Review

Biological Psychiatry

Translating Interventional Neuroscience to Suicide: It's About Time

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ABSTRACT

Despite significant advances in psychiatric and psychological treatment over the last 30 years, suicide deaths have increased. Unfortunately, neuroscience insights have yielded few translational interventions that specifically target suicidal thoughts and behaviors. In our view, this is attributable to two factors. The first factor is our limited integration of neurocircuitry models with contemporary suicide theory. The second challenge is inherent to the variable nature of suicide risk over time. Few interventional neuroscience studies evaluate how temporal fluctuations in risk affect treatment, despite evidence that temporality is a key component distinguishing suicide phenotypes. To wit, individual variability in risk trajectories may provide different treatment targets to engage as a patient moves between suicidal ideation and attempt. Here, we first review contemporary ideation-to-action theories of suicide from a neurobiological perspective, focusing on valence and executive function circuits and the key role of state-induced (e.g., within stressful contexts) functional modulation on longitudinal risk trajectories. We then describe neural correlates of suicide reduction following various interventions, ranging from circuit specific (i.e., transcranial magnetic stimulation) to broader pharmacological (i.e., ketamine, lithium) to psychological (i.e., brief cognitive therapy). We then introduce novel strategies for tracking risk in naturalistic settings and real time using ecological momentary interventions. We provide a critical integration of the literature focusing on the intersection between targets and temporality, and we conclude by proposing novel research designs integrating real-time and biologically based interventions to generate novel strategies for future suicide reduction research.

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Since 1999, suicide deaths in the United States have increased by 35% (1). In response, investment in research has increased significantly. The U.S. National Institutes of Health's increased spending on suicide research paralleled the rise in mortality, growing approximately 13% from 2011 to 2019 after adjusting for inflation. Despite increased investment, few novel, neuroscience-based suicide interventions have been developed. Although recent psychosocial research has promoted wider appreciation for the important temporal aspects of suicide, spurring development of more complex, biopsychosocial models (2–4), these models are not fully integrated into clinical research.

Here, we argue that greater incorporation of critical psychosocial perspectives into clinical neuroscience will accelerate suicide treatment innovation. Toward this goal, we first introduce contemporary models of suicide emphasizing temporality—a key aspect of phenotypic variance. Next, we provide a focused review of the neuroimaging of suicide and summarize the state of the science of suicide treatment. We conclude with recommendations for improving research designs emphasizing interdisciplinary approaches and real-time risk tracking.

CONTEMPORARY PSYCHOSOCIAL MODELS OF SUICIDE

Early psychosocial models posited that particular distal factors [e.g., sociological (5), psychache (6), emotional dysregulation (7), diathesis–stress (8)] drove periods of heightened suicide risk and were influential in guiding the development of assessments and interventions. However, recent evidence recommends these models' refinement, demonstrating that common distal risk factors are, at best, modest predictors of behavior (9), failing to identify who will make future attempts (10). This is critical because most who contemplate suicide never attempt (11,12).

Contemporary ideation-to-action models of suicide explicitly address this shortcoming, taking the perspective that suicide comprises stages of variable risk. These models seek to identify who is at risk of attempt and when their risk is greatest [e.g., three-step theory (13), interpersonal-psychological theory (14), integrated motivational-volitional model (15), fluid vulnerability theory (FVT) (16)]. These models treat ideation and attempt as distinct stages, and each variant defines a suicidogenic pathway wherein key factors [e.g., belongingness and burdensomeness (14), defeat and entrapment (15), pain and hopelessness (13)] govern transitions from ideation to behavior. Ideation-to-action models have identified several factors demarcating which individuals may attempt suicide (13). However, because they largely treat suicidogenic pathways as static, most struggle to account for recent evidence that risk processes are heterogeneous (17) and vary substantively over time (17–20).

FVT (16) is distinguished from its ideation-to-action counterparts by its focus on suicide risk as a temporally dynamic

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process and its consideration of multiple interacting risk pathways. FVT posits that stable, preexisting vulnerabilities to suicide (e.g., genetics, stress responsiveness, neurocognitive function) are exacerbated or triggered by life stressors, intensifying risk states (e.g., hopelessness, anger, isolation, sleep deprivation), thereby driving immediate fluctuations and longer-term patterns of risk over time (16,20). Thus, FVT accounts for evidence that suicide attempt risk is a moving, nonlinear target fluctuating rapidly over brief periods [i.e., hours to days (17,19,20)]. FVT's interactionist perspective also aligns with naturalistic suicidal behavior and machine learning insights underscoring the complex, interacting nature of risk factors (21,22). In essence, FVT conceptualizes risk escalation as a perfect storm of stable and dynamic factors in time and space whose emergence is influenced by longer-term vulnerabilities (e.g., phenotypic factors).

THE NEUROCIRCUITRY OF SUICIDE

Progress requires a temporally sensitive theoretical framework of suicide, integrating knowledge of risk processes across clinical presentations. Distinct pathophysiologies may underlie suicide phenotypes, defined in part by temporal trends in individuals' risk (4,23,24). Because neuroimaging investigations primarily use cross-sectional designs for practical reasons, this hypothesis is largely untested. Moreover, because structure-function is typically compared between suicidal and nonsuicidal individuals within diagnoses, the generalizability of relevant neuroimaging to phenotypes and temporality remains unclear. These caveats notwithstanding, we now highlight findings potentially localizing key pathways and affective and behavioral traits to specific brain networks. In keeping with FVT's interactionist perspective, we highlight how state factors (e.g., sleep, substance use, stress) and accelerating/decelerating phenotypic tendencies influence circuits.

Functional Brain Networks and Suicide

Functional networks are constellations of brain regions serving common functional domains (e.g., vision, language). Prior neuroimaging implicates the valence (or reward), default, and cognitive control networks in suicide (25). The valence network processes feedback signals appraising the rewarding value of current or anticipated events that are central to emotion and learning (Figure 1). The default mode network (DMN) (Figure 1) is involved in autobiographical memory, prospection, and social cognition (26–30). Cognitive control, i.e., the adaptive control of thought and behavior (Figure 1), modulates processing in other brain networks toward goal-directed thought and action (31). Functional decrements in these networks map to suicidal processes in FVT [e.g., impaired future orientation, attentional biases, emotional dysregulation, problem-solving deficits (32)] differing between phenotypic presentations and map to specific circuits. Because these networks interact functionally via the cortico-striatal-thalamocortical loops (33), impairment in one has repercussions in other networks. Moreover, this detail of brain architecture facilitates recursive interactions between stable and dynamic factors underlying the "perfect storm." Unless stated otherwise, imaging studies below compare individuals with suicidal thoughts and behaviors (STBs) to diagnostic controls.

The Valence Network: Emotion, Learning, and Decision-Making Biases

Valence and arousal signals are central to emotion (34) (Figure 1). Functional magnetic resonance imaging (fMRI) activation in the pars orbitalis/orbitofrontal cortex is attuned to negative affect in those with mood disorders and STBs. In adults with depression, orbitofrontal cortex activation is more robust during passive viewing of negative emotional faces (35,36). Valence and arousal functional connectivity is also affectively biased in adolescents with bipolar disorder and attempt(s), who exhibit hyperconnectivity while viewing negative faces, but hypoconnectivity for positive emotion (37). Privileged negative emotional processing may confer stable vulnerability underlying depressive suicide phenotypes (23). These biases may influence interpersonal interactions, strong drivers of momentary risk (38).

Valence biases may also broadly influence feedback learning and decision making in STBs. Attempt history is associated with sunk cost bias (39,40), excessive loss aversion (39,41), short-term reward preference (42–44), and decision-making patterns reflecting inadequate feedback and/or anticipatory processing (45). fMRI evidence links the valence network to feedback bias (orbitofrontal cortex, win $>$ loss bias) [(46), but see (36)] and blunted anticipatory signaling [ventromedial prefrontal cortex (PFC) (44)] in older adults with depression and prior attempt (44) and to risk processing abnormalities in youths with attention deficits and ideation (47). These deficits promote riskier, short-term–focused decision making, trait impulsivity, and perhaps, under proximal stress, suicide (45).

These findings highlight valence network emotion and feedback learning pathways that influence stable risk, proximal risk, and phenotypic expression. Other valence correlates of ideation (48,49), attempt (50–55), and attempt lethality (43,56,57) have also been reported. Research is needed to address biases associated with nondepressive phenotypes (e.g., reward hypersensitivity in bipolar disorder or borderline personality disorder [BPD]). The circuitry underlying phenotypic interactions with proximal factors or how they amplify the impact of stress/trauma is also poorly understood. Examining how valence phenotypes influence attention in STBs (58) will be important for understanding suicide in posttraumatic stress disorder (59).

The Default Network: Prospection and Social Cognition

Midsagittal DMN regions integrate episodic memories [posterior cingulate cortex and precuneus (26)] with context and affect (medial PFC) into a self-referential framework (60). This is the foundation of our personal narratives and, to an extent, our future because experience guides prospection (30). Negative reinforcements are more readily recalled [reviewed in (61)], amplifying valence biases' sway over prospection. Several studies of attempt in depression illustrate valence's influence over DMN and memory prioritization. Posterior cingulate cortex activation while viewing positive self-referential images is attenuated in adolescents (62). By contrast, the posterior cingulate cortex is hyperactive in adults viewing pictures of suicidal means (63). Such biases may reinforce maladaptive

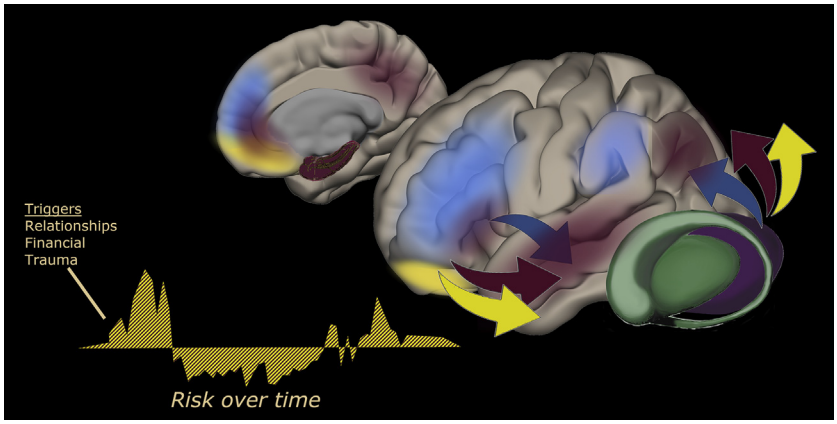

Figure 1. Target engagement along suicide risk trajectories. The valence (yellow), default (fuchsia), and cognitive control (blue) networks hold special relevance for suicide phenotypes. The cortico-striatal-thalamocortical loops integrate information across these distributed networks; thus, alterations in one network may impact functioning in other networks. Arousal and salience regions also interact with these networks, both directly and via the anatomical loop system. The development of suicidal ideation is influenced by the valence network's sensitivity to positive and negative stimuli, including high-stress triggers, and the impact of valence bias on prospection and social cognition in the default network. Although cognitive control does influence longer-term patterns of risk, e.g., potential impulsive phenotypes, its most significant impact may be on momentary stress responses and transitions between risk states. Notably, cognitive control deteriorates in the aftermath of changes in cognition, behavior, emotion, and physiology that may occur secondary to triggers—this is the fluid vulnerability theory's "perfect storm," the confluence of stable and dynamic factors in time and space that rapidly escalate risk. Thus, it may be more efficient for treatments for longer-term factors to target valence and default networks, whereas targeting the control network may be a better strategy for rapid symptom reduction and improved regulation.

cognitive patterns [e.g., rumination and self-conceptual distortions (8,14), prospective impairments (64)] long associated with suicidality.

Function in the theory of mind (ToM) subnetwork (65) (Figure 1) may contribute to social-cognitive suicide risk factors [e.g., hypermentalization (66), perceived burdensomeness (14)]. ToM network fMRI activation during social exclusion is elevated in women with depression and attempt history (67). Vulnerabilities rooted in ToM dysfunction may enhance stress responses, accelerating risk. Indeed, ToM coactivation with arousal/stress regions during exclusion scales with perceived burdensomeness (68). Differences in network volume are common in disorders/symptoms associated with attempts [BPD (51,69), psychosis (70), schizophrenia (55)]. Although understudied, the transdiagnostic nature of ToM observations is aligned with interpersonal difficulty as a universal driver of intensifying proximal risk (38).

Despite the clear relevance of the DMN's function to the phenomenon of suicide, it is comparatively understudied. Future work should investigate how broad DMN disruptions (e.g., resting hyperactivity) associated with general psychopathology (71), such as rumination (60) and intrusions, specifically contribute to suicide. The plasticity of the DMN in chronic stress (72) also merits attention given its potential to undermine encoding of positive memories while preserving negative ones, entrenching hopelessness.

Cognitive Control: Transitions From Ideation to Attempt

Although cognitive control influences suicide, its role is unclear, with the strength of its association varying substantially between clinical populations [reviewed in (73)]. Still, despite these discrepancies and because of its modulatory nature, cognitive control is a likely determinant of the acceleration/deceleration of risk processes and transitions to suicidal behaviors. Here, we consider cognitive control's contributions to three elements critical for weathering the perfect storm: decision processes, emotional regulation, and inhibitory control.

One recent perspective on suicide casts it as a disorder of aberrant decision making (45). Although it emphasizes the neurobiology of valence, paradoxical findings on the delay-discounting task supporting this model suggest a role for cognitive control. There is a robust association between histories of more/less lethal or planned attempts and the exaggerated/limited ability to delay gratification in older adults with depression (42,43,74). Subjective value comparison during delay-discounting evokes fMRI activation in the dorsolateral PFC (DLPFC) (75), a central cognitive control hub. This activation is reduced in older adults with histories of more planned attempts during delay discounting (74). Reduced engagement of the DLPFC in attempters during performance of other risk evaluation tasks (36) reinforces linkage of decision making, cognitive control, and suicidal behavior (45). Superior cognitive control may, paradoxically, be a stable vulnerability associated with a high-risk phenotype (23,25,45). Because higher control function is typically associated with better coping skills and psychiatric health, it will be important to fully specify when superior control is a liability.

Our allusion to the interplay between traits and naturalistic state factors is relevant to the DLPFC's role in emotional regulation and suicide. Poor regulation is a transdiagnostic risk factor for self-injurious behaviors (76). Emotional regulation is the control-dependent modification of reactions to emotionally evocative events (77); this regulation evokes DLPFC activation [reviewed in (78)]. The inclusion of emotional feedback in decision-making tasks generally alters prefrontal dynamics, but more so in adult suicide attempters than clinical control subjects (79). DLPFC recruitment also distinguishes depressed adolescents with/without STBs during explicit regulation (80), but not passive tasks (80,81). Individuals for whom regulation is more biologically costly may be more vulnerable under "perfect storm" scenarios conducive to rapid temporal escalation of proximal risk. One can imagine higher-risk scenarios where situational factors, such as weeks of impaired sleep, reduce capacity for reactive control during immediate stressors.

Ventrolateral PFC (VLPFC) inhibition may also shape STB manifestation, especially under proximal stress. The VLPFC

facilitates the suppression/countermanding of thoughts and actions (82,83), often in response to conflict signals from arousal or salience circuits (84,85). Although speculative, stronger functional connectivity between these circuits may enable conflict detection, driving fluctuations in ideation and negative affect and rumination. Indeed, functional connectivity between the VLPFC and salience circuits is elevated in young adults with mood disorders and ideation (86). Two antecedents of risk escalation, hypomania and negative urgency, are associated with differential VLPFC activity in more impulsive individuals (87) at a greater lifetime risk for STBs. Aberrant VLPFC suppression activation has also been noted in STBs with psychosis (88,89).

The hypothesis that cognitive control modulates the acceleration/deceleration of risk state transitions awaits further evaluation. Unfortunately, control function is often treated as a static resource in neuroimaging, limiting insight into risk's naturalistic, nonlinear evolution, escalating as a function of multiple suicide pathways. This missed opportunity is important given control's central role in regulation, and because indicators of increased proximal risk [i.e., sleep (90), substance abuse (91), mood/energy shifts (92)] reduce control capacity [e.g., in depression (93,94), anxiety (95)]. Within-subjects examination of circuit function under varying levels of stress or control demand will be essential to revealing its role in suicide and relationship to impulsivity-related phenotypes and temporal risk trends (23,45). Although we advocate for the employ of state-trait interaction logic, we would be remiss not to acknowledge its limitations—within-subjects test-retest reliability and the potential for practice-related performance change.

Neuroimaging Summary

These findings highlight the valence, default, and cognitive control circuits' significance to suicide, phenotypes, and risk temporal dynamics. Contradictory conclusions, however, indicate that much work remains. Transdiagnostic approaches that can identify both irrelevant variance and universal commonalities across clinical presentations will be essential for progress. Integrating high temporal resolution methodologies with imaging (see Opportunities in Suicide Research) may illuminate temporally delineated phenotypes. Other limitations include overemphasis on depression, modest delineation between ideation and attempt, and reliance on cross-sectional designs.

INTERVENTIONAL APPROACHES TO SUICIDE REDUCTION

Several treatments developed primarily for depression have efficacy for suicide reduction. Here, we consider interventions for rapid reduction of suicidality and longer-term chronic risk factors, including treatments that have nonspecific impacts on function (i.e., medications) and those aimed at specific circuits or processes (i.e., neurostimulation, cognitive training). A few important caveats to this literature warrant attention. A number of studies consisted of secondary analyses utilizing single items extracted from various depression rating scales, limiting dimensionality and knowledge about the nature of the suicidal ideation or behavior. Moreover, the paucity of robust clinical trial effects may reflect their measurement over broad temporal windows aliasing rapid fluctuations in suicidality during high-risk periods.

Longer-term Nonspecific Interventions

Clozapine. Clozapine is approved by the United States Food and Drug Administration for reduction of attempts in schizophrenia or schizoaffective disorder (96). An early, unblinded study of clozapine in treatment-resistant patients found an 88% reduction in attempts (97). Another small study found superior reductions in self-directed aggression and suicide risk after clozapine over haloperidol (98). The largest trial to date, comparing clozapine (n = 479) to olanzapine (n = 477), found superior reductions in suicidal behavior favoring clozapine (99). Despite clear efficacy, the prominent side effect burden associated with clozapine (e.g., anticholinergic side effects, weight gain, leukopenia, cardiotoxicity, and increased suicide risk after discontinuation) has limited its use (100,101).

Lithium. Lithium is a mood stabilizer and augmentation agent used to treat bipolar disorder and major depressive disorder (MDD). Long-term lithium (>18 mo) reduces suicidality (102). A meta-analysis associated lithium with reduced suicide risk versus placebo and was generally better than other pharmacotherapies, although statistically superior only to carbamazepine (103). Partial randomized controlled trial (RCT) data suggest that lithium does not reduce deliberate self-harm in depression (104) or attempts during a 1-year controlled trial (105). A cohort study of patients with bipolar disorder found that lithium and valproic acid were the only specific agents associated with reduced suicide; lithium's lower mortality risk led to its recommendation for patients with bipolar disorder at risk for suicide (106). Lithium concentrations in drinking water have also been linked to reduced suicide rates and psychiatric hospital admissions (107). Lithium's larger antisuicidal than mood episode effect in a meta-analysis (103) suggests that independent, unidentified mechanisms could be at play. fMRI in healthy subjects showed that lithium modulated striatal reward anticipation and prediction error coding (108). However, lithium's inconsistent benefits across diagnoses and side effects (e.g., tremor, dizziness, sedation) limit its role as a suicide treatment.

Rapid Nonspecific Interventions

Electroconvulsive Therapy. Electroconvulsive therapy (ECT) has been used for decades for the rapid relief of ideation in individuals with refractory symptoms of depression, mania, and psychosis (109). ECT is an inpatient procedure administered under anesthesia, involving the application of electrical current to the scalp in a dose sufficient to induce a generalized tonic-clonic seizure. Two studies of depression, one using bilateral ECT and the other right unilateral, found that it reduced ideation (110,111), with effects persisting up to 12 weeks after completion. These clinical studies cannot address neural mechanisms of suicidality reductions, but they likely involve networks implicated in ECT response [e.g., visual, limbic, default networks (112)], also implicated in the broader neurobiology reviewed above.

Ketamine and Esketamine. Ketamine (delivered intravenously) and esketamine (delivered as a nasal spray) are emerging rapid pharmacotherapies acting primarily as NMDA receptor antagonists. Both are fast-acting antidepressants for

treatment-resistant symptoms (113,114) and promising antisuicidal treatments (115). RCTs in patients with depression at imminent risk have demonstrated efficacy for reducing ideation within 24 hours of drug initiation [i.e., ketamine vs. midazolam in bipolar disorder with ideation (116), ketamine vs. midazolam for MDD with ideation (117), adjunctive esketamine vs. placebo for MDD with ideation (118,119)]. Small sample sizes, sample heterogeneity, and inadequate control for nonspecific effects [e.g., effect sizes for midazolam- vs. saline-controlled studies (120)] contribute to inconsistencies across trials [e.g., (119,121)], but aggregated evidence was sufficiently compelling for the Food and Drug Administration's approval of esketamine for MDD with acute STBs. Ketamine/esketamine's acute side effects, including dizziness, sedation, nausea, and dissociation, have posed challenges to blinding in trials; side effects and the need for intensive vital signs monitoring limit broad applicability for treating STBs (122–124). Connectome fingerprinting following ketamine administration found evidence of weakening functional connectivity within the control network but enhanced connectivity to external networks (125).

Longer-term Circuit-Specific Interventions

Psychotherapies. There is a wide body of literature that describes neurobiological changes associated with psychotherapy [e.g., reviewed in (126)]. Different psychotherapy paradigms target—and modify—brain regions and circuits involved in impulse control, cognitive reappraisal, and emotion regulation. Co-occurring pharmacological treatment may augment these neurobiological changes. There remains a paucity of neuroimaging studies providing insight into mechanisms underlying psychotherapy's antisuicidal effects.

Psychotherapies: Cognitive Behavioral Therapy. Cognitive behavioral therapy (CBT) for suicide has reduced suicide attempts (127). In brief CBT for suicide (BCBT), a time-limited version of CBT, patients complete training in three control-dependent skills—cognitive reappraisal, problem solving, and emotional regulation—and develop and rehearse a relapse prevention plan. RCTs in patients with a wide range of psychiatric diagnoses found that those receiving CBT/BCBT were 50% to 60% less likely to attempt suicide and more likely to remain in treatment (128); however, there is still room for improvement.

Psychotherapies: Dialectical Behavior Therapy. Dialectical behavior therapy was initially designed to treat patients with suicidal behavior and BPD and has demonstrated efficacy for reducing attempt (129). Patients focus on developing skills in mindfulness (including cognitive reappraisal), distress tolerance, emotion regulation, and interpersonal effectiveness, with STBs targeted in an individualized hierarchy (130). RCTs indicate that patients receiving dialectical behavior therapy are less likely to engage in self-directed violence, are more likely to remain in therapy, and have fewer hospitalizations versus treatment as usual (129) or psychoanalysis (130). Dialectical behavior therapy skills depend on cognitive control, but with greater emphasis on emotional regulation. Despite its effectiveness, its time- and resource-intensive nature hinders wider implementation.

Transcranial Magnetic Stimulation. Recently, transcranial magnetic stimulation (TMS), a noninvasive form of therapeutic brain stimulation, has received attention as an antisuicidal treatment. TMS uses rapidly fluctuating magnetic fields to induce electrical activity in targeted brain regions (131). When efficacious, several weeks of daily TMS leads to downstream changes in neural networks (132). TMS is cleared for pharmacoresistant MDD and has demonstrated efficacy in other disorders associated with suicide risk.

In suicide research, stimulation is commonly applied over the DLPFC to target cognitive and affective control regions (133). Clinical trials of TMS for suicide have been conducted in more than 500 patients, and TMS consistently reduces depressive symptoms [reviewed in (134)]. Reductions in suicidality were promising, albeit less robust. Studies' limitations included unblinded designs, modest samples, reliance on single-item measures, and frequent exclusion of higher-risk participants. Newer forms of stimulation such as theta burst TMS demonstrated fewer suicide attempts and hospitalizations 1 year following stimulation (135).

Rapid Circuit-Specific Interventions

Multiple daily applications (accelerated TMS) have reported rapid reductions in suicidal thoughts (136), although RCT findings were less robust (137). Most recently, an unblinded study demonstrated that accelerated theta burst TMS had a rapid antisuicidal effect (138). Questions remain, such as whether it is best used as a rapid stabilizing agent or longer-term intervention (or both), but TMS shows promise as a rapid circuit-based suicide intervention.

OPPORTUNITIES IN SUICIDE RESEARCH

Recent methodological advances permit increasingly novel approaches to suicide research. Here, we highlight advances in temporal sampling, transdiagnostic analyses, biological components of suicide reduction, and individualized treatment. Broader integration of the following approaches with neuroimaging may advance the development of more efficacious intervention and prevention strategies.

Intensive Proximal Risk Sampling

Proximal predictors influencing risk in the weeks, days, and hours before suicide are not well understood. Longitudinal methodologies (139) involving intensive daily samplings such as ecological momentary assessment (EMA) can address this gap. EMA enables the naturalistic investigation of risk processes at high temporal resolutions. This capacity permits the characterization of suicidal phenotypes (18) distinguished by temporal variability [e.g., ideation chronicity vs. lability, cyclicity (140)]. Moreover, its naturalistic administration facilitates examination of the complex interplay between proximal factors as suicidality evolves (92,141). Integrating EMA with neuroimaging research is one strategy for overcoming MRI constraints precluding examination of temporality. Mapping EMA-based suicide typologies to circuits will ground temporal phenotypes in neurobiological circuits.

Digital phenotyping [e.g., smartphones, wearables; reviewed in (142,143)] permits intensive sampling of potential objective suicide risk indicators (e.g., sleep, speech). Mapping

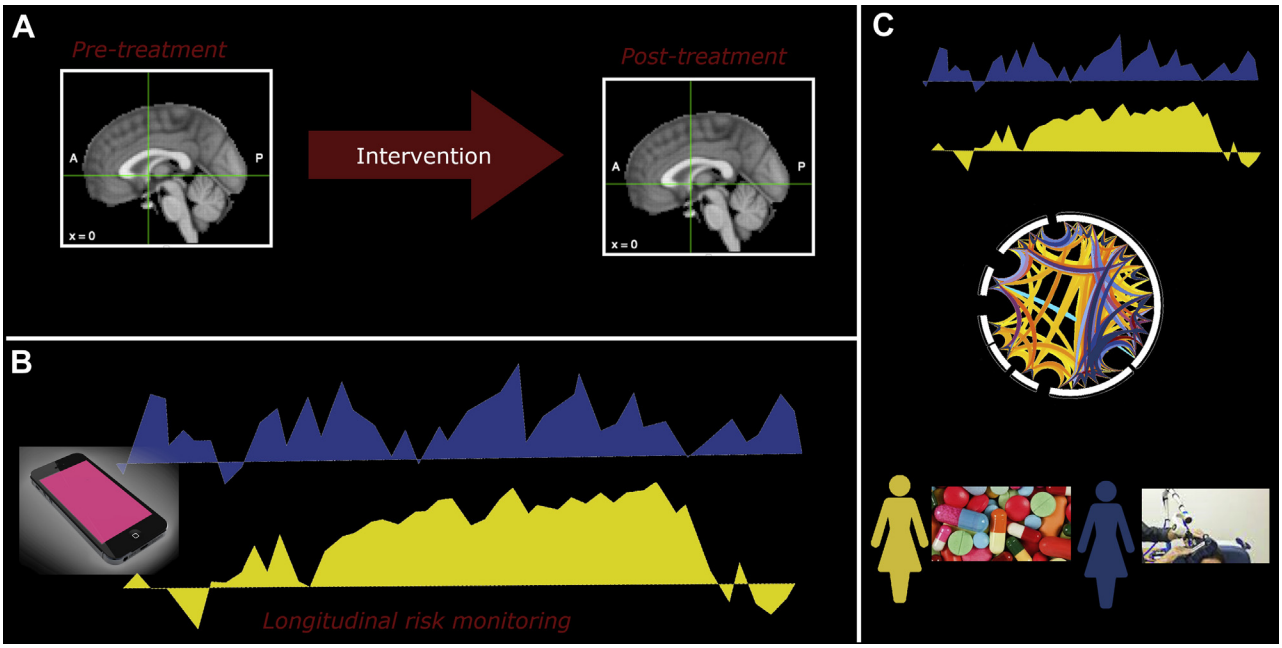

Figure 2. Incorporating longitudinal methods into suicide intervention research. Integration of methods providing insight into biological mechanisms and temporality is critical for the advancement of neuroscience-based interventions for suicide. **(A)** One approach is to measure participants' brain activity via neuroimaging or electrophysiological methods before and following the administration of intervention procedures **(B)** while concurrently and/or subsequently monitoring risk with devices providing real-time information (e.g., actigraphy, smartphone applications). More intensive designs may include collection of serial mechanistic data from multiple time points across the course of the intervention and follow-up period, especially during high-risk periods such as the 2 weeks immediately after an inpatient hospitalization. **(C)** Mapping temporal phenotypes derived from digital phenotyping to neuroimaging is one approach toward bridging magnetic resonance imaging's temporal limitations. Matching treatment outcomes to digital phenotypes and biotypes can advance efforts toward personalized medicine approaches to suicide prevention and intervention; for example, phenotypic data could inform the selection of treatments or implementation parameters (e.g., functional magnetic resonance imaging to guide which circuits are targeted via transcranial magnetic stimulation). A, anterior; P, posterior.

finer-grained sensor data to EMA-derived phenotypes is an avenue toward personalized, real-time intervention. Ecological momentary interventions or just-in-time adaptive interventions use short-term indices of risk to trigger the delivery of suicide interventions, creating opportunities for intervention outside of provider interactions, when attempts are most likely to occur. Integrating with neuroimaging would allow even greater personalization, e.g., individualized targeting and neuromodulation of valence circuits triggered by reduction in the nature or frequency of patients' typical social media use.

Understanding Transdiagnostic Risk

Suicide is a transdiagnostic behavior, often occurring in individuals with complex symptomatology and at higher rates in patients with symptom clusters crossing categorical diagnosis [e.g., mixed depressive episodes (144)]. Prior work heavily focuses on diagnostic samples with high rates of ideation [e.g., depression (134)], limiting generalizability to varied symptom profiles (e.g., depression comorbid with trauma, BPD). Deploying the integrated strategies discussed above (see Intensive Proximal Risk Sampling) across a broader range of symptom profiles will enable transdiagnostic characterization of suicide risk. This inclusive approach paves the way for the definition of phenotypes emerging from transdiagnostic symptom clusters and the characterization of related circuit-level vulnerabilities. We note, however, that adopting this enriched modeling approach will necessitate appropriate penalization for model complexity to ensure broad generalizability.

Predictors and Mechanisms of Phenotypic Response. A significant portion of patients respond inadequately to treatment, experiencing continued high ideation and subsequent reattempts (145). Interdisciplinary treatment designs providing mechanistic data are critical for addressing this problem. Integrating measures of distal risk processes (e.g., neuroimaging, electrophysiology) and variation in risk processes over time (e.g., EMA, sensors) with intervention studies creates an opportunity to define predictors of treatment responsiveness associated with distinct phenotypes. These designs will be critical for improving outcomes via personalized prescription and target engagement guided by individuals' EMA-derived risk phenotype.

Interdisciplinary Personalized Interventions

Developing personalized interventions is essential for improving treatment outcomes. Combining interdisciplinary treatments targeting different aspects of suicidal risk (e.g., augmenting CBT with circuit neuromodulation, modifying dosage/delivery by real-time indicators) may improve intervention outcomes. Combining brain stimulation with

psychotherapy has been developed in other areas [e.g., (146,147)] and is under investigation for suicide (148). Optimizing implementation by phenotype (e.g., fMRI-guided circuit targeting for neurostimulation) (Figure 2) is another path forward. A preliminarily exemplar from depression (149) demonstrates localization of temporal risk patterns to circuits, although not to an intervention.

CONCLUSIONS

Quelling the rise in suicide requires the refinement of existing treatments and the development of novel intervention strategies that are optimized for its complex, multidetermined nature. Integrating approaches capturing critical temporal elements of suicide risk with circuit-focused methodologies is essential for progress. Mapping temporality to circuits can guide personalized treatment tailored to individual biological vulnerabilities and indicators of near-term risk.

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