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Anhedonia in Relatives of Patients with Major Depressive Disorder

Shimaa Ibrahim Amin, Ramadan Abdelbr Hussein, Usama M Youssef, Mahmoud Ibrahim Ahmed Elsawy, Basha A M

Department of Psychiatry, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Mahmoud Ibrahim Ahmad EL-Sawy ,
E-mail: Mahmoud.elsawy@rocketmail.com

Abstract:

Anhedonia is a hallmark feature of depression and is highly prevalent among individuals with mood disorders. The history and neurobiology of anhedonia has been most extensively studied in the context of unipolar Major Depressive Disorder (MDD), with converging lines of evidence indicating that marked anhedonia heralds a more chronic and treatment-refractory illness course. Furthermore, findings from neuroimaging studies suggest that anhedonia in MDD is associated with aberrant reward-related activation in key brain reward regions, particularly blunted reward anticipation-related activation in the ventral striatum.

Keywords: Anhedonia, major depressive disorder, behavior.

Introduction:

Individuals closely related to patients with major depressive disorder (MDD) are at a nearly three-fold greater risk of developing depression than the general population. Studying unaffected individuals with a family history of MDD may provide clues to the mechanisms underlying risk for MDD **(1).**

Several studies have shown that, compared with individuals without a family history of psychiatric disorders, unaffected first-degree relatives of MDD patients are characterized by elevated neuroticism and depressive cognitive styles, and that these traits are stable over time. Relatives of MDD patients also display a range of neurobiological abnormalities similar to those observed in patients with MDD, suggesting a possible genetic basis for these traits **(2).**

MDD is a disorder with considerable heterogeneity with a broad constellation of presentations and symptoms. Anhedonia, which is defined as reduced interest or pleasure in all or almost all previously enjoyed activities, is a hallmark symptom of MDD. It affects more than half of individuals with current MDD **(3).**

In patients with MDD, anhedonia is characterized by impairments in anticipatory pleasure and integration of reward-related information from past experiences and is related to greater severity of clinical symptoms and poorer treatment response. Anhedonia has emerged as a key dimension that predicts recovery and is related to a longer time to remission, especially in young adults with depression **(4).**

- **Reward Circuits and Anhedonia in MDD:**

Previous research has demonstrated that structural and functional alterations in the reward pathways of the brain are highly relevant to anhedonia and aberrant reward-related perception and memory in depression. The key brain areas of the reward pathway related to anhedonia in depression include the ventral and dorsal striatum, ventromedial PFC (vmPFC), orbitofrontal cortex (OFC), and ACC **(5).**

Structural magnetic resonance imaging (MRI) studies have reported that anhedonia in depression is associated with reduced gray matter volume in the OFC and caudate nucleus. In addition, diffusion tensor imaging studies have reported that abnormal structural connectivity of the reward network is related to anhedonia in patients with depression **(1).**

Microstructural alterations in the segment of the superolateral medial forebrain bundle connecting the VTA with the medial OFC are related to anhedonia and depression severity. Moreover, aberrant white matter microstructural integrity of the cingulum and uncinate fasciculus is negatively correlated with anhedonia in patients with depression **(2).**

Furthermore, disrupted structural connectivity between the bilateral anterior thalamic radiation and the left corticospinal tract is significantly linked to the severity of anticipatory anhedonia in MDD patients. Previous findings suggest that the frontostriatal and mesocorticolimbic circuit systems are involved in anhedonia-related reward processing in patients with depression **(6).**

Resting-state functional MRI (fMRI) research has revealed that a biotype of depression that is characterized by hyperconnectivity of the frontostriatal and thalamic networks is associated with anhedonia and psychomotor retardation **(7).**

In addition, reduced functional connectivity (FC) and regional homogeneity within the ventral striatum and vmPFC are correlated with greater anhedonia in MDD patients, and decreased functional coupling between NAc subregions and frontoparietal areas is also linked to anhedonia in patients with depression **(6).**

Moreover, the constructs of anhedonia in depression appear to have dissociated neural underpinnings; increased intrinsic function of the left dorsal ACC and reduced cortical thickness of the left rostral ACC and lateral OFC are respectively correlated with anticipatory and consummatory anhedonia **(4).**

Task fMRI research has demonstrated that when encountering pleasurable stimuli, the aberrant connectivity between the posterior vmPFC and the mesolimbic reward system is negatively correlated with anhedonia in patients with MDD. When individuals with depression receive an unexpected reward, they exhibit abnormal frontostriatal hypoactivation, especially in the OFC and ventral striatum **(3).**

Moreover, reduced activation in the ventral striatum during reward anticipation is correlated with anhedonia and depression severity in patients with MDD. Reward anticipation is assessed by measuring prediction error, which is defined as the response to the discrepancy between anticipated and received rewards **(7).**

NAc activity is associated with an inverse correlation between reward anticipation and prediction error in healthy controls, and a lower correlation may predict greater anhedonia in individuals with MDD. In addition, reduced neural reward prediction-error signaling in the medial OFC and ventral striatum is inversely correlated with anhedonia severity, which reflects reward processing deficits in MDD **(5).**

During reward processing tasks, reward liking and reward wanting in depression is associated with striatal hypoactivation, alongside mPFC and dorsolateral PFC hyperactivation and OFC hypoactivation, whereas reward learning is related to blunted frontostriatal sensitivity to positive feedback **(1).**

Mapping activation and connectivity patterns of reward networks may help understand the neural basis of reward deficits associated with anhedonia in patients with MDD. The identification of brain functional circuits linked to anhedonia may enable a better understanding of the heterogeneity of MDD and help track one of its core symptoms **(7).**

Aberrant metabolite status of neurotransmitters in reward processing regions has also been implicated in reward deficits and anhedonia. In depression, dysfunction of the ACC in the reward neural circuitry is highly relevant to anhedonia. Reduced glutamine and γ-aminobutyric acid (GABA) levels in the pregenual ACC are associated with anhedonia in adolescents with depression**(2).**

Additionally, glutamine/glutamate imbalance in the rostral ACC is associated with anhedonia in depression patients. Moreover, a subtype of depression, characterized by increased peripheral inflammation and glutamate

level in the left basal ganglia, has been reported to be associated with anhedonia and reduced network integrity within reward processing regions **(6).**

Neuroinflammation and oxidative stress likely contribute to reductions in glutathione in the occipital cortex, which results in glutamate and dopamine dysregulation; this, in turn, affects the reward circuitry and induces anhedonia in patients with MDD. Thus, reward deficits, alongside functional and neurochemical alterations within and beyond the reward circuitry, may give rise to anhedonia in depression patients **(7).**

- **Aversion Circuits and Anhedonia in MDD:**

The neural basis of anhedonia is closely related to dysfunctional aversion circuits. LHb is a key brain structure for mediating behavioral responses to aversive stimuli.64 In rodents, increased expression of a specific calcium protein kinase in the LHb mediates depressive behaviors, such as anhedonia and despair behavior **(3).**

Stimulation of LHb neurons establishes connections with distinct subpopulations of VTA neurons and triggers aversion-associated behavior in mice; thus, the dysregulation of the LHb–VTA pathway may be a key mechanism underlying aversion processing deficits and depression pathogenesis. Additionally, individuals with MDD have larger habenula volumes and greater left habenula activation, which correlate with the severity of depressive symptoms and anhedonia **(4).**

The brain circuits that mediate aversive processing in depression patients include the PFC, amygdala, and caudate. Patients with MDD show greater amygdala activation in response to negative than positive facial expressions, and reduced amygdala responsiveness to positive stimuli is associated with higher physical anhedonia scores **(7).**

Patients who have recovered from depression have abnormal neural responses, whereby activation in the caudate nucleus while viewing aversive stimuli is increased, and neural responses in the PFC to both pleasant and aversive conditions are diminished **(5).**

Moreover, adolescents at a high risk of depression show attenuated neural responses to aversive stimuli, with a decrease in activation of the vmPFC and pregenual ACC. In line with the emotion context insensitivity theory of depression, blunted aversion observed both before depression onset and during the residual phase may be a trait marker of the illness **(1).**

- **Treatments for Anhedonia in Patients with MDD:**

Anhedonia and cognitive deficits are typically resistant to first-line antidepressant treatments. Previous clinical studies have suggested that selective serotonin reuptake inhibitors are ineffective for anhedonia. Vortioxetine is a multimodal-acting antidepressant that may be effective in ameliorating anhedonia, especially in female patients with MDD **(2).**

Ketamine may rapidly alleviate anhedonia in depression patients because of its direct effect on mitochondrial energy metabolism. In addition, kappa-opioid receptor antagonists that target the ventral striatum, one of the core hubs of the reward system, may improve the rate of reward learning and alleviate anhedonia **(6).**

Bupropion is a dopaminergic and noradrenergic reuptake inhibitor and has been offered as a treatment for reward-related deficits and blunted affect in patients with MDD and may increase neural responses to anticipation, effort and consummation of rewards, and aversive stimuli **(3).**

However, despite the growing number of studies on treatments, the efficacy of interventions remains unsatisfactory. Besides, new psychological treatments such as positive affect treatment and positive affect stimulation and sustainment that target the Positive Valence Systems are providing promise for anhedonia **(4).**

Abnormal neural responses to rewards and aversion that are associated with anhedonia may be potential targets for intervention and prevention strategies for depression. Moreover, understanding the neural substrates of anhedonia in depression patients is vital for identifying neurobiological treatment markers **(1).**

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