Toward a Better Understanding of the Mechanisms and Pathophysiology of Anhedonia: Are We Ready for Translation?

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Anhedonia—the loss of pleasure or lack of reactivity to pleasurable stimuli—remains a formidable treatment challenge across neuropsychiatric disorders. In major depressive disorder, anhedonia has been linked to poor disease course, worse response to psychological, pharmacological, and neurostimulation treatments, and increased suicide risk. Moreover, although some neural abnormalities linked to anhedonia normalize after successful treatment, several persist—for example, blunted activation of the ventral striatum to reward-related cues and reduced functional connectivity involving the ventral striatum. Critically, some of these abnormalities have also been identified in unaffected, never-depressed children of parents with major depressive disorder and have been found to prospectively predict the first onset of major depression. Thus, neural abnormalities linked to anhedonia may be promising targets for prevention. Despite increased appreciation of the clinical importance of anhedonia and its underlying neural mechanisms, important gaps remain. In this overview, the author first summarizes the extant knowledge about the pathophysiology of anhedonia, which may provide a road map toward novel treatment and prevention strategies, and then highlights several priorities to facilitate clinically meaningful breakthroughs. These include a need for 1) appropriately controlled clinical trials, especially those embracing an experimental therapeutics approach to probe target engagement; 2) novel preclinical models relevant to anhedonia, with stronger translational value; and 3) clinical scales that incorporate neuroscientific advances in our understanding of anhedonia. The author concludes by highlighting important future directions, emphasizing the need for an integrated, collaborative, cross-species, and multilevel approach to tackling anhedonic phenotypes.

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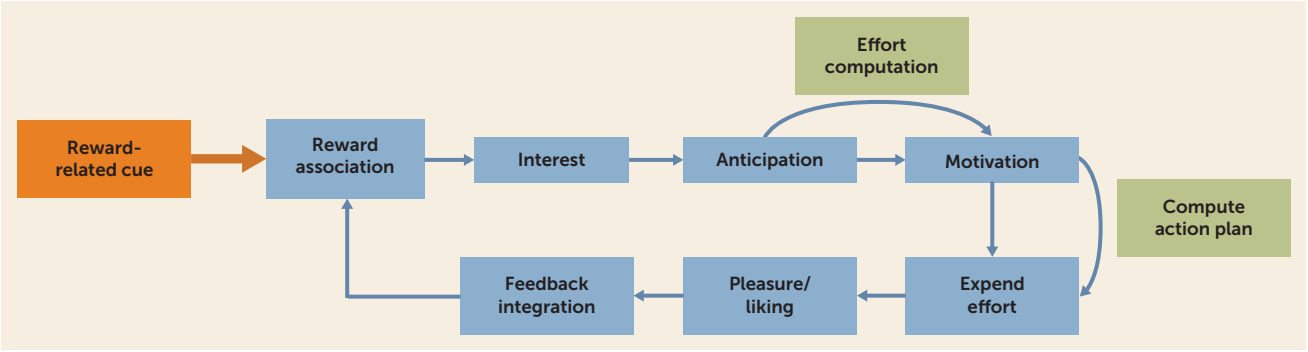
Victoria, a middle-aged professional and a dedicated long-distance runner since young adulthood, has totally lost interest in running. When asked by her partner about this change, she explains that what used to be her favorite hobby does not provide any joy and, in fact, has become a burden. Concerned by her mounting sleep difficulties (mostly early awakening) and weight loss, Victoria reconnects with the psychiatrist who successfully treated her first major depressive episode a decade ago. At the intake session, Victoria discloses multiple ongoing stressors, including her mother's progressing dementia, difficulties at work, and growing financial debt. Unfortunately, the selective serotonin reuptake inhibitor (SSRI) that had previously led to remission does not work this time, and augmentation strategies bring little benefit. After 9 months of unabating symptoms, Victoria's mental state worsens, and she is hospitalized after attempting suicide.

With the lifting of COVID-related restrictions, Antonne's parents had hoped that he would reconnect with his friends and be eager to return to in-person classes. Throughout the pandemic, Antonne, a timid 14-year-old boy, has been isolating himself from his friends and falling behind in school. A reserved child from early age who often needed encouragement to socialize, Antonne has spent an increasing amount of time playing video games in his room. Alarmed by his apathic demeanor and failing grades, his parents reach out to their pediatrician, who is unsure how best to help. When prompted about these developments, Antonne describes no motivation in initiating social activities. He acknowledges that he still enjoys spending time with one soccer teammate who is also a gamer, but most of the time he does not feel like doing anything.

Victoria and Antonne are fictional, but they illustrate a key point. Specifically, although they both exhibit anhedonic behaviors, those behaviors are different and are likely associated with distinct pathophysiologies (1–3), which may respond to different treatment strategies. Victoria exhibits anhedonia as it is classically understood: she shows loss of pleasure, which may have been triggered by chronic, uncontrollable stressors. Antonne, on the other hand, can experience pleasure but has difficulty initiating behavior in pursuit of some pleasurable experiences. Such difficulty

FIGURE 1. Subprocesses and subdomains implicated in reward processing[a]



[a] Specific anhedonic behaviors may be chiefly associated with disruption in one or several of these subdomains. (Modified after references 18, 19.)

emerged early in development, apparently without any objective external trigger.

As exemplified by these fictional cases, anhedonia is complex and its treatment remains a critical, unmet need. One of the two cardinal symptoms of major depressive disorder (MDD), anhedonia is reported by 37%–72% of individuals with MDD (4–6). In MDD, anhedonia has been linked to chronic disease course (7), worse outcome (8), poor response to pharmacological (9), psychological (10), and neurostimulation treatments (11), and increased risk of completed suicide (12). Critically, and highlighting the clinical relevance of anhedonia, individuals with MDD conceptualize remission as the restoration of positive affect, rather than the alleviation of depressive symptoms (13, 14). Why has the treatment of anhedonia remained such an unmet need, despite decades of preclinical and clinical research?

In this overview, I attempt to answer this question by identifying three areas that require attention. These areas pertain to the need for 1) appropriately controlled clinical trials, especially those embracing an experimental therapeutics approach to probe target engagement; 2) novel preclinical models relevant to anhedonia with stronger translational value; and 3) clinical scales that incorporate neuroscientific advances in our understanding of anhedonia. Before addressing these points, I summarize the extant knowledge about the pathophysiology of anhedonia, which may provide a road map toward filling these knowledge gaps.

THE NEUROBIOLOGY OF ANHEDONIA

Decades of neuroscientific research in experimental animals and humans has emphasized the role of the mesocorticolimbic circuit in different subdomains of reward processing, including *reward responsiveness* (e.g., reward anticipation, reward consumption), *reward learning* (e.g., positive reward prediction errors, which encode that an outcome is better than expected and is critically implicated in reward learning), and *reward valuation* (e.g., deciding to exert effort to pursue a possible reward) (15–17). These findings have contributed to an understanding of anhedonia as being composed of discrete subcomponents (2, 3, 18, 19) (Figure 1), which has also been captured by the Research Domain Criteria (RDoC) initiative from the National Institute of Mental Health (NIMH) (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/positive-valence-systems).

Originating from the ventral tegmental area (VTA), the dopaminergic (DA) mesocorticolimbic pathway projects to the ventral (nucleus accumbens [NAc]) and dorsal (caudate, putamen) striatum, and then runs to the orbitofrontal cortex (OFC), more dorsal aspects of the prefrontal cortex (PFC), and various subregions of the anterior cingulate cortex (ACC) (3, 20, 21). The main regions of the reward system (e.g., VTA → nucleus accumbens) are anatomically connected by the medial forebrain bundle (20, 22)—a white matter tract that has been strongly implicated in the experience of pleasure and motivated behavior (23, 24). Although a detailed summary of neurobiological mechanisms implicated in anhedonic behaviors is beyond the scope of this overview, abundant preclinical data highlight that anhedonic phenotypes in experimental animals, which are often induced by exposure to chronic, uncontrollable, and inescapable stressors, are linked to blunted DA transmission in the ventral striatum, with potentiated DA transmission in the VTA and medial PFC (or functionally homologous regions in rodents) (3). In particular, rodent models relevant to depression have linked anhedonia and reduced goal-directed behaviors to increased phasic bursting and excitability of VTA DA neurons, which characterized only vulnerable animals and could be reversed by chronic antidepressant treatment (21, 25–27). Similarly, optogenetic activation of VTA DA neurons during chronic social defeat stress exacerbated depressive phenotypes (28, 29), whereas optogenetic inhibition of VTA-NAc DA neurons reversed anhedonia elicited by chronic social defeat (30). Collectively, these data demonstrate that normative hedonic behaviors are supported by an adaptive and flexible DA-mediated interplay among the VTA, the striatum (especially the ventral striatum), and the PFC.

The Neural Correlates of Anhedonia

The past decade has seen substantial progress with respect to neural mechanisms that underlie anhedonia and reward

processing dysfunction in MDD. Several recent reviews focusing on functional neuroimaging have highlighted frontostriatal abnormalities in MDD during different reward processes, including incentive motivation (reward anticipation), valuation (reward consumption), and reward learning (31–34). Specifically, in depression, reduced dorsal (e.g., caudate, putamen) and ventral (NAc) activation and reduced perigenual anterior cingulate cortex (pgACC) activation have emerged in tasks probing reward consumption (35, 36), reward anticipation (3, 35, 37, 38), and reward learning (39–42). Reduced ventral striatal activation to reward receipt was associated with anhedonic symptoms (38), whereas larger reward prediction error signals (which captured the difference between expected and actual reward outcome) in the ventral striatum predicted reduced anhedonia 6 months later (43). In addition, during reward consumption or anticipation, MDD has been linked to reduced activation in the dorsal anterior cingulate cortex (dACC) (36) as well as the central and medial OFC (44), with blunted reward-related central OFC (areas 11 and 13) activation correlating with more anhedonic symptoms in adolescents with MDD (44). In tasks harnessing computational modeling to estimate expected value and reward prediction errors during Pavlovian, instrumental, or reversal learning tasks, MDD has been linked to reduced reward prediction error in the ventral and dorsal striatum (39–41; but see also 45, 46), pgACC (47), dACC (42), and medial OFC (46). Similarly, in the decision phase of an instrumental reinforcement learning task, MDD was characterized by reduced reward value encoding in the pgACC but higher subgenual anterior cingulate cortex (sgACC) activation (48). Notably, reward-related blunting in these regions has been accompanied by hyperactivation in the medial prefrontal cortex (mPFC), ventromedial prefrontal cortex (vmPFC; including the sgACC), and dorsolateral prefrontal cortex (dlPFC) (33, 38, 49). Findings highlighting disruption in key hubs of the brain reward system have been complemented by reports that functional connectivity between the caudal vmPFC and various reward regions (NAc, VTA, OFC) while listening to pleasant music was negatively correlated with anhedonia (50).

Several recent findings deserve special emphasis. First, frontostriatal abnormalities in MDD emerge early in the disease course, as demonstrated by reduced striatal and pgACC activation—but potentiated PFC (specifically mPFC, dlPFC) activation—during reward consumption in children and adolescents with MDD (33, 51, 52), with blunted pgACC activation during reward consumption correlating with higher anhedonia (51). Across studies, mPFC and dlPFC overrecruitment during reward processing was interpreted as pointing to possible overcompensation for reduced striatal responses to rewards (33, 52, 53). Critically, in a large sample of youths (N=1,576; mean age, ~14 years), reduced ventral striatal activation during reward anticipation was associated with anhedonia and predicted transition to depression 2 years later among previously healthy youths (54; see also 55). Along similar lines, blunted striatal activation during reward anticipation predicted greater increases in adolescent depressive symptoms over 2 years (55).

Second, while some abnormalities, such as blunted reward-related striatal activation (56) and reduced reward prediction error signals in the ventral striatum (57), normalize after remission, others persist and point to possible trait-like abnormalities. Abnormalities that do not normalize include blunted OFC activation to rewards (58), reduced ability to sustain ventral striatal activation to positive cues (56), and greater reward prediction error in the VTA (42). Along similar lines, never-depressed children of parents with MDD showed blunted striatal activation during reward anticipation (59) and consumption (60) as well as reduced NAc activation in response to happy faces (61). Altogether, these studies suggest that reward-related dysfunction can precede the initial onset of MDD and thus represents a vulnerability risk.

Third, some of these abnormalities show acute treatment-related changes. For example, a single ketamine infusion was associated with normalization of sgACC hyperactivation to positive incentives (which was associated with more anhedonia) as well as dACC hypometabolism (62, 63). Similarly, administration of a single low dose of amisulpride—hypothesized to increase DA transmission via autoreceptor blockade—normalized frontostriatal abnormalities in unmedicated individuals with MDD. Specifically, relative to placebo, 50 mg of amisulpride increased ventral and dorsal striatal hypoactivation to reward-related cues and decreased lateral OFC and vmPFC hyperactivation in MDD (64, 65).

Fourth, evidence of frontostriatal abnormalities has emerged not only in reward tasks but also during resting (i.e., task-free) states. In the Adolescent Brain Cognitive Development (ABCD) study, among children ages 9–10 years from unreferred community samples (N=2,455), decreased resting-state functional connectivity (rsFC) between the ventral striatum and the cingulo-opercular network was observed in children with anhedonia but not those with low mood (66), which highlights specificity in relation to anhedonia. In a notable study involving a large community-based sample of 9-year-old children (N=637), rsFC between the ventral striatum and other key reward hubs (vmPFC, dACC, VTA) predicted new onset of depressive disorders 3 years later, but not attention deficit hyperactivity disorder, anxiety disorders, or substance use disorders (53). Thus, disrupted frontostriatal coupling not only characterizes current MDD but also represents a vulnerability marker for MDD. The same research group recently extended these findings (67, in this issue) by analyzing data from the IMAGEN Consortium (N=305, ages 13–15 years at baseline) and examining intrinsic FC between the ventral striatum and the rest of the brain reward network. Several interesting findings emerged. First, in logistic regression models, right ventral striatal intrinsic FC at baseline (age 14) was positively associated with depressive disorders (but not anxiety disorders) at age 14. Similarly, left ventral striatal intrinsic FC at baseline correlated positively with anhedonia (but not low mood) at age 14. Second, structural equation modeling showed that left ventral

striatum FC predicted anhedonia 2 years later, whereas right ventral striatum FC predicted anhedonia 4 years later. Based on these findings, the authors speculate that excessive FC between the ventral striatum and the rest of the reward network may reflect a lack of flexibility to respond to reward-related cues in the environment. Future studies incorporating ecological momentary assessments probing flexible responding to potential rewards in daily activities would be well positioned to evaluate this interesting interpretation.

Finally, evidence of disrupted mesocorticolimbic pathways in anhedonia has also emerged from structural studies. For example, studies probing the integrity of the medial forebrain bundle have found that anhedonia in MDD is associated with decreases in tract volume and the number of tracts in the left superolateral branch of the medial forebrain bundle (68, 69), which projects through the anterior limb of the internal capsule and connects the VTA to the PFC. Notably, severity of anhedonia was also associated with *increased* structural connectivity between the VTA and the medial PFC (69), a finding interpreted as reflecting a possible compensatory mechanism in severe anhedonia. These structural connectivity findings have been complemented by reports of reduced striatal (in particular, dorsal) and OFC volume correlating with anhedonia (35, 70) or polygenic risk for anhedonia (71).

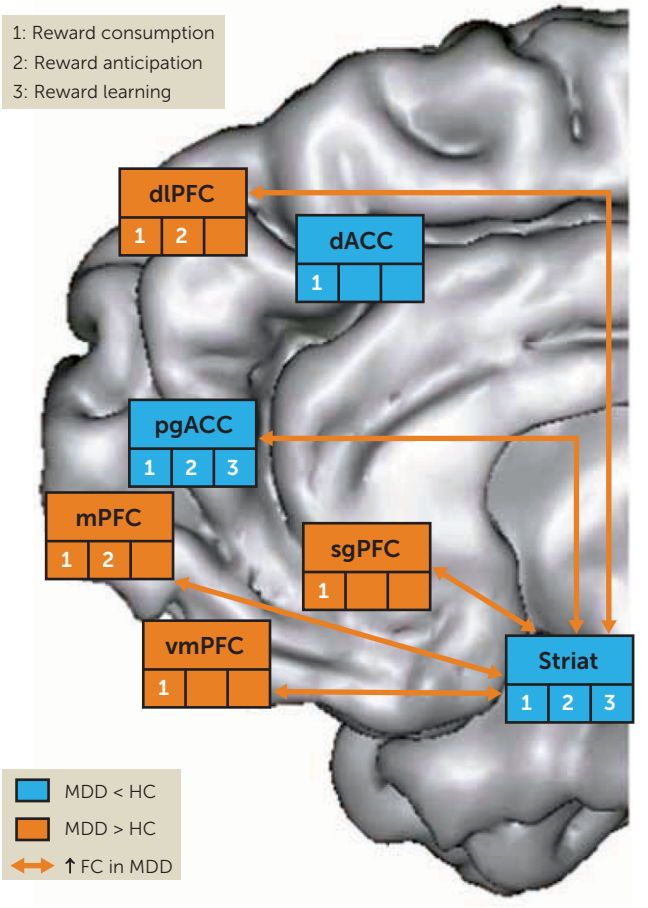
Interim Summary

Across tasks probing different subdomains of reward processing but also during task-free (resting) states, MDD has been linked to abnormal activation within and functional connectivity across nodes of the brain reward pathways (Figure 2). Although some inconsistencies exist, MDD is generally characterized by reduced activation to reward-related cues within ventral and dorsal striatal regions, perigenual and dorsal ACC regions, and central and medial OFC. These hypoactivations contrast with overrecruitment of medial frontal pole (BA10), vmPFC (including sgACC), and dlPFC regions in response to reward-related cues, which has been interpreted as reflecting a compensatory mechanism owing to reduced reward-related striatal activation. Highlighting the clinical importance of these findings, some of these markers were cross-sectionally and prospectively related to anhedonia and predicted first onset of MDD. Complementing these findings, certain abnormalities—specifically, reduced reward-related striatal activation and frontostriatal resting-state functional connectivity—were also observed in unaffected, never-depressed children of parents with MDD, indicating that they may represent vulnerability markers. A key question for future research is whether such vulnerability markers might be targeted for prevention.

THE NEED FOR PLACEBO-CONTROLLED CLINICAL TRIALS WITH AN EXPERIMENTAL THERAPEUTICS APPROACH

As mentioned above, the treatment of anhedonia in MDD remains a formidable challenge. These challenges are present

FIGURE 2. Summary of abnormalities emerging from functional MRI in individuals with major depressive disorder (MDD) or at risk for MDD using tasks probing reward-related processes or evaluating resting-state functional connectivity within the brain reward system[a]



[a] Regions highlighted in orange and blue show higher activation and lower activation, respectively, in MDD samples than in healthy control samples (HC). Orange arrows denote higher functional connectivity (FC) in MDD samples than healthy control samples. dACC=dorsal anterior cingulate cortex; dlPFC=dorsolateral prefrontal cortex; mPFC=medial prefrontal cortex; pgACC=perigenual anterior cingulate cortex; sgACC=subgenual anterior cingulate cortex; Striat=striatum; vmPFC=ventromedial prefrontal cortex. (Modified after reference 34.)

in both first-line psychological (e.g., cognitive-behavior therapy) and pharmacological treatments. In light of these unmet needs, several targeted psychological interventions have been developed in recent years, including behavioral activation treatment (e.g., 72) and positive affect treatment (73). Positive affect treatment, in particular, was specifically designed to target deficits in reward sensitivity, and it includes modules involving planning for pleasurable activities (reward approach-motivation), reinforcing connections between behaviors and mood effects (reward learning), and "in-the-moment" savoring (reward consumption). Initial results are promising (73), and future studies should evaluate whether this intervention normalizes neural abnormalities associated with anhedonia. (For promising evidence that

modulation of reward-related neural circuitry may underlie reduction in anhedonia with behavioral activation, see reference 74.)

With respect to pharmacological treatments, anhedonia has received surprisingly modest attention vis-à-vis rigorous placebo-controlled trials. For example, in a recent qualitative review, Cao and colleagues (75) summarized results from 17 studies that evaluated the efficacy of different pharmacotherapies for anhedonia. These strategies included melatonergic antidepressants (agomelatine; eight studies), SSRIs (escitalopram, sertraline, fluoxetine; four studies), serotonin-noradrenaline reuptake inhibitors (extended-release venlafaxine, extended-release levomilnacipran; two studies), norepinephrine-dopamine reuptake inhibitors (bupropion; one study), serotonin-norepinephrine-dopamine reuptake inhibitors (amitifadine; one study), reversible inhibitors of monoamine oxidase A (moclobemide; one study), tricyclic antidepressants (clomipramine; one study), glutamatergic agents (ketamine and riluzole; one study), stimulants (methylphenidate; one study), and psychedelics (psilocybin; one study). Of note, nine of these 17 studies were open-label, and 10 included 30 or fewer patients in each treatment arm. Agomelatine showed some promise in alleviating anhedonia, but none of the eight studies published included a placebo-control arm. Although the low number of studies and high level of heterogeneity prevented a quantitative meta-analysis, Cao and colleagues concluded that melatonergic antidepressants (agomelatine), monoaminergic antidepressants, glutamatergic agents, psychedelics, and stimulants have shown initial promise in addressing anhedonia.

Recently, three relatively novel mechanisms have attracted substantial interest as promising antianhedonic treatments: kappa opioid receptor (KOR) antagonism, potassium channel (KCNQ) modulation, and NMDA receptor antagonism.

Kappa Opioid Receptor Antagonists

KOR antagonism has been proposed as a possible treatment for anhedonia based on robust preclinical data implicating these receptors in modulating reward processing and stress regulation (76, 77). Specifically, preclinical studies had previously shown that stressors trigger release of dynorphin, which binds to KOR receptors and inhibits DA release in the NAc via ventral tegmental area neurons (77–81). KOR antagonists have been hypothesized to exert antianhedonic effects by blocking CREB-mediated upregulation of dynorphin function, which in turn normalizes the mesolimbic DA system (81). Consistent with this hypothesis, in rodents KOR antagonists have shown antidepressant effects (e.g., 82–84); moreover, when delivered in the NAc, KOR antagonists led to a 175% increase in DA release in this region (85). In a transdiagnostic sample of 89 individuals with MDD, bipolar disorder, or anxiety disorders with some level of anhedonia, a KOR antagonist (aticaprant, formerly JNJ-67953964) was associated with greater pre- to posttreatment changes in self-reported, behavioral (performance on the probabilistic reward task [PRT]), and neural (i.e., ventral striatal activation during reward anticipation) measures of anhedonia (86, 87) relative to placebo. Moreover, on the PRT, which uses an asymmetric reinforcement schedule to objectively assess participants' ability to learn from rewards, trial-level computational modeling indicated that the KOR antagonist affected learning rate (the ability to learn from rewards) while leaving reward sensitivity (the hedonic response) unaffected.

KCNQ Channel Modulators

A different strategy to restore DA signaling consists of affecting membrane excitability by means of modulation of membrane-bound ion channels (88). Interestingly, in mice exposed to chronic social defeat, resilient animals were characterized by upregulation of KCNQ2/3 channels in the VTA, which was associated with normative phasic firing of the VTA and protection against anhedonic behaviors. Of note, administration of ezogabine (a selective KCNQ2/3 channel opener) restored VTA homeostasis and reversed anhedonic and pro-depressive behaviors among defeated animals (89). Inspired by these preclinical findings, Tan and colleagues evaluated the effects of 10 weeks of treatment with ezogabine (900 mg/day) on self-reported, behavioral (performance on the PRT), and neural measures of anhedonia, using an open-label single-arm design (90). Participants included 18 individuals with MDD and clinically significant symptoms of anhedonia. From baseline to the 10-week endpoint, ezogabine increased reward learning on the PRT and reduced depression severity and anhedonia. Two additional, notable findings emerged. First, the decrease in anhedonic symptoms remained after controlling for depression severity. Second, improvements in self-reported anhedonia correlated with reduced rsFC between the ventral caudate and the midcingulate cortex, a region that has been implicated in responding to salient stimuli (91). These findings were recently confirmed and extended by the same group (92), who randomized 45 individuals with MDD and elevated anhedonia to 5-week treatment with ezogabine (900 mg/day; N=21) or placebo (N=24). Relative to placebo, ezogabine was associated with a larger reduction in depressive and anhedonic symptoms and an increase, short of significance, in ventral striatal activation during reward anticipation.

NMDA Antagonists (e.g., Ketamine)

Ketamine, an NMDA receptor antagonist, is a glutamatergic modulator that has attracted substantial interest due to its rapid antidepressant effects (e.g., 93). NMDA-receptor-mediated inhibition of inhibitory GABAergic interneurons in the PFC has been implicated in ketamine's antidepressant mechanism of action (94). Preclinical studies have shown that increased synaptic glutamate release leads to potentiated AMPA receptor activation and, ultimately, synaptic plasticity via the mTOR pathway (95). This, in turn, has been hypothesized to increase DA tone in mesocorticolimbic pathways (96) and thereby exert antianhedonic effects. In line with these hypotheses, retrospective analyses combining

data from multiple studies (N=203 individuals with MDD) showed that treatment with four intravenous infusions of racemic ketamine (0.50–0.75 mg/kg) over the course of 1–2 weeks was associated with significant reductions in self-reported anhedonia (97). Interestingly, reductions in anhedonia partially mediated reductions in symptoms of depression, anxiety, and suicidal ideation (for a recent review of ketamine's antianhedonic effects, see reference 9). These findings have been complemented by reports that reduced anhedonia after ketamine infusion correlated with 1) increased glucose metabolism in the dACC (63, 98), putamen (98), and OFC (63); 2) increased rsFC within a frontostriatal network involving the PFC, OFC, and pgACC (99); and 3) normalization (i.e., reduction) of sgACC hyperactivation to positive feedback. This latter finding was particularly interesting in light of recent findings in marmosets implicating sgACC hyperactivation in anhedonic behaviors (100).

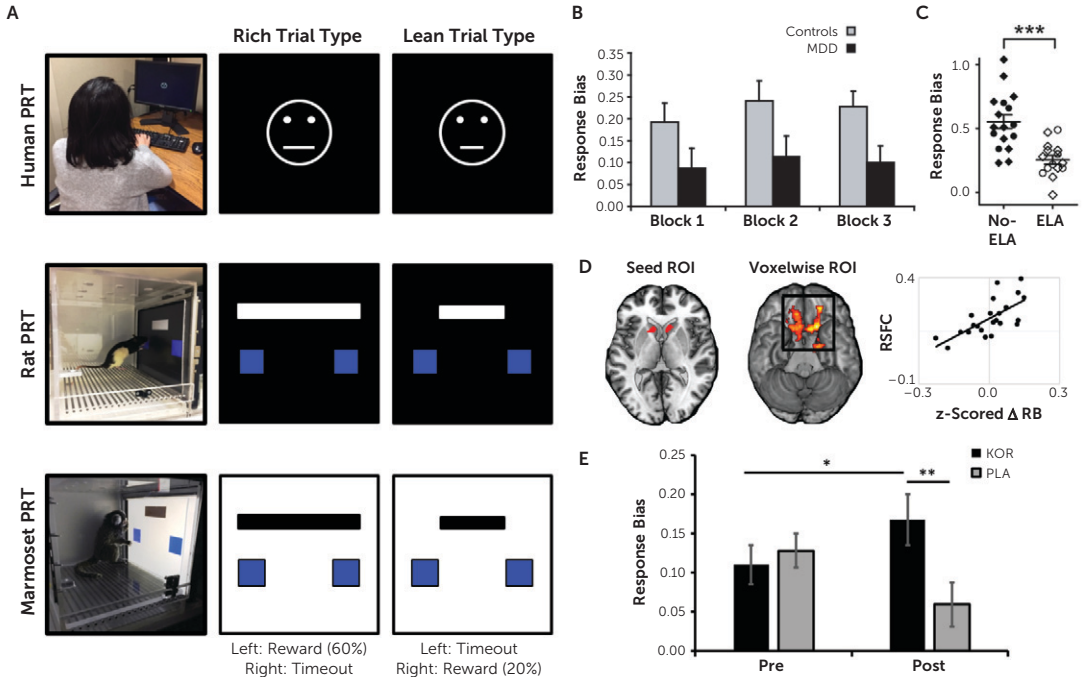
Interim Summary

Findings from these studies are exciting not only because they point to potentially novel mechanisms for tackling anhedonia but also because they show that reduced anhedonia correlates with changes in the brain reward system (9, 86, 90). Thus, by taking an experimental therapeutics approach, these studies provided important corroboration that the "target" (in this case, ventral striatal activation to reward cues) was engaged. Although an in-depth discussion of this point is beyond the scope of this overview (for elaboration, see references 101–103), the importance of an experimental therapeutics approach in order to avoid false positive findings and meaningfully interpret failed clinical trials cannot be overemphasized. Harnessing this approach early in drug discovery will be critically important to accelerate the development of better treatment for anhedonia and to avoid investing resources and time in therapeutics that do not show target engagement. I believe that this approach, coupled with the use of preclinical models with more direct translational value (see the next section), offers the strongest path forward.

THE NEED FOR STRONGER CROSS-SPECIES TRANSLATIONAL MODELS OF ANHEDONIC BEHAVIORS

As highlighted by several recent reviews (e.g., 15, 18, 104), one important limitation and potential translational "leak" is the use of vastly different approaches to assess anhedonia across species. Whereas human studies overwhelmingly rely on clinical scales, rodent (and sometimes nonhuman primate) studies rely on the sucrose preference test or other tasks involving palatable food, and in the case of rodents, intracranial self-stimulation (e.g., within the medial forebrain bundle). Despite the evolutionary conservation of brain reward pathways, and acknowledging that these approaches have contributed to important discoveries, the translational value of this work remains unclear. As a result, in recent years there has been growing interest in developing and optimizing experimental procedures that are functionally analogous—and, in some cases, identical—across species, with the hope that these platforms might accelerate translation. A comprehensive review is beyond the scope of this overview, but the interested reader is referred to several recent reviews on this topic (105–107). Here, I briefly highlight our experience using the PRT, which assesses reward learning or the ability to modulate behavior as a function of rewards. Originally developed for humans (108), the PRT has been back-translated to nonhuman primates (109), rats (110), and mice (unpublished), most recently using touchscreen technology (Figure 3A). Using tasks with identical reinforcement contingencies (e.g., 3-to-1 reward ratio for correct identification of one stimulus vs. another), identical sensory modalities (e.g., visual stimuli), and similar psychometric properties (e.g., overall accuracy between 70% and 90%), and using identical signal-detection equations to derive measures of response bias (i.e., the preference for the more frequently rewarded stimulus), our lab and others have described similar findings in humans and rodents given interventions hypothesized to increase or decrease DA signaling (e.g., pramipexole, stimulants, nicotine withdrawal) or exposed to stressors (111–116). Critically, anhedonic symptoms among depressed individuals (Figure 3B), as well as anhedonic behavior induced by early-life stress in rats (Figure 3C), were associated with similarly blunted reward learning on the PRT (117, 118). Finally, in humans, individual differences in the ability to acquire a response bias have been linked to functional, electrophysiological, and molecular markers of the mesocorticolimbic system (119, 120) (Figure 3D). Interestingly, a recent study in rats (116) showed that blunted reward learning after exposure to chronic mild stress could be reversed by systemic injection of a low dose of the D_2/D_3 antagonist amisulpride (hypothesized to increase DA signaling in the striatum via autoreceptor blockade) (116). Thus, transient increase of DA signaling in the striatum rescued stress-induced anhedonic behavior in rats, which parallels prior findings in MDD showing that a single low dose of amisulpride (50 mg) normalized blunted reward-related activation in the dorsal and ventral striatum (64, 65). Finally, and highlighting potential clinical utility, two recent studies in independent samples showed that more normative PRT reward learning before treatment predicted better antidepressant and antianhedonic response to bupropion (121) and pramipexole (122). Critically, in the study by Ang and colleagues (121), better reward learning predicted better response to bupropion after failing to respond to 8 weeks of treatment with the SSRI sertraline. If replicated, these findings suggest that objectively assessed anhedonic phenotypes may be more homogeneous than the syndrome of "MDD," which may facilitate treatment selection for at least a subgroup of depressed individuals. Future studies should also evaluate whether subgrouping patients based on objective measures of anhedonia might outperform self-reported assessments of anhedonia (for initial evidence, see references 123, 124), particularly when using "first-generation" clinical

FIGURE 3. Cross-species reward learning assay[a]



[a] Panel A shows task schematics for the human (top) (108), rat (middle) (110), and marmoset (bottom) (109) probabilistic reward task (PRT) (for a review, see reference 137). Using a signal-detection approach involving an asymmetric reinforcement schedule and two difficult-to-discriminate stimuli, the PRT objectively assesses subjects' ability to develop a response bias toward a more frequently rewarded stimulus, which is taken as a measure of reward learning. (Reprinted by permission from Springer Nature GmBH, Toward a quantification of anhedonia: unified matching law and signal detection for clinical assessment and drug development, Luc OT et al, Perspect Behav Sci, Copyright 2021.) In panel B, relative to healthy control subjects, unmedicated individuals with major depressive disorder (MDD) have significantly lower response bias (117). (Reprinted from J Psychiatr Res, vol 43, no 1, Pizzagalli et al, Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task, pp 76–87, Copyright 2008, with permission from Elsevier.) In panel C, relative to a no-stress (control) group, rats exposed to early-life adversity (ELA) (limited bedding and nesting paradigm) between postnatal days 2 and 9 were characterized by significantly blunted response bias (118). (Reprinted with permission.) In panel D, among healthy control subjects, individual differences in response bias (RB) are positively associated with resting-state functional connectivity (RSFC) between the ventral striatum and the ventromedial prefrontal cortex (as assessed with functional MRI) and negatively associated with dopamine transporter binding potential (not shown; as assessed using positron emission tomography). The latter finding suggests that low dopamine transporter availability, and thus higher dopamine availability in the synaptic cleft, is associated with better reward learning abilities (119). (Reprinted from Kaiser RH et al, Frontostriatal and dopamine markers of individual differences in reinforcement learning: a multi-modal investigation, Cereb Cortex, 2018, vol 28, no 12, pp 4281–4290, by permission of Oxford University Press.) In panel E, in a placebo-controlled clinical trial, a kappa-opioid receptor antagonist (KOR) was associated with better response bias than placebo (PLA) in a transdiagnostic sample with elevated anhedonia (87). (Reprinted with permission.)

anhedonia scales, which, as discussed next, do not differentiate among different subdomains of reward processing.

THE NEED FOR NEUROSCIENTIFICALLY INFORMED, PSYCHOMETRICALLY SOUND CLINICAL SCALES OF ANHEDONIA

Informed by historical conceptualizations of anhedonia, early scales focused exclusively on the assessment of pleasure (consummatory anhedonia) (for a recent review, see reference 125). For example, the Snaith-Hamilton Pleasure Scale (SHAPS) (126), which is arguably the most widely used self-report scale of anhedonia, assesses the ability to experience pleasure in the context of five type of rewards (food/drinks, sensory experiences, social interaction, pastimes, and achievements). Similarly, the Chapman Anhedonia Scale focuses exclusively on consummatory pleasure (125). Feasibly, individuals such as Antonne—who, as described at the start of this article, can experience pleasure but has difficulty mounting motivated behavior in pursuit of potentially pleasurable experiences—may not generate high scores on such measures, despite clearly displaying anhedonic phenotypes. Consistent with this speculation, a recent meta-analysis comparing SHAPS scores across neuropsychiatric disorders concluded that use of the SHAPS may underestimate the number of depressed individuals with anhedonia (127). To address these limitations, and informed by more modern (neuroscientific) conceptualizations of anhedonia, second-generation scales, such as the Dimensional Anhedonia Rating Scale (128) and the Temporal Experience of Pleasure Scale (129), have been developed to probe different subdomains, including anticipatory versus consummatory anhedonia. Finally, a recently published scale, the Positive Valence Systems Scale (130), explicitly uses domains and subdomains from the NIMH RDoC initiative (131) to provide a more fine-grained assessment of anhedonic behaviors, by parsing seven subdomains (reward valuation, reward expectancy, effort valuation, reward anticipation, action

selection, initial responsiveness, and reward satiation). Future studies should use these more modern anhedonia scales to identify what are expected to be more biologically homogeneous subgroups of patients. In addition, studies are needed to confirm the hypothesis that patients featuring dysfunction in specific reward processing subdomains are indeed characterized by different neural alterations. Collectively, these studies might suggest how best to conceptualize treatment approaches for the individuals in such subgroups.

CONCLUSIONS AND FUTURE DIRECTIONS

Treating anhedonia associated with MDD as well as with other neuropsychiatric disorders (for a full overview, see reference 132) remains a daunting clinical challenge. Loss of pleasure, as well as blunted motivation to pursue pleasurable activities and learn from them, negatively impacts our ability to see purpose in life, to function across domains (e.g., family, work, society), and to be resilient when challenged by life stress. Restoring motivation and the ability to feel pleasure is seen by individuals as pivotal to remission. Thanks to substantial progress in our understanding of reward processing across species, but also to novel conceptualizations of psychopathology (e.g., the RDoC initiative), the past 10 years have seen remarkable innovation and promise in addressing anhedonia. Such progress has been fueled by several developments, including 1) an appreciation that different reward processing subdomains are governed by partially nonoverlapping brain networks; 2) the development and optimization of objective tasks to probe reward processing subdomains that are functionally identical across species; and 3) the identification of novel (nonmonoaminergic) targets for anhedonia treatment. Moreover, this knowledge has spurred significant innovation, including the development of psychological treatments that specifically target anhedonia (such as positive affect treatment [73]) and the harnessing of virtual reality to address anhedonic symptoms (133); the evaluation of the medial forebrain bundle as a novel target for deep brain stimulation (23, 134); and the development of second-generation, circuity-targeted neurostimulation strategies targeting anhedonia (11).

Despite this progress and promise, there are important remaining gaps and future directions the field will need to pursue. First, there is insufficient understanding of how specific anhedonic phenotypes should be treated: should Victoria and Antonne, as described at the beginning of this review, be treated similarly or differently? Treatment studies with large samples that afford the use of machine learning or clustering approaches are needed to identify reward-related biotypes and their response to treatments (135). For instance, it is unclear why individuals with a more normative brain reward system at baseline (as evidenced by a better ability to learn from rewards and by stronger functional coupling between the NAc and the pgACC) fail to benefit from an 8-week treatment course with an SSRI (sertraline) but go on to respond to an atypical antidepressant (bupropion) (121; see also 122). Do these findings challenge the traditional pharmacology deficiency model (e.g., SSRI ↔ monoaminergic hypothesis of MDD), and do they suggest that anhedonia might follow a capitalization model, which assumes that a treatment should be provided to match relative strengths rather than deficits? (For a discussion of the capitalization vs. compensation approaches in the context of psychotherapy for depression, see reference 136.) If specific neural markers (e.g., blunted striatal recruitment while anticipating or receiving rewards, and/or disrupted rsFC between the ventral striatum and other key reward hubs) are present in young, unaffected, never-depressed children of depressed parents, should we implement preventive strategies to thwart the emergence of MDD and anhedonia? If so, which strategies should we use? Ultimately, for people like Victoria and Antonne, the best chances for remission will stem from a rigorous, integrated, cross-species, multilevel investigation of anhedonia, which promises to lead to much-needed therapeutic and preventive breakthroughs.

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