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Anhedonia in Behavioral Addiction

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Abstract

In schizophrenia and major depressive disorder, anhedonia (a loss of capacity to feel pleasure) had differently been considered as a premorbid personological trait or as a main symptom of their clinical picture. Anhedonia is a diminished capacity to experience pleasure. It describes the lack of interest and the withdrawal from all usual pleasant activities. It was defined two different types of hedonic deficit: physical anhedonia and social anhedonia. Physical anhedonia represents an inability to feel physical pleasures (such as eating, touching and sex). Social anhedonia describes an incapacity to experience interpersonal pleasure (such as being and talking to others). In the schizophrenic sample, anhedonia seems to be a specific subjective psychopathological experience of the negative and disorganised forms of schizophrenia. In the depressed sample, anhedonia seems to be a specific subjective psychopathological experience of those major depressive disorder forms with a marked clinical depression severity.

Keywords: Anhedonia, Schizophrenia, Major Depressive disorder.

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1. Introduction

Clinical research findings indicate that patients with schizophrenia are less responsive than those with depression to treatments for anhedonia. For schizophrenia, atypical antipsychotics are superior to typical antipsychotics in reducing negative symptoms, such as anhedonia; however, none of them have achieved the threshold for clinically significant improvement [1]. Intermittent theta-burst stimulation over the dorsomedial PFC has also been shown to have little effect on ameliorating anhedonia in patients with schizophrenia. Thus, anhedonia in schizophrenia patients cannot be effectively treated with current treatments, which highlights the crucial need for more effective interventions. Anhedonia is considered a trait-marker of schizophrenia and is highly relevant to the dysfunction of reward and aversion systems [2]. Therefore, elucidating neurobiological mechanisms underlying anhedonia may help in identification of potential treatment targets for schizophrenia [3].

2. Transdiagnostic Brain Alterations in major depressive disorder (MDD) and Schizophrenia

Anhedonia is recognized as a transdiagnostic symptom of depression and schizophrenia and is linked to deficits in the reward and aversion systems. Anhedonia shares common neurobiological alterations of the frontostriatal network and mesocorticolimbic circuits for reward and aversion processing in both patients with MDD and schizophrenia. A transdiagnostic meta-analysis reported that consummatory anhedonia is associated with decreased activation of the ventral basal ganglia region in both disorders, and anticipatory anhedonia is linked to areas of the frontostriatal circuitry, which include the ventral striatum, dorsal ACC, middle frontal gyrus, and medial frontal gyrus. Additionally, in MDD and schizophrenia patients, reward deficits are associated with hypoconnectivity between the NAc and the DMN and hyperconnectivity between the NAc and the cingulo-opercular network (CON); moreover, reward responsivity impairments are associated with DMN hyperconnectivity and diminished connectivity between the DMN and CON.

Volumetric abnormalities in the putamen and cerebellum have been reported to negatively correlate with anhedonia scores in both MDD and schizophrenia patients, which suggests that volumetric alterations within the puta men–cerebellum network mediate reward-related goal-directed behaviors in both disorders. Inflammation and cytokines may affect dopamine neurotransmission, which mediates several aspects of anhedonic behavior. In addition to the dysfunction of dopaminergic signaling, dysregulation of glutamate and serotonin are also involved in anhedonia. Furthermore, anhedonia has shared genetic influences across multiple diagnostic categories, and the genetic risk of anhedonia also influences brain structure, especially regions associated with reward and pleasure processing. Thus, the shared genetic and inflammation factors may contribute to the common alterations in the reward and aversion pathways, which results in the manifestation of anhedonia in patients with depression and schizophrenia [4]. Dissociable or disorder-specific alterations in brain pathways are also linked to anhedonia among different clinical diagnostic categories.

The spatial distribution of reward processing regions differs between depression and schizo phrenia patients during reward learning; patients with MDD exhibit reduced prediction error signaling in striatum and midbrain, whereas

those with schizophrenia show reduced prediction signaling in the dorsal striatum, thalamus, and limbic regions [5]. Moreover, abnormal prediction error encoding in MDD patients gives rise to anhedonia symptoms by attenuating reward learning events, whereas disturbed signal encoding in schizophrenia patients contributes to psychotic symptoms by driving aberrant salience toward external and internal stimuli. Depression and schizophrenia likely reflect illness-specific neural valuation and incentive salience formation associated with reward and aversion processing. Both depression and schizophrenia groups show reduced activation in the mPFC in response to unexpected rewards, with activation being significantly more aberrant in schizophrenia patients than in depression patients [6]. The severity of depressive symptoms in patients with schizophrenia negatively correlates with ventral striatum activation during receipt of a reward, which indicates impaired hedonic reward processing contributes to development of depressive symptoms in schizophrenia.

Furthermore, from a cellular perspective, dopaminergic neurons are reclassified according to specific projection subtypes and thus may contribute uniquely to the processing of rewards and aversion. In addition to the heterogeneous cellular structure, dopaminergic, GABAergic, and glutamatergic neurons engage in complex interactions to modulate network activity. Thus, adaptations of both dopaminergic and glutamatergic functions within the VTA and NAc may differ in directionality according to cell type and stress paradigm [7]. Anhedonia-associated reward and aversion pathways. The figure displays key regions of the frontostriatal network and mesocorticolimbic circuits that are linked to the reward and aversion processing underlying anhedonia in patients with depression and schizophrenia. (A) The red curve represents the reward circuit, and the blue curve represents the aversion circuit. Purple dots represent major depressive disorder (MDD). Green dots represent schizophrenia (SCZ). Yellow dots represent healthy controls (HC). PFC, prefrontal cortex. The upward arrow indicates increases, and downward arrow indicates decreases. (B) Key regions of reward circuit from lateral and axial views. (C) Key regions of aversion circuit from lateral and axial views.

Abbreviations: OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; NAc, nucleus accumbens; VTA, ventral tegmental area; SN, substantia nigra; FC, functional connectivity; ReHo, regional homogeneity; CT, cortical thickness; GMV, gray matter volume; L, left; R, right.

3. Understanding anhedonia from a genomic perspective

Anhedonia is a core clinical feature of depression that commonly presents across various other forms of psychopathology including schizophrenia, posttraumatic stress disorder, and substance use disorder. Highlighting its potential import, across psychopathologies, anhedonia has been associated with increased severity and comorbidity as well as reduced response to treatment. Despite evidence that anhedonia and related constructs are moderately-largely heritable, the genomic sources of this heritability remain poorly understood [8].

4. Circuit Mechanisms of Reward, Anhedonia, and Depression

Anhedonia is defined as the reduced ability to feel pleasure in normally pleasurable situations and is a transdiagnostic key symptom for several psychiatric disorders such as MDD and schizophrenia. The clinical phenotype of anhedonia is thought to reflect a dysfunctional processing of reward on a neurobiological level. Since it was first described in the late 19th century, the knowledge about reward processing has evolved and it has become clear that anhedonia is an umbrella term including a number of different components of reward processing that are necessary for the ability to feel pleasure in response to an event. Reward processing is a multi-step process starting with establishment of an association between a given stimulus and a connected reward, which is then followed by development of interest, desire, and anticipation defined as “state of readiness for a reward”. Based on balance between expected value of a given stimulus and expected effort to gain this reward, a “cost-benefit calculation” is performed and motivation in favor or opposed to initiation of goal-directed behavior is formed. If motivation is strong enough, thus expected reward subjectively exceeds the necessary effort, an action plan is constructed, followed by behavioral component of reward in which sustained energy is expended to gain expected reward.

If the goal is achieved, the consummatory phase of reward processing occurs, leading to hedonic response. This whole cascade of events is then subject to feedback integration and reward-based learning, influencing future reward related processes [9]. The definitions of these different subdomains shown to be relevant for understanding of neurobiological processes underlying reward processing, because modulation of distinct circuits or local transmitters shown to influence these in a specific manner. In remitted bipolar patients, for example, who display increased levels of anhedonia compared to healthy volunteers, only some aspects of hedonic capacity, namely inter ests and social interactions, seem to be impaired. In animal models of depression, dopamine depletion in nucleus accumbens (NAc) was shown to lead to a lack of motivation as expressed by reduction of appetitive seeking but not to a reduction of liking (orofacial expression to sucrose and disgust reaction to quin ine). Furthermore, it suggested that treatment does not influence all aspects of reward processing to same extent, with some studies showing stronger effects on reward anticipation than consummatory aspects of reward. In humans, anhedonia can be assessed with questionnaires or reward-specific tasks as used in neuroimaging studies, for example [10].

5. Which networks for reward have been detected?

A number of reviews focusing on reward circuits in animals and humans have been published. The most consist ently described reward network is the dopaminergic mesolim bic pathways originating in the ventral tegmental area (VTA) and spreading onto the NAc located in the ventral striatum (VS), bed nucleus of the stria terminalis, amygdala, and hippocampus. This evidence was recently fur ther investigated in an animal study using optogenetics, which showed that activation of the VTA leads to dopamine release in the NAc. A total 60% of efferent projections of the VTA are dopaminergic, although it contains glutamatergic and GABAergic neurons also. The NAc has also mixed dopaminergic and glutamatergic afferent connections from the VTA and the thalamus, prefrontal cortex (PFC), hippocampus and amygdala, and efferent GABAergic projections to the ventral pallidum and the VTA via its primary outputs, which run through the medi odorsal

thalamus to the cortex. The complex relationship and interconnections of the involved regions outline the role of the NAc as integral hub for corticolimbic circuitry. In addition to this main reward axis, the medial PFC (mPFC) has been considered as core region of "reward pro cessing," which, together with the VTA and the NAc, forms the classical "mesocorticolimbic reward circuit".

It was investigated the modulatory relationship between the striatum and the PFC and the neurobiological correlates of reward-seeking behavior in rats using a multimodal approach including functional magnetic resonance imaging (fMRI) and optogenetics. This study led to a number of relevant results. The optogenetic stimulation of dopaminergic neurons in the midbrain led to ipsilateral increases of the blood oxygenation level dependent (BOLD) signal in the dorsal and VS. On a behavioral level, blue light, inducing dopaminergic stimu lation, was self-administered by the rodents as an expression of its rewarding effect. Furthermore, increased excitability of the mPFC, as shown in depression, led to reductions of BOLD signal [11-12]. ing of reward-related behavior. Disruption of this circuit as dem onstrated by increased mPFC excitability might be a correlate for dysfunctional reward processing and anhedonia. Besides the mPFC, the orbitofrontal cortex (OFC) was shown to be implicated in reward processing. It was stated that the OFC is "best thought as an important nexus for sen sory integration, emotion processing and hedonic experience". However, the importance of the OFC has been challenged in this and other work. Importantly, it has to be highlighted that ventromedial PFC (vmPFC) and the OFC, although they differ in terms of function, are two highly interconnected, overlapping regions with limited possibilities to clearly distinguish these two areas in lesioning and other stud [13].

Ies depending on the methodology. More recently, it was shown that additional regions are involved in reward-related processes in a differentiated man ner; thus, the hypothalamus, lateral habenula (LHb), and dorsal striatum have been detected as major players in this regard. The LHb has dopaminergic projections to the substantia nigra pars compacta and the VTA as well as serotonergic pro jections to the median and dorsal raphe nuclei. It was shown that the LHb has an inhibitory influence on dopaminergic neurons via GABAergic interneurons in the rostromedial tegmental nucleus, which is reflected by the fact that lesioning of the habenula leads to an increase of cortical and striatal dopamine levels. On a behavioral level, it was shown that the habenula has an inhibi tory effect on dopaminergic neurons in reinforcement learning. Thus, using a reward prediction error paradigm in monkeys with a smaller than expected reward led to activation of LHb neurons, whereas a larger than expected reward led to their inhibition. For a review on habenula func tion, see [14]. In terms of fibers that mediate reward, the medial forebrain bundle (MFB) has gained increased attention, as it has become a potential target for DBS treatment (see below). This structure connects the VTA with the NAc via the mesolimbic dopamin ergic connection and the VTA with the PFC via the mesocortical dopaminergic connection [15].

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