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Anhedonia in depression: biological mechanisms and computational models

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Abstract

Anhedonia is a severe condition that describes a near-complete absence of enjoyment, motivation, and interest. A core feature of depression, clinical manifestations of anhedonia can include deficits in experiencing pleasure, approach-related motivated behavior, and learning how to match expectations to the environment. To date, the precise neurobiological mechanisms of anhedonia in major depression are still poorly understood. We have previously argued that contradictory findings and the inability to identify specific neurobiological substrates for anhedonic symptoms may result from sample heterogeneity, suboptimal methods of assessment, and the challenge of dissociating between different components of anhedonia. Recently, however, computational advances to the operationalization of psychiatric symptoms have enhanced the ability to evaluate the neurobiology of constituent elements of this symptom domain. In this paper, we review (1) advances in behavioral and computational methods of assessing reward processing and motivation and (2) the development of new self-report, neurological, and biological methods of subtyping that may be useful in future pursuits to expand our understanding of the neurobiology of anhedonia in depression.

Anhedonia, a core feature of depression, is a multi-faceted symptom that includes deficits in the experience of pleasure, reduced approach-related motivated behavior, and/or impaired learning about rewards in the environment (see Box 1). [1]. We have previously argued that the elusiveness of neurobiological substrates for anhedonia in depression results from the use of suboptimal methods of assessment, which fail to dissociate between these different

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components of anhedonia and result in pathophysiological heterogeneity. Anhedonia in mood disorders has long been hypothesized to be related to a reduction in dopamine (DA) transmission [2–4]. While neuroimaging and pharmacological manipulations have provided some support for the hypothesis that DA may be affected in at least some individuals with major depression [5–7], findings remain mixed (For a review, see [1]), and more work is needed to understand the neurobiology of anhedonia in depression.

Box 1

Anhedonia – What's in a name?

Despite significant progress in the study of reward-related symptoms, there remains considerable disagreement regarding the precise definition of anhedonia and its degree of conceptual overlap with other commonly used terms (e.g., avolition, anergia, apathy, alexithymia, etc.). This lack of clarity is likely due at least in part to the DSM, which offers two distinct definitions for anhedonia depending on whether the diagnostic context is depression or schizophrenia. In the case of the schizophrenia spectrum, anhedonia is defined narrowly as "the decreased ability to experience pleasure from positive stimuli or a degradation in the recollection of pleasure previously experienced" (DSM V p. 88), and is included among 4 other symptoms (alogia, avolition, asociality, and diminished emotional expression) that together comprise the broader "negative symptom" domain. In other words, anhedonia is a *subordinate* construct within the negative symptom criterion for schizophrenia spectrum disorders. In the context of major depression, however, anhedonia is a *supraordinate* construct; here it is used as a general criterion that may be satisfied through different clinical presentations, such as the loss of motivation or interest in hobbies ('wanting'), or the ability to enjoy activities ('liking') and so on (DSM V p. 163). Consequently, the term "anhedonia" in depression is more akin to the term "negative symptoms" in the schizophrenia spectrum in that both are the supraordinate labels for a general domain. These competing definitions for anhedonia have caused confusion in the literature, especially for the translation of preclinical models [33]. Moreover, the use of anhedonia as an "umbrella term" in the nosology of major depression is inconsistent with its greek etymology implying a specific deficit related to the "absence of pleasure". We have previously suggested that new clinical terminology be introduced in subsequent versions of the DSM to facilitate transdiagnostic definitions of symptoms in the anhedonia domain of depression [1]. Until such changes are enacted, however, we have chosen to remain aligned to the current nomenclature defining anhedonia as a supraordinate construct that is comprised of distinct features related to both motivation and pleasure that may satisfy the A2 anhedonia criterion in the diagnosis of depression.

Within the last five years the field of psychiatry has moved in several new directions that hold promise for improving methods of assessment and increasing our understanding of the underlying neurobiology, including the possible role of DAergic deficits. In this review, we outline two new lines of research: First, the emergence of computational psychiatry [8] has encouraged the application of computational methods to improve our understanding of mental illness, including the use of computational modeling for making inferences regarding

the underlying mechanisms that generate observed behavior in psychiatric groups [9,10] (Figure 1). This includes the use of behavioral paradigms and computational models that have been previously linked to DAergic signaling in animal models and human subjects, providing opportunities to evaluate the prevalence of DA-related deficits in patients with depression and anhedonia. Here we focus on advances in the use of reinforcement learning and effort-based choice to evaluate reward processing and motivational deficits.

Second, recent work has also encouraged the identification of subgroups within heterogeneous disorders for which individualized treatments can be developed [9], and has resulted in increased efforts to identify behaviorally, neurologically, or biologically distinct subgroups within and across diagnostic categories. One candidate sub-group with growing empirical support is the so-called “inflammatory sub-type” [11], which may be driven by immune-induced alterations in DAergic tone and basal ganglia function. In the sections that follow, we outline recent work in these domains and advocate for further integration of these lines of research to extend our understanding of neurobiological mechanisms associated with anhedonia in depression.

Computational Psychiatry in Depression: Reinforcement Learning

A fundamental premise of computational psychiatry is the idea that behavioral manifestations of clinical symptoms may be best conceptualized in terms of computational components that can be used to infer underlying mechanisms [1,8] (See Figure 1). In the case of depression, anhedonic symptoms have long been viewed in terms of failure within reinforcement systems (e.g. a fundamental deficit in response to positive reinforcement [12]). This idea, coupled with the early advances linking reinforcement learning (RL) models to midbrain DA neurons [13], presented an initial opportunity for the study of anhedonia using computational approaches. This body of research has focused primarily on the role of DAergic mesocorticolimbic pathways, including ventral and dorsal striatal targets for midbrain DA neurons, in the signaling of reward prediction errors (RPEs). More recently, an important direction in computational assessment has been to link behaviorally or computationally-derived measures of reward reactivity, learning, and decision-making to emotional experience and mood states that may be disrupted in mood disorders [14,15]. Specifically, Rutledge et al. (2014) modeled subjective feelings of happiness in healthy volunteers from the combined influence of recent reward expectations and associated (plausibly DAergic) prediction errors during a risky decision task [16] and showed that pharmacologically manipulating dopamine affected both choices and happiness ratings [17]. Thus, mechanisms of reinforcement learning provide a potential means of linking DAergic response to rewards to disrupted mood regulation as well as a mechanism of examining aberrant reinforcement processing in depression (See [18], for a review).

To date, however, evidence supporting the link between anhedonic symptoms and failures within reward learning has been mixed. One widely-used paradigm, the probabilistic reward task (PRT), employs a signal-detection methodology to test the development of an implicit bias towards rewarding stimuli. Patients with major depression exhibit reduced ability to modulate behavior in response to rewards [19,20]—a pattern that persists even after reported remission [21]. Further, depressed patients with high symptoms of anhedonia show

diminished reward learning on the PRT relative to those with low symptoms [19,20]. A recent re-analysis of these data using an RL framework [22] compared healthy controls to both individuals with high symptoms of anhedonia and patients with MDD and found that the primary difference in behavior for both groups was related to reductions in reward sensitivity, and *not* reductions in learning from rewards *per se* [22]. This distinction is significant, as it is learning behavior in this task that has been clearly linked to both manipulations of and individual differences within the mesolimbic DA system [23]. Consequently, the question of whether associations between anhedonic symptoms and PRT performance in patients with depression are exclusively linked to a DAergic deficit remains unresolved.

A parallel body of work has suggested that depression-related differences in reinforcement learning may be driven by disruptions in goal-directed reasoning that depend on formulating a model of the reward environment (often referred to as "model-based" valuation) rather than prediction error signaling (also known as "model free") [15,24]. In support of this idea, Rutledge et al. (2017) used a mixed gambles task designed to elicit RPEs in the absence of learning and found that patients with moderate depression showed no difference from healthy controls in striatal reward prediction error signaling, and that symptoms of anhedonia were not related to striatal RPE signaling. Moreover, an analysis using a similar task in a large community sample of individuals with varying self-reported symptoms of depression as measured by the Beck Depression Inventory [25] found no effect of depressive or anhedonic severity on the relationship between momentary mood and outcome, though baseline mood did correspond to depression severity [15]. These results were interpreted as suggesting that the integrity of DAergic reward prediction error signaling is intact in depressive anhedonia, and that the previously-observed attenuations in ventral-striatal signaling during reinforcement learning in patients with depression may be related to impaired model-based valuation (For a review of model-based vs. model-free decision-making in depression, see [25]).

While this hypothesis is certainly plausible and worthy of pursuit in future studies, an alternative explanation for these null findings is that deficits in DAergic model-free signaling may be a marker of particular sub-types of depression. Consequently, the ability to detect alterations in RL signaling may depend on symptom severity of the sample populations, sample inclusion criteria, and symptom heterogeneity. These paradigms will be critical for evaluating and quantifying reward processing and reward learning in heterogeneous samples with anhedonia or motivational impairments that are thought to be related to DAergic functioning, ideally among individuals with similar behavioral manifestations.

Computational Psychiatry in Depression: Motivation and Effort-based Decision-Making

In addition to reinforcement learning, another common behavioral manifestation of anhedonia in depression is reduced motivation [26]. In depressed patients, several laboratory paradigms have thus been developed to explore reward motivation and its relationship with anhedonia. One such paradigm developed by our group, the Effort-Expenditure for Rewards

Task (EEfRT) [27], has shown reduced willingness to expend effort for reward in patients with subsyndromal depression, first-episode depression, and remitted depression compared to controls [28,29]. Additionally, self-reported symptoms of anhedonia have been found to correlate with willingness to exert effort in patients [29] and in undergraduates with a wide range of trait anhedonia [27]. Other effort-based decision-making paradigms have shown similar associations between willingness to exert effort for rewards among patients with unipolar depression [30] and in correlation with measures of apathy among otherwise healthy participants [31]. Taken together, studies using these measures in depressed patients are consistent with clinical observations of reduced motivation as a core feature of the disorder. Like measures of RL, effort-based decision-making paradigms can be readily analyzed using computational models [32] that may provide objective methods of quantifying reduced motivation associated with anhedonia.

As with RL processes, studies of the willingness to expend greater effort in order to obtain larger or preferred rewards have repeatedly implicated disruption of corticostriatal DA as a critical substrate [33,34]. In both humans and animals, potentiation or attenuation of DA signaling respectively increases or decreases effort expenditure for rewards [35–38], and intra-individual variation in striatal DA availability predicts individual differences in effort-based discounting [39,40]. In addition to striatal DA, human and animal studies suggest several potential regions of interest for future studies examining the neurobiology of reduced motivation in anhedonia. Specifically, functional magnetic resonance imaging (fMRI) studies in humans have identified a role for the dorsal anterior cingulate cortex (dACC) and anterior insula (aI) in the subjective discounting of rewards as a function of required effort [41], as well as activity in ventromedial prefrontal cortex (vmPFC) and supplementary motor area (SMA) that drive behavior toward reward maximization or effort minimization, respectively [42]. Finally, the dorsomedial and dorsolateral prefrontal cortices have been shown to play a role in encoding both effort devaluation [41] and effort learning signals [43]. Further, these studies have also indicated that reduced motivation may be linked to decreased connectivity between SMA and ACC [44] as well as decreased striatal activation. Taken together, these studies highlight the importance of cortical networks in guiding effortful behavior. Future studies are needed to test this corticostriatal network as a substrate for reductions in effortful behavior associated with anhedonic symptoms in depression.

Evidence for pathophysiologically distinct anhedonic sub-types

As noted in the prior sections, a clear role for DAergic impairments as a primary cause for deficits in reinforcement learning or effort expenditure in anhedonia in depression has yet to be established. One explanation for this body of inconsistent findings is the presence of distinct subtypes. Indeed, growing appreciation for the multi-faceted nature of individual symptoms and diagnostic categories (see Box 1) has spurred the development of increasingly sophisticated methods of assessment. Self-report measures of anhedonia have expanded to separately capture aspects of motivation and pleasure [45], and anticipatory and consummatory aspects of pleasure [46]. The development of assessment methods has also advanced to include the application of computational methods to identify different profiles within a heterogeneous symptom domain. For example, the newly developed Apathy Motivation Index was created and validated using factor analysis and latent profile analysis

to distinguish aspects of apathy associated with behavioral, social, and emotional domains and profiles associated with depression, anhedonia, and fatigue [47]. These methods may be useful in identifying specific components of anhedonia and associating them with comorbid symptoms and diagnoses. Additionally, subtyping efforts have also benefitted from the use of machine learning techniques. Applied to resting fMRI data of patients with depression, these techniques have been used to identify anhedonia-related patterns of connectivity and have potential to aid in the identification of subgroups that may benefit from targeted treatments (see [48]).

While innovative self-report methods and neurologically-based classification efforts show great promise in identifying subtypes of patients within and across diagnostic categories, recent studies of brain-immune interactions in depression have also highlighted the existence of heterogeneous pathophysiologies for anhedonic symptoms in depression. Peripheral markers of inflammation are frequently increased in depressed patients [49–51]. Moreover, a wealth of data has established that in both humans and laboratory animals, chronic administration of cytokines or cytokine-inducers is associated with decreased striatal dopamine release and blunted striatal responsivity to reward [52–54] as well as reports of anhedonic symptoms [55,56]. Indeed, it is increasingly understood that DA acts as major regulator of immune cell function within the brain [57] and conversely, the elevation of cytokines has been found to down-regulate processes that govern pre-synaptic DA availability and function [52,54].

Interestingly, the possible contribution of inflammation to the etiopathophysiology of depression may help resolve some of the inconsistencies in detection of DAergic alterations in depressed samples. While administration of cytokine inducers like interferon-alpha (IFN) therapy can produce severe depressive episodes in individuals with no prior history of depression, this response only occurs in approximately 30%–50% of drug recipients [58]. In a further study, IFN therapy was found to blunt DA synthesis capacity as well as striatal BOLD responses to reward [53]. Importantly, the magnitude of this effect varied across patients, and IFN-induced change correlated with change in motivational symptoms as measured by the Multidimensional Fatigue Inventory [53]. Given that substantial increases in inflammation occur in almost everyone receiving interferon-alpha therapy, this finding suggests that the onset of depressive symptoms may reflect a particular vulnerability to the down-stream effects of increased immune signaling.

Intriguingly, a recent study by Menard and colleagues found direct evidence for such a vulnerability. Following exposure to chronic social stress, mice that went on to develop a depressive phenotype–but not stress resilient mice–were found to have developed a “leaky” blood-brain barrier (BBB) in the NAcc that permitted increased trafficking of the inflammatory cytokine interleukin-6 (IL-6) from the periphery into the CNS [59]. Critically, this enhanced permeability was detected around the NAcc, but not prefrontal cortex or hypothalamus, providing a possible explanation for the potential selectivity of the “inflammatory subtype” and DA-linked anhedonia symptoms (See Figure 2). Given that periods of significant life stress are one of the major risk factors for the development of a first depressive episode [60], sensitivity to stress-induced vulnerability of the BBB may be a critical moderating variable in determining whether markers of abnormal striatal DA

function will be present. Moreover, the importance of BBB permeability as a potential mediator for vulnerability to inflammation may help explain inconsistencies in the effects of inflammatory challenges on reward behavior in healthy individuals (e.g [61]).

Consistent with the results of Menard et al., a recent study by our group also observed that individual differences in the effects of an acute stressor on NAcc prediction error signals measured with fMRI were dependent on the magnitude of change in IL-6 following acute stress [62]. Finally, blockade of inflammation using the tumor necrosis factor (TNF-alpha) antagonist infliximab was found to relieve reward-related symptoms in depressed patients with high–but not low–inflammation [63]. Taken together, these data suggest the possibility that neurobiological sensitivity to inflammatory stimuli–possibly mediated by BBB integrity around the NAcc–may drive the link between stress and anhedonic symptoms for a subset of patients, thereby forming the basis for an “inflammatory subtype”. While this tantalizing model needs to be translated to further clinical studies, it suggests the possibility that patients with depression in the context of high inflammation may show selective benefit from treatments aimed at reducing inflammation or increasing DAergic tone [64,65].

Summary and Future Directions

We have highlighted several recent advances in the assessment of reward processing and motivational deficits in depression and anhedonia through behavioral and computational methodology, and have reviewed recent efforts to identify neurologically and biologically distinct subtypes within the diagnostic construct of depression. We are optimistic that this work will progress toward the identification of neurobiology associated with subtypes within anhedonia and lead to targeted treatment approaches. While both of these fields have led to novel and informative work, we advocate that further integration of these research trajectories will be critical for increasing our understanding of the neurobiology of anhedonia and depression, specifically regarding reward processing and motivational deficits, and for developing targeted treatment strategies.

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Highlights

- Discrete cognitive processes underlying anhedonia can be computationally operationalized
- Approaches include models of reinforcement learning and effort-based decision-making
- Mixed findings in both domains may reflect the presence of pathophysiological subtypes
- One candidate sub-type is the presence of chronic inflammation

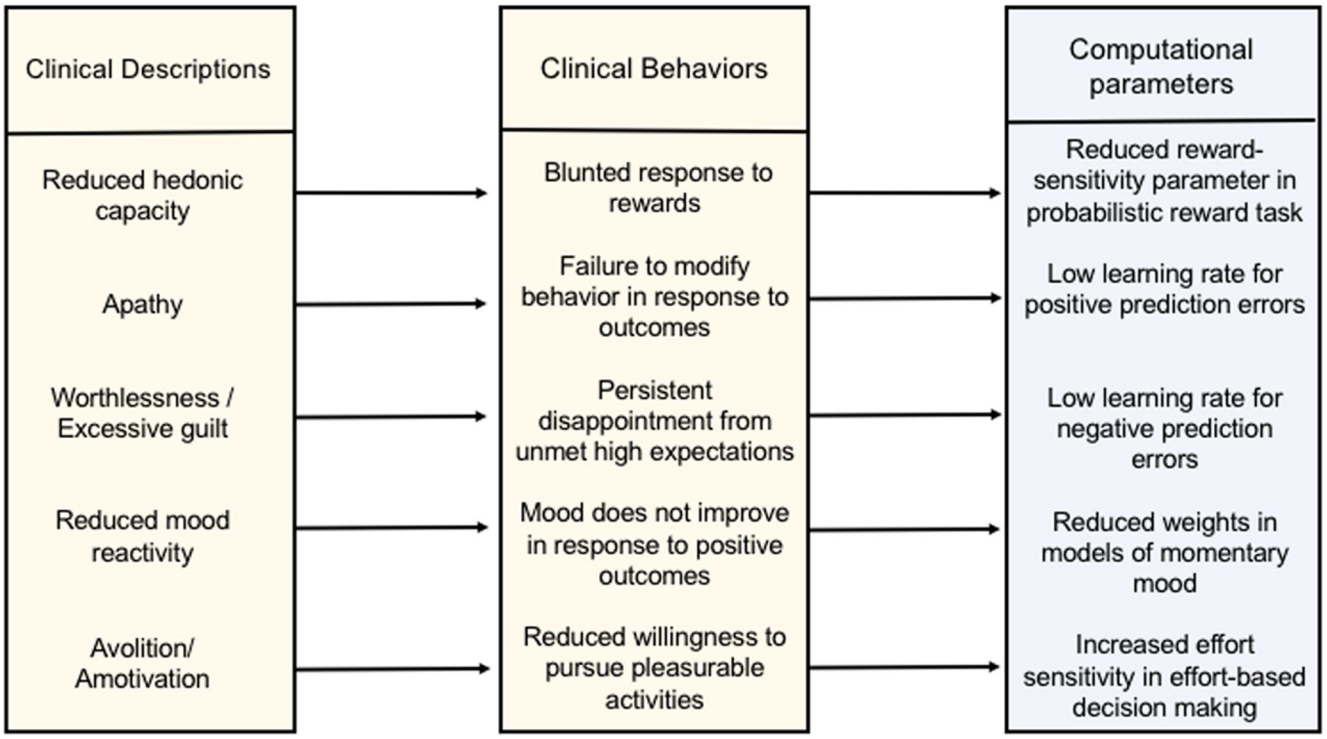

Figure 1.

The computational approach to assessing anhedonia and related symptoms. This conceptual diagram outlines the hypothetical operationalization of behavioral manifestations of anhedonia and related symptoms within a computational psychiatry framework. Clinically defined facets of anhedonia have typically been associated with behavioral manifestations that are difficult to quantify or measure directly and are often confused with other related symptoms. However, computational approaches allow for objective assessment through association with computational parameters. To date, there is insufficient data to support specific mapping between behavioral and computational terms, but we present this hypothetical example as a representation of the potential to operationalize clinical behaviors using computational approaches.

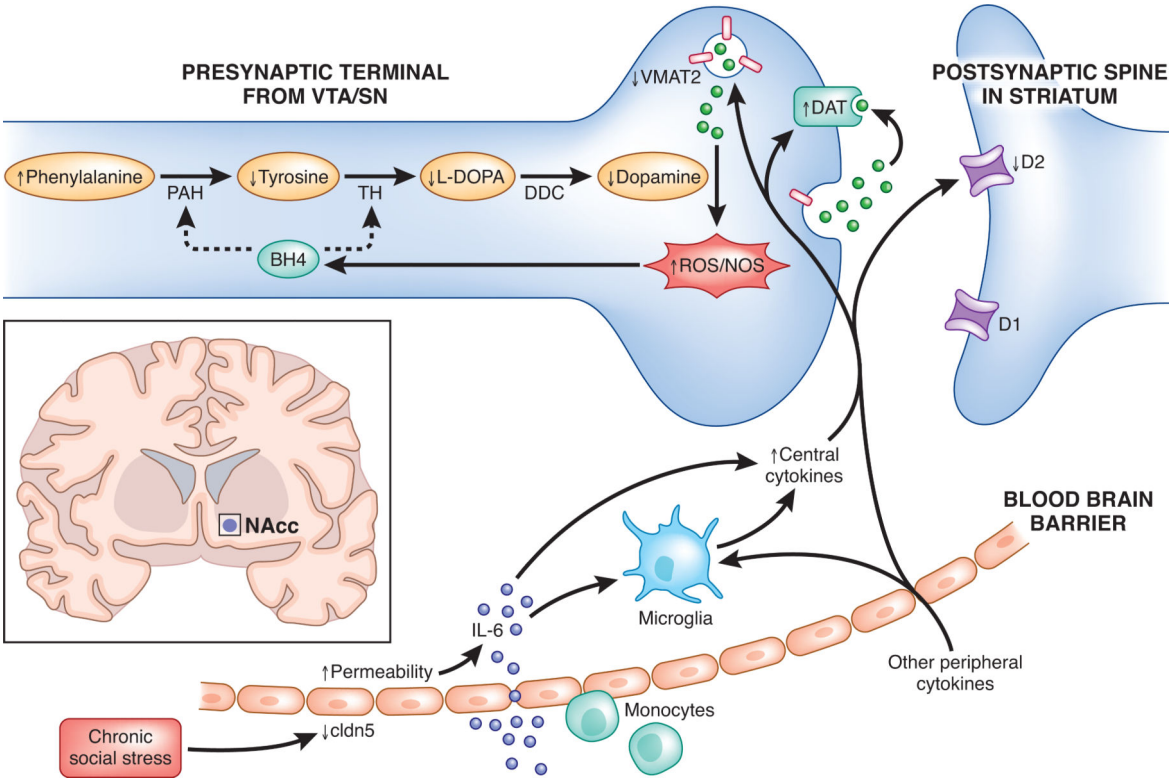

Figure 2.

Potential signaling pathways linking peripheral inflammation to disruption of dopaminergic function. Adapted from [66]. As suggested by one recent study [59], individuals who go on to develop a depressive phenotype following stress show increased permeability of the blood brain barrier (BBB) to peripheral cytokines such as IL-6. The peripheral cytokines that cross the blood brain barrier, as well as central cytokines produced by activated microglia, may contribute to oxidative stress and reactive oxygen species (ROS) generation. This, in turn, may increase the oxidation of tetrahydrobiopterin (BH4), a cofactor required for the conversion of phenylalanine to tyrosine and tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), thereby impeding DA synthesis. Additionally, central inflammatory cytokines may decrease the expression or function of the vesicular monoamine transporter 2 (VMAT2) as well as increase the expression or function of the dopamine transporter (DAT), increasing DA and leading to increased generation of ROS. Finally, inflammatory cytokines may also decrease DA signaling by reducing DA D2 receptors. D1, dopamine 1 receptor 1; D2, dopamine 2 receptor; DDC, dopamine decarboxylase; NOS, nitric oxide synthase; PAH, phenylalanine hydroxylase; ROS, reactive oxygen species; SN; substantia nigra; TH, tyrosine hydroxylase; VTA, ventral tegmental area.