Anhedonia and Suicide

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Abstract Suicide is a leading cause of death, and presently, there is no definitive clinical indicator of future suicide behaviors. Anhedonia, a transdiagnostic symptom reflecting diminished ability to experience pleasure, has recently emerged as a risk factor for suicidal thoughts and behaviors (STBs). This overview, therefore, has the

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following aims. First, prior research relating anhedonia to STBs will be reviewed, with a particular focus on clarifying whether anhedonia is more closely associated with suicidal thoughts versus behaviors. Second, the National Institute of Mental Health's Research Domain Criteria Positive Valence Systems provide a useful heuristic to probe anhedonia across different units of analysis, including clinical symptoms, behaviors, neural mechanisms, and molecular targets. Accordingly, anhedonia-related constructs linked to STBs will be detailed as well as promising next steps for future research. Third, although anhedonia is not directly addressed in leading suicide theories, this review will provide potential inroads to explore anhedonia within diathesis-stress and interpersonal suicide frameworks. Last, novel approaches to treat anhedonia as a means of reducing STBs will be examined.

Keywords Anhedonia · Positive Valence Systems · Reward processing · Suicidal behavior · Suicidal ideation

1 Introduction

Suicide is a major public health concern and a leading cause of death (CDC 2019). Despite considerable global efforts to enhance access to prevention and intervention services (Mann et al. 2021), each year approximately 700,000 people die by suicide worldwide (WHO 2019). Given the clinical imperative to stem the rising prevalence of suicidal thoughts and behaviors (STBs), research has sought to clarify risk factors contributing to the emergence of suicidal thoughts as well as those that facilitate the transition from ideation to action. Although definitive clinical predictors of suicide remain unclear (Franklin et al. 2017), there is recent evidence supporting anhedonia – a transdiagnostic symptom reflecting diminished ability to experience pleasure – as a promising risk factor for STBs (Bonanni et al. 2019; Ducasse et al. 2018). Accordingly, the following aims will be addressed. *First*, we will summarize extant findings – with a particular focus on clarifying whether anhedonia is more closely associated with suicidal thoughts versus behaviors (e.g., aborted, interrupted, and actual attempts). *Second*, several anhedonia-related constructs within the National Institute of Mental Health's Research Domain Criteria (RDoC) Positive Valence Systems have been linked to STBs, and thus, we will detail promising findings as well as highlight potential inroads for future research. *Third*, we will outline the role of anhedonia within leading suicide theories, with a particular focus on diathesis-stress and interpersonal frameworks. *Last*, we will explore how leading treatment approaches target anhedonia in the service of reducing suicide risk.

2 Anhedonia as a Risk Factor for STBs

At present, research implicating anhedonia as a precursor to STBs is inconclusive. Core questions about the association between anhedonia and STBs remain regarding: (1) the specificity to suicidal thoughts versus behaviors, (2) developmental differences, and (3) the differential impact of state versus trait anhedonia. Within this body of research, there is substantial diagnostic heterogeneity (e.g., mood disorders, schizophrenia), which has important clinical implications, and critically, few studies focus on completed suicide. Recent meta-analyses have focused specifically on establishing the anhedonia-suicidal ideation relationship (e.g., (Ducasse et al. 2018)). Thus, this review emphasizes studies examining associations between anhedonia and suicide behavior, as nonfatal suicide attempts are markedly more related to future suicide deaths relative to suicide ideation (Nock et al. 2008).

2.1 Anhedonia and Suicidal Behaviors

A substantive body of research has found that anhedonia severity associates with suicidal ideation, above and beyond depression symptom severity (Ducasse et al. 2018). Less research has definitively linked anhedonia to suicide death or attempts. To the best of our knowledge, only two studies have demonstrated a link between anhedonia and suicide death. In a large sample of psychiatric patients, primarily diagnosed with mood disorders, anhedonia was predictive of suicide death within a year of initial assessment (Fawcett et al. 1990). Similarly, among patients diagnosed with schizophrenia, the presence of anhedonia (based on the Structured Clinical Interview for the DSM) was more common among those who died by suicide compared to those dying of other causes (Kelly et al. 2004).

Generally, research testing the impact of anhedonia on suicide attempts has used either a cross-sectional, retrospective case-control design – that is, examining whether anhedonia is more severe among attempters versus ideators – or has prospectively tested whether anhedonia severity contributed to an attempt. Results from case-control studies among adult patients also are equivocal. There is evidence that among patients diagnosed with major depressive disorder, but not schizophrenia, social anhedonia was more common among attempters relative to non-attempters (Sagud et al. 2021), suggesting that specific aspects of anhedonia (e.g., social versus physical) may confer increased vulnerability to suicidal behaviors. By contrast, Yaseen and Colleagues (2016) found no differences in anhedonia among inpatients, primarily diagnosed with mood disorders, with and without a suicide attempt history (Yaseen et al. 2016).

Longitudinal research is equivalently mixed, with findings generally relating anhedonia severity to suicidal behaviors (but see (Loas 2007)). For example, secondary data analyses of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial explored dynamic changes in anhedonia within patients

who attempted or died by suicide. In the 6-month follow-up, there was increased acuity of suicidal ideation and loss of interest prior to the occurrence of suicidal behaviors (Ballard et al. 2016). In a large sample of psychiatric outpatients diagnosed with mood disorders, baseline anhedonia severity was related to attempts over the subsequent 3 years, however, this effect was non-significant when accounting for sociodemographic and other clinical factors (Ducasse et al. 2021). There also is partial support for a model in which baseline anhedonia severity mediates the relationship between depression symptoms and STBs. However, this study did not differentiate between suicidal thoughts versus behaviors, and based on the design (Amazon Mechanical Turk) and self-report measure used (i.e., Suicide Behaviors Questionnaire-Revised (Osman et al. 2001)), findings most likely reflect a global measure of current and past ideation as opposed to behaviors (Zielinski et al. 2017). By contrast, among psychiatric outpatients anhedonia severity was cross-sectionally related to ideation severity but unrelated to attempt history, and at the 1-month follow-up assessment, anhedonia was not predictive of suicide attempts (Hawes et al. 2018). Collectively, although there is a consistent relationship between anhedonia and suicidal ideation (Bonanni et al. 2019; Ducasse et al. 2018; Loas 2014), cross-sectional and longitudinal research has yet to definitively link anhedonia severity to suicide behaviors. Studies also varied widely in their sample characteristics, measurement of suicide behaviors, and longitudinal time scale, all of which may affect this association. Thus, further research is needed to better understand whether there are specific types of anhedonia that may be more predictive of suicidal behaviors, particularly as this may differ as a function of clinical diagnosis.

2.2 Youth, Anhedonia, and STBs

Compared with research in adults, less research has investigated associations between anhedonia and STBs in youth. Earlier work in children reporting non-suicidal self-injury indicated that anhedonia severity differentiated patients with and without a suicide attempt history (Nock and Kazdin 2002). These findings were in line with our own work among psychiatrically hospitalized adolescents showing that anhedonia severity distinguished adolescents with a suicide attempt history from depressed adolescents with suicidal ideation – an effect that persisted when accounting for current depression, anxiety, and suicidal ideation severity (Auerbach et al. 2015). Interestingly, among psychiatric adolescent inpatients, lower positive affect scores – a proxy for anhedonia – predicted the occurrence of suicidal events (i.e., suicide attempt, psychiatric hospitalization, emergency department visit) within 6 months post-discharge (Yen et al. 2013). Though promising, these studies included relatively modest sample sizes (Stewart et al. 2019a), and cross-sectional findings did not replicate in larger samples (Stewart et al. 2017a, b, 2019b), underscoring the urgent need for more research within younger patient populations.

2.3 State Versus Trait Anhedonia and STBs

It is believed that anhedonia includes both state and trait characteristics. State-based anhedonia is more variable and often fluctuates with the intensity of a depressive state (Treadway and Zald 2011). By contrast, trait-based anhedonia is believed to be stable, perhaps reflecting a personality predisposition (Conway et al. 2019). Accordingly, suicide research has begun exploring the differential impact of state versus trait anhedonia on the emergence of STBs. Whereas acute increases in anhedonia severity (state) relate to increases in suicidal ideation, trait measures have demonstrated less consistent results as well as difficult to interpret effects whereby lower trait anhedonia related to greater ideation (e.g., (Yang et al. 2020a, b; Loas et al. 2019; Winer et al. 2016)).

Probing state versus trait anhedonia reflects a promising growth area for suicide research as this has been understudied in the context of suicidal behaviors. Prior research has primarily investigated this association in non-clinical settings using methodological approaches that may be ill-suited to capture dynamic changes in anhedonia (i.e., state-based questionnaires relying on retrospective recall over extended periods). Advances in smartphone technology, however, allow assessment of changes in affect (e.g., ecological momentary assessment) and behavior (e.g., accelerometer, geolocation data) that may reflect changes in *real-time* anhedonia acuity (Allen et al. 2019). These approaches are sensitive to subtle differences in psychomotor and behavioral disturbances that distinguish healthy from remitted depressed individuals (e.g., Auerbach et al. 2022a), and thus, hold enormous promise as a means of detecting clinically significant changes in state anhedonia that may precede suicide, which, ultimately, could facilitate the development of just-in-time interventions.

3 RDoC Positive Valence System (PVS) and Suicide

The NIMH RDoC initiative provides a framework for conceptualizing transdiagnostic neurocognitive mechanisms, across units of analysis (e.g., genes, molecules, brain systems, behavior), that can be used to characterize psychiatric disorders (Cuthbert 2014; Insel et al. 2010). This transdiagnostic approach is well suited for studying STBs, which occur across a range of disorders (Glenn et al. 2017, 2018; Stewart et al. 2019a). Further, rather than treating anhedonia as a monolithic entity (Treadway and Zald 2011; Der-Avakian and Markou 2012; Rizvi et al. 2016), RDoC *Positive Valence Systems* (PVS) (sub)constructs can be used to probe a wide range of dimensions and features that map onto anhedonia (e.g., deficits in reward anticipation [wanting] versus initial response to reward [liking] versus discounting of effort required to achieve reward). This RDoC approach, therefore, allows processes underlying anhedonia to be operationalized more concretely. For example, at the neural level, anhedonia is often characterized by alterations within reward

circuitry involving fronto-striatal regions (e.g., (Der-Avakian and Markou 2012; Auerbach et al. 2017, 2022b; Gabbay et al. 2013; Schlaepfer et al. 2008)), and prior research also has implicated structural and functional alterations in reward-related circuitry in relation to STBs (Schmaal et al. 2020). Neuroimaging studies of STBs in youth are limited (Auerbach et al. 2021), and the few studies that have examined the neurocognitive underpinnings of STBs, particularly in youth, have not been well integrated into the RDoC framework (Glenn et al. 2017; Stewart et al. 2019a). Consequently, although research exploring PVS-STB relationships is a promising area of research, it currently warrants additional attention.

3.1 PVS: Reward Responsiveness

The RDoC Reward Responsiveness construct consists of three proposed sub-constructs: initial response to reward, reward anticipation, and reward satiation. These characterize different phases of hedonic responding over time from the representation of potential future rewards (wanting), current experience of reward (liking), and updating the incentive value of a past reward as it is consumed or experienced. To the best of our knowledge, studies have not examined differences in reward satiation in relation to STBs.

Simple monetary guessing tasks (Levinson et al. 2017; Helfinstein et al. 2013; Luking et al. 2014; Delgado et al. 2000) are often used to study initial response to reward. Event-related potential (ERP) studies tend to probe the reward positivity (RewP) reflecting activity comparing reward versus loss feedback (or alternatively the feedback negativity (FN) indexing activity stemming from loss versus reward feedback), which has been linked to ventral striatal activation in the context of functional magnetic resonance imaging (fMRI) (Carlson et al. 2011). Of note, children of parents with a lifetime suicide attempt history exhibit a blunted ERP (smaller RewP/larger FN) in response to winning versus losing money, though this is potentially driven by loss trials (Tsypes et al. 2019). Other work, however, has found no significant difference in adolescent girls' RewP based on maternal STB history but did find that a blunted RewP moderated the association between maternal STB history and girls' depression outcomes (Burani et al. 2021). Beyond family history, a blunted RewP has been noted among children with a history of recent suicidal ideation, compared to those with no recent ideation (Tsypes et al. 2017). More broadly, the association between a blunted RewP and suicide ideation has been confirmed in meta-analytic work, but there does not seem to be a clear signal that relates to individuals reporting a history of suicide attempts (Gallyer et al. 2021). One neuroimaging study found higher activation in dorsal prefrontal cortex (PFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) to wins versus losses between depressed adults with an attempt history compared to those with a history of depression but no attempts ((Olie et al. 2015); c.f., (Jollant et al. 2010)). In another gambling task, depressed adults with an attempt history exhibited greater insula deactivation to subjective loss compared to depressed adults with no attempt

history and psychiatrically healthy adults (Baek et al. 2017), but, perhaps surprisingly, no clear differences emerged within striatal regions. Overall, findings on reward responsivity are somewhat mixed but suggest potential associations with ideation rather than attempts. Intriguingly, these findings tend to be driven by loss sensitivity.

Experimental designs such as the Monetary Incentive Delay Task (Knutson et al. 2000) allow for separation of the neural processes underlying reward anticipation from receipt of reward. In an ERP study, whereas adults with no suicide attempt history exhibited a stronger P3 ERP to incentive versus neutral cues – thought to reflect attentional allocation to reward-predicting stimuli – adults with an attempt history exhibited less differentiation of cue types (Tsypes et al. 2021). In a gambling task, depressed adults with an attempt history exhibited blunted subgenual ACC and amygdala response to potential gain compared to depressed adults with no attempt history and psychiatrically healthy adults (Baek et al. 2017). Neuroimaging research also suggests decreased activation to reward cues in the putamen, amygdala, and OFC among self-injuring adolescent girls (mix of non-suicidal self-injury and STBs), compared to girls with no history of self-injury (Sauder et al. 2016). Taken together, there seems to be preliminary evidence that individuals with a history of STBs are characterized by blunted response to reward-predicting cues; though this does not necessarily stem from differential activation in striatal regions.

3.2 PVS: Reward Learning

The RDoC Reward Learning construct consists of three proposed sub-constructs: probabilistic and reinforcement learning, reward prediction error, and habit learning. These represent different processes by which one learns about stimulus-reward contingencies and updates one's internal schematic based on differences between expected and actual reward. These vary in their cognitive intensiveness, e.g., habits can result from reward learning, require little effort, but often do not update to changing contingencies. To the best of our knowledge, studies have not explicitly examined reward prediction error or habit learning in relation to STBs.

Probabilistic and reinforcement learning tasks have examined how individuals learn uncertain reward/punishment conditions and adapt to changing contingencies. Computational models can be used to ascertain latent parameters of behavior and estimate expected value of choices on a trial-by-trial basis. Adults, ages 60 years and older, with an attempt history showed impaired probabilistic reversal learning compared to depressed and nondepressed participants. Specifically, computational modeling suggested that adults with an attempt history discounted information about previous reward outcomes in favor of basing choice on prior trial outcomes (Dombrovski et al. 2010). In a probabilistic reversal learning study on late-life depression, participants with an attempt history exhibited weaker ventromedial PFC response to high expected reward and their pregenual cingulate responses tracked reinforcement history less reliably compared to depressed and nondepressed

participants with no attempt history (Dombrovski et al. 2013). Meta-analyses suggest worse performance on the Iowa Gambling Task among individuals with an attempt history compared to those without any attempt history (Perrain et al. 2021; Richard-Devantoy et al. 2014; Sastre-Buades et al. 2021). Though work is limited and largely in late-life adults, findings suggest potential deficits in reward learning in relation to suicide attempts.

3.3 PVS: Reward Valuation

The RDoC Reward Valuation construct consists of three proposed sub-constructs: delay discounting, probability discounting, and effort discounting. These represent processes by which the value of a reward is computed as a function of its magnitude versus the time, chance/risk, or effort required to obtain it. Anhedonic deficits may stem from alterations in these valuation processes, e.g., an individual may devalue the potential enjoyment of an activity because of the perceived effort it requires.

Delay discounting paradigms present participants with choices between sooner but smaller rewards versus later but larger rewards. Though delay discounting also has been conceptualized within an impulsivity framework or in relation to future orientation, RDoC places this process within a reward valuation context, i.e., how one weights/discounts the value of a potential reward based on the time required to obtain it. Interestingly, meta-analytic work suggests that steeper delay discounting (preference for sooner, smaller rewards) is seen across numerous disorders, including mood disorders, schizophrenia, and eating disorders (Amlung et al. 2019). This is similarly observed among individuals with self-harming or suicidal behaviors (McHugh et al. 2019; Bryan and Bryan 2021; Liu et al. 2012; Dougherty et al. 2009; Mathias et al. 2011). This could be accounted for by associations between stress and delay discounting (Fields et al. 2014, 2015) or potentially, thoughts of death and mortality salience, which can shift delay discounting to favor sooner, smaller rewards (Kelley and Schmeichel 2015). Work in older adults also suggests differences in delay discounting as a function of attempt lethality and planning (Dombrovski et al. 2011) and related delay discounting to putamen structure (Dombrovski et al. 2012). Suicide attempts also associated with deactivation of the lateral PFC in response to value difference favoring the immediate option (Vanyukov et al. 2016). Overall, despite a common focus on impulsivity, delay discounting differences in suicidal behavior may be more related to inconsistent reward valuation rather than a true preference for immediate reward (Tsypes et al. 2022).

Probability discounting paradigms present participants with choices between surer but smaller rewards versus riskier but larger rewards. Though preference for surer, sooner rewards have been observed in a number of psychiatric conditions (Dai et al. 2016; Hart et al. 2019), and a number of studies have examined decision making under probabilistic conditions (reward learning), to the best of our knowledge, only one study has examined probability discounting in relation to suicide.

Compared to adults with depression but no attempt history and psychiatrically healthy adults, adults with an attempt history exhibited greater discounting under conditions of potential monetary loss but not monetary gain, i.e., more often chose definite, but smaller loss over the probability of a larger loss (Baek et al. 2017). Similarly, there is some work suggesting greater risk aversion among depressed adults with an attempt history compared to depressed adults with no attempt history and psychiatrically healthy controls, in related paradigms (e.g., Balloon Analogue Risk Task) with less explicit probability frameworks (Ji et al. 2021). Though, other work does find lower loss aversion among adolescents with an attempt history compared to those with no attempt history (Hadlaczky et al. 2018). In other paradigms, adults with an attempt history also exhibited decreased frontal response to risky versus safe choices (Olie et al. 2015; Jollant et al. 2010). Taken together, although probability discounting has not been seen with monetary gains, there is some evidence for altered discounting with losses among individuals with an attempt history.

Effort discounting paradigms present participants with choices between smaller versus larger rewards that require less or more physical effort, respectively, e.g., number of button presses or intensity of grip strength. Although effort discounting deficits have been examined in relation to anhedonia in depression (Treadway 2016; Treadway et al. 2009, 2012a; Treadway and Zald 2013) and schizophrenia (Reddy et al. 2015; Horan et al. 2015; Green et al. 2015; Gold et al. 2013), research is very limited in STBs. In our prior work, we found that depressed attempters were less willing to choose the difficult option for reward than ideators, but only when rewards were uncertain. Further, while ideators were significantly more likely to choose the difficult option on trials proceeding winning money, attempters did not show this effect (Auerbach et al. 2015).

3.4 PVS: Molecular Pathways

PVS functioning and anhedonic deficits implicate a number of neurotransmitters and fronto-striato-limbic brain systems. Herein, we will expand on dopaminergic systems in relation to the PVS, particularly as it relates to a potential pathway to STBs; in spite of such focus, it is important to note the growing evidence for the involvement of other systems, including glutamate (Der-Avakian and Markou 2012), in PVS-related circuitry.

Initial theories suggested that dopamine is central to the experience of pleasure, but our understanding has since been refined (Wise 2008). Pleasure or "liking" is not fully contingent on dopamine, as alterations in dopaminergic systems are intimately involved in reward anticipation ("wanting"), modulation of striatal reward response, motivation, stimulus-reward pairing, and reward prediction errors (Wise 2008; Berridge and Kringelbach 2015; Bressan and Crippa 2005; Glimcher 2011). Dopamine is primarily synthesized by midbrain neurons, specifically the ventral tegmental area and substantia nigra pars compacta. Tegmental neurons project

widely to the PFC and critically to the nucleus accumbens in the ventral striatum (Glimcher 2011), while substantia nigra dopamine neurons project mainly to the dorsal striatum (Ilango et al. 2014). The majority of dopamine neurons respond to positive rewards (Schultz 2010), including carrying tonic signal encoding average reward rate during task, via the accumbens (Niv et al. 2007). Phasic dopamine responses occur on top of tonic dopamine levels, which are modulated by cortico-striatal control (Grace 1991), and play a key role in building associations between predictive stimuli and rewards (Wise 2008). Particularly, dopamine neurons encode reward prediction error signals that are used to guide learning (Glimcher 2011).

In human research, dopaminergic systems have been linked to RDoC PVS function. Striatal regions, receiving dopaminergic innervation, are centrally implicated in reward responsiveness in numerous human neuroimaging paradigms, particularly nucleus accumbens response to rewards relative to loss (Delgado et al. 2000; May et al. 2004). A meta-analysis of fMRI studies has shown robust blunting of reward-related responses in youth and adult depression that was localized to the striatum (Keren et al. 2018). Further, midbrain dopamine transporter availability correlates with ventral striatal fMRI activation during initial responsiveness to reward (Dubol et al. 2018). Midbrain neural activation has been shown to track with reward prediction errors calculated through temporal difference models (Klein-Flugge et al. 2011). Further, increased dopamine enhances willingness to exert physical effort to obtain reward, mediated by fronto-striatal mechanisms (Chong et al. 2015; Treadway et al. 2012b; Wardle et al. 2011). Behavioral and neuroimaging work also suggests an adolescent peak in reward responsivity, increasing over childhood into the adolescence (Galvan 2010; Luking et al. 2016, 2019), which may contribute to adolescent increases in depression and STBs.

A variety of studies have observed dopaminergic deficits in adult STBs, though work in youth is notably limited. For example, adults with an attempt history exhibited reduced peripheral metabolites of dopamine compared to those with no attempt history (Lester 1995; Roy et al. 1986, 1989; Träskman et al. 1981), which also predicted re-attempt within 5 years (Roy et al. 1989). Additionally, there is post-mortem evidence among people who died by suicide of reduced striatal dopamine turnover (Bowden et al. 1997a) and striatal receptor differences (Bowden et al. 1997b; Fitzgerald et al. 2017). Relatedly, STB increases can be noted with dopamine agonists and dopamine disruption in Parkinson's (Flament et al. 2011; Struhal et al. 2012). Adults with major depression with elevated suicide risk and who died by suicide showed lower striatal dopamine transporter availability via single photon emission computed tomography (Pettorruso et al. 2020; Pizzagalli et al. 2019). Finally, STBs have been linked to polymorphisms in dopamine pathway genes, including those involved in dopamine synthesis, degradation, and receptors (Brezo et al. 2008; Kia-Keating et al. 2007; Suda et al. 2009). Together, this provides evidence for dopaminergic deficits in suicide risk in adults, which underscores the importance of probing dopamine deficits in vivo in youth using less invasive methods.

4 Contextualizing Anhedonia in Leading Suicide Theories

Current suicide theories have not directly accounted for anhedonia as a risk factor; however, as anhedonia is a transdiagnostic symptom that cuts across a wide range of psychiatric disorders and profoundly shapes social behavior, it may play a prominent role in both the diathesis-stress (Mann et al. 1999) and interpersonal frameworks (e.g., Interpersonal Theory of Suicide [IPTS], Three Step Theory [3ST] (Joiner 2005; Klonsky and May 2015)). Further, preliminary evidence suggests that including anhedonia as a construct within leading theories of suicide may enhance our understanding of STBs (Yang et al. 2020a, 2021).

4.1 Anhedonia and Diathesis-Stress Model

Within the diathesis-stress model of suicide (van Heeringen and Mann 2014), the diathesis, generally believed to be a psychiatric disorder, is necessary but not sufficient for a suicide behavior to occur. Though mood disorders, substance use, and schizophrenia are observed among the majority of people who attempt or die by suicide (Conner et al. 2019; Mullins et al. 2022), only 5–8% of those diagnosed with psychiatric disorders die by suicide (Nordentoft et al. 2011). The diathesis, however, heightens the likelihood that a stressful event, typically interpersonal in nature, triggers a suicidal behavior (van Heeringen 2012). Although the diathesis-stress framework emphasizes the importance of the disorder, each disorder is characterized by extraordinary heterogeneity in terms of the symptom constellation. That is, the symptoms one experiences both within and across disorders vary significantly from patient to patient. Yet, within each of these disorders, anhedonia is a prominent transdiagnostic symptom (Whitton et al. 2015), and for major depression alone, 37–70% of depressed cases exhibit clinically significant anhedonia (Pelizza and Ferrari 2009; Yorbik et al. 2004). Accordingly, anhedonia may be the key vulnerability factor within this diatheses-stress framework, rather than the presence of a disorder broadly, that potentiates risk for suicide following interpersonal stress exposure.

For example, it is well documented that chronic stress and early life adversity contribute to anhedonia (Pizzagalli 2014). When stress occurs, the hypothalamic-pituitary-adrenal axis secretes glucocorticoids (i.e., cortisol), negatively affecting reward-based dopaminergic pathways. Prolonged stress, which may be common among high-risk patients, further reduces dopamine neuron availability in the ventral tegmental area (Douma and de Kloet 2020; Sugama and Kakinuma 2016), and is believed to reduce motivation, impair incentive-based learning, and increase social withdrawal (Lloyd and Dayan 2016). As social withdrawal increases, associated reductions in social support may occur, which may increase sensitivity to future stress and enhance STB vulnerability. This is consistent with preliminary findings showing that the co-occurrence of blunted cortisol levels (in response to a social stress task) and peer stress exposure together increased risk for suicidal behaviors,

above and beyond depression symptom severity (Eisenlohr-Moul et al. 2018). A critical next step for future research will be to test whether anhedonia – inclusive of PVS phenotypic, biological, and molecular markers – increases vulnerability to suicide attempts or death following stress exposure, and further, whether models focusing on anhedonia specifically versus psychiatric disorders generally are more predictive.

4.2 Anhedonia and Interpersonal Theories of Suicide

Interpersonal theories of suicide have expanded upon the diathesis-stress model by highlighting factors central to the transition from suicidal ideation to behaviors. The IPTS (Joiner 2005; Van Orden et al. 2010) disaggregates specific interpersonal elements – namely, thwarted belongingness and perceived burdensomeness – that hasten the transition from ideation to action. Thwarted belongingness is comprised of loneliness (i.e., feeling disconnected from others) or a lack of interpersonal support (e.g., social withdrawal, family conflict), whereas perceived burdensomeness reflects feeling expendable (Van Orden et al. 2010). According to the IPTS, the highest risk for suicidal ideation occurs when thwarted belongingness and perceived burdensomeness are both elevated, and risk for suicidal behaviors increases when there also is the capability to act on suicidal thoughts. Similarly, the 3ST (Klonsky and May 2015) separates components contributing to suicidal ideation versus behaviors. Psychache (i.e., psychological pain (Shneidman 1993)) and hopelessness are believed to be critical potentiators for suicidal ideation, and acquired capability (e.g., enhanced tolerance of pain), for some, increases risk for suicidal behaviors. Although not specified in these models, anhedonia, and particularly social anhedonia, pervades across key elements within these interpersonal frameworks.

Social anhedonia impacts interpersonal relationships (Llerena et al. 2012) and thus, may heighten risk for STBs. Recent research has shown that a loss of interest in friends was the only type of anhedonia that related to suicidal ideation severity (Yang et al. 2021), and interestingly, anhedonia moderated the relationship between thwarted belongingness and suicide attempts (Loas et al. 2018). In the context of the IPTS model, it is possible that thwarted belongingness leads to social anhedonia (e.g., social withdrawal), thereby augmenting feelings of disconnectedness. A continued cycle of disconnectedness and social withdrawal – perhaps due to perceptions of being a burden – may increase hopelessness and intensify suicidal ideation. Another possibility more consistent with the 3ST is that hopelessness and psychache may override feelings of connectedness with others. This lack of connectedness over time may contribute to anhedonic behaviors and exacerbate the risk for severe suicidal ideation. Moreover, social anhedonia (e.g., not engaging with a relationship, apathy about social closeness) may increase vulnerability to experiencing interpersonal stress. Across frameworks, interpersonal stress typically precedes suicidal behaviors (Paul 2018; Stewart et al. 2019b). Consequently, for those who have acquired capability (e.g., desensitization to pain, prior attempts), social anhedonia may be a key contributor to suicidal behaviors.

5 Targeting Anhedonia in Treatments for Suicide

Currently, there are several treatments that reduce the intensity of STBs (e.g., cognitive behavior therapy, dialectical behavior therapy, antidepressant medication); however, these approaches were not specifically designed to target anhedonia. In our recent systematic review (Mann et al. 2021), we detailed preventative intervention strategies most effective for reducing suicidal behaviors. The majority of scalable approaches relate to enhanced screening, particularly within non-psychiatrist physician settings. Consistent with precision medicine initiatives (Manchia et al. 2020), increasingly there is a need to match discrete clinical presentations with optimal treatments. Given the equifinal nature of suicide – it is unlikely that a single approach will be effective for all patients, underscoring the importance of developing anti-anhedonic approaches in the service of reducing the needless loss of life.

For example, Positive Affect Treatment (PAT) targets constructs within the RDoC PVS ((Craske et al. 2016); for recent review, see Sandman and Craske 2022). This transdiagnostic treatment employs strategies focused on improving positive affect through normalizing reward anticipation, initial response to reward, and reward learning (Sandman and Craske 2022). In a recent randomized clinical trial, depressed and anxious adults were recruited from the community. Participants were randomized to either PAT or Negative Affect Treatment (NAT), which was a combination of strategies derived primarily from cognitive behavioral therapy approaches for depression and anxiety. At 6-months post-treatment, compared to NAT, participants receiving PAT reported greater positive affect as well as reductions in negative affect, depression, and anxiety. Interesting, there also was a reduction in suicidal ideation occurrence (derived through a 1-item self-report measure) (Craske et al. 2019). These findings are promising, and perhaps, provide a novel inroad to reduce STBs among high-risk, anhedonic patients.

Additionally, ketamine, an N-methyl-D-aspartate receptor antagonist and glutamatergic modulator, has received widespread attention given potential rapid anti-suicidal ideation effects. Indeed, across several investigations, infusion of a subanesthetic-dose ketamine rapidly reduced suicidal thoughts within hours (Diazgranados et al. 2010; Larkin and Beautrais 2011; Murrough et al. 2015; Zarate et al. 2012; Price et al. 2009; Grunebaum et al. 2018). Moreover, in a recent meta-analysis, ketamine reduced suicidal ideation for up to 1 week, which was independent of antidepressant effects (Wilkinson et al. 2018). Interestingly, within the context of treatment-refractory major depressive disorder, ketamine trials also showed reductions in anhedonia (DeWilde et al. 2015), which, in patients diagnosed with bipolar disorder, were independent of depressive symptoms (Lally et al. 2014). Accordingly, post-hoc analyses across several clinical trials tested whether ketamine's anti-suicidal effects corresponded to the attenuation of anhedonia. Among patients with treatment-resistant major depressive disorder or bipolar disorder, improved anhedonia related to reductions in suicidal ideation 1-day post-ketamine administration – an effect that was above and beyond changes in depression symptom severity (Ballard et al. 2017). Though the specific mechanism of

action for these effects remains unclear, there was some preliminary evidence that anti-anhedonic effects following ketamine administration may relate to decreased glucose metabolism in the OFC in patients diagnosed with major depressive disorder (Lally et al. 2015) or increased metabolism in the dorsal ACC among patients with bipolar disorder (Lally et al. 2014).

Addressing an alternative pathway, recent evidence has linked inflammation with the pathophysiology of anhedonia (Miller and Raison 2016), specifically showing that peripheral elevations in pro-inflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α], C-reactive protein) associated with anhedonia severity, neural circuitry alterations related to the PVS, and suicide attempts (Pedigo et al. 2016; Yin et al. 2019; Felger et al. 2016; Janelidze et al. 2011). Interestingly, among patients diagnosed with bipolar I or II disorder in a current depressive episode, compared with a saline placebo, the use of infliximab – an anti-TNF-α agent – resulted in reduced anhedonia severity. Moreover, reductions in anhedonia severity for those receiving infliximab corresponded to decreased plasma concentrations of TNF-α (Lee et al. 2020). These preliminary effects on anhedonia may be a key first step toward developing innovative treatments for STBs.

6 Conclusion

Suicide remains a major clinical problem and definitive risk markers are lacking. Anhedonia represents a promising transdiagnostic factor that likely contributes to suicidal thoughts and may facilitate the transition from ideation to action. Given the heterogeneity within anhedonia (Treadway and Zald 2011; Der-Avakian and Markou 2012; Rizvi et al. 2016) as well as the diversity of disorders through which suicidal behaviors often manifest, a more refined approach to concretely link anhedonia to suicide is needed, particularly when integrating within our current theoretical models of suicide risk. Use of real-time approaches (e.g., ecological momentary assessment, mobile sensor tracking), which have the potential to capture state-based changes in anhedonia, in combination with probing PVS brain-behavior markers that increase vulnerability to anhedonia and susceptibility to suicidal behaviors will serve to enrich our understanding of patients who may be most at risk for suicide death.

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