



HHS Public Access

Author manuscript

Am J Psychiatry. Author manuscript; available in PMC 2023 July 01.

Published in final edited form as:

Am J Psychiatry. 2022 July ; 179(7): 458–469. doi:10.1176/appi.ajp.20220423.

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

Diego A. Pizzagalli, PhD

Department of Psychiatry, Harvard Medical School & McLean Hospital, USA

Abstract

Anhedonia – the loss of pleasure or lack of reactivity to pleasurable stimuli – remains a formidable treatment challenge across neuropsychiatric disorders. In major depressive disorder (MDD), 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—e.g., blunted activation of the ventral striatum to reward-related cues and reduced functional connectivity involving the ventral striatum—persist. Critically, some of these abnormalities have also been identified in unaffected, never-depressed children of parents with MDD, and have been found to prospectively predict the first onset of MDD. Thus, neural abnormalities linked to anhedonia might 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, we first summarize extant knowledge about the pathophysiology of anhedonia, which might provide a roadmap towards novel treatment and prevention strategies. We then highlight 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. We conclude by highlighting important future directions, emphasizing the need for an integrated, collaborative, cross-species, and multi-level approach to tackle anhedonic phenotypes.

A dedicated long-distance runner since young adulthood, Victoria – a middle-aged professional – has totally lost interest in running. When asked by her partner about this change, Victoria 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 debts. Unfortunately, the selective serotonin reuptake inhibitor (SSRI) that had previously led to remission does not work this time,

and additional augmentation strategies bring little benefit. After nine 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 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 might 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 emerged early in development, apparently without any objective external trigger.

As exemplified by these fictive cases, anhedonia is complex and 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, we 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, we summarize extant knowledge about the pathophysiology of anhedonia, which may provide a roadmap towards 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 (<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, 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 focused 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, as well as 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 vs. actual reward outcome) in the ventral striatum predicted reduced anhedonia six 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 central and medial OFC (44), with blunted reward-related central OFC (areas 11 and 13) activation correlating with more anhedonic symptoms among 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 (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 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 subgenual anterior cingulate cortex, 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 over-recruitment during reward processing was interpreted as pointing to possible over-compensation for reduced striatal responses to rewards (33, 52, 53). Critically, in a large sample of youth (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 youth ((54); see also (55)). Along similar lines, blunted striatal activation during reward anticipation predicted greater increases in adolescent depressive symptoms over two 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 hyper-activation to positive incentives (which was associated with more anhedonia), as well as dACC hypo-metabolism (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 not only emerged in reward tasks, but also during resting (i.e., task-free) states. In the Adolescent Brain Cognitive Development (ABCD) study, among children aged 9 to 10 years from unreferred, community samples (N=2455), 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 three years later new onset of depressive disorders, but not ADHD, anxiety or substance use disorders (53). Thus, disrupted frontostriatal coupling not only characterizes current MDD but also represents a vulnerability marker for MDD. The same group recently extended these findings (see current issue of the *Journal*) by analyzing data from the IMAGEN Consortium (N=305, 13–15 years old at baseline) and examining intrinsic FC between the ventral striatum and the rest of the brain reward network (67). 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 at age 14 (but not low mood). Second, structural equation modeling showed that left ventral striatum FC predicted anhedonia two years later, whereas right ventral striatum FC predicted anhedonia four years later. Based on these findings, the authors speculated that excessive FC between the ventral striatum and the rest of the reward network might 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 supero-lateral 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 over-recruitment of medial frontal pole (BA10), vmPFC (including sgACC) and dlPFC regions in response to reward-related cues, which has been interpreted as reflecting 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 might 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 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 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 might underlie reduction in anhedonia with Behavioral Activation, see (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: (1) melatonergic antidepressants (agomelatine; 8 studies); (2) SSRIs (escitalopram, sertraline, fluoxetine; 4 studies); (3) serotonin-noradrenaline reuptake inhibitors (SNRIs; venlafaxine ER, levomilnacipran ER; 2 studies); (4) norepinephrine-dopamine reuptake inhibitors (NDRI; bupropion; 1 study); (5) serotonin-norepinephrine-dopamine reuptake inhibitors (SNDRIs; amitifadine; 1 study); (6) reversible inhibitor of monoamine oxidase A (MAOI-A; moclobemide; 1 study); (7) tricyclic antidepressants (TCAs; clomipramine; 1 study); (8) glutamatergic agents (ketamine and riluzole; 1 study); (9) stimulants (methylphenidate; 1 study); and (10) psychedelics (psilocybin; 1 study). Of note, 9 of these 17 studies were open-label, and 10 of 17 included 30 or fewer patients in each treatment arm. Agomelatine showed some promise in alleviating anhedonia, but none of the 8 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 anti-anhedonic 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 anti-anhedonic 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 levels of anhedonia, a KOR antagonist (Aticaprant, formerly JNJ-67953964) was associated with greater pre-to-post treatment changes in self-reported, behavioral (performance in the Probabilistic Reward Task (PRT)), and neural (i.e., ventral striatal activation during reward anticipation) measures of anhedonia (86, 87), relative to placebo. Moreover, in 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 a 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-week treatment with ezogabine (900 mg/day) on self-reported, behavioral (performance in 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 in 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 mid-cingulate 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 larger reduction in depressive and anhedonic symptoms and a trend-level increase 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 mTOR pathway (95). This, in turn, has been hypothesized to increase DA tone in mesocorticolimbic pathways (96), and thereby exert anti-anhedonic effects. In line with these hypotheses, retrospective analyses combining data from multiple studies (N=203 individuals with MDD) showed that four IV infusions of racemic ketamine (0.50–0.75 mg/kg) over the course of 1–2 weeks were associated with significant reduction 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 anti-anhedonic effects, see (9)). These findings have been complemented by reports that reduced anhedonia after ketamine infusion correlated with: (i) increased glucose metabolism in the dACC (63, 98), putamen (98), and OFC (63); (ii) increased rsFC within a frontostriatal network involving the PFC, OFC, and pgACC (99); and (iii) 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 not only exciting because they point to potentially novel mechanisms to tackle anhedonia, but because they also showed that reduced anhedonia correlated 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 the current overview (for elaboration, see (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 into therapeutics that do not show target engagement. We 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 non-human 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, we 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 non-human 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), similar psychometric properties (e.g., overall accuracy between 70–90%), 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 in 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 D2/D3 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 anti-anhedonic 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 8-weeks of treatment with the SSRI sertraline. If replicated, these findings suggest that objectively assessed anhedonic phenotypes might be more homogenous than the syndrome of “MDD”, which might 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 (123, 124)), particularly when using “first-generation” clinical 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 (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 Scales focuses exclusively on consummatory pleasure (125). Feasibly, individuals such as Antonne – who can experience pleasure but has difficulty mounting motivated behavior in pursuit of potentially pleasurable experiences – might 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 might 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 (DARS; (128)) and the Temporal Experience of Pleasure Scale (TEPS; (129)), have been developed to probe different subdomains, including anticipatory vs. consummatory anhedonia. Finally, a recently published scale – the Positive Valence Systems Scale (PVSS) (130) – explicitly uses domains and subdomains from the NIMH Research Domain Criteria 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, reward satiation). Future studies should use these more modern anhedonia scales to identify what are expected to be more biologically homogenous 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 conceptualize treatment approaches for the individuals in such subgroups.

Conclusions and Future Directions

Treating anhedonia associated with MDD, as well as in other neuropsychiatric disorders (for a full overview, see (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. 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 non-overlapping 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 (non-monoaminergic) targets for anhedonia treatment. Moreover, this knowledge has spurred significant innovation, including: developing psychological treatments that specifically target anhedonia (such as Positive Affect Treatment; (73)) and harnessing virtual reality to address anhedonic symptoms (133); evaluating the medial forebrain bundle as a novel target for deep brain stimulation (23, 134); and developing second-generation, circuitry-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 8-week treatment 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 capitalization vs. compensation approach in the context of psychotherapy for depression, see (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 and multi-level investigation of anhedonia, which promises to lead to much-needed therapeutic and preventive breakthroughs.

Acknowledgments

During preparation of this manuscript, the author was supported by grants from the National Institute of Mental Health (NIMH) of the National Institutes of Health (P50 MH119467, R01 MH095809, R37 MH068376) and by a Distinguished Investigator Award from the Brain and Behavior Research Foundation. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

Financial Disclosures

Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (former BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka Pharmaceuticals, Sunovion Pharmaceuticals, and Takeda Pharmaceuticals; honoraria from the Psychonomic Society (for editorial work) and Alkermes, and research funding

from NIMH, Dana Foundation, Brain and Behavior Research Foundation, Millennium Pharmaceuticals. In addition, he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (former BlackThorn Therapeutics), and Neuroscience Software. Finally, Dr. Pizzagalli has a financial interest in Neumora Therapeutics (former BlackThorn Therapeutics), which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Massachusetts General Brigham in accordance with their conflict-of-interest policies. No funding from these entities was used to support the current work, and all views expressed are solely those of the author.

References

1. Klein DF: Endogenomorphic depression. A conceptual and terminological revision. *Arch Gen Psychiatry* 1974; 31:447–54 [PubMed: 4420562]
2. Treadway MT, Zald DH: Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev* 2011; 35:537–55 [PubMed: 20603146]
3. Pizzagalli DA: Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annu Rev Clin Psychol* 2014; 10:393–423 [PubMed: 24471371]
4. Pelizza L, Ferrari A: Anhedonia in schizophrenia and major depression: state or trait? *Ann Gen Psychiatry* 2009; 8:145–155
5. Cao B, Park C, Subramaniapillai M, et al. : The Efficacy of Vortioxetine on Anhedonia in Patients With Major Depressive Disorder. *Front psychiatry* 2019; 10
6. Tang W, Liu H, Chen L, et al. : Inflammatory cytokines, complement factor H and anhedonia in drug-naïve major depressive disorder. *Brain Behav Immun* 2021; 95:238–244 [PubMed: 33794316]
7. Moos RH, Cronkite RC: Symptom-based predictors of a 10-year chronic course of treated depression. *J Nerv Ment Dis* 1999; 187:360–368 [PubMed: 10379723]
8. Spijker J, Bijl RV, de Graaf R, et al. : Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatr Scand* 2001; 103:122–130 [PubMed: 11167315]
9. Klein ME, Grice AB, Sheth S, et al. : Pharmacological treatments for anhedonia. *Curr Top Behav Neurosci* 2022;
10. Sandman CF, Craske MG: Psychological treatments for anhedonia. *Curr Top Behav Neurosci* 2021;
11. Siddiqi SH, Haddad N, Fox MD: Circuit-targeted neuromodulation for anhedonia. *Curr Top Behav Neurosci*
12. Auerbach RP, Pagliaccio D, Kirshenbaum JS: Anhedonia and Suicide. *Curr Top Behav Neurosci* 2022;
13. Demyttenaere K, Donneau AF, Albert A, et al. : What is important in being cured from depression? Discordance between physicians and patients (1). *J Affect Disord* 2015; 174:390–396 [PubMed: 25545606]
14. Zimmerman M, McGlinchey JB, Posternak MA, et al. : How should remission from depression be defined? The depressed patient's perspective. *Am J Psychiatry* 2006; 163:148–150 [PubMed: 16390903]
15. Husain M, Roiser JP: Neuroscience of apathy and anhedonia: A transdiagnostic approach. *Nat Rev Neurosci* 2018; 19:470–484 [PubMed: 29946157]
16. Treadway MT, Zald DH: Parsing Anhedonia: Translational Models of Reward-Processing Deficits in Psychopathology. *Curr Dir Psychol Sci* 2013; 22:244–249 [PubMed: 24748727]
17. Der-Avakian A, Markou A: The neurobiology of anhedonia and other reward-related deficits. *Trends Neurosci* 2012; 35:68–77 [PubMed: 22177980]
18. Rizvi SJ, Pizzagalli DA, Sproule BA, et al. : Assessing anhedonia in depression: Potentials and pitfalls. *Neurosci Biobehav Rev* 2016; 65
19. Kring AM, Barch DM: The motivation and pleasure dimension of negative symptoms: neural substrates and behavioral outputs. *Eur Neuropsychopharmacol* 2014; 24:725–736 [PubMed: 24461724]
20. Haber SN, Knutson B: The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology* 2009; 35:4–26

21. Knowland D, Lim BK: Circuit-based frameworks of depressive behaviors: The role of reward circuitry and beyond. *Pharmacol Biochem Behav* 2018; 174:42–52 [PubMed: 29309799]
22. Nieuwenhuys R, Geeraedts LMG, Veening JG: The medial forebrain bundle of the rat. I. General introduction. *J Comp Neurol* 1982; 206:49–81 [PubMed: 6124562]
23. Coenen VA, Schlaepfer TE, Maedler B, et al. : Cross-species affective functions of the medial forebrain bundle-implications for the treatment of affective pain and depression in humans. *Neurosci Biobehav Rev* 2011; 35:1971–1981 [PubMed: 21184778]
24. Bracht T, Doidge AN, Keedwell PA, et al. : Hedonic tone is associated with left supero-lateral medial forebrain bundle microstructure. *Psychol Med* 2015; 45:865–874 [PubMed: 25124530]
25. Han MH, Nestler EJ: Neural Substrates of Depression and Resilience. *Neurotherapeutics* 2017; 14:677–686 [PubMed: 28397115]
26. Lowes DC, Chamberlin LA, Kretsge LN, et al. : Ventral tegmental area GABA neurons mediate stress-induced blunted reward-seeking in mice. *Nat Commun* 2021; 12
27. Cao JL, Covington HE, Friedman AK, et al. : Mesolimbic dopamine neurons in the brain reward circuit mediate susceptibility to social defeat and antidepressant action. *J Neurosci* 2010; 30:16453–16458
28. Berton O, McClung CA, Dileone RJ, et al. : Essential Role of BDNF in the Mesolimbic Dopamine Pathway in Social Defeat Stress. *Science (80-)* 2006; 311:864–868
29. Wook Koo J, Labonté B, Engmann O, et al. : Essential Role of Mesolimbic Brain-Derived Neurotrophic Factor in Chronic Social Stress-Induced Depressive Behaviors. *Biol Psychiatry* 2016; 80:469–478 [PubMed: 26858215]
30. Chaudhury D, Walsh JJ, Friedman AK, et al. : Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* 2013; 493:532–536 [PubMed: 23235832]
31. Keren H, O'Callaghan G, Vidal-Ribas P, et al. : Reward processing in depression: A conceptual and meta-analytic review across fMRI and EEG studies. *Am J Psychiatry* 2018; 175:1111–1120 [PubMed: 29921146]
32. Admon R, Pizzagalli DA: Dysfunctional reward processing in depression. *Curr Opin Psychol* 2015; 4
33. O'Callaghan G, Stringaris A: Reward processing in adolescent depression across neuroimaging modalities: A review. *Z Kinder Jugendpsychiatr Psychother* 2019; 47:535–541 [PubMed: 30957688]
34. Pizzagalli DA, Roberts AC: Prefrontal cortex and depression. *Neuropsychopharmacology* 2022; 47:225–246 [PubMed: 34341498]
35. Pizzagalli DA, Holmes AJ, Dillon DG, et al. : Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry* 2009; 166:702–710 [PubMed: 19411368]
36. Forbes EE, Christopher May J, Siegle GJ, et al. : Reward-related decision-making in pediatric major depressive disorder: an fMRI study. *J Child Psychol Psychiatry* 2006; 47:1031–1040 [PubMed: 17073982]
37. Zhang WN, Chang SH, Guo LY, et al. : The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. *J Affect Disord* 2013; 151:531–539 [PubMed: 23856280]
38. Borsini A, Wallis ASJ, Zunszain P, et al. : Characterizing anhedonia: A systematic review of neuroimaging across the subtypes of reward processing deficits in depression. *Cogn Affect Behav Neurosci* 2020; 20:816–841 [PubMed: 32472419]
39. Kumar P, Waiter G, Ahearn T, et al. : Abnormal temporal difference reward-learning signals in major depression. *Brain* 2008; 131:2084–2093 [PubMed: 18579575]
40. Kumar P, Goer F, Murray L, et al. : Impaired reward prediction error encoding and striatal-midbrain connectivity in depression. *Neuropsychopharmacology* 2018; 43:1581–1588 [PubMed: 29540863]
41. Gradin VB, Kumar P, Waiter G, et al. : Expected value and prediction error abnormalities in depression and schizophrenia. *Brain* 2011; 134:1751–1764 [PubMed: 21482548]
42. Ruppacher S, Romaniuk L, Series P, et al. : Blunted medial prefrontal cortico-limbic reward-related effective connectivity and depression. *Brain* 2020; 143:1946–1956 [PubMed: 32385498]

43. Eckstrand KL, Forbes EE, Bertocci MA, et al. : Anhedonia Reduction and the Association between Left Ventral Striatal Reward Response and 6-Month Improvement in Life Satisfaction among Young Adults. *JAMA Psychiatry* 2019; 76:958–965 [PubMed: 31066876]
44. Xie C, Jia T, Rolls ET, et al. : Reward Versus Nonreward Sensitivity of the Medial Versus Lateral Orbitofrontal Cortex Relates to the Severity of Depressive Symptoms. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2020; 6
45. Rutledge RB, Moutoussis M, Smittenaar P, et al. : Association of neural and emotional impacts of reward prediction errors with major depression. *JAMA Psychiatry* 2017; 74:790–797 [PubMed: 28678984]
46. Rothkirch M, Tonn J, Köhler S, et al. : Neural mechanisms of reinforcement learning in unmedicated patients with major depressive disorder. *Brain* 2017; 140:1147–1157 [PubMed: 28334960]
47. Ubl B, Kuehner C, Kirsch P, et al. : Altered neural reward and loss processing and prediction error signalling in depression. *Soc Cogn Affect Neurosci* 2014; 10:1102–1112
48. Rupprechter S, Stankevicius A, Huys QJM, et al. : Abnormal reward valuation and event-related connectivity in unmedicated major depressive disorder. *Psychol Med* 2020; 2020 Jan 7
49. Zhang B, Lin P, Shi H, et al. : Mapping anhedonia-specific dysfunction in a transdiagnostic approach: an ALE meta-analysis. *Brain Imaging Behav* 2016; 10:920–939 [PubMed: 26487590]
50. Young CB, Chen T, Nusslock R, et al. : Anhedonia and general distress show dissociable ventromedial prefrontal cortex connectivity in major depressive disorder. *Transl Psychiatry* 2016; 6:e810
51. Rzepa E, Fisk J, McCabe C: Blunted neural response to anticipation, effort and consummation of reward and aversion in adolescents with depression symptomatology. *J Psychopharmacol* 2017; 31:303–311 [PubMed: 28093022]
52. Forbes EE, Hariri AR, Martin SL, et al. : Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am J Psychiatry* 2009; 166:64–73 [PubMed: 19047324]
53. Pan PM, Sato JR, Salum GA, et al. : Ventral striatum functional connectivity as a predictor of adolescent depressive disorder in a longitudinal community-based sample. *Am J Psychiatry* 2017; 174:1112–1119 [PubMed: 28946760]
54. Stringaris A, Belil PVR, Artiges E, et al. : The brain s response to reward anticipation and depression in adolescence: Dimensionality, specificity, and longitudinal predictions in a community-based sample. *Am J Psychiatry* 2015; 172:1215–1223 [PubMed: 26085042]
55. Morgan JK, Olino TM, McMakin DL, et al. : Neural response to reward as a predictor of increases in depressive symptoms in adolescence. *Neurobiol Dis* 2013; 52:66–74 [PubMed: 22521464]
56. Admon R, Pizzagalli DA: Corticostriatal pathways contribute to the natural time course of positive mood. *Nat Commun* 2015; 6:10065
57. Geugies H, Mocking RJT, Figueroa CA, et al. : Impaired reward-related learning signals in remitted unmedicated patients with recurrent depression. *Brain* 2019; 142:2510–2522 [PubMed: 31280309]
58. Dichter GS, Kozink RV., McClernon FJ, et al. : Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes. *J Affect Disord* 2012; 136:1126–1134 [PubMed: 22036801]
59. Gotlib IH, Hamilton P, Cooney RE, et al. : Neural processing of reward and loss in girls at risk for major depression. *Arch Gen Psychiatry* 2010; 67:380–387 [PubMed: 20368513]
60. Sharp C, Kim S, Herman L, et al. : Major depression in mothers predicts reduced ventral striatum activation in adolescent female offspring with and without depression. *J Abnorm Psychol* 2014; 123:298–309 [PubMed: 24886004]
61. Monk CS, Klein RG, Telzer EH, et al. : Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *Am J Psychiatry* 2008; 165:90–98 [PubMed: 17986682]
62. Morris LS, Costi S, Tan A, et al. : Ketamine normalizes subgenual cingulate cortex hyper-activity in depression. *Neuropsychopharmacology* 2020; 45:975–981 [PubMed: 31896116]

63. Lally N, Nugent AC, Luckenbaugh DA, et al. : Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *J Psychopharmacol* 2015; 29:596–607 [PubMed: 25691504]
64. Admon R, Kaiser RH, Dillon DG, et al. : Dopaminergic enhancement of striatal response to reward in Major Depression. *Am J Psychiatry* 2017; 174:378–386 [PubMed: 27771973]
65. Liu Y, Admon R, Mellem MS, et al. : Machine learning identifies large-scale reward-related activity modulated by dopaminergic enhancement in major depression. *Biol Psychiatry Cogn Neurosci Neuroimaging*
66. Pornpattananangkul N, Leibenluft E, Pine DS, et al. : Association between childhood anhedonia and alterations in large-scale resting-state networks and task-evoked activation. *JAMA Psychiatry* 2019; 76:624–633 [PubMed: 30865236]
67. Pan PM et al. : Longitudinal trajectory of the link between ventral-striatum and depression in adolescence. *Am J Psychiatry*
68. Bracht T, Horn H, Strik W, et al. : White matter microstructure alterations of the medial forebrain bundle in melancholic depression. *J Affect Disord* 2014; 155:186–193 [PubMed: 24252169]
69. Bracht T, Mertse N, Walther S, et al. : Link between structural connectivity of the medial forebrain bundle, functional connectivity of the ventral tegmental area, and anhedonia in unipolar depression. *NeuroImage Clin* 2022; 34
70. Auerbach RP, Pisoni A, Bondy E, et al. : Neuroanatomical prediction of anhedonia in adolescents. *Neuropsychopharmacology* 2017; 42:2087–2095 [PubMed: 28165037]
71. Howard DM, Adams MJ, Clarke T-K, et al. : Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci* 2019; 22:343–352 [PubMed: 30718901]
72. Dimidjian S, Hollon SD, Dobson KS, et al. : Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *J Consult Clin Psychol* 2006; 74:658–670 [PubMed: 16881773]
73. Craske MG, Meuret AE, Ritz T, et al. : Positive affect treatment for depression and anxiety: A randomized clinical trial for a core feature of anhedonia. *J Consult Clin Psychol* 2019; 87:457–471 [PubMed: 30998048]
74. Nagy GA, Cernasov P, Pisoni A, et al. : Reward Network Modulation as a Mechanism of Change in Behavioral Activation. *Behav Modif* 2020; 44:186–213 [PubMed: 30317863]
75. Cao B, Zhu J, Zuckerman H, et al. : Pharmacological interventions targeting anhedonia in patients with major depressive disorder: A systematic review. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; 92:109–117 [PubMed: 30611836]
76. Jacobson ML, Browne CA, Lucki I: Kappa opioid receptor antagonists as potential therapeutics for stress-related disorders. *Annu Rev Pharmacol Toxicol* 2020; 60:615–636 [PubMed: 31914893]
77. Carlezon WA, Krystal AD: Kappa-opioid antagonists for psychiatric disorders: From bench to clinical trials. *Depress Anxiety* 2016; 33:895–906 [PubMed: 27699938]
78. Brujinzeel AW: kappa-Opioid receptor signaling and brain reward function. *Brain Res Rev* 2009; 62:127–46 [PubMed: 19804796]
79. Muschamp JW, Van't Veer A, Carlezon WA: Tracking down the molecular substrates of stress: New roles for p38 α mapk and kappa-opioid receptors. *Neuron* 2011; 71:383–385 [PubMed: 21835335]
80. Wee S, Koob GF: The role of the dynorphin-kappa opioid system in the reinforcing effects of drugs of abuse. *Psychopharmacology (Berl)* 2010; 210:121–35 [PubMed: 20352414]
81. Carlezon WA Jr., Beguin C, Knoll AT, et al. : Kappa-opioid ligands in the study and treatment of mood disorders. *Pharmacol Ther* 2009; 123:334–343 [PubMed: 19497337]
82. McLaughlin JP, Li S, Valdez J, et al. : Social defeat stress-induced behavioral responses are mediated by the endogenous kappa opioid system. *Neuropsychopharmacology* 2006; 31:1241–1248 [PubMed: 16123746]
83. Reindl JD, Rowan K, Carey AN, et al. : Antidepressant-like effects of the novel kappa opioid antagonist MCL-144B in the forced-swim test. *Pharmacology* 2008; 81:229–235 [PubMed: 18176093]

84. Shirayama Y, Ishida H, Iwata M, et al. : Stress increases dynorphin immunoreactivity in limbic brain regions and dynorphin antagonism produces antidepressant-like effects. *J Neurochem* 2004; 90:1258–1268 [PubMed: 15312181]
85. Maisonneuve IM, Archer S, Glick SD: U50,488, a kappa opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. *Neurosci Lett* 1994; 181:57–60 [PubMed: 7898771]
86. Krystal AD, Pizzagalli DA, Smoski M, et al. : Application of the “Fast-Fail” approach to evaluating the potential of selective Kappa Opioid Antagonism as a treatment for anhedonia: A randomized proof of mechanism trial assessing effects on the ventral striatum. *Nat Med*
87. Pizzagalli DA, Smoski M, Ang YS, et al. : Selective kappa-opioid antagonism ameliorates anhedonic behavior: evidence from the Fast-fail Trial in Mood and Anxiety Spectrum Disorders (FAST-MAS). *Neuropsychopharmacology* 2020; 45:1656–1663 [PubMed: 32544925]
88. Russo SJ, Murrough JW, Han MH, et al. : Neurobiology of resilience. *Nat Neurosci* 2012; 15:1475–1484 [PubMed: 23064380]
89. Friedman AK, Juarez B, Ku SM, et al. : KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. *Nat Commun* 2016; 7
90. Tan A, Costi S, Morris LS, et al. : Effects of the KCNQ channel opener ezogabine on functional connectivity of the ventral striatum and clinical symptoms in patients with major depressive disorder. *Mol Psychiatry* 2020; 25
91. Shackman AJ, Salomons TV, Slagter HA, et al. : The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* 2011; 12:154–167 [PubMed: 21331082]
92. Costi S, Morris LS, Kirkwood KA, et al. : Impact of the KCNQ2/3 Channel Opener Ezogabine on Reward Circuit Activity and Clinical Symptoms in Depression: Results From a Randomized Controlled Trial. *Am J Psychiatry* 2021; 178:437–446 [PubMed: 33653118]
93. Wilkinson ST, Ballard ED, Bloch MH, et al. : The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis. *Am J Psychiatry* 2018; 175:150–158 [PubMed: 28969441]
94. Zanos P, Gould TD: Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry* 2018; 23:801–811 [PubMed: 29532791]
95. Shinohara R, Aghajanian GK, Abdallah CG: Neurobiology of the Rapid-Acting Antidepressant Effects of Ketamine: Impact and Opportunities. *Biol Psychiatry* 2021; 90:85–95 [PubMed: 33568318]
96. Pulcu E, Guinea C, Cowen PJ, et al. : A translational perspective on the anti-anhedonic effect of ketamine and its neural underpinnings. *Mol Psychiatry* 2022; 27:81–87 [PubMed: 34158619]
97. Rodrigues NB, McIntyre RS, Lipsitz O, et al. : Changes in symptoms of anhedonia in adults with major depressive or bipolar disorder receiving IV ketamine: Results from the Canadian Rapid Treatment Center of Excellence. *J Affect Disord* 2020; 276:570–575 [PubMed: 32871688]
98. Lally N, Nugent AC, Luckenbaugh DA, et al. : Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Transl Psychiatry* 2014; 4:e469 [PubMed: 25313512]
99. Mkrтчian A, Evans JW, Kraus C, et al. : Ketamine modulates fronto-striatal circuitry in depressed and healthy individuals. *Mol Psychiatry* 2021; 26:3292–3301 [PubMed: 32929215]
100. Alexander L, Gaskin PLR, Sawiak SJ, et al. : Fractionating Blunted Reward Processing Characteristic of Anhedonia by Over-Activating Primate Subgenual Anterior Cingulate Cortex. *Neuron* 2019; 101:307–320.e6
101. Krystal AD, Pizzagalli DA, Mathew SJ, et al. : The first implementation of the NIMH FAST-FAIL approach to psychiatric drug development. *Nat Rev Drug Discov* 2018; 18:82–84
102. Paul SM, Mytelka DS, Dunwiddie CT, et al. : How to improve R&D productivity: the pharmaceutical industry’s grand challenge. *Nat Rev Drug Discov* 2010; 9:203–214 [PubMed: 20168317]
103. Insel TR: The NIMH experimental medicine initiative. *World Psychiatry* 2015; 14:151–153 [PubMed: 26043323]

104. Der-Avakian A, Pizzagalli DA: Translational assessments of reward and anhedonia: A tribute to Athina Markou. *Biol Psychiatry* 2018; 83:932–939 [PubMed: 29615189]
105. Lewis LR, Benn A, Dwyer DM, et al. : Affective biases and their interaction with other reward-related deficits in rodent models of psychiatric disorders. *Behav Brain Res* 2019; 372
106. Kangas BD, Der-Avakian A, Pizzagalli DA: Probabilistic Reinforcement Learning and Anhedonia. *Curr Top Behav Neurosci* 2022;
107. Treadway MT, Salamone JD: Vigor, Effort-Related Aspects of Motivation and Anhedonia. *Curr Top Behav Neurosci* 2022;
108. Pizzagalli DA, Jahn AL, O’Shea JP: Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biol Psychiatry* 2005; 57:319–327 [PubMed: 15705346]
109. Wooldridge LM, Bergman J, Pizzagalli DA, et al. : Translational Assessments of Reward Responsiveness in the Marmoset. *Int J Neuropsychopharmacol* 2020;
110. Kangas BD, Wooldridge LM, Luc OT, et al. : Empirical validation of a touchscreen probabilistic reward task in rats. *Transl Psychiatry* 2020; 10
111. Der-Avakian A, D’Souza MSS, Pizzagalli DAA, et al. : Assessment of reward responsiveness in the response bias probabilistic reward task in rats: implications for cross-species translational research. *Transl Psychiatry* 2013; 3:e297 [PubMed: 23982629]
112. Pergadia ML, Der-Avakian A, D’Souza MS, et al. : Association between nicotine withdrawal and reward responsiveness in humans and rats. *JAMA Psychiatry* 2014; 71:1238–1245 [PubMed: 25208057]
113. Pizzagalli DA, Evins AE, Schetter EC, et al. : Single dose of a dopamine agonist impairs reinforcement learning in humans: Behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology (Berl)* 2008; 196:221–232 [PubMed: 17909750]
114. Bogdan R, Santesso DL, Fagerness J, et al. : Corticotropin-releasing hormone receptor type 1 (CRHR1) genetic variation and stress interact to influence reward learning. *J Neurosci* 2011; 31:13246–13254
115. Lamontagne SJ, Melendez SI, Olmstead MC: Investigating dopamine and glucocorticoid systems as underlying mechanisms of anhedonia. *Psychopharmacology (Berl)* 2018; 235:3103–3113 [PubMed: 30136143]
116. Lamontagne SJ, Wash SIJ, Irwin SH, et al. : Effects of dopamine modulation on chronic stress-induced deficits in reward learning. *Cogn Affect Behav Neurosci* 2022;
117. Pizzagalli DA, Iosifescu D, Hallett LA, et al. : Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J Psychiatr Res* 2008; 43:76–87 [PubMed: 18433774]
118. Kangas BD, Short AK, Luc OT, et al. : A cross-species assay demonstrates that reward responsiveness is enduringly impacted by adverse, unpredictable early-life experiences. *Neuropsychopharmacology* 2022; 47:767–775 [PubMed: 34921225]
119. Kaiser RH, Treadway MT, Wooten DW, et al. : Frontostriatal and dopamine markers of individual differences in reinforcement learning: A multi-modal investigation. *Cereb Cortex* 2018; 28:4281–4290 [PubMed: 29121332]
120. Santesso DL, Dillon DG, Birk JL, et al. : Individual differences in reinforcement learning: behavioral, electrophysiological, and neuroimaging correlates. *Neuroimage* 2008; 42:807–16 [PubMed: 18595740]
121. Ang YS, Kaiser R, Deckersbach T, et al. : Pretreatment reward sensitivity and frontostriatal resting-state functional connectivity are associated with response to bupropion after sertraline nonresponse. *Biol Psychiatry* 2020; 88:657–667 [PubMed: 32507389]
122. Whitton AE, Reinen JM, Slifstein M, et al. : Baseline reward processing and ventrostriatal dopamine function are associated with pramipexole response in depression. *Brain* 2020; 143
123. Whitton AE, Kumar P, Treadway MT, et al. : Mapping disease course across the mood disorder spectrum through a Research Domain Criteria framework. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2021;
124. Guffanti G, Kumar P, Admon R, et al. : Depression genetic risk score is associated with anhedonia-related markers across units of analysis. *Transl Psychiatry* 2019; 9

125. Wang S, Leri F, Rizvi SJ: Clinical and Preclinical Assessments of Anhedonia in Psychiatric Disorders. *Curr Top Behav Neurosci* 2022;
126. Snaith RP, Hamilton M, Morley S, et al. : A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry* 1995; 167:99–103 [PubMed: 7551619]
127. Trøstheim M, Eikemo M, Meir R, et al. : Assessment of Anhedonia in Adults With and Without Mental Illness: A Systematic Review and Meta-analysis. *JAMA Netw open* 2020; 3
128. Rizvi SJ, Quilty LC, Sproule BA, et al. : Development and validation of the Dimensional Anhedonia Rating Scale (DARS) in a community sample and individuals with major depression. *Psychiatry Res* 2015; 229:109–119 [PubMed: 26250147]
129. Gard DE, Gard MG, Kring AM, et al. : Anticipatory and consummatory components of the experience of pleasure: a scale development study. *J Res Pers* 2006; 40:1086–1102
130. Khazanov GK, Ruscio AM, Forbes CN: The Positive Valence Systems Scale: Development and Validation. *Assessment* 2020; 27:1045–1069 [PubMed: 31416336]
131. Insel T, Cuthbert B, Garvey M, et al. : Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 2010; 167:748–751 [PubMed: 20595427]
132. Pizzagalli DA: Anhedonia: Preclinical, translational, and clinical integration. Springer Nature Switzerland AG, Springer, 2022
133. Chen K, Barnes-Horowitz N, Treanor M, et al. : Virtual reality reward training for anhedonia: A pilot study. *Front Psychol* 2021; 11
134. Coenen VA, Bewernick BH, Kayser S, et al. : Superolateral medial forebrain bundle deep brain stimulation in major depression: a gateway trial. *Neuropsychopharmacology* 2019; 44:1224–1232 [PubMed: 30867553]
135. Williams LM: Precision psychiatry: a neural circuit taxonomy for depression and anxiety. *The lancet Psychiatry* 2016; 3:472–480 [PubMed: 27150382]
136. Cheavens JS, Strunk DR, Lazarus SA, et al. : The compensation and capitalization models: a test of two approaches to individualizing the treatment of depression. *Behav Res Ther* 2012; 50:699–706 [PubMed: 22982085]

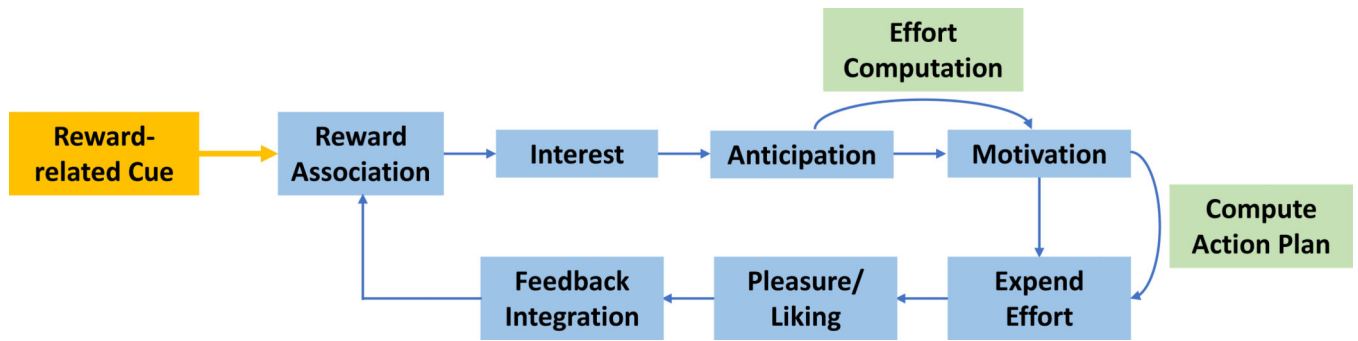


Figure 1: Subprocesses and subdomains implicated in reward processing (modified after (19) and (18)). Specific anhedonic behaviors might be chiefly associated with disruption in one or several of these subdomains.

1: Reward Consumption
2: Reward Anticipation
3: Reward Learning

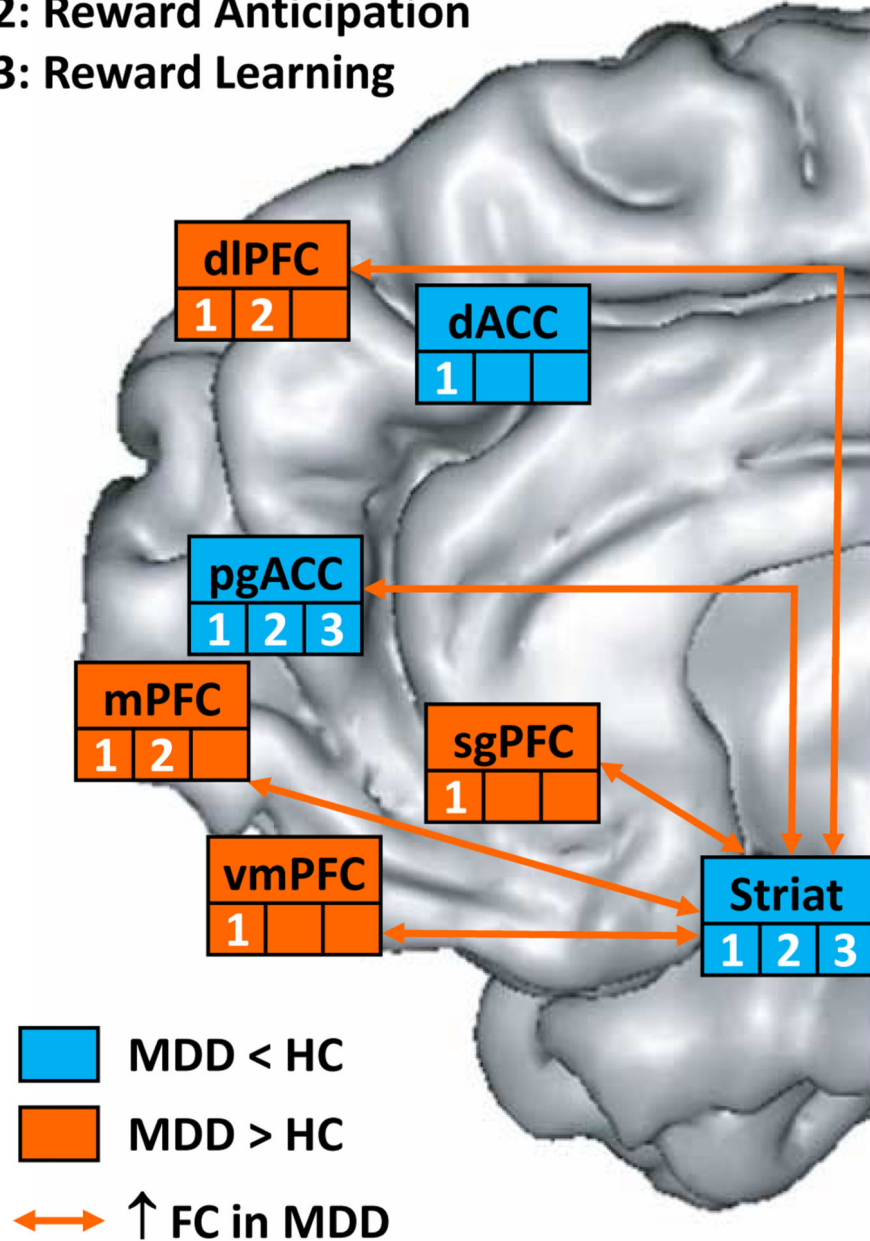


Figure 2: Summary of abnormalities emerging from functional magnetic resonance imaging (fMRI) in individuals with major depressive disorder (MDD) or at risk for MDD using tasks probing reward-related processes or evaluating resting state functional connectivity within the brain reward system. Regions highlighted in orange and blue show higher activation and lower activation, respectively, in MDD samples than healthy controls (HC). Orange arrows denote higher functional connectivity in MDD samples than healthy controls. 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 (34).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

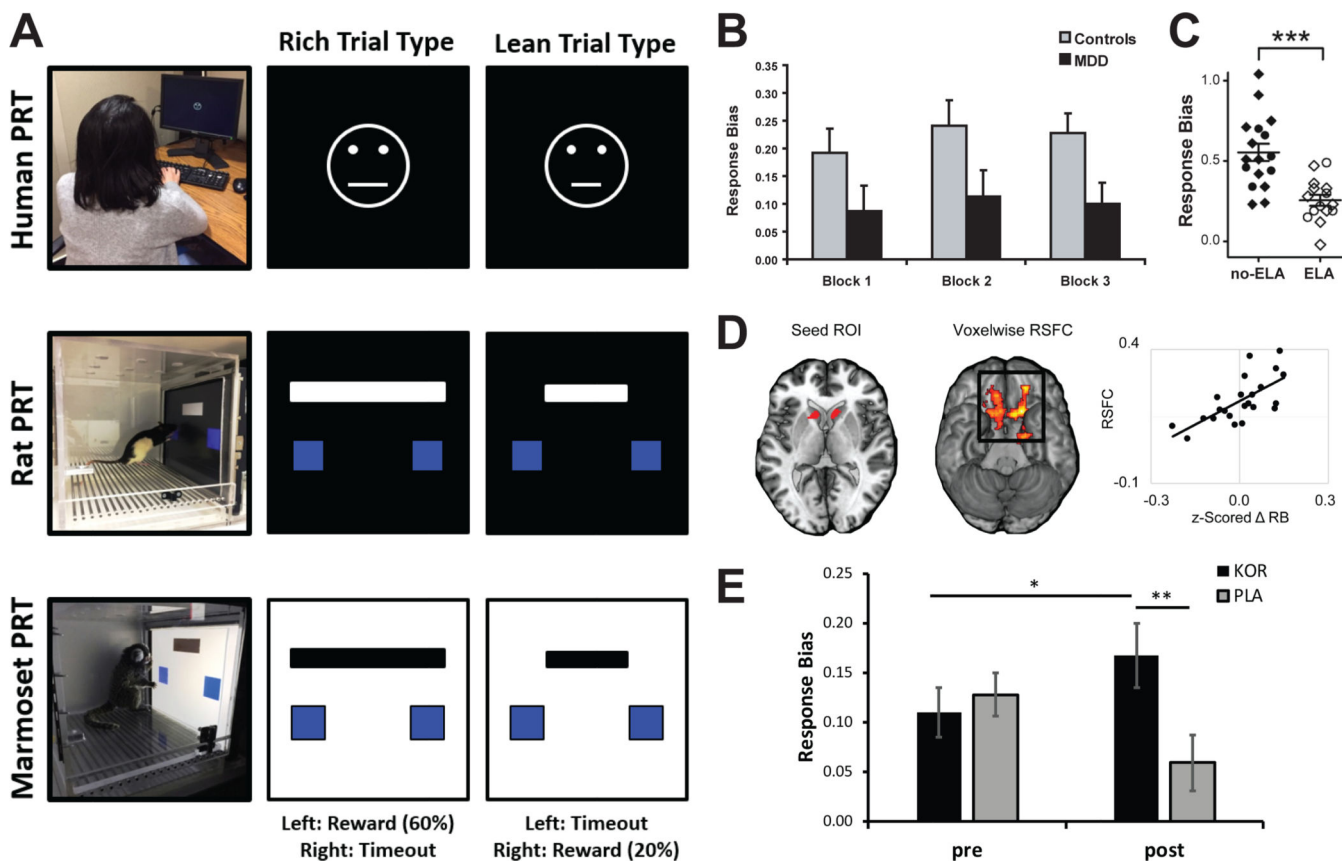


Figure 3: Cross-species Reward Learning Assay. **(A)** Task schematics for the human (top; (108)), rat (middle; (110)), and marmoset (bottom; (109)) Probabilistic Reward Task (PRT). Using a signal-detection approach involving an asymmetric reinforcement schedule and two difficult-to-discriminate stimuli, 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. **(B)** Relative to healthy controls, unmedicated individuals with major depressive disorder (MDD) have significantly lower response bias (117). **(C)** Relative to a no-stress (control) group, rats exposed to early life stress (limited bedding and nesting paradigm) between P2 and P9 were characterized by significantly blunted response bias (118). **(D)** Among healthy controls, individual differences in response bias are positively associated with resting state functional connectivity between the ventral striatum and the ventromedial prefrontal cortex (as assessed with fMRI) 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). **(E)** In a placebo-controlled clinical trial, a kappa opioid antagonist was associated with better response bias among a transdiagnostic sample with elevated anhedonia (87). Figures reproduced with permissions from the publishers.