nonrestorative sleep)	Bernert, Turvey, Conwell, & Joiner, 2014; Pigeon, Pinguart, & Conner, 2012	Self-report
		Dysfunction in rapid eye movement (REM); lower sleep efficiency; longer sleep latency (assessed via EEG)	Agargun & Cartwright, 2003; Sabo, Reynolds, Kupfer, & Berman, 1991	Physiology
Circadian rhythms	“Endogenous self-sustaining oscillations that organize the timing of biological systems to optimize physiology and behavior, and health.”	Diurnal variation ⁵	Erazo, Baumert, & Ladwig, 2004; Preti & Miotto, 2001	
		Seasonal variation ⁵	Altamura, VanGastel, Pioli, Mannu, & Maes, 1999; Erazo et al., 2004	
Arousal	“Sensitivity of the organism to stimuli, both external and internal.”	Psychiatric disorders with core symptoms of hyperarousal, such as psychomotor agitation in depression, increased goal-directed behavior in bipolar disorder, hypervigilance in posttraumatic stress disorder	Nock et al., 2012; Nock, Hwang, et al., 2010	Self-report
		Agitated affective states ⁶	Busch, Fawcett, & Jacobs, 2003; Hendin et al., 2001; Sadeh & McNiel, 2013	Self-report
		Emotion reactivity ⁶	Nock, Wedig, Holmberg, & Hooley, 2008 (SI/SA)	Self-report

¹Definitions for each construct are drawn from the RDoC Matrix website: <https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml>

²As defined by RDoC, aggression is a heterogeneous construct. In the RDoC framework, different forms of aggression are categorized based on their distinct antecedents and motivations (NIMH, 2011). For instance, *Negative Valence: frustrative nonreward* is distinguished from defensive aggression (categorized under *Negative Valence: acute threat*) and offensive (proactive) aggression (categorized under the *Social Processes* domain). Unfortunately, previous suicide research lacks the specificity needed to make these fine-grained distinctions. Moreover, there remains debate about where aggression should be most appropriately included in the matrix. For the purposes of this review, we discuss aggression within *Negative Valence: frustrative nonreward*, but recognize that this may not be the most accurate classification.

³Executive attention falls under *cognitive control* (instead of *attention*) due to its involvement in input selection (within the *goal selection, updating, and representation* subconstruct).

⁴Indicates examples of factors that *decrease* risk for suicidal behaviors.

⁵These examples are proxies for *circadian rhythms* and therefore no specific unit of analysis is indicated. Of note, the *Arousal and Regulatory Systems* workgroup chose not to include seasonal oscillations within the *circadian rhythms* construct, noting there is “little evidence to support the presence of seasonal oscillations in the human mammal” (NIMH, 2012). However, given the seasonal patterns in rates of suicide deaths, we decided this was relevant to include in our review.

⁶These studies confound arousal and valence and therefore it is unclear how much risk is conferred by increased *arousal* specifically.

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