Conceptualizing anhedonias and implications for depression treatments

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Abstract: Anhedonia has been implicated as a core symptom of depression and schizophrenia, and studying anhedonia has yielded a wide array of important findings aiding the understanding and identification of psychological disorders. However, anhedonia is a complex and multifaceted construct; indeed, the term anhedonia has been defined in psychological and psychiatric research as many different concepts, a number of which are theoretically and methodologically independent of one another. In this review alone, we discuss research that separates social aspects of anhedonia from the physical contexts of anhedonia, with the former emphasizing interpersonal relationships as important to anhedonic symptoms, and the latter emphasizing biological and brain-related impairment as potential causes of chronic anhedonia states. We highlight research that distinguishes between interest in (wanting) or experience of (liking) potential pleasure as definitions of anhedonia and also disambiguate methodologically and theoretically distinct ways of assessing 1) trait-level dispositional tendencies, 2) state-level cross-sectional assessments, and 3) symptom-based recent changes from baseline, all of which have been used to indicate anhedonia. Lastly, we describe cutting-edge translations of basic anhedonia research into treatment and discuss how different conceptualizations of anhedonia, guided by recent theoretical and methodological advances, have begun to usher in a science of anhedonia that is consistent with increasingly personalized assessment and treatment. We conclude with a note for future research, emphasizing that continued application of theoretically based operationalizations of anhedonia and sound design are paramount to continue the recent progress toward meaningful and specific use of the anhedonia construct in clinical research.

Keywords: wanting, liking, recent changes, state, trait, interest, pleasure, reward

Introduction

Anhedonia is a complex and multifaceted construct. As this review describes, the term anhedonia has been defined in psychological and psychiatric research in many ways, a number of which are theoretically and methodologically independent of one another. This paper reviews research on anhedonia that has attempted to separate its social or physical context, with the former emphasizing interpersonal relationships as important to anhedonic symptoms, and the latter emphasizing a deficiency in the ability to experience physical pleasures, such as eating or touch. In addition, we also review research that considers biological and brain-related impairment as potential causes of chronic anhedonia states. Consideration of social factors that lead to the experience of anhedonia, especially when anhedonia is conceptualized as a symptom and not a trait, run somewhat contrary to considerations of anhedonia as the result of...
biologically based impairment, and each conceptualization has implications for prospective treatment.

We then highlight research that distinguishes between two definitions of anhedonia that are associated with the potential experience of pleasure: anticipatory anhedonia, or the interest in potential pleasure (wanting)\(^4\) and consummatory anhedonia, or the experience of (liking)\(^3\) potential pleasure. The distinction between anticipatory and consummatory experience of pleasure has some overlap with the aforementioned social/physical distinction, but a relatively independent line of research has implicated deficits in anticipatory pleasure, in particular, as a candidate for intervention.

We will also disambiguate methodologically and theoretically distinct ways of assessing 1) trait-level dispositional tendencies, 2) state-level cross-sectional assessments, and 3) symptom-based recent changes from baseline,\(^2,4,9-11\) all of which have been used to operationalize anhedonia. As has been previously noted by our research team and others,\(^2,4,9-14\) these distinctions are of crucial importance when studying anhedonia, and we will summarize why each of these three conceptualizations is, for the most part, independent from one another and quite likely to indicate differential considerations in patients or nonclinical populations. A discussion of specific measures that tap into these methodologically and theoretically distinct anhedonias is beyond the scope of this review, and the reader is referred elsewhere.\(^15,16\) Instead, we emphasize the distinction and application of these theoretically based operationalizations of anhedonia, as they continue to foster meaningful research in clinical science and treatment.

We will then compare cutting-edge translations of basic anhedonia research into treatment.\(^17-20\) These treatments focus on increasing and sustaining positive affect, ie, the experience of positively valenced subjective emotional states. Anhedonia is often operationalized as the absence of positive affect, or the loss of interest in or inability to experience positive emotions, so these treatments carry with them the promise of more personalized approaches for the treatment of depression.

We close with a discussion of how different conceptualizations of anhedonia, guided by recent theoretical and methodological advances, have begun to usher in a science of anhedonia that is consistent with increasingly personalized assessment and treatment. We conclude with a note for future research, emphasizing that continued application of sound design and theoretically based operationalizations of anhedonia – as well as considerations of when anhedonia may indicate complex devaluation of reward instead of dysfunction\(^13\) – are paramount to continue the recent progression toward meaningful and specific use of the anhedonia construct in clinical research and treatment.

**Anhedonia in biological context**

The biological context for anhedonia begins with central functions of reward in brain systems, as affective states may be elicited by rewards when they are anticipated or obtained. The relationship between these systems for reward and pleasure, including those involved in sensory analysis, valuation of reward, and, ultimately, decision-making is often conceptualized as a neural architectural framework.

Biological decision-making processes related to reward and anhedonia involve communication among complex brain structures, and the type of reward, how it is valued, and the choices one has to make in relation to obtaining or experiencing reward make understanding interactions among these systems even more complex. Nonetheless, neurobiological studies have attempted to delineate structures and mechanisms that are associated with reward, the experience of pleasure, and disorders related to prospective dysfunction in these areas.\(^21\) Many of these studies emphasize the role of neuroanatomical connections and dopamine (DA) at a neurobiological level.\(^22\) Although nondopaminergic mechanisms also play a role in the experience of pleasure, DA has received considerable attention due to its effects on reward anticipation, learning, motivation, and “wanting” of pleasurable stimuli.\(^23\) Thus, anhedonia may be considered at both a molecular (eg, deficits in DA production) and at a structural level (eg, deficient processing among brain structures).

**Anhedonia at a molecular level**

The ventral tegmental area (VTA) is the origin of dopaminergic neurons, which give rise to the nigrostriatal, mesolimbic, and mesocortical pathways.\(^24\) Connections within the nigrostriatal pathway are involved in motor control and habit formation, whereas the mesolimbic pathway is implicated in learning, reward motivation, and reinforcement.\(^23\) The mesocortical pathway includes projections to cortical regions, such as the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC), and is involved in working memory, attention, and executive functioning.\(^23\) Overall, core “wanting” reactions appear to be generated in the mesolimbic pathway, given DA’s association with a willingness to work for and obtain reward, and modulate functioning in other brain structures associated with the experience of pleasure and reward.\(^25\)

In recent decades, much research has promoted the hypothesis that negative symptoms of schizophrenia (eg,
avolition and hedonic deficits) are a result of a deficiency in DA in the mesocortical pathway, starting from the VTA in the midbrain and projecting to areas of the prefrontal cortex.26 A similar process has been proposed to occur in major depression, wherein anhedonia is a result of functional deficits associated with dopaminergic transmission, especially in the mesolimbic and mesocortical dopaminergic pathways.26,27

**Anhedonia at a structural level**

When considering connections among brain structures themselves, multiple cortical areas and sensory systems (eg, the temporal visual cortex and the anterior portion of the insula) determine what stimulus is present. An important area that receives input from these regions is the OFC, although the ACC and amygdala also receive information at this stage.22 In human subjects, the OFC is associated with the experience of pleasure produced via different sensory rewards.22,28 The OFC projects to areas of the temporal lobe, including the amygdala, cingulate cortex, ventral striatum, the ventromedial prefrontal cortex (vmPFC), as well as the VTA.29,30 These connections ultimately influence decision-making behaviors and response to emotion and novelty.30

The OFC also involves other important functions and is likely the first stage of cortical processing wherein the value of reward is explicitly represented.25 For example, activation in the OFC is related to the subjective pleasantness and satiety of consumed stimuli, such as the flavor of liquids or foods.31 Perhaps more importantly, this area also appears to play a fundamental role in reward-guided decision, with accumulating evidence that neurons in this region carry information related to reward probability, reward magnitude, and risk.32 In sum, evidence from neuroscience literature suggests that neurons in the OFC are fine-tuned to different sensory experiences and are able to represent more abstract dimensions of reward (eg, probability), which in turns leads to the decision to seek reward.21

The amygdala also plays a role in the representation of sensory features, such as taste and odor, of primary rewards.33 Although the function of the amygdala is similar to the OFC in that it serves affective and value-related functions, it is less directly related to experienced pleasure. That is, it allows conditioned associations (ie, links between a certain response and rewarding or punishing stimuli) to influence one’s affective state, as well as decision-making behavior.34 Across human neuroimaging research, converging evidence suggests the ACC also responds in a similar fashion to the OFC, but contains specific projections to cingulate motor areas that are involved in preparation of actions (eg, the mid-cingulate cortex), which further link actions to reward attainment.23

Together, the OFC, amygdala, and ACC provide the ability to represent the value of primary and sensory rewards that ultimately translate neural reward value representations into behavioral choices.35 With this shift from valuing reward to choice, the vmPFC plays a central role. For example, a corpus of findings indicate that activation in this region is associated with subjective value during decisions when considering immediate and delayed rewards,36–38 expected reward value based from one’s own experience,39,40 and a willingness to pay for primary rewards, such as food.41,42 Although the vmPFC plays a formative role in decision-making processes, behavioral output is also guided by information regarding value of outcomes signaled by the OFC.21 Decision-making in relation to reward is thus extraordinarily complex, especially considering that there are other structures involved in the decision-making process (such as the striatum) that are not always associated with rewarding stimuli or affective experiences.25 Due to this complexity, dysfunction at any of these sites or as a result of their dysfunctional interactivity represents potential candidates for associations with self-reported or behavioral43 indicators of anhedonia.

**Evaluating anhedonia in a biological context**

In sum, when considering anhedonia in a biological context, its phenomenology may be due in part to deficits or dysfunction at the molecular or structural level. At a molecular level, DA appears to play a crucial role in incentive-based salience processing and motivational aspects of pleasure. At a structural level, any impairments in these areas associated with ultimate decision-making may lead to different expressions of anhedonias. Taken together, even just at the biological level, there is need to continue to consider anhedonia as more than merely reduced subjective experience of pleasure.23 The need is even more readily apparent when considering theory and method of examining anhedonia in social context.

**Anhedonia in social context**

Social anhedonia may be defined as the experience of decreased pleasure or interest in previously enjoyed activities due to social withdrawal or isolation. Anhedonia emerging in social context can sometimes be overshadowed by research in pursuit of biological causal agents that are potential sites for medical interventions. However, when considering differential types of anhedonia that predict different pathologies
discriminately, assessment of the social causes of distress are at least as important as assessment of the biological ones.

A quintessential example of the discriminant nature of social anhedonia is seen in the longitudinal investigation of changes in social anhedonia over time by Blanchard et al. They found that social anhedonia was a stable individual difference over time in individuals with schizophrenia, whereas those with major depressive disorder (MDD) had increases in social anhedonia only during depressive episodes. Indeed, other research also suggests that waxing and waning of social anhedonia is predictive of symptoms that are more indicative of depression, while more trait-like expression of social anhedonia and physical-related hedonic deficits emerge more robustly in relation to other schizophrenia-spectrum symptoms; some findings even suggest that social anhedonia, at least when measured in relation to recent changes, as is done longitudinally, is predictive of distress among individuals with severe depressive symptoms. Although the distinction between social and physical anhedonia has some conceptual overlap with the distinction between anticipatory and consummatory anhedonia, recent research suggests that these social aspects may be more likely to instead interact with anticipatory differences, the latter of which seem to be predictive of both depression and schizophrenia.

The implications of social anhedonia, and especially changes, in social anhedonia, being potentially able to discriminate between depression and schizophrenia are important. Depression is often conceptualized as a brain disorder: individuals who are depressed are caused to feel pleasure ambiguates important temporal or phenomological aspects, which can differ among individuals. Methodologically and theoretically distinct anhedonias may serve as differential vulnerability factors.

Recent changes in anhedonia vs trait anhedonia

Historically, anhedonia has primarily been assessed as a trait or state construct, with early measures focusing on anhedonia as a focal life-long neurological dysfunction associated with schizophrenia. Thus, those with schizophrenia may have never had any interest in or ability to derive pleasure from social interactions. Along these lines, anhedonia is a widely studied negative symptom of schizophrenia. More recently, anhedonia has also been conceptualized as a biological vulnerability for the development of schizophrenia spectrum disorders, ie, a premorbid personality trait predisposing patients to development of an overt disorder. Anhedonia here is considered an innate trait leading to (or inferring risk for) onset of psychotic symptoms, given that a long-term loss of pleasure can manifest
prior to the prototypical symptoms of schizophrenia, such as eccentric behavior and speech.26 Such a trajectory led to the notion that there was an underlying hereditary defect of the central nervous system, which, in tandem with numerous psychosocial stressors or an unfavorable environment, would lead to the development of schizophrenia.26,48

In addition, anhedonia has also been historically considered a diathesis that could eventually develop into unipolar depression, following a significant amount of stress.26 That is, that individuals who were “hypohedonic” were predisposed to develop MDD.26 However, this trait distinction often focuses on a loss of the ability to feel pleasure, not on other aspects of anhedonia, such as loss of interest in engaging in activities that were once pleasurable.23 Given the heterogeneity of depression, these other elements of anhedonia are important, however. For example, one may have clinical depression without anhedonia, and the presence of anhedonia is related to different symptoms and long-term outcomes, such that anhedonic depression is associated with psychomotor retardation, appetite loss, and rumination.48 Thus, the presence of anhedonia may not be a predictor of a depressive disorder per se, rather, a predictor of different constellations of depressive symptoms.

So, trait measures of anhedonia are commonplace when assessing anhedonia in schizophrenia and depression research, as well as other disorders (eg, substance abuse).1,7,46 However, at least at the level of clinical diagnostic assessment, anhedonia is indicated by a decrease in the ability to derive pleasure.46 That is, if one does not enjoy a particular activity and never enjoyed it in the past, he or she is not endorsing anhedonia with regard to a depressive diagnosis. This is an important clinical distinction, as many extant measures—even beyond trait measures—do not examine changes from baseline, but instead evaluate cross-sectional state experiences within a particular time frame.2,49 In fact, without any baseline, it is often difficult to distinguish between state and trait anhedonia. For example, many state anhedonia measures emphasize the ability to experience pleasure within a particular time frame (such as the past 2 weeks). Trait measures, on the other hand, focus on one’s general ability to experience pleasure, without a temporal component. Thus, a global trait inability to experience pleasure may also be reflected with a state anhedonia assessment.50

What differs when assessing recent changes in anhedonia is a comparative evaluation of one’s current interest in or experience of pleasure with one’s previous interest in or experience of pleasure. For example, one may have never enjoyed being with family or friends (trait anhedonia). In addition, one may have not enjoyed being with family or friends within the past few days (state anhedonia). However, assessing whether or not one has enjoyed being with family or friends as much as one used to (a change in the experience of or interest in pleasure) provides valuable information not otherwise captured by trait or state assessments. Indeed, such measures of recent changes have empirically evidenced incremental validity in this manner compared to trait and state measures, especially in relation to depressive symptoms.2

In summary, recent changes in anhedonia uniquely identify clinically significant symptoms with a built-in baseline. This is potentially vital, as having the ability to recognize recent changes in anhedonia, as opposed to measuring a life-long lack of pleasure or interest, may inform more personalized treatments, as well as it may allow researchers and clinicians to better identify recent distress.39

Social anhedonia vs physical anhedonia
Social anhedonia refers to deriving little or no pleasure from interpersonal situations, whereas physical anhedonia refers to deriving little or no pleasure from nonsocial physical sensations, such as smell, touch, or sound.1,48 Examples of physical anhedonia include lack of enjoyment from sexual activity, lack of interest in listening to music, and lack of pleasure from eating palatable foods. Examples of social anhedonia, on the other hand, may include disinterest in making new friends, lack of closeness with friends and family members, and disinterest in having conversations with others. In addition, these two constructs are not entirely separable, as one can certainly engage in pleasurable physical activities in a social setting (such as eating dinner with friends). This notion is supported by research showing strong correlations between measurements of social and physical anhedonia.7,52 Such aspects of anhedonia have been examined extensively in relation to schizophrenia.1 For example, deficits in intimacy and emotional involvement in a variety of social relations have been documented in patients with schizophrenia26 as well as deficits in physical pleasure.1

In relation to MDD, there is evidence that both physical and social anhedonia are episodically affected. For example, depressed patients with anhedonic symptoms are likely to experience both social withdrawal and appetite loss than patients without anhedonic symptoms, although not all anhedonic patients lack pleasure or interest in all domains.48 That is, some patients may experience a generalized loss of pleasure, though some may only have diminished pleasure in a specific domain (eg, social contact), whereas their experience of pleasure in other domains remain unchanged. Further,
there are also some temporal differences between these two aspects. Some evidence suggests that physical anhedonia in the context of major depression is more trait-like and associated with symptom severity, whereas social anhedonia may decline over time as a result of symptom remission.48

Anticipatory vs consummatory anhedonia

Anhedonia may also be differentiated into anticipatory and consummatory facets.25,53 Anticipatory anhedonia is a tendency to not look forward to pleasurable events, whereas consummatory anhedonia is a tendency not to derive pleasure from in-the-moment experiences.53 For example, one who evidences anticipatory anhedonia may have difficulty becoming excited about the prospect of attending a social event that includes many friends. Conversely, one who evidences consummatory anhedonia may experience difficulty deriving pleasure from eating one’s favorite meal. Although physical and consummatory anhedonia share some logical overlap, some evidence suggests that increased anticipatory and consummatory anhedonia are both related to increased physical anhedonia.53 However, the relationship between anticipatory anhedonia and physical anhedonia may be explained by the fact that assessment of anticipatory anhedonia also covers physical pleasure in addition to social pleasure.

Thus, while anticipatory and consummatory anhedonia both include aspects of physical anhedonia, the main difference between anticipatory and consummatory anhedonia is temporal, although there are likely bidirectional relationships between the two. For example, most often, one can only want something that has been previously liked or enjoyed, with evidence indicating that the more one looks forward to a reward, the more one enjoys the reward when he or she actually obtains it.48 The distinction between anticipatory and consummatory anhedonia has also played an important role in delineating different neurobiological underpinnings of reward and pleasure, such as the distinction between deficits in motivation and consummation in relation to anhedonia.23,25 At a more basic level, there are “wanting”, “liking”, and “learning” processes associated with pleasure (and lack thereof). Wanting refers to motivation for, or incentive salience of a reward, closely associated with anticipatory pleasure, whereas liking is in line with consummatory pleasure, referring to the actual pleasure or hedonic impact of a reward.25 Learning processes include associations, representations, and predictions about future rewards based on one’s past experience, indicating that these processes include aspects of both anticipatory and consummatory pleasure.25,27 Thus, anhedonia may be a product of deficient processing in either one of these components (see section “Anhedonia in biological context” for more detail).

In sum, anhedonia may likely function as a transdiagnostic construct, depending on how it is operationalized. Whereas anhedonia is often conceptualized in relation to schizophrenia and MDD, aspects of anhedonia are present in other disorders as well.48 However, the phenomenology of anhedonia may differ across disorders. Researchers and clinicians are thus well-served to carefully consider how anhedonia is conceptualized, which keys how and why anhedonia would be associated with different symptoms and disorders.

Cutting-edge translational treatments

Existing depression treatments often place an emphasis on understanding and reducing negative affect; however, individuals experiencing anhedonia may be less responsive to these treatments if they predominantly experience reduced positive affect.54 Indeed, some studies examining treatment outcomes for anhedonia have found low positive affect or sustained symptoms of anhedonia to be a significant predictor of poorer treatment outcomes.2,17 Thus, recent interventions have emerged that target increased positive affect to attempt more personalized interventions for individuals experiencing anhedonia.17–20

Positive affect stimulation and sustainment (PASS)

Individuals who are depressed often have difficulty maintaining positive affect, thus PASS was developed to target positive affect functioning (PAF).19 PASS incorporates skills from behavioral activation by focusing on planned events and enhancing the positive emotions associated with them, in line with traditional behavioral treatment. It also incorporates the savoring component of positive psychotherapy with the added focus on extending the effect of positive experiences to past daily activities.19

PASS also incorporates behavioral and cognitive strategies to increase savoring of positive emotions by having individuals recall and write about a recent, vivid, positive event.19 Additionally, individuals associate this event with future positive events to increase anticipatory savoring. Lastly, they are asked to identify their behavioral contributions to this event and make positive attributions about their role in the positive event.

PASS has produced initially heartening results of decreased depression beyond treatment as usual interventions in a developmental trial aimed at increasing PAF.55 However,
PASS is conceptualized as a component to add to existing cognitive behavioral treatment, not as a fully formed treatment.

Positive affect treatment (PAT)

PAT was also developed to target the deficits in reward processing that are associated with anhedonia and has the advantage of being conceptualized as a protocol-based and standalone treatment. To improve positive affect, PAT targets three subdomains that are associated with reward processing affect: anticipation, consumption, and learning of reward. Treatment consists of three different modules to address these subdomains over 15 different sessions.

The first module, pleasant events scheduling, targets anticipation and learning of reward by first having individuals schedule activities that are enjoyable to them or were in the past and then focusing on increasing positive reinforcement by associating positive emotions with the planned activity, similar to behavioral activation. These two aspects are then combined with consumption of learning by helping individuals savor the positive emotions associated with the activity.

The second module focuses on three cognitive exercises that can help individuals identify positive stimuli, recognize behavioral contributions to positive outcomes, and imagine future positive events. The first exercise allows individuals to repeatedly identify any positive aspects of situations to help train them to orientate their attention toward positive information. The second exercise focuses on attributing positive outcomes to the self and savoring the positive emotions associated with these outcomes. The third exercise aims to build positive mood by having individuals imagine the positive aspects associated with a future event.

The last module places an emphasis on the consumption of reward by having individuals cultivate and savor their positive experiences through audio scripts. These sessions include practicing loving-kindness to the self, engaging in daily acts of generosity, wishing happiness on the self and others, and being grateful.

Positive activity intervention (PAI)

Somewhat similar to PAT, Taylor et al detail a ten-session treatment protocol called PAI, another novel treatment approach that aims to train one’s attention to positive events, as well as savor positive experiences that are in turn associated with increased positive emotions and subjective well-being. In their initial sessions, patients undergo psychoeducation regarding the nature and utility of positive emotions. They also learn to monitor and document positive events, such as writing about events from the past week for which they are grateful.

As patients come to understand the nature of positive emotions, they turn to increasing the awareness of their personal strengths, identify important personal values, and undergo a variety of activities to foster these positive emotions in themselves and others (eg, by recalling another’s kindness and writing a gratitude letter). Lastly, participants learn to develop a “positive activity plan”, working with a clinician to create a plan that promotes continued commitment to engagement in these positive activities after termination.

Compared to a no intervention control group, Taylor et al found that those who engaged in the PAI protocol evidenced significantly greater increases in positive affect, as well as a significant reduction in negative affect-related outcomes, such as reduced anxiety and depressive symptoms. Thus, PAI is a very promising treatment protocol that may be beneficial in reducing anhedonic symptoms.

Augmenting traditional CBT

A rather interesting line of recent research has emphasized additional techniques and strategies to supplement CBT by targeting anhedonia specifically. Traditionally, some researchers argue that CBT emphasizes identifying behaviors and cognitions associated with increases in negative mood, whereas thoughts and behaviors that lead to a decrease in positive mood are neglected. Indeed, elevated negative affect is rarely the sole component of depression, and, as this review emphasizes, diminished interest and/or pleasure is an important clinical phenomenon deserving of a greater dialog between the affective and clinical sciences.

To this end, one can implement an integrationist approach by drawing ideas from other treatments, such as acceptance and commitment therapy or mindfulness-based cognitive therapy. For example, a clinician may seek to validate concerns a depressed or anhedonic patient may have in approaching positive or pleasurable activities. When introducing this agenda, the clinician may acknowledge that feeling happy can be difficult when depressed and that initial efforts to engage in positive activities may not warrant immediate success. In addition, depressed patients can be taught to facilitate processing of positive experiences by learning to savor these in-the-moment experiences, similar to the techniques detailed in the modules provided by PAT and PAI.

One recent protocol aimed at treating anhedonia and increasing well-being specifically is augmented depression therapy (ADepT). Drawing from a behavioral activation and
an individualized therapy approach, replete with solution-focused and cognitive techniques, ADepT consists of 15 acute treatment sessions with up to 5 booster sessions. Primary sessions consist of patients and clients clarifying their values, setting behavioral goals that meet these values, and breaking down these goals into reasonable steps and systematically working toward completing these steps. Clinicians work with patients and clients to provide encouragement in carrying out the steps, while building the capability to reach these goals. Preliminary results with a group of 13 depressed patients indicate that the treatment led to significant improvements in levels of well-being and reductions in anhedonic symptoms, as well as overall depressive symptoms. Thus, initial findings are promising, and the pilot randomized clinical trial (RCT) for ADepT may provide more detailed information about which strategies and techniques may best augment a brief cognitive-behavioral approach to the treatment of anhedonia.

Ketamine
A novel biologically based treatment that may positively impact severe anhedonia and associated suicidal ideation is intravenous ketamine treatment. Ketamine is an antagonist of N-methyl-d-aspartate that prospectively acts on glutamatergic receptors and enhances release of neurotransmitters related to mood regulations. A recent comprehensive meta-analysis found a large and significant effect of ketamine decreasing suicidal ideation, though the overall evidence was deemed quite low because of the relatively few number of existing RCTs. In contrast to other antidepressants that may have lag times of weeks in improving depressive symptoms, ketamine has been shown to improve depressive symptoms, including anhedonia and suicidal ideation, within hours of administration. Moreover, reported improved mood was sustained for a week after a single dose of ketamine.

So, there is only budding evidence of ketamine’s overall efficacy. However, a recent longitudinal study that found a relationship between ketamine treatment and reduced suicidal ideation also found that shifts in anhedonia may be a mechanism through which ketamine causes reduction in suicidal ideation, even when considered independently of other depressive symptoms. Thus, further research examining ketamine as a biological treatment of anhedonia is warranted.

Amygdala neurofeedback and depressive symptoms
Expanding upon potential biological treatments afforded by ketamine, one recent RCT evaluated the effects of real-time functional MRI neurofeedback (rtfMRI-nf) from the amygdala in depressed patients. By utilizing an rtfMRI-nf approach, patients receive information regarding their blood-oxygen-level-dependent signal in real-time and learn to self-modulate this signal. As mentioned previously, the amygdala plays an important role in relation to depressive symptoms, with the logic behind rtfMRI-nf being that enhancement of processing of positive stimuli in the amygdala may provide treatment gains not otherwise seen in traditional therapy.

To this end, Young et al compared participants randomly assigned to receive rtfMRI-nf from either 1) the left amygdala or 2) the intraparietal sulcus, a region not readily activated in emotion regulation. Participants in both conditions were instructed to retrieve positive emotions while monitoring their own blood flow to the associated regions. Results suggest that training to enhance the amygdala’s hemodynamic response to positive memory recall was associated with a significant reduction in depressive symptoms in participants presenting with clinically significant symptoms. Although this approach has produced initial efficacious results, it may also prove beneficial to patients presenting with anhedonic symptoms, as general autobiographical recall is an important clinical correlate across depression and schizophrenia.

Evaluating novel anhedonia treatments
Overall, these treatments hold the promise of targeting reward processing deficits associated with anhedonia in a more precise manner than traditional depression treatments. The interventions discussed above aim to target positive affect and increasing positive experiences through sustainment and reward anticipation, unlike traditional depression treatments, including cognitive-behavioral therapy, which focuses mainly on targeting negative affect and reducing negative experiences. Although these traditional treatments have been shown to improve positive affect, even first-line treatments often fail to sustain these gains due to multiple obstacles to sustained symptom remission; thus, these treatments focusing on sustaining positive affect through savoring and attribution, and biologically based treatments have promise. Moreover, they have produced initially heartening results beyond treatment as usual interventions.

However, there are two important considerations that will need to be addressed by future research on these novel treatments. The first is empirical and will be answered by more well-controlled studies that can raise the evidence base. Additionally, future studies should further examine both these novel interventions and traditional depression treatments in order to investigate the effectiveness of the different
treatments in reducing negative affect and increasing positive affect. The second is theoretical and will be answered by careful contemplation of why some anhedonic individuals not only approach positive events but also actively avoid them.

**Moving forward with anhedonia research: the challenge of reward devaluation theory**

So far, a corpus of research outlines different elements of anhedonia (or entirely unique conceptualizations of anhedonia) that are core predictors of differential psychopathological states. Biopsychosocial context informs these assessments and has resulted in novel treatments, which suggest hope for a way forward for precision medicine approaches to anhedonia interventions.

However, extant interventions privilege increased and expanded experience of positive affect with the assumption that positivity is merely being undervalued (or processed dysfunctionally) by anhedonic individuals. These conceptual and treatment-based models do not address whether positive affect is being devalued because of its positive content due to fear of negative results, however.

In other words, a crucial consideration moving forward is how to cross the intersection of social and biological contexts when considering reward devaluation. Potentially all biological findings demonstrating deficits in reward learning and positive affect are limited by the possibility that some individuals with anhedonia may have a complex relationship with positivity that is only cursorily explained via brain dysfunction and impairment. This is because some individuals may exhibit attentional biases away from positive information due to a previous association of positivity with negative outcomes. Although prospective positivity may have once been viewed as rewarding, it is likely that it ended up being harmful and thus resulted in disappointment. Repeated disappointment in response to positive information may have thus created lasting, learned associations of positivity with negative outcomes; positive information is then viewed as a threat and can become more dangerous than neutral or even negative information.

The learned association that positivity has come to represent potential threat results in individuals devaluing positivity and avoiding what was once viewed as reward. Reward devaluation theory thus posits that individuals who devalue reward do not simply lack the ability to find positive information rewarding, but they instead actively avoid this information by diverting their attention away from positivity when exposed to it.

Extensive meta-analytic evidence supporting this theory suggests that depressed individuals exhibit such avoidance to positivity, consistent with other evidence of depressed individuals’ tendency to initially approach positive information but quickly avoid it due to their association of positivity with threat. Importantly, both depressed individuals and other clinical groups exhibit vigilance toward threat, but avoidance of positivity is unique to individuals with primary symptoms of depression.

Recent changes in anhedonia that include loss of interest or pleasure may be specific to individuals avoiding positivity. Thus, avoidance of reward is a crucial candidate variable for future research that will unpack how and why individuals develop and maintain anhedonic symptoms.

**Conclusion**

Anhedonia can be conceptualized and measured in a number of unique ways. This review has included considerations of social and physical context; of interest in (wanting) or experience of (liking) potential pleasure; and of the comparison of trait-level dispositional tendencies, state-level cross-sectional assessments, and symptom-based recent changes from baseline. We have also described translations of basic anhedonia research into treatment that hold future promise, including psychosocial (eg, PAT and PAI) and biological (eg, ketamine) treatments. We lastly offered a challenge to the field to consider how reward devaluation theory might expand upon current conceptualizations of anhedonia to include motivated avoidance of positivity as a potential target for research hypotheses and personalized treatment.

Anhedonia, as we have seen, is a complex and multifaceted construct. Future work should emphasize continued application of theoretically based operationalizations of anhedonia to continue the recent progress toward meaningful and specific use of the anhedonia construct in theory, clinical research, and treatment.

**Disclosure**

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