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REVIEW ARTICLE

Anhedonia and its intervention in depressive adults: New developments based on Research Domain Criteria (RDoC) in mental illnesses

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ABSTRACT

Anhedonia, as one of the core symptoms of depression, is of great significance for the diagnosis and treatment of depression. Traditionally, anhedonia has been referred to as "loss of pleasure", while the recent research emphasizes that anhedonia is a complex and multidimensional construct based on reward processing impairment. Exploring different manifestations of anhedonia and developing the corresponding interventions have become indispensable in the current research of depression. Based on the positive valence system of the Research Domain Criteria (RDoC), this paper firstly demonstrates that the anhedonia of depressive adults are mainly characterized by the impairments in anticipatory pleasure, incentive motivation/effort, and reward learning based on subjective rating, behavioral, and neurophysiological evidences, while the existing evidences for the consummatory anhedonia of depression are inconsistent. Additionally, we introduce the vulnerability–stress model, as the mainstream theory of anhedonia in depression, and also emphasize the role of dopamine system abnormalities and altered brain structures or functional networks underpinning reward processing in the pathogenesis of anhedonia. Furthermore, to reinstate reward processing in depressed adults, various effective interventions for anhedonia have been developed, including direct psychosocial interventions, indirect working memory training, and real-time neurofeedback training with functional magnetic resonance imaging (fMRI). Future research needs to deeply investigate the role of stress and gene polymorphisms in the etiology and mechanism of anhedonia in depression. Besides, more attention should be paid to social anhedonia in depressed individuals. And we also emphasize the need to further promote translational studies on the clinical interventions of anhedonia.

1 Introduction

Depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease [1]. In the Diagnostic and Statistical Manual of Mental

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Disorders 5th editon (DSM-5), anhedonia and depressive mood have been viewed as the two core symptoms of depression [2].

As one of the most salient endophenotypes of depression [3], anhedonia plays a critical role in the clinical diagnosis and treatment of depression. Many studies have demonstrated that anhedonia is a valid predictor of the course and severity of depression, suicidal ideation, and suicidal behaviors [4–8]. Particularly, the presence of anhedonia symptom can predict the poor outcome of antidepressant treatment (e.g., selective serotonin reuptake inhibitor) [9–11].

2 Defination and classification of anhedonia in depressed adults

Anhedonia is defined as loss of pleasure and interest in previous pleasurable or rewarding activities [2]. In contrast to early opinions, which regarded anhedonia as a unitary construct, accumulating studies have proved that anhedonia is a complex and multifaceted clinical symptom, which is essentially manifested as deficits in reward processing system. Using animal models, Berridge and Robinson have isolated the "wanting" system and "liking" system of reward [12]. Correspondingly, anticipatory pleasure and consummatory pleasure are not only dissociable but closely related structures in human's hedonic system [12–16]. Klein also indicated that distinguishing between anticipatory and consummatory pleasures was crucial to understanding and treating symptoms of anhedonia in depression [15]. Additionally, researchers have also proposed other structures, such as decisional anhedonia [16] and reward learning impairment [12, 17, 18].

The Research Domain Criteria (RDoC) in mental illnesses proposed by the National Institute of Mental Health (NIMH) provides a reliable framework for the structural classification of anhedonia. RDoC emphasizes to deconstruct currently defined higher order "criterion" symptoms into lower order functions, and promotes a units-of-analysis approach to study psychopathology that extends up to clinical variations and down to genetic and molecular levels [17, 19]. Among the six domains of RDoC, positive valence system is primarily responsible for responses to positive motivational situations or contexts, which can reflect different aspects of reward processing (Table 1). Different types of anhedonia in depressed adults based on this system were elaborated as follows.

2.1 Anticipatory anhedonia

Anticipatory anhedonia, closely related to the "wanting" system, refers to decreased pleasure in anticipation of upcoming activities, as well as the impaired ability to imagine stimulus, which is associated with motivation and goal-directed behaviors [12, 14, 15].

2.1.1 Evaluation methods

Self-reported scales. Temporal Experience of Pleasure Scale (TEPS), which is widely used in different population, has been developed to distinguish between anticipatory and consummatory pleasure only focusing on physical

Table 1 Constructs of positive valence system in RDoC

	Reward responsiveness	Reward learning	Reward valuation
Subconstructs	Reward anticipation	Probabilistic and reinforcement learning	Reward (ambiguity/risk)
	Initial response to reward	Reward prediction error	Delay
	Reward satiation	Habit	Effort

Source: https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/definitions-of-the-rdoc-domains-and-constructs.shtml

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pleasure [14]. In contrast, the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) is a self-report measure that evaluates individual differences in capacity to look forward to and enjoy social interactions. As noted, ACIPS theoretically contains anticipatory social anhedonia, but this component cannot be directly separated structurally [20, 21].

Experimental tasks. Monetary incentive delay (MID) [22] and affective incentive delay (AID) tasks [23], as established paradigms that differentiate anticipatory and consummatory phases, have been extensively used to investigate behavioral and neural responses of individuals to the processing of monetary or social rewards and punishments [24]. Typically, these tasks require individuals to make a quick response to the target (target response phase) after a delay that is preceded by a cue (anticipatory phase). The response is followed by a feedback (feedback phase). The limitation of MID/AID is that the pure appetitive motivation may not be measured in reward anticipatory phase, given that this phase precedes the rapid response rather than the potential reward [16]. Additionally, the gambling task, such as card-guessing [25], is another popular paradigm to examine neural responses during reward anticipation.

2.1.2 Empirical evidence

Studies have consistently shown that relative to healthy controls, depressed adults including depressed patients and subclinical depressed individuals report higher anticipatory anhedonia on self-reported scales [26–29]. However, the evidence on both behavioral measurements and subjective emotional ratings was mixed in depressive patients. For example, some studies found that patients with major depressive disorder (MDD) rated reward cue during anticipatory phase less positive as compared to controls [30, 31]. And patients also showed weaker reward-related reaction time modulation than healthy individuals, indicating blunted affective responses to gains in MDD [31]. However, other studies using the same tasks failed to show differences between the two groups on some indices [32, 33]. These mixed findings may reflect insensitivities of behavioral indexes in the prediction of depression.

In the level of neural activation, frontostriatal circuitry has been proven to play an important role in reward anticipatory/prediction processing [34]. But a variety of neuroimaging studies have found that depressed patients show abnormal activation in the frontal lobe and striatum during the reward anticipation. When anticipating monetary rewards, adult patients with MDD showed lower activation than controls in several brain areas related to reward processing, such as ventral striatum [33, 35], caudate [36], orbito-frontal cortex [23, 33], putamen [31], hippocampus [23], anterior cingulate cortex (ACC) [23, 35, 36], and middle frontal gyrus [36]. Yet, other studies have found different activation patterns [31, 32, 37]. Accordingly, using meta-analysis, Zhang et al. revealed significantly hypoactivation in the left caudate [38], but hyperactivation in the bilateral middle frontal gyrus and right anterior cingulate during anticipation of monetary rewards in MDD relative to healthy controls. Thus, although ventral striatum is considered to be a key area involved in reward anticipation [39], depressed patients do not exhibit abnormalities in the activation of ventral striatum compared to healthy individuals. Of note, hyporesponsivity in the caudate is more significant in MDD, which indicates a weaker perceived association between action and outcome [40]. And a previous research has found that bilateral caudate volume is inversely related to anhedonia symptoms [31], which further highlights the importance of structural and functional abnormalities of the caudate nucleus in understanding anticipatory

anhedonia. In addition, neuroimaging results have shown greater frontal area activation for the monetary anticipation in patients, wherein middle frontal gyrus is strongly related to monitoring incentive-based behavioral responses [41], and the dorsal ACC is related to affective conflict monitoring and value encoding of expected rewards [32, 37, 42]. Hyperactivation in such regions demonstrates that MDD patients may need to recruit relatively greater neural resources to encode and represent the value of anticipated rewards [38]. Moreover, for anticipation of pleasant image/social rewards, MDD patients have shown reduced brain activity associated with preparing for task-related action in the anterior paracingulate gyrus and supplementary motor cortex, compared to controls. Further, prior studies found relatively greater right putamen activation to monetary than to social rewards in MDD rather than in controls, suggesting that patients are less sensitive to social reward anticipation than to monetary rewards [23]. This account was supported by subclinical findings of impaired appetitive motivation to pursue rewards in hedonic deficit of subclinical depression [29].

Taken together, findings reviewed above indicate that depressed individuals, whether clinical or subclinical, show deficits in anticipatory pleasure. Neuroimaging studies consistently emphasize the role of dysfunction of frontal-dorsal striatal pathways in the deficit of anticipatory pleasure in depression [38, 43]. A most recent study has suggested that this phenomenon of anticipatory anhedonia should be accounted for by the deficits of episodic future thinking for positive events in depression [44].

2.2 Consummatory anhedonia

Consummatory anhedonia, dominated by impaired "liking" system, emphasizes the decrease of in-the-moment pleasure and hedonic response to reward stimulus, which reflects the abnormalities in reward satiation and resolution of desire [15].

2.2.1 Evaluation methods

Self-reported scales. In addition to TEPS and ACIPS, the most widely used questionnaire is Snaith-Hamilton Pleasure Scale (SHAPS), which is a cross–cultural scale and encompasses multiple domains of hedonic experiences [45, 46]. Due to measuring state anhedonia, SHAPS may be more sensitive to changes in anhedonia [47]. Fawcett–Clark Pleasure Capacity Scale (FCPS), another state questionnaire, also covers several domains of anhedonia [48]. However, FCPS can only measure part of the hedonic capacity, and its cross-cultural generalizability is undetermined compared to SHAPS [49]. In addition, the Chapman Anhedonia Scale (CAS) has been designed to measure trait, as opposed to state anhedonia in patients with schizophrenia, which is less used in depressed individuals [50]. Finally, the Dimensional Anhedonia Rating Scale (DARS) is a comprehensive scale integrating different types of anhedonia and reward deficits, which is specifically developed for the assessment of depression-related anhedonia. And one study has found that DARS can better predict treatment resistant status than SHAPS in MDD patients [51].

Experimental tasks. The first type of paradigms is the same as that used for anticipatory anhedonia. This line of paradigms focus on the feedback phase that reveals individual response to reward receipt during the assessment of consummatory anhedonia [23, 31, 52]. The second one is the emotional experience task that requires individuals to watch or process positively valenced stimulus implicitly or explicitly [53, 54]. The third one is the sweet taste test that provides another approach to assess consummatory pleasure [55, 56], which may be affected by taste sensitivity [57].

2.2.2 Empirical evidence

Using the self-reported measurements, there is

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mixed evidence for impaired consummatory hedonic capacity in depressed patients. Consistent with widely clinical observation, patients suffering from depression all reported significantly lower consummatory pleasure ratings [27, 29, 33]. Similarly, some studies found that patients showed reduced positive affect in response to positive stimulus [53, 58–60] and gain feedback [31], compared to healthy individuals. By contrast, some studies showed intact hedonic capacity in depressed adults using sweet taste [55, 56, 61], affective ratings of social reward or positive stimulus [23, 27, 62, 63]. The discrepancies above may be affected by the sensitivity of the paradigm to subjective evaluation, heterogeneity of depressed patients as well as individual differences in taste sensitivity.

In terms of physiological indices, depressive individuals exhibited significantly fewer facial expressions and electrodermal reactivity in response to the positive stimuli than nondepressed individuals [58, 60, 63]. Correspondingly, in terms of the startle reflex, an index sensitive to emotional valence, patients with high depression and anhedonia showed less startle reflex inhibition when watching positive film clips than healthy group, whereas patients with low depression/ anhedonia showed the same pattern as normal group, indicating reduced reactivity to positive stimuli in highly depressed patients [59, 64].

In the neuroimaging level, a bulk of evidence has demonstrated that depressed patients show abnormal reward-related brain activation during consummatory phase. For example, studies investigating neural responses to positive stimuli have found that patients in depression exhibit blunted activation in ventral striatum [65], putamen [66, 67], amygdala [54, 68], as well as parts of the temporal lobe [68–70], but greater activation in regions such as middle frontal gyrus [69, 70], relative to controls. In addition, patients have shown lower activation than healthy subjects when gaining monetary or social rewards in brain areas, such as mesial prefrontal cortex, putamen, caudate, nucleus accumbens, ACC, middle frontal gyrus, and insula [23, 31, 32, 36]. Notably, anhedonia in depression is associated with decreased caudate volume [31]. In contrast to this, several studies failed to find differences in brain activation between two groups during reward presentation [23, 33]. Hence, Zhang et al. conducted a meta-analysis of the neural responses to consummatory pleasure (excluding the results of emotional experience task) [43], which revealed that MDD patients exhibited significant hypoactivation to rewards of gain in left globus pallidus, right caudate body, left putamen, right insula, and left ACC, compared to healthy controls. These abnormalities in areas associated with reward processing may reflect the impairments of depressed patients in the representation of immediate hedonic value and incentive perception processing.

There are few studies focusing on consummatory anhedonia in subclinical depressed individuals. However, existing studies in subclinical depression have yielded inconsistent findings. A study has found no difference in consummatory scores on the TEPS between individuals with and without subsyndromal depression, indicating intact self-reported consummatory pleasure [29]. By contrast, other studies have shown significantly higher trait consummatory anhedonia on TEPS [26], as well as less positive affects in response to winning money in subclinical depression compared to healthy group [71].

Altogether, depressed patients show impairments in their ability to experience immediate pleasure to some extent, which is suggested to be independent of patients' current depressive state [56]. Yet, whether consummatory pleasure in subclinically depressed individuals is blunted remains to be further studied. Thus compared

with the clear anticipatory anhedonia in depressed adults, the importance of the consummatory hedonic capacity in depression is undetermined, which contradicts traditional conceptualization of anhedonia in depression.

2.3 Deficits in reward learning

Reward learning is a process by which individuals acquire information about stimuli, actions, and contexts that predict positive outcomes, and by which behaviors are modified according to one's experience of environment. The probabilistic reward task (PRT) [72] and reinforcement learning tasks, such as the Pavlovian reward-learning paradigm [73], the instrumental reward learning task [74], and probabilistic reversal learning task [75], are commonly used paradigms in laboratory research. In the PRT, participants are instructed to make a quick response to identify which type of stimuli (only two types) has been presented. And an asymmetrical reinforcement ratio is used, which means that the probability of receiving reward for correctly identifying one stimulus ("rich stimulus") is higher than that for another one ("lean stimulus"). Therefore, the task provides an objective measure of individuals' ability to regulate behaviors as a function of prior reinforcements [76], which can be well assessed by response bias. In addition, the ability of reinforcement learning is generally evaluated by learning rate, a core parameter calculated by computational model, which reflects the efficiency of utilizing prediction error information to update the value function [77].

With regard to behavioral performance, the available studies have consistently demonstrated that compared to healthy control, depressed adults show significantly blunted responsiveness to reinforcing stimuli in probabilistic reward learning, namely they are less likely to identify stimuli according to prior reward feedback. For instance, both clinical and subclinical depressed individuals exhibited lower response bias towards the rich stimulus than healthy group [26, 76, 78]. In particular, patients with high anhedonic symptom showed significantly impaired reward learning compared to low anhedonic patients [78]. Furthermore, a study examining reward learning in remitted MDD patients has also found that relative to controls, adults with remitted MDD show diminished reward responsiveness to the rich stimulus [79]. Consequently, impaired probabilistic reward learning in depressed individuals may be a trait-like abnormality, which could also positively predict the persisting diagnosis of MDD after 8-week treatment [78].

However, previous studies have reported mixed findings regarding depression-related reward learning using reinforcement learning tasks. On the one hand, consistent with the depression-related abnormality observed in probabilistic reward learning task, the study by Cooper et al. showed that subclinical depressed group performed worse and switched more between options than healthy control in reinforcement learning task [80]. Specifically, they over-learned from negative than from positive prediction errors, leading to more frequent switching and poorer reward maximization [80]. Further, several studies also reported diminished reward learning rate in depressive patients especially in suicide attempters relative to controls [81, 82]. Anhedonia was also positively correlated with impaired reward learning rate [81]. On the other hand, some studies have not found blunted reward learning rate among MDD patients, regardless of whether they have suicidal ideation or behavior [74, 75]. One possible explanation for this discrepancy is the heterogeneity of illness severity and reward-sensitivity in MDD. In addition, the type of reinforcer (water drops vs. correct/incorrect feedback) may be another influence factor. Water drops used by Gradin et al. are a specific primary reward, and there

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should be a strong motivation to meet physiological needs after water-need deprivation, which may partially mask the effects of depression/anhedonia [75]. By contrast, correct/incorrect feedback used by Chase et al. is a more abstract reinforcer that requires cognitive processing [81]. Depressed patients are more likely to exhibit blunted reward processing owing to impaired cognitive functions [77].

At the neural level, reward prediction error (RPE), another important aspect of reward learning, is defined as the discrepancy between expected and actual outcome, which plays a key role in predicting stimuli-outcome linking. Considerable evidence indicates that RPE signals are primarily calculated by dopamine neurons in the midbrain region (e.g., ventral tegmental area (VTA)) and then projected to other brain areas (e.g., striatum) [83–85]. Yet, several neuroimaging studies have suggested that depressive patients show abnormal RPE signals especially in VTA and ventral striatum relative to healthy individuals during reward learning. As for VTA, findings showed that the reward-learning signals appeared to be increased in VTA in middle-aged MDD patients [73] and remitted unmedicated patients with recurrent depression [86], compared to healthy controls. However, Gradin et al. have found that the VTA signals of MDD patients are weaker than that of the healthy group [74]. In this regard, Kumar and coworkers suggested that the increased VTA signal might reflect the compensation effect to the impairments in signal-receiving areas such as ventral striatum [73]. In contrast, Gradin et al. demonstrated that depressed patients exhibited overall RPE signal reduction in the mesolimbic dopamine system [74]. The difference between Pavlovian reward learning task and the instrumental reward learning task may have contributed to this inconsistency.

Additionally, compared to healthy controls, depressed patients show significantly blunted RPE signals in ventral striatum, which may be affected by antidepressants. To support this, studies revealed that individuals in a medicated state, including MDD patients and healthy groups, exhibited reduced reward-learning signals in ventral striatum in comparison with unmedicated controls [73, 74]. But recent studies on unmedicated MDD patients and medication-free remitted recurrent depression patients all failed to replicate this impairment [86, 87]. The role of antidepressants in reward learning mechanism in the brain remains to be further explored.

Overall, depressed adults exhibit a trait-related abnormality in reward learning, which is characterized by impairments in integrating reinforcement information and in modulating their own behavioral responses based on prior reinforcement history. And anhedonic symptom is a good predictor of this dysfunction.

2.4 Deficits in motivation/efforts

The motivation and efforts of reward pursuit are strongly associated with anticipatory pleasure. Accordingly, the motivation of obtaining rewards or willingness to make efforts for rewards plays an important role in anhedonia. The most common paradigm adopted in experimental study is the effort expenditure for rewards task (EEfRT) [88], which requires individuals to use the information about probability and magnitude of reward to choose between a "high-cost/high-reward" (HC/HR) and a "low-cost/low-reward" (LC/LR) option, in order to gain more monetary rewards ultimately. More difficult task choices denote higher motivation to obtain rewards.

Convergent evidence has revealed that compared to controls, both depressed patients and subclinical samples are less willing to expend efforts to obtain rewards, indicating significant impairment of incentive motivation. Specifically, clinical samples were less likely to choose

HC/HR option, and exhibited blunted ability to use reward information of magnitude and probability to guide choice behavior in comparison with healthy group [28, 29, 89]. And anhedonia was a strong predictor of lower HC/HR choices [29]. Similarly, Sherdell et al. also showed that anticipatory anhedonia in MDD patients could predict decreased motivation to make efforts for cartoon rewards [27]. In addition, a study using the incentive force task has found that potential monetary rewards fail to energize grip force production in depressed group [90]. In accordance with findings in patients, individuals with subclinial depression showed less preference for HC/HR options in EEfRT as well [29]. Furthermore, dysphoric compared with healthy individuals also showed blunted cardiovascular responses to effort mobilization for monetary [91, 92] and social rewards [93, 94], such as less motivated to enter own name in a public "best list", or to communicate with other participants to get more information about upcoming experiments through internet.

Together, the above evidence consistently suggests that depressive individuals, whether clinical or subclinical, exhibit impaired incentive motivation, and anticipatory anhedonia is a good predictor of reduced efforts for obtaining rewards. However, motivational deficits may be state-like, which appear to diminish with the relief of depressive symptoms [29]. Notably, the conclusion of motivational impairments in depressed samples is mainly based on objective indexes through behavioral or physiological recordings. It needs to be indicated that, in terms of subjective experience, depressed individuals reported similar or even higher efforts and motivation for gaining rewards than healthy individuals [90, 93]. This suggests that blunted motivation may lead depressed individuals to more laborious efforts during easy tasks [90].

In summary, anhedonia is a complex clinical symptom with multiple structures, and different subtypes of anhedonia are relatively independent in definition and research methods. However, contrary to the historical view of overall loss of pleasure, recent evidence for consummatory anhedonia in depression is mixed. Instead, impairment or abnormality in anticipatory pleasure, incentive motivation, and reward learning exhibited a more consistent prediction for anhedonia and major depression [94].

3 Theory and mechanism of anhedonia in depression

The onset of anhedonia in depression can be well explained by vulnerability–stress model. Vulnerability is a stable but changeable endogenous trait that includes genetic (biological) and psychological factors [95]. For anhedonia, Loas has demonstrated that hedonic ability is influenced by genetic factors [96]. Many studies have examined the effects of gene polymorphisms on different aspects of reward processing. During reward anticipation, Met/Met genotype of catechol-O-methyltransferase (*COMT*) genes has been associated with increased activation in ventral striatum (VS) and lateral prefrontal cortex (PFC) [97–99] and larger stimulus-preceding negativity (SPN) relative to Val carriers [100]. One study has also shown that individuals with the 9-repeat allele of a 40-bp variable number of tandem repeats (VNTR) polymorphism in the 3′ untranslated region of the dopamine transporter gene (*DAT1*) activate VS more than 10-repeat allele homozygotes [97, 101, 102]. And Jia et al. have found that during anticipation phase, the C allele of the sixth intron of the vacuolar protein sorting-associated protein 4A (*VPS4A*) gene locus is linked to decreased striatal node activation [103]. Moreover, as for consummatory hedonic capacity, research focusing on COMT Val/Met polymorphism has revealed that individuals with

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Met homozygotes show greater orbitofrontal cortex (OFC) activation [97] and larger the feedback negativity (FN) [100] to reward receipt than Val allele carriers. Boecker-Schlier et al. also reported that only for individuals with Met/Met genotype [98], their childhood family adversity was positively associated with left ACC and right VS activation in response to reward. And for *DAT1*, participants with 9-repeat allele have exhibited higher dorsolateral PFC, anterior PFC [97], and VS [52] reactivity compared to those with 10-repeat allele homozygotes. Furthermore, functional polymorphism in the dopamine receptor gene could also modulate the activation of reward-related brain regions during reward reception. For example, studies have found that relatively elevated VS activation is exhibited by individuals with A2 allele on the Taq1A dopamine receptor D2 gene (*DRD2*) site [104], the deletion (Del) allele of DRD2-141C insertion (Ins)/Del [52], and the 7-repeat allele of 48-bp VNTR within the dopamine receptor D4 gene (*DRD4*) [25]. In addition to dopamine-related genes, research has also paid attention to other genes. Dillon et al. found that *TREK1* gene had an effect on consummatory reward processing [105]. Specifically, compared to individuals in the at-risk groups, those in protected groups, namely with "protective allele" of *TREK1* gene (A allele carriers at rs10494996, G homozygotes at rs12136349 and rs2841616, C homozygotes at rs2841608), have shown greater basal ganglia responses to gains [105]. Moreover, research showed that the number of T alleles of rs322931 on chromosome 1 was positively associated with left VS activation during receipt the reward [106]. For reward learning, studies have demonstrated that Val allele carriers of *COMT* gene exhibit diminished reward learning capacity than Met homozygotes [107–109]. Meanwhile, other researchers found that S or L_G allele carriers of the serotonin-transporter-linked polymorphic region (5-HTTLPR) [110] and individuals with A homozygotes of the corticotropin-releasing hormone type 1 receptor gene (*CRHR1*) at rs12938031 showed greater stress-induced reward learning deficits [111]. All studies mentioned above have emphasized the effect of gene polymorphism at a single gene locus on reward processing, imaging genetics studies have also demonstrated that the multilocus genetic profile for dopamine signaling can better predict reward-related neural responses during reward processing [112, 113]. But notably, few studies have linked genetic polymorphisms to reward processing in depression [114]. In terms of psychological factors, the maladaptive attentional bias of depressed individuals, which is characterized by attentional biases toward negative stimuli and away from positive stimuli [80, 115–117], is closely related to anhedonia [118, 119].

The role of various environmental stressors has been also emphasized in this model. Converging evidence across species has shown a strong link between stress and the emergence of anhedonic-like symptoms [39, 120]. For example, chronic stress in rodents can induce decreased preference and intake of sucrose liquid [121], decreased motivation to obtain sucrose and social motivation [122, 123]. Similarly, exposure to stress can reduce self-reported rating of pleasure [124, 125] or reinforcement learning in humans [110, 111, 126].

In addition, anhedonia in depressed individuals is associated with abnormal neurophysiological mechanisms. At the molecular level, dopamine plays an important role in reinforcement learning and motivation salience [127, 128]. Originating from VTA and the pars compacta of the substantia nigra (SNpc), dopamine is projected to other brain regions through the nigrostriatal, mesolimbic, and mesocortical pathways [129]. Importantly, the mesolimbic and mesocortical dopamine pathways are implicated in reward processing. In depression, studies have found that

dopamine metabolites and dopamine transporter binding are reduced [39, 130], which may lead to abnormalities in reward processing in them. Notably, Pizzagalli has suggested, in the integrated model of depression, stress and anhedonia, that stress-induced anhedonic behaviors may be caused by altering mesolimbic dopamine system, such as downregulating the mesolimbic dopamine pathway and/or reducing dopamine transporter level [39]. Moreover, stress-induced anhedonia can in turn strengthen the relationship between stress and depression. At the structural level, anhedonia patients show abnormal brain structure and functional connectivity related to reward processing. For instance, MDD patients with severe anhedonia have exhibited reduced bilateral caudate volumes [31]. And compared with those without anhedonia, children with anhedonia have shown hypoconnectivity between the arousal-related cingulo-opercular network and reward-related ventral striatum area [131].

4 Psychological interventions for anhedonia in depression

Given that anhedonia has a negative impact on depression treatment, it is necessary to develop effective interventions for anhedonia to accelerate the remission of depression. Thus, we summarized existing studies of psychotherapies for anhedonia in depression, as in the following sections.

4.1 Positive imagery cognitive bias modification

Based on two cognitive targets: mental imagery and interpretation, Holmes et al. have developed positive imagery cognitive bias modification (PI-CBM), which can improve individual positive emotion [132], imagery ability, and interpretative bias [133–135]. This training may be used as an independent intervention or as a complement to existing treatments [136].

PI-CBM involves repeated generation of positive solutions through mental imagery when faced with fuzzy situations, so as to help individuals form an adaptive cognitive bias, which is to automatically carry out positive imagery in daily ambiguous situations [132, 137]. During this training, situation materials are presented in two ways including audio descriptions and picture-word pairs [133, 134, 137, 138]. Participants are instructed to imagine themselves in the scenarios as if actively going through them.

A multitude of studies have proved the effectiveness of PI-CBM. Such training has been shown to increase positive affects and positive interpretative bias in healthy and subclinical depressed samples [132, 133, 138]. Experimental studies of depressed patients not only found improvements in depressive symptoms, interpretative bias and imagery ability following this training [135, 139, 140], but also found reductions in symptoms of anhedonia [136, 141]. Specifically, PI-CBM could boost engagement in potentially rewarding activities in clinical samples [142].

Therefore, as a promising intervention that can be implemented based on Internet, PI-CBM has a significant effect on reducing anhedonia in depressed individuals.

4.2 Positive affect stimulation and sustainment

Positive affect stimulation and sustainment (PASS), which is an integral part of existing cognitive behavioral therapy, is mainly aimed at sustaining positive affective states. PASS uses the written disclosure paradigm to enhance and maintain positive emotions by savoring positive events, establishing positive attribution and expectancies. Based on behavioral activation, positive psychotherapy, and well-being therapy, this intervention enables individuals to better experience positive affects in positive events and emphasizes linking current positive events to positive expectations for future events [143].

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McMakin et al. found that female adults with dysphoric symptoms showed increased self-reported positive emotions from pre to post writing sessions and decreased depression symptoms from pre to post treatment, an effect absent with the control subjects [143]. These results indicated the efficacy of PASS on positive affective functioning, which describes cognitive, behavioral, and subjective manifestations of positive emotions.

4.3 Positive affect treatment

Positive affect treatment (PAT) is a stand-alone treatment scheme targeting the deficits of reward system in anhedonic individuals, which involves improvements in anticipatory pleasure, consummatory pleasure and reward learning. PAT is composed of three modules. The first module is the modified pleasant events scheduling, which increases positive reinforcement and improves anhedonia by listing and savoring activities that make individuals feel happy, valuable, or in control. The second one consists of some positive cognitive trainings, including identifying positive stimuli, recognizing contributions to positive outcomes and imagining positive future events. The last module is mainly designed to help individuals to savor and cultivate different kinds of positive experiences such as loving-kindness, generosity, appreciative joy and gratitude via audio-scripts [17].

Empirical evidence has confirmed that the techniques involved in PAT can enhance positive emotions and improve the components of the reward system. However, the therapeutic effect of PAT on anhedonia in depressed patients still needs further verification.

4.4 Positive activity intervention

Positive activity intervention (PAI), which is a new transdiagnostic treatment protocol, is designed to increase positive attentional bias and abilities to anticipate, experience, and maintain positive emotions [144]. In this intervention, the therapists assist individuals to increase positive emotional experience and awareness of personal strengths and values by writing about relevant information, participating in activities, savoring and imaging positive events, etc. Participants also need to engage in prosocial behaviors and activities, and cultivate emotions, such as kindness and gratitude, to promote the relationship between individuals and others. Through these processes, individuals can learn to monitor and record positive events well. Finally in the last module, individuals are required to work with therapists to develop personalized positive activity plans, which help them continue to be active after treatment [144].

In a small sample intervention study, Taylor et al. reported that compared to waitlist group, individuals with PAI treatment for anxiety and depression displayed more positive emotions and psychological well-being, as well as fewer negative affects and symptoms of anxiety and depression [144]. Meanwhile, these improvements were greatly maintained over 6-month following the end of treatment. Hence, PAI may be conducive to improvements in positive affect system and anhedonia in clinical anxiety and/or depression patients.

4.5 Positive attention training

Cooper et al. used the dot probe task, a positive attention training task, to improve the ability of reward learning in subclinical depressed individuals [80]. The results showed that on the reward maximization task, subclinical individuals who received placebo training performed worse and were more likely to switch to the sub-optimal choice following the negative reward prediction error than healthy control. However, there was no difference between dysphoric group with the training and non-depressive

controls on task performance and learning rate in positive and negative prediction errors, which demonstrated that reward learning deficits in depressive individuals could be effectively alleviated by positive attention training.

4.6 Amygdala-based real-time fMRI neurofeedback training

Real-time functional magnetic resonance imaging-neurofeedback (rtfMRI-nf) training allows individuals to receive information about the BOLD signal in a specific brain region in real time and learn to self-regulate the signal [145]. Evidence has suggested that amygdala, which plays the critical role in neurobiological models of MDD [146], is important for emotional processing and responses to positive stimuli [147], including autobiographical memories [148]. Thus, rtfMRI-nf training targeting amygdala may provide a promising way to regulate responses to positive stimuli in depressed individuals, resulting in increased positive emotions.

In this training, MDD patients are randomly assigned to receive rtfMRI-nf either from left amygdala or from horizontal segment of the intraparietal sulcus that is independent of emotional processing. The patients are instructed to retrieve positive autobiographical memories to raise the BOLD signal from the target region to a target level. Young and colleagues found that amygdala training group significantly upregulated BOLD signal in amygdala relative to their own baseline and control group [149, 150]. And the training effects were still retained in both the immediate transfer test and in the baseline test one week after the first training session. In addition, experimental group resulted in significantly larger increases in happiness ratings, as well as larger reductions in anxiety ratings from pre to post training, compared to control group.

Thus, depressed patients can successfully elevate the responses of amygdala to the recall of positive autobiographical memories and subsequently improve their positive emotional states using amygdala-based rtfMRI-nf training. And this training may have good short-term and long-term transfer effects.

4.7 Working memory training

Empirical researches have supported that anhedonia shares overlapping neural substrates with working memory, such as the prefrontal cortex and the striatum, which implies the potential effectiveness of working memory training on relieving anhedonia [151]. Zhang et al. used the dual N-back task to conduct a 20-session training for college students with and without subclinical depression [152, 153]. The results showed that this training significantly improved working memory performance and self-reported pleasure in both groups. However, the motivation index obtained in the affective incentive delay task (AID) and depressive symptoms were improved only in subclinical depressed samples after working memory training. And the changes in depressive symptoms were significantly correlated with improvements in anticipatory anhedonia [151].

Therefore, working memory training may be helpful in reducing symptoms of depression and anhedonia, especially anticipatory anhedonia.

These existing interventions, which have produced preliminary therapeutic effects, provide promising means for the treatment of anhedonia in depression. Among the interventions, PASS, PAT, and PAI all underline the critical role of savoring, positive attribution, and positive future imagination in treatments, while other interventions treat anhedonia from different perspectives, such as neurofeedback and working-memory trainings.

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5 Limitations and future directions

There are several limitations that need to be further addressed. First, the sample size of existing studies is small and the scope of population who benefit from the interventions is limited. For example, the efficacy of PASS has only been proven in female subclinical depressed individuals. Consequently, future research needs to further evaluate the intervention effect in a broader population, such as depressed patients of different gender, age, and those with or without medication at different stages of disease, etc. Secondly, the evaluation of intervention effect mainly focused on subjective measures (e.g., positive emotional experience rating), but less on objective measures. Thus, it is necessary to comprehensively evaluate the effectiveness of interventions by specific anhedonia scales, objective behavioral indices and neurobiological measures. Thirdly, most of the current interventions are based on positive valence system advocated by RDoC. However, the interaction between this system and other systems, such as negative valence system and cognitive system, also needs to be systematically evaluated [17]. In particular, the development of regulatory flexibility and thus avoiding over-emphasis on positive affect are highlighted in the intervention of depression [153]. This should be taken into account in future studies of anhedonia and its intervention.

Fourthly, as for the pathogenesis of anhedonia in depression, for one thing, the effect of gene polymorphisms on different components of anhedonia should be emphasized in gene research, especially on motivation deficits. Moreover, as mentioned above, it is necessary to further explore the relationship between gene and anhedonia in depressed populations. For another, recent research has emphasized the prominent role of stress in anhedonia of depression and its neurobiological mechanism in the synthesis and integrated model [39]. However, this account is mainly based on the preclinical evidence, and few studies to date have investigated the impact of stress on anhedonia in human subjects. In particular, though there is behavioral evidence of stress-induced anhedonia, whether the evidence is also associated with abnormalities in dopamine pathways, which has been proven in animals, needs to be further examined [39].

Lastly, research on different types of reward processing in depressed patients should be strengthened, especially with regards to social rewards. To date, most of research on reward processing in anhedonia focused on non-social rewards (e.g., money, sweet food/liquid), though social rewards are more crucial for humans' social functions. Social anhedonia, related to impairment in social reward processing, is manifested by deriving significantly less or even no pleasure from social situations [154], as well as diminished social interests [155]. Though current research extensively explored the impairment of social functions in patients suffering from depression, few studies have directly investigated social anhedonia in clinical population, particularly by comparing neurophysiological correlates between social reward and non-social reward processing in clinical samples, like depressive patients [156].

In conclusion, as a clinical symptom that is typical of depression, anhedonia is no longer a general concept of reduced ability to experience pleasure, but a multifaceted concept that includes anticipatory anhedonia, consummatory anhedonia, decreased motivation/effort, as well as impaired reward learning. Importantly, in these subcomponents, compared with consummatory anhedonia, anticipatory anhedonia and impairments in motivation and reward learning may play a more pivotal role in the symptoms of depression. In addition, a number of treatments

have been developed to address anhedonia in depressed individuals, which have changed the treatment of depression from targeting negative effects to strengthening that of positive effects. Future research needs to deepen the exploration of pathological and neurobiological mechanism of anhedonia using diversified technologies and methods, so as to provide more effective clinical diagnosis and treatment.

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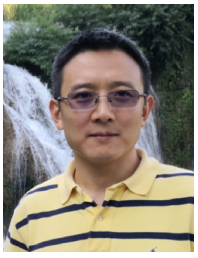

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