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Suicide Risk and the Menstrual Cycle: A Review of Candidate RDoC Mechanisms

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Abstract

Purpose of review: Risk for suicidal behavior may fluctuate across the menstrual cycle. Here, we use the RDoC framework to review potential mechanisms by which the cycle may increase acute suicide risk.

Findings: The menstrual cycle impacts the majority of RDoC constructs linked to suicide risk, particularly among hormone-sensitive women, such as those with premenstrual dysphoric disorder or premenstrual exacerbation of a psychiatric disorder. Despite this, there are no published studies examining suicidal ideation, planning, or behavior longitudinally across the cycle.

Summary: More work is needed to understand how hormone sensitivity may relate to both trait and state suicide risk. Intensive multilevel investigations of cyclical hormone effects on suicide risk through specific RDoC mechanisms are suggested. This is a fertile research area and may provide key insights regarding the mechanisms of acute suicide risk.

Keywords

Suicide; RDoC; Menstrual Cycle; Estradiol; Progesterone

Introduction

Suicide remains a poorly understood and devastating public health problem. It is the 10th leading cause of death in the United States, representing \$58.4 billion of the annual fatal injury cost (1,2). Despite years of research, suicide has increased in recent decades, with steeper rates of increase for women¹ (45%) compared to men (16%) (3). Prevention efforts have been impeded by a focus on stable, trait-level risk factors (4,5). Effective prevention requires models focused on fluctuating, state-level risk factors—especially those that move beyond self-report (6). The Research Domain Criteria (RDoC) framework, which describes mental processes within five transdiagnostic domains, is well-suited to guide development of biobehavioral models of both trait and state suicide risk (6). Each RDoC construct is

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¹Although we use the term "women" throughout for readability, we wish to clarify that we use this word to indicate those assigned female at birth who are currently experiencing natural menstrual cycles. This may include transgender men and nonbinary-identified individuals.

dimensional, measurable on a spectrum from normative to functionally impairing, and can be measured at various units of analysis ranging from self-report and behavior to cells and molecules. Therefore, in addition to structuring discussion of trait suicide risk (5), the RDoC framework can guide our search for markers of state suicide risk.

One understudied source of acute changes in suicide risk is the female menstrual cycle. This review highlights some of the strongest recent evidence that the menstrual cycle can trigger changes in RDoC risk factors that increase acute risk for suicidal behavior. First, we briefly introduce the menstrual cycle, hormone sensitivity, and the small literature on the menstrual cycle and directly-measured suicidal behavior. Second, we provide an RDoC-structured review of potential mechanisms by which the cycle might cause changes in acute suicide risk. We will focus on evidence from within-person studies of the cycle and will primarily describe self-report and behavioral levels of analysis. We will not comprehensively review neurobiological and animal work regarding hormone mechanisms in behavior, because such reviews are already available (7). In line with experimental and epidemiologic evidence, we assume that any functionally significant cyclical behavioral changes are driven primarily by women with some degree of hormone sensitivity, and do not occur in all women.

Psychiatric Hormone Sensitivity and Suicide Risk

At puberty, suicidal ideation and behavior dramatically increase and a female-biased difference in depression and suicide attempts appears (8). For many females, increased risk may be driven by increased flux in the ovarian hormones estradiol (E2) and progesterone (P4), which begin to fluctuate predictably across the monthly menstrual cycle (see Figure 1 for illustration of a typical 28-day cycle). Experimental work demonstrates prominent individual differences in neurobiological sensitivity to normal hormone changes, with normal monthly flux causing adverse mood and behavior changes only in some “hormone sensitive” females (9). This sensitivity may exist on a continuum, whereby the severity of cyclical symptom change can be absent, mild, moderate, or severe (10). At the extreme end of this spectrum is the DSM-5 disorder **Premenstrual Dysphoric Disorder (PMDD)**. Diagnosis requires five or more emotional, behavioral, or physical symptoms emerging between ovulation and the onset of menses and remitting fully by the end of menstrual bleeding. Core emotional symptoms include mood swings, rejection sensitivity, irritability, interpersonal conflict, depressed mood, hopelessness, feelings of worthlessness and guilt, and anxiety; at least one of these must be present for diagnosis (11). Although prevalence of diagnosable PMDD is estimated at 3–8%, up to 20% of reproductive-aged report clinically significant symptoms (12). In addition to PMDD, many women with psychiatric disorders experience **premenstrual exacerbation (PME)** in which chronic symptoms worsen prior to and during menses; for example, up to 60% of women with depressive disorders demonstrate PME of at least one symptom (13).

The pathophysiology of hormone sensitivity remains poorly understood, but some known risk factors for suicide also appear to predict hormone sensitivity. Early life adversity (14), proximal stress (15,16), and markers of impulsivity (17,18) each predict both suicide and hormone sensitivity. Further, many disorders characterized by externalizing behaviors and elevated suicide risk show a high risk of PME, including eating disorders (19), borderline

personality disorder (BPD; (20), bipolar disorder (21), substance abuse (22), and post-traumatic stress disorder (23). This overlap between hormone sensitivity, externalizing, and suicide risk raises the possibility that females with suicidality are at elevated risk of hormone sensitivity (i.e., perimenstrual exacerbation of suicidal behavior) due to various shared etiological mechanisms, or alternatively, that hormone sensitivity promotes externalizing and suicide risk.

Evidence for Changes in Suicide Risk Across the Menstrual Cycle

To our knowledge, no published studies have prospectively examined cyclical changes in daily suicidal ideation or behavior. However, many cross-sectional studies, reviewed by Saunders and Hawton (24), document perimenstrual increases in risk of hospitalization for suicidal behavior (relative to hospitalization for accidents) in the *perimenstrual* weeks (i.e., the weeks before and during menses). Since the publication of that review, three additional studies have found associations between the early follicular/menstrual phase and suicidal behavior, and one found no significant association (25–28). Methods have been rudimentary, utilizing self-reported last menses and single hormone measures to examine phase effects on admissions for suicide attempt (vs. accidents or other ailments). Nonetheless, the preponderance of the evidence indicates elevated perimenstrual risk for suicidal ideation and behavior, and forthcoming longitudinal and experimental evidence from our laboratory also supports a role for the cyclical hormone changes in acute risk for daily suicidal ideation, planning, and intent (29). Given the evidence that the menstrual cycle may drive predictable changes in risk for suicide, it is critical to identify potential mechanisms (e.g., RDoC systems) of this cycling risk.

Overview of RDoC Domains and Suicidality

A comprehensive review of RDoC systems and suicidality is provided elsewhere (5). However, below we review key RDoC systems and subconstructs relevant to the intersection of the cycle and suicidality.

RDoC Negative Valence Systems and Suicide

Negative Valence Systems respond to aversive contexts; both negative experiences and maladaptive responses may elevate suicide risk. The aversive contexts most frequently linked to suicidal behavior align with the RDoC constructs of **loss** (deprivation of shelter, status, control, and relationships), **acute/potential threat** (present or potential danger), **sustained threat** (prolonged exposure to aversive or harmful stimuli) and **frustrative nonreward** (inability to obtain or removal of rewarding stimuli following persistent effort). Both occurrence of negative events and deleterious biological, psychological, and behavioral responses to negative life events are associated with suicidal behavior (25–28).

RDoC Positive Valence Systems and Suicide

Positive Valence Systems respond to rewarding stimuli or contexts. The most relevant subconstructs of this domain include **reward responsiveness** (responses to impending reward, receipt of reward, and repeated reward or satiation) and **reward valuation** (processes by which probability and benefits of a prospective outcome are computed). Both

hyper-responsiveness to reward and indifference to reward (e.g. anhedonia) have been associated with suicide. Delay discounting, the act of overvaluing short-term rewards relative to long-term rewards, leads to decision-making deficits in suicidal women (31), and trait-level anhedonia (lack of responsiveness to reward) is also linked to suicide (32).

RDoC Cognitive Systems and Suicide

Cognitive systems regulate how individuals receive, process, and recall information and utilize information to enact behavior. Deficits in subconstructs related to executive cognitive functioning, such as **attention**, **cognitive control** (inhibition), and **working memory**, have been linked to suicidal behavior. These cognitive deficits increase suicide risk by facilitating impulsive action-taking and impairing problem-solving abilities. Reduced inhibitory control facilitates the transition from suicidal thoughts to suicidal actions; while many individuals experience suicidal ideation, reductions in inhibitory control distinguish the few who attempt (33). Cognitive changes in the **perception of pain** may also predict suicide risk; increased pain tolerance is hypothesized to increase the likelihood of suicide attempts by decreasing aversion to painful suicide methods (34).

RDoC Systems for Social Processes and Suicide

Systems for Social Processes influence interpersonal interactions, including perceptions of self and other and behavioral responses to social stimuli. Relevant subconstructs include **affiliation and attachment** (engagement in positive social interactions, social bondedness), **perception and understanding of self** (including self-esteem and self-criticism), **perception and understanding of others**, and **communication** (including both reception and production, facial and non-facial communication). Perceived social rejection increases suicidal desire and is a key component of leading suicide theories (e.g. (35,36). Low self-concept and feelings of worthlessness predict suicidal behavior longitudinally (37,38). Neural reactivity to negative facial expressions are greater in those with a history of suicide attempt vs. those with depression but no history of suicidal behavior (39,40), and negative interpretive bias during neutral facial expressions predicts suicidal ideation and planning (e.g. 118).

RDoC Arousal and Regulatory Systems and Suicide

The Arousal and Regulatory Systems are responsible for homeostatic regulation and context-appropriate activation of neural circuits. **Sleep-wakefulness** in particular has been linked to suicide. A recent meta-analysis found problems with sleep-wakefulness to be associated with suicide risk independent of depression symptoms; low sleep efficiency, subjectively low sleep quality, and dysfunction in rapid eye movement (REM) sleep have all be linked to elevated risk for suicidal thoughts and behaviors (42,43).

Menstrual Cycle Fluctuations within the RDoC Domains

Negative Valence Systems Across the Menstrual Cycle

Loss Across the Menstrual Cycle.—PMDD causes temporary but impairing perimenstrual losses of status, achievement, and interpersonal roles. These include declines in productivity, effectiveness, and work attendance, impaired relationships with spouses, and

decreased ability to parent effectively (12,44,45). Women with PMDD (vs. healthy controls) rate stressors as more severe and aversive premenstrually (46,47). Loss experiences may increase suicidal ideation via emotions such as sadness, loneliness, guilt, and shame; women with PMDD (13,20,48) or PME of other psychiatric disorders (13,20) demonstrate perimenstrual increases in these emotions, whereas healthy women do not (49,50). Cyclical hormone changes also alter biological systems associated with responses to loss in ways that may be relevant to acute suicide risk. The amygdala, a brain region involved in emotional processing, demonstrates increased reactivity to aversive stimuli perimenstrually (vs. mid follicular (51) and late follicular (52,53) phases). Inflammatory immune activity, which has been implicated in depression (54), loss-related suicidal ideation and behavior (55), and violent suicide attempts (56), also peaks perimenstrually (57).

Frustrative Nonreward Across the Menstrual Cycle.—Anger, irritability, and interpersonal conflict which often occur in the context of frustrative nonreward, are among the most commonly-reported and severe symptoms of PMDD (58–62). Women with BPD, who may be at elevated risk of PME (20), similarly demonstrate a midluteal worsening and a perimenstrual peak in anger, irritability and interpersonal conflict (17,20).

Acute and Potential Threat Across the Menstrual Cycle.—Perimenstrual increases in anxiety are observed among women with PMDD (62,63) and PME of BPD (20) and elevated startle responses (64). Many women with high trait-level anxiety (65), post-traumatic stress disorder (23) and panic disorder (66) also experience PME of their symptoms, although it seems clear that this does not occur in all women with these disorders (63). Women high in anxiety sensitivity (AS; fear of behaviors and sensations associated with anxiety) demonstrate more uncontrollable and threatening appraisals of panic symptoms during a CO₂ challenge during the premenstrual phase (vs. follicular phase), but no differences in physiological panic symptoms (67).

Sustained Threat Across the Menstrual Cycle.—Although the symptomatic consequences of sustained threat may fluctuate, sustained threat itself is considered a relatively stable historical factor that would not cycle. However, the moderators and mediators of sustained threat effects on suicide risk may cycle, including emotion regulation (68) and physiological stress system dysregulation. Sustained threat (e.g., childhood abuse) may reduce the capacity for **emotion regulation** and cause altered **HPA axis activity and responses** to stress, both of which have been linked to suicidal behavior (69).

Emotion Regulation Across the Menstrual Cycle. PMDD symptoms include a sense of emotional overwhelm and difficulty coping, signaling the role of compromised premenstrual emotion regulation (62). Premenstrually, women with PMDD exhibit reduced cognitive reappraisal, greater use of maladaptive coping (47), and more self-focused attention (70).

Some work suggests that women high in neuroticism exert greater attempts at cognitive reappraisal premenstrually, but are less successful in reducing sadness and galvanic skin response (71). Anxiety control and rumination may also worsen premenstrually among many women with poor trait emotion regulation (20,72).

HPA Axis Function Across the Menstrual Cycle.: There is some evidence that women with cyclical hormone sensitivity also have blunted baseline cortisol levels and responses to challenge, regardless of cycle phase or history of abuse (73,74). A substantial body of literature also demonstrates normative luteal increases in HPA axis function across the menstrual cycle, with exogenous or endogenous progesterone elevations causing a potentiation of ACTH and cortisol responses (75). It is possible that this normative luteal rise and fall in HPA axis output could have more deleterious cyclical effects on suicide risk among those with blunted or otherwise compromised HPA axis function due to sustained threat exposure.

Cyclicity in Negative Valence Systems and Acute Suicide Risk: Summary and Recommendations.—Multi-level cyclical changes in experiences of and responses to negative life events may elevate perimenstrual suicide risk in hormone-sensitive women. Hormone-sensitive women report perimenstrual increases in both low-arousal (e.g., depressed mood) and high-arousal (e.g., anxiety, irritability) affective symptoms, both in general and in response to negative events. These experiences are sustained and exacerbated by perimenstrual reductions in effective emotion regulation and perimenstrual increases in negative appraisals of physiological symptoms. Increases in the frequency of self-generated negative events during this period may also contribute to these affective changes, but objective measurements of stressful events and use of stressful laboratory paradigms are needed to confirm this association. In addition, future research should utilize longitudinal and experimental study designs, and should incorporate levels of analysis other than self-report.

Positive Valence Systems Across the Menstrual Cycle

Reward Responsiveness Across the Menstrual Cycle.—Women with PMDD often experience reductions in interest or motivation in the luteal phase (59). Additionally, perimenstrual increases in anhedonia appear to be common in women with depression (13) and BPD (20). In unselected samples, neural sensitivity to expected rewards and reward magnitude appears to increase during the perimenstrual and mid-follicular phases. The mid-follicular (vs. midluteal) phase was associated with increased activation in orbitofrontal cortex and amygdala during reward anticipation, and increased activation in the midbrain, striatum, and left ventrolateral prefrontal cortex during reward outcome (76). The early follicular/menstrual phase was also associated with increased orbitofrontal cortex sensitivity to gain magnitude as well as increased early ventral striatum and anterior cingulate cortex sensitivity to loss magnitude (77). The premenstrual phase (vs. the late follicular phase) was linked to increased ventral striatum activity during the anticipation of reward compared, particularly among those with elevated premenstrual symptoms (78). Appetitive urges like substance craving and sexual desire are also higher in the follicular (vs. midluteal) phase (79–81).

Reward Valuation Across the Menstrual Cycle.—Delay discounting decreases from the early follicular phase to the late follicular phase (82,83). These effects were moderated by COMT gene allelic variation; COMT^{Val} carriers had the greatest mid-cycle declines in

preference for immediate rewards (83). As COMT^{Val} carriers have lower prefrontal dopamine, this cyclicity may be caused by E2-related changes in dopaminergic function.

Cyclicity in Positive Valence Systems and Acute Suicide Risk: Summary and Recommendations.—Cyclical fluctuations in reward systems are a critically understudied potential mechanism for proximal suicide risk. Elevated sensitivity to expected rewards and reward magnitude increases perimenstrual decision-making deficits and corresponding risk for suicidal behavior. Future research should examine the interactive effects of fluctuations in reward processing and inhibitory control (see cognitive section below) on suicide risk. Future research should examine reward-related processes and behavioral measures of anhedonia across the cycle in women with a range of hormone sensitivity.

Cognitive Systems Across the Menstrual Cycle

Attention and Working Memory Across the Menstrual Cycle.—Difficulty concentrating (i.e., self-reported problems with attention) is a common symptom of PMDD (59), and many women with depression demonstrate PME of concentration and attention difficulties (13). In the largest study of healthy women (n=68 across two cycles), no robust effects of the cycle on attention or working memory were observed (84). Further, two experimental studies in healthy women found that neither suppression of ovarian hormone cycling with a GnRH agonist nor luteal-level hormone addback influenced attention or working memory (85,86). These individual differences in cognitive hormone sensitivity appear to be determined in part by COMT^{Val} status and associated risk for impulsive traits (18,87,88).

Inhibitory Control and Impulsive Behaviors Across the Menstrual Cycle.—Perimenstrual reductions in inhibitory control and associated cortical activity have been documented in several studies (82,89–91), although findings are not entirely consistent (92). COMT^{Val} status also appears to confer risk for perimenstrual reductions in inhibitory control (87), and play a role in the expression of hormone sensitivity in PMDD (93). Many impulsive behaviors peak in the luteal phase or perimenstrually, including substance use frequency and craving (94–97) and binge eating (19,98). Impulsivity-related neural activation demonstrates similar patterns across the cycle in those with hormone-sensitivity; women with PMDD have decreased medial orbitofrontal cortex activity during inhibitory responses to negative emotional stimuli in the premenstrual phase as compared to the mid-to-late follicular phase, while healthy women do not (91,99).

Pain Perception Across the Menstrual Cycle.—Although evidence regarding the role of the cycle in pain perception in unselected samples is mixed (100,101), women with PMDD (vs. controls) have lower pain thresholds regardless of cycle phase, but describe pain as significantly more unpleasant in the luteal phase (102). Since high pain tolerance has been linked with increased capability of engaging in lethal suicidal behaviors (35), the low pain tolerance in certain phases of the cycle may act as a protective barrier to acting on suicidal thoughts for some hormone-sensitive women.

Cyclicity in Cognitive Systems and Acute Suicide Risk: Summary and

Recommendations.—Hormone sensitive women experience consistent luteal and perimenstrual deficits in executive function deficits and increased impulsive behaviors; the best evidence suggests that healthy women do not. In contrast, pain tolerance (thought to increase suicide risk) decreases during the perimenstrual period, which may be a protective factor. While cognitive research is strengthened by use of behavioral tasks, future research should also link tasks with real-life decision-making tasks as well as daily self-reported cognitive symptoms and suicidal processes. Additionally, given the centrality of interpersonal stress in suicide risk (35), studies should examine fluctuating cognitive control deficits in the context of psychosocial stressors, social problem-solving tasks, and dyadic interactions.

Systems for Social Processes Across the Menstrual Cycle

Affiliation and Attachment Across the Menstrual Cycle.—Interpersonal symptoms and social impairments are among the most commonly reported in women with PMDD; in one large PMDD sample ($n=1081$), 56% of women reported impairment in family functioning, while 52% reported impairment in social functioning during the premenstrual period (60). Women with PMDD also demonstrate more perimenstrual social-support seeking following stressors perceived as uncontrollable (47), although given their coincident increases in anger/irritability and interpersonal conflict, this may not always be effective. Women with PME of BPD also demonstrate midluteal and perimenstrual (vs. all other phases) exacerbations in interpersonal conflict, and perimenstrual and early-to-mid follicular (vs. all other phases) exacerbations of rejection sensitivity, shame, and felt invalidation (20). Women with histories of suicidal ideation demonstrated early follicular increases in perceived burdensomeness to others (103). Even in unselected samples there are significant perimenstrual (vs. mid-follicular) increases in interpersonal sensitivity (48), as well as menstrual (vs. periovulatory) reductions in task-derived motivation for social affiliation (104).

Self-perception and Self-understanding Across the Menstrual Cycle.—Among women with PMDD, worthlessness and guilt represent core emotional symptoms that arise in the luteal phase, peak perimenstrually, and remit during menses (Pearlstein et al., 2005). Many women with depressive disorders demonstrate PME of worthlessness and guilt (i.e., social emotion (13). Similarly, among women in high BPD traits, low daily levels of E2 (as in the perimenstrual phases) are related to increased identity disturbance (17). One study also found reduced premenstrual (vs. late follicular) perceptions of self-image in healthy women (48).

Other-Perception and Communication Across the Menstrual Cycle.—Rigorous within-person studies of healthy women find no cyclic changes in facial recognition (105). However, women with PMDD show a negative bias in perception of facial expressions premenstrually (106). These findings align with higher levels of rejection sensitivity in perimenstrual phases among women with PMDD, and may explain increases in perceived invalidation during this period among women with PME of BPD (20).

Cyclicity in Social Processes and Acute Suicide Risk: Summary and

Recommendations.—Ovarian hormone fluctuations appear to elicit changes in multiple risk-related social processes. For some women, perimenstrual hormone changes coincide with decreases in positive self-perception and increases in rejection sensitivity, perceived burdensomeness, felt invalidation, and interpersonal conflict. Given an overreliance on self-report in this area, it is unclear how these perceptual changes influence and are influenced by social behaviors and responses from the social environment. In-vivo dyadic interaction tasks are needed to determine how hormone-driven changes in appraisal alter social behavior and how hormone-driven changes in behavior elicit social responses that contribute to negative appraisals. Perimenstrual elevations in negative evaluations of the self and social interactions may increase risk for suicidal behavior, but more longitudinal and experimental research with behavioral tasks could clarify how social behavior and social perceptions interact to influence risk.

Arousal and Regulatory Systems Across the Menstrual Cycle

Sleep Across the Menstrual Cycle.—Both healthy women and women with PMDD report lower subjective sleep quality and lower sleep efficiency during the premenstrual and menstrual phases compared to the mid-follicular and early or mid-luteal phases, as well as increases in Stage 2 sleep and slight decreases in rapid eye movement (REM) sleep during the luteal phase (107–111). In addition to these cycle effects, women with PMDD have slower reaction times, decreased saccadic eye velocity, decreased parasympathetic activity during sleep, increased perceived daytime sleepiness and fatigue, and increased anxiety associated with subjective sleep disturbance in the premenstrual (vs. follicular) phase compared to healthy controls (108,112–116). These women also have more slow-wave sleep and lower levels of melatonin compared to healthy controls throughout the cycle (109,112).

Cyclicity of Arousal and Regulatory Systems as a Mechanism of Suicide Risk:

Summary and Recommendations.—Subjective sleep disturbance and objective changes to sleep composition in the premenstrual period may elevated suicide risk, potentially via executive function and negative affect (117). Future research should examine these potential pathways and use behavioral tasks to assess the cyclical effects of subjective and objective sleep disturbance on cognitive and affective risk for suicide.

Conclusion

Among hormone sensitive women with PMDD or PME, the perimenstrual (i.e., late luteal and early follicular) phases of the cycle may increase suicide risk via short-term changes in emotional, behavioral, and physiological risk factors. These women demonstrate perimenstrual surges in negative affect and sensitivity to emotional stimuli in response to negative life events; for some women, elevations in depressed mood appear to persist even into the mid-follicular phase. Corresponding reductions in effective emotion regulation further increase risk in this phase and may contribute to social detachment or discord as well as loss of occupational function. Perimenstrual cognitive deficits and changes in reward processing may also elevate risk; these women demonstrate perimenstrual elevations in sensitivity to expected rewards and reward magnitude. Such changes interact with cyclic executive function deficits and diminished inhibitory control to reduce effective decision-

making and increase impulsive behavior. In addition, the perimenstrual phase is linked to more negative appraisals of social interactions and the self, a less positive self-perception, and increases in feelings of perceived burdensomeness, rejection sensitivity, felt invalidation, and perceived conflict. All of these perimenstrual problems may be caused or exacerbated by perimenstrual disturbances in sleep structure and quality. In sum, perimenstrual changes in emotional, behavioral, and physiological factors across RDoC domains may interact to cause acute suicide risk among hormone-sensitive women.

Women being treated for suicidality should be screened for symptom cyclicity by tracking symptoms against the menstrual cycle (10). Cyclical suicidal symptoms should be addressed using established algorithms for the treatment of premenstrual disorders, including treatments that stabilize ovarian hormones or buffer their impact on neurobiological function (118). Additional support should come from behavioral interventions such as dialectical behavior therapy (119) that teach patients to proactively cope with negative emotion, urges to act impulsivity, and negative social perceptions.

Integration of the menstrual cycle and suicide risk literatures using the RDoC framework highlights how cyclical changes in acute risk may be mediated by cognitive, affective and psychosocial alterations in women who are neurobiologically sensitive to hormone changes (e.g., PMDD, PME). By examining a biological cause of within-person changes in risk, this approach provides a model for moving beyond trait-like, time-invariant predictors that have failed to improve suicide prevention efforts. Longitudinal and experimental designs, sufficient sample sizes for moderation by hormone sensitivity, and multilevel statistical models are needed. Ultimately, this work can clarify the complex mechanisms of suicide and build novel interventions targeting proximal risk.

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Figure 1.
 Suicide risk across the female menstrual cycle in hormone-sensitive women.