REVIEW ARTICLE OPEN

The characteristics of anhedonia in depression: a review from a clinically oriented perspective

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Anhedonia, as one of the core symptoms of major depressive disorder (MDD), has been regarded as a potential endophenotype of the disease. Multiple studies have evaluated the potential mechanisms of anhedonia in MDD, and found that MDD patients with anhedonia showed different functions in clinical features. In this review, we focus on the clinical research to explore the differences between MDD patients with and without anhedonia in the clinical manifestations and biological alterations, and elaborate the treatments and prognosis of anhedonia. It is demonstrated that anhedonia is associated with adverse outcomes including more severe depressive episode and suicidality, and poor prognosis in patients with MDD. At the biological level, MDD patients with anhedonia seem to present higher levels of inflammatory factors, abnormal metabolic function and hypermetabolism of BDNF. In brain imaging studies, there are some structural and/ or functional changes in multiple brain regions of subcortical and cortical areas, as well as the limbic system in MDD patients with anhedonia. Meanwhile, preliminary research findings have also indicated that there are associations between intestinal flora imbalance and anhedonia. Moreover, evidence indicated the benefit of some selective serotonin reuptake inhibitors seemed limited on anhedonia, and other treatments including psychotherapy, physical therapy and probiotic interventions has remained to be explored but has interesting potential. Therefore, increased awareness of the anhedonic symptoms and the unique clinical features would benefit improved early diagnosis and therapeutic effects in MDD.

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INTRODUCTION

Major depressive disorder (MDD) is one of the most common and disabling psychiatric disorders, which contributes a large health and economic burdens in the world [1]. In the last 30 years, it is estimated that the global prevalence of MDD has increased by almost 64%, and currently approximately 5% of adults suffer from depression [2]. The clinical course of MDD is often chronic and recurrent, and the disease is accompanied by heightened risk of suicide [3]. Moreover, MDD is widely considered as not a homogeneous entity but as a multidimensional syndrome. Subdivisions in different subtypes of depression based on different symptoms have received special emphasis in the literature due to the highly heterogeneous and diverse clinical manifestations of MDD [4, 5]. The strategic framework of personalized and precision medicine also highlights that a further discrimination of clinical characterization is crucial for individualized diagnosis and therapies of MDD patients.

Anhedonia has been highlighted in the diagnosis of depression and is a core feature of MDD. In depressed individuals, anhedonia has been demonstrated to have different functions in clinical features and prominently be associated with more severe depressive episode [6], more suicidality [7, 8] and poor response to anti-depressive treatments [9]. Meanwhile, accumulated studies have revealed that MDD patients with anhedonia showed different neurobiological characteristics including immune-inflammation, metabolism, brain structure and function, and others when compared with MDD patients without anhedonia [10–13]. Therefore, anhedonia may be a potential phenotype of MDD with some unique clinical and biological features, which needs paid more attention in clinical diagnosis and treatment. In this review, we focus on the clinical research to explore the differences between MDD patients with and without anhedonia in the clinical manifestations and biological alterations, and elaborate the treatments and prognosis of anhedonia. It would help to improve the understanding of anhedonia in MDD.

DEFINITIONS AND FEATURES OF ANHEDONIA

Anhedonia is defined as a loss of interest and/ or the capacity to experience pleasure in previously enjoyed activities. The word anhedonia was coined by a French psychologist in 1896 firstly referred to the total loss of both physical and psychic pleasure in melancholia. In the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III diagnostic criteria of MDD, anhedonia was first positioned as one of core symptoms of depression and had a clear definition as "loss of interest or pleasure in all or almost all usual activities and pastimes", which was similar to the current DSM-5 diagnostic criteria [14]. Unlike other features of sensory or

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cognitive, the actual experience of pleasure is an additional hedonic gloss generated by hedonic brain circuits. Different conceptualizations of anhedonia have been described based on the different perspective in the fields of psychology and neuroscience. Evidence from studies of hedonia suggests reward processing consists of three phases: wanting (the motivation for, or incentive salience of a reward), liking (the actual pleasure or hedonic impact of a reward), and learning (associations, representations, and predictions about future rewards based on past experience), which relate to the appetitive, consummatory and satiety phases of the pleasure cycle [15]. Based on this conceptualize, anhedonia is regarded as impairments in some or all of these processes, which to a great extent, reflected the composition in Positive Valence Systems of the Research Domain Criteria (NIMH) [16].

Therefore, anhedonia was initially characterized by a reduced ability to experience pleasure or interest in pleasurable rewarding stimuli. Currently, it could be roughly divided into two categories: anticipatory anhedonia (a reduced ability to experience pleasure in anticipation of rewarding events) and consummatory anhedonia (a reduced ability to experience pleasure from activities) [17]. MDD patients with anhedonia may manifest reduced motivation to participate in enjoyable activities, difficulty in planning and initiating activities, lack of enthusiasm or excitement for future events, difficulty to experience positive emotions during various activities, reduced enjoyment and frequency of social and entertainment activities [18]. Meanwhile, anhedonia is not a stable trait as it seems appears to change with progression of disease. Usually, the symptom is more severe during the acute phase of a depressive episode, however, is may also persist during the rehabilitation period [19].

ASSESSMENT OF ANHEDONIA

Anhedonia in MDD patients can be assessed in many ways, such as using one item from the Hamilton Depression Rating Scale (HAMD) or the Montgomery-Asberg Depression Rating Scale (MADRS), as well as using the direct symptom scales. One of the most common scales is the Snaith-Hamilton Pleasure Scale (SHAPS), which is a self-reported scale consisting of 14 items used to assess anhedonia in four domains (interests and pastimes, social interactions, sensory experiences and diet) [20]. The SHAPS is considered as the gold standard for measuring anhedonia in depression [21] and is used to distinguish the presence or absence of anhedonia in some previous studies [10, 22–24]. Besides, the Temporal Experience of Pleasure Scale (TEPS) is an 18-items self-report questionnaire and included two subscales that is designed to distinguish between anticipatory and consummatory pleasure [25] and the Dimensional Anhedonia Rating Scale (DARS) is a 17-item self-report questionnaire and could reflect the anhedonia in different domains of hobbies, social activities, food/drink, and sensory experience [26]. Moreover, some behavioral tasks combine with neuroimaging are helpful to identify the neurobiological underpinnings of anhedonia in MDD patients, which are more commonly used in research rather than in clinical practice [21].

CLINICAL MANIFESTATIONS OF ANHEDONIA

Prevalence

In depressed individuals, the prevalence of anhedonia is usually quite high, but varies depending on the population studied and the regions. Previous research has indicated that approximately 70% of patients with MDD showed clinically features of anhedonia [27]. Although the prevalence of depression is generally higher in women compared to men, there is no existing evidence of MDD with anhedonia for gender differences. Anhedonia occurs in MDD patients across the age spectrum, and is commonly observed in adolescents as well as adults. In adolescence, rates of depression increase significantly between 13–18 years [28] and the incidence of anhedonia was also relatively high, reported as approximately 74% [29]. In adult patients with MDD, a recent study utilizing data-driven approach demonstrated adult MDD patients (18–55 years) with anhedonia had older age, however, this work still be limited by the sample size [30]. Available evidence suggests that childhood trauma (CT) is also correlated with anhedonia, deprivation predicted anhedonia levels and trajectory in MDD [31]. In young adult patients with MDD, the degree of anhedonia was reported to be associated specific types of CT. Among them, emotional neglect had a stronger correlation with anhedonia in depression [32]. Moreover, Fan et al. reported that MDD individuals with moderate-to-severe CT suffered more severe state anhedonia than participants with no or low exposure and found that CT has effects on specific types of trait anhedonia and on core reward system [33].

Accompanied symptoms

Evidence demonstrated that patients with anhedonia have a different pattern of symptoms relative to those without anhedonia. An early article reported that MDD patients with extreme anhedonia were younger, more severely depressed and hopeless, while less neurotic than the patients with normal pleasure capacity [34]. In the investigation, the author found that the capacity to experience pleasure showed no improvement before other depressive symptoms get better when analyzed the clinical changes from hospital admission to discharge, while vegetative symptoms of depression such as sleep disturbance, weight loss, and fatigue, had no effect on the ability to discriminate anhedonic and hedonic depressed patients [34]. In the follow-up study, anhedonia has been demonstrated to have some relationships with other depressive symptoms. Lemke et al. interested in the relationship between anhedonia and psychomotor retardation in depressed patients and found that a significant correlation between the two symptoms when assessed with German version of the SHAPS and the Widöcher Retardation Scale (WDRS), respectively [35]. Moreover, Buckner et al. recruited 564 young adults with MDD to explore the influences of the presence or absence of anhedonia and sadness on the remaining DSM depressive symptoms as well as the symptom expression and clinical characteristics of MDD. In the study, the presence of anhedonia was found associated with severe social dysfunction, such as higher rates of social withdrawal and social impairment, reactivity of mood brooding about past events and diurnal mood variation (worst in mornings) [36].

Studies have established a relation between anhedonia and sleep disorders in MDD. A 14-day diary study including a hundred and seventy-one women conducted by Kalmbach et al. found that higher levels of depression-specific anhedonia predicted longer sleep-onset latency (SOL), shorter self-reported total sleep time (TST), and poor sleep quality (SQ) [37]. Besides, Wieman et al. conducted a supplementary study on two-hundred and sixty undergraduate students to explore the association between sleep disturbance and different stages of anhedonia and reward system functioning and found that poorer sleep quality, shorter sleep duration, and increased awakening after sleep onset are closely related to the reduction of anticipation and satisfaction reward response, while longer sleep start latency and poor sleep efficiency were only related to the impairment of satisfaction reward reactivity [38]. Similar findings were also demonstrated in neuroimaging studies of sleep disorders, which suggested the MDD patients with anhedonia more easily into comorbid clinical states over time [39, 40].

Deficits in cognitive function as a contributory factor to the psychosocial disabilities in MDD may throughout the whole course of the disease and hinder the achievement of complete remission of MDD [41]. In depressive individuals, previous evidence had

indicated that cognitive dysfunction and anhedonia were are closely related and interacted with each other. A longitudinal study compared the cognitive performance in the melancholic and non-melancholic subtypes of MDD and found that compared with non-melancholic MDD patients, melancholic MDD patients showed more severe impairment of executive control performance. After controlling for the severity of depression, the melancholic group showed worse performance in cognitive function tests [42]. As we known, melancholic depression is one of the common subtypes characterized by several specific symptom clusters, in which anhedonia has traditionally been conceptualized as one of the core symptoms and the key features of melancholic depression [43]. This evidence indirectly indicated the correlation between anhedonia and poor cognitive function. Moreover, a study of 369 MDD patients reported a significant correlation between self-rated cognitive impairment and anhedonia, as well as after adjusting for illness severity, which suggested MDD patients with anhedonia were more likely to show cognitive deficits [44]. Beyond that, a recent large sample investigation of 1400 patients with first episode of depression and 487 patients with recurrent depression indicated that recurrent depressive patients presented broader cognitive impairment and anhedonia symptoms, while cognitive decline was significantly related with the many aspects of anhedonia in both MDD groups [45].

Suicidality

The suicidal risk in anhedonic patients has attracted much attention in recent years. Previous research has shown that anhedonia was closely associated with suicidality in major affective disorder. Oei et al. conducted a cross-sectional study of 46 patients with depressive symptoms and found that among the patients, seventy one percent of these patients with anhedonia presented suicidal ideation. Meanwhile, the level of anhedonia was positively associated with suicidal ideation scores [46]. A cohort of 586 persons from the Netherlands Mental Health Survey and Incidence Study also reported the significantly related between suicidality and anhedonia in depressive spectrum disorder [7]. Fawcett et al. studied 954 psychiatric patients with major affective disorders and found that nine clinical features including anhedonia were associated with suicide occurring after one year. The symptom of anhedonia was considered as one of the traits of suicide attempters [47].

Moreover, anhedonia attached great importance to predict suicidal ideation in MDD patients. Winer et al. conducted a study to examine the relationship between anhedonia and suicidal ideation at baseline, at termination, and over time in a large psychiatric inpatient sample ($N = 1529$) and found that the two symptoms are significantly correlated cross-sectionally at baseline and at termination [48]. Moreover, longitudinal observations from baseline to termination have discovered the changes in anhedonia could predict the changes in suicidality and the level of suicidality at termination. Ballard et al. found the anhedonia, independent of other depressive symptoms, was associated with suicidal ideation [49] and it could be decreased by treatment to reduce the risk of suicidality, which were was confirmed in other non-clinical and clinical investigations [50]. A meta-analysis including 15 observational case–control studies conducted by Ducasse et al. aimed to investigate the anhedonia differences in individuals with and without current suicidal ideation and reported higher level of anhedonia in patients with current suicidal ideation than those without current suicidal ideation with a medium effect size. When the factors of depression and psychiatric disorders were controlled for, there still remained a significant association between anhedonia and current suicidal ideation, which suggested that anhedonia remained a robust protective predictor of suicidal ideation independent of depressive symptoms [51]. Recently, Ding et al. conducted a study based on a national multi-centered prospective cohort ($N = 1461$) to explore the trajectories and predictors of suicidal ideation (SI) in MDD patients and found that compared to those with a consistently low SI trajectory, a higher score of anhedonia was associated with an increased risk of experiencing persistently mild (RRR = 1.20, 95% CI: 1.05, 1.38) and slowly declined SI (1.54, 95% CI: 1.32, 1.80), which suggested anhedonia might be a core risk factor for suicidality and treatment or intervention targeted anhedonia are critical for suicidal prevention [52].

With deepening exploration on different dimensions of anhedonia, some studies made extension upon prior research. Sagud et al. used revised Physical Anhedonia Scale (RPAS) and the revised Social Anhedonia Scale (RSAS) to divided the physical and social anhedonia in MDD, schizophrenia, and health controls and found that MDD patients with physical and social anhedonia (respectively referring to an inability to feel physical pleasure and a diminished capacity for pleasure in social activities) showed greater rates of recent suicidal ideation, while only MDD patients with social anhedonia presented a higher frequency of individuals with life-time suicide attempts [53]. Meanwhile, considering the roles of state and trait anhedonia in suicidality, Yang et al. conducted two studies in two undergraduate samples and found state social anhedonia was positively associated with suicidal ideation and it was a margin significant predictor of suicidal ideation [54]. However, trait social anhedonia is not a directly factor for suicidal ideation, it indirectly effected suicidality by other risk factors such as thwarted belongingness, perceived burdensomeness [54]. In psychiatric outpatients, Hawes et al. reported similar results that patients with acute, state-like anhedonia showed higher levels of suicidal ideation when compared to the patients without anhedonia, while no differences of suicidal ideation were found between patients without chronic, trait-like anhedonia and the patients without anhedonia [55]. However, the conclusions of the effect of different anhedonia for suicidality remain inconsistent. Two studies including 2189 undergraduate students both showed that recent changes in anhedonia, but not trait and state anhedonia were associated with recent suicidal ideation [50]. Hein et al. also reported that trait anhedonia in patients with severe major depressives associated with recent suicidal ideation, while in mild or moderate depression, the recent change of anhedonia had a correlation with recent suicidal ideation [56]. A recent meta-analysis of 20 studies and 11,212 individuals conducted by Gillissie et al. had a more comprehensive assessment in aspects of suicidality and components of anhedonia. The results of the study demonstrated all general, anticipatory and consummatory domains of anhedonia were significant correlation with suicidality in both general and psychiatric populations, which further supported that anhedonia was a risk factor for suicidal behaviors [57].

BIOLOGICAL INDICATORS OF ANHEDONIA

Inflammatory markers

Inflammatory changes have been received much attention in the field of onset and development of depression in recent years. Hundreds of literatures demonstrated that, when compared with healthy controls (HCs), MDD patients exhibited low-level inflammation with mean increases in systematic inflammatory molecules, including elevation of inflammatory cytokines, chemokines, adhesion molecules and acute phase proteins in peripheral blood [58–60]. Meanwhile, excessive inflammation has been demonstrated to be closely related to the pathological process of anhedonia and depression. Previous clinical and animal studies demonstrated that inflammation impacts brain neural circuit and neurotransmitter system involving multiple and complex biochemical pathways, including reducing the synthesis, release and reuptake of dopamine, increasing synaptic and additional synaptic glutamate, and activating the metabolites of the kynurenine pathway, thus leading to reduced motivation and loss of interest

in MDD [61]. Felger et al. reported that hyperinflammation, especially C-reaction protein (CRP) and interleukin (IL)-6 levels, was closely related to abnormal functional connections of reward processing in the brain in MDD [62]. Besides, Jha et al. found that higher levels of IL-17, Th1-, Th2- and non-T- cell markers were associated with greater severity of anhedonia in MDD which highlighted the effect of immune dysfunction on depressive symptoms, specifically on anhedonia [63]. In addition to these indirect evidences, increasing clinical studies have directly compared the different levels of inflammatory factors between MDD patients with anhedonia and without anhedonia and found the increased inflammatory factors levels in anhedonic MDD. Lu et al. found that plasma IL-6 levels in MDD patients with anhedonia, but not in MDD patients without anhedonia, were higher than those in HCs, which were also positively correlated with the severity of anhedonic symptoms in MDD patients [12]. Tang et al. found that MDD patients with anhedonia presented higher levels of IL-6 and complement Factor H than patients without anhedonia, which extended our results [10]. Similarly, Li et al. found higher serum levels of IL-2, IL-6, and CRP in anhedonic MDD than in nonanhedonic MDD, and proposed a combination of IL-6, CRP, and cortisol could be used to distinguish anhedonic MDD with optimal predictive value [24]. Felger et al. indicated that the higher scores of anhedonia in MDD patients showed higher concentrations of plasma CRP than those with low anhedonia. The authors found that higher plasma CRP had a power to predict high anhedonia by logistic regression in both males and females [64]. Moreover, in adolescents, it was reported by Freed et al. that only symptom of anhedonia rather than depressive symptom was associated with multiple inflammatory factors including TNF-α, IL-2, IL-4, IL-6, IL-10, and IL-17A [65]. Rengasamy et al. explored the longitudinal relationships of cytokines, depression and anhedonia in depressed adolescents and found that increased baseline levels of Tumor necrosis factor-alpha (TNF-α) were positively associated with baseline anhedonia as well as predicted higher anhedonia [66]. Therefore, although there are currently few small sample studies on the levels of inflammatory factors in patients with anhedonia, C-reactive protein, IL-6, TNF-α and other inflammatory factors or receptors may still be potential effective biological markers, which can help classify subtypes of anhedonia in depression.

Metabolism indicators

Recent studies reported anhedonic symptoms were associated with metabolic disorders. In patients with type 2 diabetes (T2D), it was found a significant association between anhedonia and suboptimal glycemic control [67], and similar results have also been confirmed in individuals with hypertension [68]. Meanwhile, Singh et al. conducted a neuroimaging study in forty-two MDD patients with overweight young people and found that individuals with higher levels of anhedonia showed greater insulin resistance (IR), which was associated with reduced anterior cingulate and hippocampal volumes, and increased cingulate-hippocampal network connectivity at rest [69]. Moreover, Brouwer et al. used the secondary analysis of data from a randomized, placebo-controlled, parallel-arm clinical trial in 59 patients with depression and T2D and found higher IR individuals showed more symptoms of irritability, anhedonia, fatigue and hypersomnia than those with lower IR [70]. Similar results were proved by Rashidian et al. who investigated the effect of insulin resistance (IR) on treatment response to vortioxetine in MDD patients in a secondary analysis of an 8-week, open-label clinical trial and found a significant baseline IR by time interaction for the severity of anhedonia, cognition and functional capacity when adjusted for age, gender, dose, and BMI. The authors also indicated that a higher baseline IR could predict slower improvements in anhedonia during the therapy of vortioxetine [71]. Nasca et al. reported an increased concentration of the insulin receptor substrate-1 (IRS-1) in circulating brain-enriched exosomes (L1CAM) exosomes in MDD patients, which was positively associated with anhedonia [72].

MDD patients with anhedonia had different lipid parameters and metabolic states compared with those without anhedonia, which related to adverse clinical events and all-cause mortality. Moreira et al. recruited a sample of young adults aged 24–30 years old from the community to investigate the association between anhedonia and metabolic syndrome (MetS) in individuals diagnosed with a current depressive episode, and found that depressive individuals with anhedonia had a higher prevalence of metabolic syndrome than those without anhedonia. Moreover, a significant higher level of glucose, triglycerides, total-cholesterol and low density lipoproteins (LDL)-cholesterol, but significant lower levels of high density lipoproteins (HDL)-cholesterol were observed in depressive individuals with anhedonia when compared with those without anhedonia, which suggested anhedonia may contribute to development of MetS [11]. Su et al. compared the blood lipid profile between unipolar and bipolar depressed patients, as well as in the depressed patients with anhedonia or suicidal thoughts and reported that a lower lipid levels and insulin resistance index, as well as a higher levels of T3 and FT3 in bipolar group. In subsequent analyses of the effect of anhedonia on the levels of these biochemical parameters, they found that depressed patients with anhedonia had significantly increased levels of LDL when compared with those with non-anhedonia [73]. Moreover, previous studies showed that anhedonia is independently associated with major adverse clinical events and it could predict a shorter survival time in patients with type 2 diabetes [74]. These evidences reflected the abnormal metabolic function in MDD patients with anhedonia and highlighted the importance of exploring the association between anhedonia and metabolism.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophic family and play a prominent role in the survival, differentiation, growth and development of neurons in the central nervous system including hippocampal, cortical, cholinergic, nigral dopaminergic, and serotonergic neurons [75]. BDNF is initially synthesized as a precursor protein, proBDNF, which is cleaved into mature BDNF by extra-synaptic proteases; mature BDNF acts a beneficial role in cell survival and neural development via its primary receptor tropomysin-related kinase B (trkB), however, proBDNF, in contrast to its mature version, acts as a proapoptotic chemical [76, 77]. Recent studies have demonstrated the close relationship of neuronal levels of neurotrophic factors and reward-related processes and hedonic impairment in MDD. Wu et al. investigated the dysfunction of BDNF metabolism in MDD patients with and without severe anhedonia, and reported a statistically differences in the ratio of mature brain-derived neurotrophic factor (BDNF) to precursor-BDNF in MDD patients with and without anhedonia. The authors found a higher level of the ratio of M/P and the increased plasma tPA concentrations in MDD patients with anhedonia when compared with MDD patients without anhedonia, as well as with HCs and observed a significant positive association between the ratio of M/P and the severity of anhedonia in the depressed patients, which might suggest that hypermetabolism of BDNF could be a function of anhedonia in MDD [78]. Besides, Zheng et al. observed that baseline proBDNF levels were associated with changes in anhedonic symptoms and in antianhedonic responders to repeated doses of ketamine presented higher baseline proBDNF levels than antianhedonic nonresponders, which suggests that baseline proBDNF levels may predict the antianhedonic effect in individuals with MDD treated with repeated doses of ketamine [79]. Martinotti et al. found that an increase of BDNF serum levels after a 2-week treatment with agomelatine, which were be greater in MDD patients with severer anhedonia at baseline [80].

Neuroimaging markers

Numerous evidence in humans and animals suggests that the core mechanism of anhedonia is reward circuitry or network deficits in the brain, which including ventral tegmental area (VTA), the nucleus accumbens (NAc), ventral striatum, prefrontal cortex (PFC), amygdala, hippocampus and other areas [15, 81]. The relationship and interconnections of these involved regions is complex and different brain regions present specific behavioral functions, which is linked to different stages of reward processing. Ventral striatum including the NAc as the reward center of the brain is associated with the recognition and initiating consumption of rewards. It receives dopaminergic projections from VTA constitute the classical dopaminergic mesolimbic pathways [82–84]. Different PFC subregions have the multiple reciprocal connections with the NAc, VTA, amygdala and hippocampus, as well as in each subregion, which play an important role in regulating the behavioral response to rewards [85, 86]. Moreover, the amygdala is involved in the evaluation of rewards and associated with the reward-related memories and the hippocampus is essential for the encoding and retrieval of declarative memories in working memory [87, 88].

Literatures have found that MDD patients with anhedonia seemed to present unique changes in structure and function in reward-related regions, as well as the abnormal networks. However, although dynamic information about brain function could better accurately reflect brain activity, the studies on electroencephalogram exploring the changes of MDD patients with anhedonia is rare. Zotev et al. reported the effects of simultaneous real-time functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) neurofeedback in MDD evaluated with brain electromagnetic tomography and found the relation between changes of prefrontal upper alpha density and the severity of anhedonia in MDD [89]. Therefore, following discussion reviews the differences of MDD patients with and without anhedonia based on the clinical imaging findings, which are mostly focused on the brain structure and function. Lu et al. reported that more severe atrophy in the left striatum in MDD patients with anhedonia than those without anhedonia and HCs [12] as well as the severity of anhedonia was associated with reduced bilateral caudate volume in MDD patients [90]. Enneking et al. found that higher social anhedonia was associated with reduced gray matter volume in the bilateral caudate nucleus in MDD, which independently of diagnosis, depression severity, medication status, and former course of disease [91]. Meanwhile, Wu et al. found that MDD patients presented significantly reduced volumes in the left hippocampus head when compared with HCs, and only MDD patients with anhedonia further exhibited significantly reduced volumes in hippocampal subfields, including the cornu ammonis (CA) 1, granule cell layer of the dentate gyrus (GC-ML-DG), and molecular layer (ML), which suggested that MDD patients with anhedonia exhibit unique atrophy of the hippocampus [92]. Mu et al. investigated the volume changes of various parts of the subcortical limbic (ScLimbic) system in MDD with and without anhedonia and found MDD patients with anhedonia showed volume reductions in the left bilateral fornix (Fx) and the right basal forebrain (BF) when compared with HCs. No significant difference was found in the volumes of ScLimbic system between MDD patients without anhedonia and HCs, either the two groups of MDD patients [93]. Besides, Ma et al. observed significant differences in functional connectivity (FC) values of VS, ventromedial prefrontal cortex (vmPFC), presupplementary motor area (Pre-SMA), and left thalamus (THA) regions when comparing MDD patients with and without anhedonia. Correlation analysis in the MDD group revealed that the FC between the right VS and right NAc, left THA and left cerebellum crus1 were positively correlated with anhedonia severity, and the FC between the Pre-SMA and the right caudate, vmPFC and the left medial orbital frontal gyrus in the MDD group presented negatively correlated with anhedonia severity [13]. Lu et al. found the anhedonic group showed a significantly aberrant interhemispheric functional connectivity in middle temporal gyrus and inferior parietal lobule and bilateral superior frontal gyrus when compared to the non-anheodnic group [23]. Moreover, a significantly decreased regional homogeneity (ReHo) in the left superior frontal gyrus and left middle cingulate gyrus was found in the anheodnic group when comparing to HCs, while there was no significant difference of regional homogeneity between non-anheodnic group and HCs, which suggested disturbed intrinsic brain function in the frontal-limbic regions may be associated with anhedonia in MDD patients [22]. These results suggest MDD patients with anhedonia may have unique changes in brain structures and functions.

Gut microbiota

Recently, the role of the gut microbiota in psychiatric disorders has become a research hotspot. The gut microbiota as a key regulator within the gut-brain axis impacts cognition and mood through neural, metabolic and hormonal pathways [94]. Indeed, bacterial species not only can modulate serotoninergic, noradrenergic, dopaminergic, glutamatergic, and gamma-aminobutyric acid (GABA) neurotransmission but also produce these neurotransmitters and their precursors by themselves [95]. Gut microbiota as a topic of great interest and a new frontier in biomedical research, mainly focus on the impact on depression or other psychiatry disorders, however, the research on different symptoms and subtypes needs to be done more extensively. Therefore, considering no existing clinical study has demonstrated that differences of MDD patients with and without anhedonia in gut microbiota, we review the preclinical and clinical studies to investigate the association between gut microbiota and anhedonia.

In preclinical studies, Kelly et al. carried out a fecal microbiota transplantation from depressed patients to a microbiota-deficient rat model and found that the receiving animals presented anhedonia and anxiety-like behavior, as well as alterations in tryptophan metabolism [96]. Meanwhile, Wang et al. found two microbes (*Lactobacillus intestinalis* and *Lactobacillus reuteri*) could induce the phenotype of anhedonia in antibiotic-treated mice. Clinical studies on MDD showed that lower diversity of bacteria and difference in abundance among bacterial groups [97]. In clinical studies, Minichino et al. confirmed that alpha diversity was a directly and significantly associated with anhedonia or amotivation, and the faecal levels of the endocannabinoid palmitoylethanolamide (PEA) mediated this association [98]. Mason et al. found that cluster with higher *Bacteroides* and reduced presence of *Clostridales* presented higher anhedonia scores in participants with co-occurring depression and anxiety, which suggested the reduced anti-inflammatory gut microbiota were associated with anhedonia [99]. In addition, a recent study leveraged the microbiome to understand clinical heterogeneity in depression and identified three co-occurrence networks using 16S rRNA sequencing. The symbiotic module rich in butyrate producing bacteria is significantly correlated with depression, anxiety and anhedonia in patients with depression, reflecting the relationship between different communities of gut microbiota and clinical phenotypes in MDD [100]. Subsequent research on the relationship between anhedonia subtype of depression and gut microbiota may also be a be a promising direction.

TREATMENTS OF ANHEDONIA

Evidence has indicated that some selective serotonin reuptake inhibitors (SSRIs) seem not benefited to treat hedonic impairment in MDD and most antidepressants were no obvious collinearity in the treatment of anhedonia and other depressive symptoms [27]. Meanwhile, the recent systematic review has reported that some novel antidepressants as vortioxetine, agomelatine and ketamine

seem be more effective for the treatment of anhedonia in MDD [27].

Psychological therapies are also important alternative or adjunctive interventions for MDD. Evidence revealed the cognitive behavioral therapy (CBT) and behavioral activation (BA) are only partially effective in treating anhedonia and there was no further significant improvement in anhedonia during the follow-up phase. Meanwhile, the recovery of anhedonia was even less marked than depression and more severity of baseline anhedonia could predict poorer depression treatment outcome [101]. Dunn et al. found that a novel intervention of augmented depression therapy (ADepT) was better than CBT in the treatment of anhedonia in a pilot randomized controlled trial, which need a larger multicenter pragmatic trial to test [102].

Moreover, the imaging features of anhedonia provide clues for neuromodulation intervention, which is also called noninvasive brain stimulation (NIBS). Despite that there are not many studies on this aspect, the latest systematic review including twelve articles also reported a large effect size for NIBS on anhedonia, which suggests that neuromodulation intervention may have therapeutic potential in MDD patients with anhedonia [103]. Kong et al. reported that the anodal transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex (DLPFC) significantly improved anhedonia in MDD patients, which might be a potential adjuvant therapy for anhedonia [104].

Gut microbiota modulation with probiotics is widely believed to be a novel, potential and customizable treatments in MDD and has become a hot topic in recent years. However, probiotics as medical therapies for depression subtypes are still in infancy stage; clinical evidence is still limited. Some animal studies reported that some probiotics including *L. helveticus, L. plantarum, L. paracasei, L. kefiranofaciens, B. infantis*, and *B. breve* could increase the preference of sucrose in depressed rodents and improve the symptoms of anhedonia, and more clinical data are needed [105].

OUTCOMES AND PROGNOSIS OF ANHEDONIA

Research evidence shows that anhedonia is one of most common residual symptoms in MDD [106], which would make patients lack of treatment efficacy experience, and then contribute further to reduce the therapy compliance and increase the risk for relapse of depressive episodes [107, 108]. In adolescent major depression, anhedonia as a hallmark may have the potential to predict the risk of later adult depression [109] and the severity of anhedonia was inversely correlated with the number of depressive symptoms and depression severity at admission and the discharge [110]. Meanwhile, some MDD adolescents exhibited enduring anhedonia, which were not improved significantly by discharge [110]. Similarly, Gabbay et al. found that only the high-anhedonia subgroup in adolescents with MDD manifested greater illness severity, number of MDD episodes, episode duration, and suicidality scores, which represented more severe outcomes [6]. Anhedonia in MDD have been associated with chronicity and severity in multiple investigations and have been regarded as a driver of treatment-resistance in MDD [111]. It seemed that MDD patients with anhedonia presented poorer response to some antidepressant treatments. Moreover, a large cohort of patients with MDD conducted by Vinckier et al. revealed the anhedonia was closely tied to the persistence of psychosocial dysfunction, and the authors proposed that anhedonia is one of the strongest predictors of psychosocial functioning, along with symptomatic remission [19]. In a recent systematic review, Huang et al. investigated anhedonia with health-related quality of life and/or functional outcomes in MDD and found MDD patients with symptoms of anhedonia are more likely to have worse prognosis including physical, psychological, and social functioning deficits, which suggested that anhedonia might be an important predictor and target for future therapeutic and preventative tools in MDD patients [112]. These evidences suggested that anhedonia is associated with worse course and treatment outcomes, suggesting anhedonia as depression subtype increased the complexity of clinical decision-making.

CONCLUSION

Anhedonia, as a potential endophenotype of MDD has received great attention in recent years. In depressed individuals, anhedonia is common and closely associated with the other clinical symptoms, and it is a relevant risk factor for possible suicidal behaviors, which remaining a robust protective predictor of suicidal ideation independent of depressive symptoms. At the biological level, comparing with MDD patients without anhedonia, MDD patients with anhedonia presented higher levels of inflammatory factors, abnormal metabolic function and hypermetabolism of BDNF. In brain imaging studies, there are some structural and/ or functional changes in multiple brain regions of subcortical and cortical areas, as well as the limbic system in MDD patients with anhedonia. Meanwhile, preliminary research findings have indicated that there are associations between intestinal flora imbalance and anhedonia, but this is still under investigation. Moreover, MDD patients with anhedonia seemed to have poor prognosis and is linked to treatment-resistance, the benefit of some selective serotonin reuptake inhibitors seemed limited on anhedonia, and other treatments including psychotherapy, physical therapy and probiotic interventions holds tremendous potential.

In conclusion, abundant evidence indicates that MDD patients with anhedonia have unique clinical and biological features. However, there are still some deficiencies in the present research for MDD patients with anhedonia. Firstly, anhedonia is a subjective experience, largely depending on the ability to articulate individual's feelings and/or experiences as well as the physician's impression and expertise skills. Although some scales were used to measure anhedonia in MDD patients, but the scales chosen and metric varied across studies. Meanwhile, there is still a lack of comprehensive and systematic evidence, especially in many aspects such as the differences of the dynamic changes of the brain, mass spectrometry imaging and gut microbiota in MDD patients with and without anhedonia, which might be the potential directions for future studies. Lastly, how to safely and effectively treat the patients with depressive subtype characterized by anhedonia is still a research hotspot, targeted treatment strategies are needed.

REFERENCES

1. Liu Q, He H, Yang J, Feng X, Zhao F, Lyu J. Changes in the global burden of depression from 1990 to 2017: findings from the Global Burden of Disease study. J Psychiatr Res. 2020;126:134–40.
2. Collaborators GBDMD. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9:137–50.
3. Marx W, Penninx B, Solmi M, Furukawa TA, Firth J, Carvalho AF, et al. Major depressive disorder. Nat Rev Dis Primers. 2023;9:44.
4. Kung B, Chiang M, Perera G, Pritchard M, Stewart R. Identifying subtypes of depression in clinician-annotated text: a retrospective cohort study. Sci Rep. 2021;11:22426.
5. Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD. Distinct symptom-specific treatment targets for circuit-based neuromodulation. Am J Psychiatry. 2020;177:435–46.
6. Gabbay V, Johnson AR, Alonso CM, Evans LK, Babb JS, Klein RG. Anhedonia, but not irritability, is associated with illness severity outcomes in adolescent major depression. J Child Adolesc Psychopharmacol. 2015;25:194–200.
7. Spijker J, de Graaf R, Ten Have M, Nolen WA, Speckens A. Predictors of suicidality in depressive spectrum disorders in the general population: results of the Netherlands Mental Health Survey and Incidence Study. Soc Psychiatry Psychiatr Epidemiol. 2010;45:513–21.

8. Auerbach RP, Millner AJ, Stewart JG, Esposito EC. Identifying differences between depressed adolescent suicide ideators and attempters. J Affect Disord. 2015;186:127–33.
9. Vrieze E, Demyttenaere K, Bruffaerts R, Hermans D, Pizzagalli DA, Sienaert P, et al. Dimensions in major depressive disorder and their relevance for treatment outcome. J Affect Disord. 2014;155:35–41.
10. Tang W, Liu H, Chen L, Zhao K, Zhang Y, Zheng K, et al. Inflammatory cytokines, complement factor H and anhedonia in drug-naive major depressive disorder. Brain Behav Immun. 2021;95:238–44.
11. Moreira FP, Jansen K, Cardoso TA, Mondin TC, Vieira IS, Magalhaes P, et al. Metabolic syndrome, depression and anhedonia among young adults. Psychiatry Res. 2019;271:306–10.
12. Lu S, Wu C, Jia L, Fang Z, Lu J, Mou T, et al. Increased plasma levels of IL-6 are associated with striatal structural atrophy in major depressive disorder patients with anhedonia. Front Psychiatry. 2022;13:1016735.
13. Ma Y, Guo C, Luo Y, Gao S, Sun J, Chen Q, et al. Altered neural activity in the reward-related circuit associated with anhedonia in mild to moderate major depressive disorder. J Affect Disord. 2024;345:216–25.
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.
15. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35:68–77.
16. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167:748–51.
17. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–55.
18. Serretti A. Anhedonia and depressive disorders. Clin Psychopharmacol Neurosci. 2023;21:401–9.
19. Vinckier F, Gourion D, Mouchabac S. Anhedonia predicts poor psychosocial functioning: results from a large cohort of patients treated for major depressive disorder by general practitioners. Eur Psychiatry. 2017;44:1–8.
20. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the snaith-hamilton pleasure scale. Br J Psychiatry. 1995;167:99–103.
21. Rizvi SJ, Pizzagalli DA, Sproule BA, Kennedy SH. Assessing anhedonia in depression: potentials and pitfalls. Neurosci Biobehav Rev. 2016;65:21–35.
22. Fang Z, Mu Q, Wu C, Jia L, Wang Z, Hu S, et al. The impacts of anhedonia on brain functional alterations in patients with major depressive disorder: a resting-state functional magnetic resonance imaging study of regional homogeneity. J Psychiatr Res. 2022;156:84–90.
23. Lu S, Shao J, Feng Q, Wu C, Fang Z, Jia L, et al. Aberrant interhemispheric functional connectivity in major depressive disorder with and without anhedonia. BMC Psychiatry. 2022;22:688.
24. Li Y, Yue Y, Chen S, Jiang W, Xu Z, Chen G, et al. Combined serum IL-6, C-reactive protein, and cortisol may distinguish patients with anhedonia in major depressive disorder. Front Mol Neurosci. 2022;15:935031.
25. Fawcett J, Clark DC, Scheftner WA, Gibbons RD. Assessing anhedonia in psychiatric patients. Arch Gen Psychiatry. 1983;40:79–84.
26. Rizvi SJ, Quilty LC, Sproule BA, Cyriac A, Michael Bagby R, Kennedy SH. Development and validation of the dimensional anhedonia rating scale (DARS) in a community sample and individuals with major depression. Psychiatry Res. 2015;229:109–19.
27. Cao B, Zhu J, Zuckerman H, Rosenblat JD, Brietzke E, Pan Z, et al. Pharmacological interventions targeting anhedonia in patients with major depressive disorder: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2019;92:109–17.
28. Avenevoli S, Swendsen J, He JP, Burstein M, Merikangas KR. Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. J Am Acad Child Adolesc Psychiatry. 2015;54:37–44. e32
29. Yorbik O, Birmaher B, Axelson D, Williamson DE, Ryan ND. Clinical characteristics of depressive symptoms in children and adolescents with major depressive disorder. J Clin Psychiatry. 2004;65:1654–9.
30. Lin J, Su Y, Rizvi SJ, Jagoda J, Li J, Wu Y, et al. Define and characterize the anhedonia in major depressive disorder: an explorative study. J Affect Disord. 2022;313:235–42.
31. Wang X, Lu J, Liu Q, Yu Q, Fan J, Gao F, et al. Childhood experiences of threat and deprivation predict distinct depressive symptoms: a parallel latent growth curve model. J Affect Disord. 2022;319:244–51.
32. Wang P, Zhang N, Ma S, Kang L, Wang W, Zong X, et al. Dysfunctional attitudes mediate the relationship between childhood emotional neglect and anhedonia in young adult major depression patients. Front Psychiatry. 2022;13:791230.
33. Fan J, Liu W, Xia J, Li S, Gao F, Zhu J, et al. Childhood trauma is associated with elevated anhedonia and altered core reward circuitry in major depression patients and controls. Hum Brain Mapp. 2021;42:286–97.
34. Fawcett J, Clark DC, Scheftner WA, Hedeker D. Differences between anhedonic and normally hedonic depressive states. Am J Psychiatry. 1983;140:1027–30.
35. Lemke MR, Puhl P, Koethe N, Winkler T. Psychomotor retardation and anhedonia in depression. Acta Psychiatr Scand. 1999;99:252–6.
36. Buckner JD, Joiner TE Jr., Pettit JW, Lewinsohn PM, Schmidt NB. Implications of the DSM's emphasis on sadness and anhedonia in major depressive disorder. Psychiatry Res. 2008;159:25–30.
37. Kalmbach DA, Arnedt JT, Swanson LM, Rapier JL, Ciesla JA. Reciprocal dynamics between self-rated sleep and symptoms of depression and anxiety in young adult women: a 14-day diary study. Sleep Med. 2017;33:6–12.
38. Wieman ST, Arditte Hall KA, MacDonald HZ, Gallagher MW, Suvak MK, Rando AA, et al. Relationships among sleep disturbance, reward system functioning, anhedonia, and depressive symptoms. Behav Ther. 2022;53:105–18.
39. Casement MD, Keenan KE, Hipwell AE, Guyer AE, Forbes EE. Neural reward processing mediates the relationship between insomnia symptoms and depression in adolescence. Sleep. 2016;39:439–47.
40. Holm SM, Forbes EE, Ryan ND, Phillips ML, Tarr JA, Dahl RE. Reward-related brain function and sleep in pre/early pubertal and mid/late pubertal adolescents. J Adolesc Health. 2009;45:326–34.
41. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. J Affect Disord. 2011;134:20–31.
42. Withall A, Harris LM, Cumming SR. A longitudinal study of cognitive function in melancholic and non-melancholic subtypes of major depressive disorder. J Affect Disord. 2010;123:150–7.
43. Fletcher K, Parker G, Paterson A, Fava M, Iosifescu D, Pizzagalli DA. Anhedonia in melancholic and non-melancholic depressive disorders. J Affect Disord. 2015;184:81–88.
44. McIntyre RS, Woldeyohannes HO, Soczynska JK, Maruschak NA, Wium-Andersen IK, Vinberg M, et al. Anhedonia and cognitive function in adults with MDD: results from the international mood disorders collaborative project. CNS Spectr. 2016;21:362–6.
45. Ren J, Wu Z, Peng D, Huang J, Xia W, Xu J, et al. Changes of anhedonia and cognitive symptoms in first episode of depression and recurrent depression, an analysis of data from NSSD. J Affect Disord. 2023;321:47–55.
46. Oei TI, Verhoeven WM, Westenberg HG, Zwart FM, van Ree JM. Anhedonia, suicide ideation and dexamethasone nonsuppression in depressed patients. J Psychiatr Res. 1990;24:25–35.
47. Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry. 1990;147:1189–94.
48. Winer ES, Nadorff MR, Ellis TE, Allen JG, Herrera S, Salem T. Anhedonia predicts suicidal ideation in a large psychiatric inpatient sample. Psychiatry Res. 2014;218:124–8.
49. Ballard ED, Wills K, Lally N, Richards EM, Luckenbaugh DA, Walls T, et al. Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. J Affect Disord. 2017;218:195–200.
50. Yang X, Yuan X, Liu G, Harrision P. The specific roles of loss of interest and loss of pleasure in recent suicidal ideation. Arch Suicide Res. 2022;26:861–70.
51. Ducasse D, Loas G, Dassa D, Gramaglia C, Zeppegno P, Guillaume S, et al. Anhedonia is associated with suicidal ideation independently of depression: a meta-analysis. Depress Anxiety. 2018;35:382–92.
52. Ding R, Zhu X, Feng L, Xiao L, Zhang L, He P, et al. Trajectories and predictors of suicidal ideation in clinical characteristics and pharmacological treatments for major depressive disorder: a study based on a national multi-centered prospective cohort. Transl Psychiatry. 2024;14:422.
53. Sagud M, Tudor L, Simunic L, Jezernik D, Madzarac Z, Jaksic N, et al. Physical and social anhedonia are associated with suicidality in major depression, but not in schizophrenia. Suicide Life Threat Behav. 2021;51:446–54.
54. Yang X, Liu S, Wang D, Liu G, Harrison P. Differential effects of state and trait social anhedonia on suicidal ideation at 3-months follow up. J Affect Disord. 2020;262:23–30.
55. Hawes M, Galynker I, Barzilay S, Yaseen ZS. Anhedonia and suicidal thoughts and behaviors in psychiatric outpatients: the role of acuity. Depress Anxiety. 2018;35:1218–27.
56. Hein M, Dekeuleneer FX, Hennebert O, Skrjanc D, Oudart E, Mungo A, et al. Relationships between recent suicidal ideation and recent, state, trait and musical anhedonias in depression. Int J Environ Res Public Health. 2022;19:16147.
57. Gillissie ES, Le GH, Rhee TG, Cao B, Rosenblat JD, Mansur RB, et al. Evaluating anhedonia as a risk factor in suicidality: a meta-analysis. J Psychiatr Res. 2023;158:209–15.
58. Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: double trouble. Neuron. 2020;107:234–56.

59. Harsanyi S, Kupcova I, Danisovic L, Klein M. Selected biomarkers of depression: what are the effects of cytokines and inflammation? Int J Mol Sci. 2022;24:578.
60. Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: a meta-analysis. J Affect Disord. 2020;277:940–8.
61. Lucido MJ, Bekhbat M, Goldsmith DR, Treadway MT, Haroon E, Felger JC, et al. Aiding and abetting anhedonia: impact of inflammation on the brain and pharmacological implications. Pharmacol Rev. 2021;73:1084–117.
62. Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry. 2016;21:1358–65.
63. Jha MK, Miller AH, Minhajuddin A, Trivedi MH. Association of T and non-T cell cytokines with anhedonia: role of gender differences. Psychoneuroendocrinology. 2018;95:1–7.
64. Felger JC, Haroon E, Patel TA, Goldsmith DR, Wommack EC, Woolwine BJ, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry. 2020;25:1301–11.
65. Freed RD, Mehra LM, Laor D, Patel M, Alonso CM, Kim-Schulze S, et al. Anhedonia as a clinical correlate of inflammation in adolescents across psychiatric conditions. World J Biol Psychiatry. 2019;20:712–22.
66. Rengasamy M, Marsland A, McClain L, Kovats T, Walko T, Pan L, et al. Longitudinal relationships of cytokines, depression and anhedonia in depressed adolescents. Brain Behav Immun. 2021;91:74–80.
67. Nefs G, Pouwer F, Denollet J, Kramer H, Wijnands-van Gent CJ, Pop VJ. Suboptimal glycemic control in type 2 diabetes: a key role for anhedonia? J Psychiatr Res. 2012;46:549–54.
68. Willame H, Wacquier B, Point C, Dosogne M, Al Faker M, Loas G, et al. The association between type 2 diabetes and anhedonic subtype of major depression in hypertensive individuals. J Clin Hypertens. 2022;24:156–66.
69. Singh MK, Leslie SM, Packer MM, Zaiko YV, Phillips OR, Weisman EF, et al. Brain and behavioral correlates of insulin resistance in youth with depression and obesity. Horm Behav. 2019;108:73–83.
70. Brouwer A, van Raalte DH, Lamers F, Rutters F, Elders PJM, Van Someren EJW, et al. Insulin resistance as a marker for the immune-metabolic subtype of depression. J Affect Disord. 2021;295:1371–6.
71. Rashidian H, Subramaniapillai M, Park C, Lipsitz O, Zuckerman H, Teopiz K, et al. Insulin resistance is associated with deficits in hedonic, self-reported cognitive, and psychosocial functional response to antidepressant treatment in individuals with major depressive disorder. J Affect Disord. 2021;282:448–53.
72. Nasca C, Dobbin J, Bigio B, Watson K, de Angelis P, Kautz M, et al. Insulin receptor substrate in brain-enriched exosomes in subjects with major depression: on the path of creation of biosignatures of central insulin resistance. Mol Psychiatry. 2021;26:5140–9.
73. Su M, Li E, Tang C, Zhao Y, Liu R, Gao K. Comparison of blood lipid profile/thyroid function markers between unipolar and bipolar depressed patients and in depressed patients with anhedonia or suicidal thoughts. Mol Med. 2019;25:51.
74. Nefs G, Pop VJ, Denollet J, Pouwer F. Depressive symptoms and all-cause mortality in people with type 2 diabetes: a focus on potential mechanisms. Br J Psychiatry. 2016;209:142–9.
75. Kowianski P, Lietzau G, Czuba E, Waskow M, Steliga A, Morys J. BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity. Cell Mol Neurobiol. 2018;38:579–93.
76. Azman KF, Zakaria R. Recent advances on the role of brain-derived neurotrophic factor (BDNF) in neurodegenerative diseases. Int J Mol Sci. 2022;23:6827.
77. Deinhardt K, Chao MV. Shaping neurons: long and short range effects of mature and proBDNF signalling upon neuronal structure. Neuropharmacology. 2014;76 Pt C:603–9.
78. Wu C, Lu J, Lu S, Huang M, Xu Y. Increased ratio of mature BDNF to precursor-BDNF in patients with major depressive disorder with severe anhedonia. J Psychiatr Res. 2020;126:92–7.
79. Zheng W, Gu L, Zhou Y, Wang C, Lan X, Zhang B, et al. Baseline plasma BDNF levelsare associated with antianhedonic effects of repeated-dose intravenous ketamine in major depressive disorder. Curr Neuropharmacol. 2023;21:1013–21.
80. Martinotti G, Pettorruso M, De Berardis D, Varasano PA, Lucidi Pressanti G, De Remigis V, et al. Agomelatine increases BDNF serum levels in depressed patients in correlation with the improvement of depressive symptoms. Int J Neuropsychopharmacol. 2016;19:pyw003.
81. Hoflich A, Michenthaler P, Kasper S, Lanzenberger R. Circuit mechanisms of reward, anhedonia, and depression. Int J Neuropsychopharmacol. 2019;22:105–18.
82. Del Rey NL, Garcia-Cabezas MA. Cytology, architecture, development, and connections of the primate striatum: hints for human pathology. Neurobiol Dis. 2023;176:105945.
83. Barbas H, Garcia-Cabezas MA. How the prefrontal executive got its stripes. Curr Opin Neurobiol. 2016;40:125–34.
84. Haber SN. Corticostriatal circuitry. Dialogues Clin Neurosci. 2016;18:7–21.
85. Grabenhorst F, Rolls ET. Value, pleasure and choice in the ventral prefrontal cortex. Trends Cogn Sci. 2011;15:56–67.
86. Ballard IC, Murty VP, Carter RM, MacInnes JJ, Huettel SA, Adcock RA. Dorsolateral prefrontal cortex drives mesolimbic dopaminergic regions to initiate motivated behavior. J Neurosci. 2011;31:10340–6.
87. Adcock RA, Thangavel A, Whitfield-Gabrieli S, Knutson B, Gabrieli JD. Reward-motivated learning: mesolimbic activation precedes memory formation. Neuron. 2006;50:507–17.
88. McNamara CG, Tejero-Cantero A, Trouche S, Campo-Urriza N, Dupret D. Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. Nat Neurosci. 2014;17:1658–60.
89. Zotev V, Bodurka J. Effects of simultaneous real-time fMRI and EEG neurofeedback in major depressive disorder evaluated with brain electromagnetic tomography. Neuroimage Clin. 2020;28:102459.
90. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009;166:702–10.
91. Enneking V, Krussel P, Zaremba D, Dohm K, Grotegerd D, Forster K, et al. Social anhedonia in major depressive disorder: a symptom-specific neuroimaging approach. Neuropsychopharmacology. 2019;44:883–9.
92. Wu C, Jia L, Mu Q, Fang Z, Hamoudi H, Huang M, et al. Altered hippocampal subfield volumes in major depressive disorder with and without anhedonia. BMC Psychiatry. 2023;23:540.
93. Mu Q, Cui D, Zhang K, Ru Y, Wu C, Fang Z, et al. Volume changes of the subcortical limbic structures in major depressive disorder patients with and without anhedonia. Psychiatry Res Neuroimaging. 2023;336:111747.
94. Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 2013;36:305–12.
95. Socala K, Doboszewska U, Szopa A, Serefko A, Wlodarczyk M, Zielinska A, et al. The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res. 2021;172:105840.
96. Kelly JR, Borre Y, C OB, Patterson E, El Aidy S, Deane J, et al. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res. 2016;82:109–18.
97. Wang S, Ishima T, Zhang J, Qu Y, Chang L, Pu Y, et al. Ingestion of lactobacillus intestinalis and lactobacillus reuteri causes depression- and anhedonia-like phenotypes in antibiotic-treated mice via the vagus nerve. J Neuroinflammation. 2020;17:241.
98. Minichino A, Jackson MA, Francesconi M, Steves CJ, Menni C, Burnet PWJ, et al. Endocannabinoid system mediates the association between gut-microbial diversity and anhedonia/amotivation in a general population cohort. Mol Psychiatry. 2021;26:6269–76.
99. Mason BL, Li Q, Minhajuddin A, Czysz AH, Coughlin LA, Hussain SK, et al. Reduced anti-inflammatory gut microbiota are associated with depression and anhedonia. J Affect Disord. 2020;266:394–401.
100. Chin Fatt CR, Asbury S, Jha MK, Minhajuddin A, Sethuram S, Mayes T, et al. Leveraging the microbiome to understand clinical heterogeneity in depression: findings from the T-RAD study. Transl Psychiatry. 2023;13:139.
101. Alsayednasser B, Widnall E, O'Mahen H, Wright K, Warren F, Ladwa A, et al. How well do cognitive behavioural therapy and behavioural activation for depression repair anhedonia? A secondary analysis of the COBRA randomized controlled trial. Behav Res Ther. 2022;159:104185.
102. Dunn BD, Widnall E, Warbrick L, Warner F, Reed N, Price A, et al. Preliminary clinical and cost effectiveness of augmented depression therapy versus cognitive behavioural therapy for the treatment of anhedonic depression (ADepT): a single-centre, open-label, parallel-group, pilot, randomised, controlled trial. EClinicalMedicine. 2023;61:102084.
103. Chu MY, Li SB, Wang Y, Lui SSY, Chan RCK. The effect of noninvasive brain stimulation on anhedonia in patients with schizophrenia and depression: a systematic review and meta-analysis. Psych J. 2024;13:166–75.
104. Kong S, Chen Y, Huang H, Yang W, Lyu D, Wang F, et al. Efficacy of transcranial direct current stimulation for treating anhedonia in patients with depression: a randomized, double-blind, sham-controlled clinical trial. J Affect Disord. 2024;350:264–73.
105. Yong SJ, Tong T, Chew J, Lim WL. Antidepressive mechanisms of probiotics and their therapeutic potential. Front Neurosci. 2019;13:1361.
106. Gasto C, Navarro V, Catalan R, Portella MJ, Marcos T. Residual symptoms in elderly major depression remitters. Acta Psychiatr Scand. 2003;108:15–19.
107. Israel JA. The impact of residual symptoms in major depression. Pharmaceuticals. 2010;3:2426–40.
108. Buckman JEJ, Underwood A, Clarke K, Saunders R, Hollon SD, Fearon P, et al. Risk factors for relapse and recurrence of depression in adults and how they operate: a four-phase systematic review and meta-synthesis. Clin Psychol Rev. 2018;64:13–38.

109. Wilcox HC, Anthony JC. Child and adolescent clinical features as forerunners of adult-onset major depressive disorder: retrospective evidence from an epidemiological sample. J Affect Disord. 2004;82:9–20.
110. Gutkovich Z, Morrissey RF, Espaillat RK, Dicker R. Anhedonia and pessimism in hospitalized depressed adolescents. Depress Res Treat. 2011;2011:795173.
111. Kelly CA, Freeman KB, Schumacher JA. Treatment-resistant depression with anhedonia: integrating clinical and preclinical approaches to investigate distinct phenotypes. Neurosci Biobehav Rev. 2022;136:104578.
112. Wong S, Le GH, Phan L, Rhee TG, Ho R, Meshkat S, et al. Effects of anhedonia on health-related quality of life and functional outcomes in major depressive disorder: a systematic review and meta-analysis. J Affect Disord. 2024;356:684–98.

AUTHOR CONTRIBUTIONS

CCW reviewed the literature, collected the data, and drafted the manuscript; QLM and WJG provided critical revisions; SJL conceived and designed the present study.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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