Is depression associated with dysfunction of the central reward system?

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Abstract

The neural substrates of MDD (major depressive disorder) are complex and not yet fully understood. In the present review, I provide a short overview of the findings supporting the hypothesis of a dysfunctional dopamine system in the pathophysiology of depression. Because the mesocorticolimbic dopamine system is involved in reward processing, it has been hypothesized that a reduced function of this system could underlie the anhedonia and amotivation associated with depression. This hypothesis is supported by several observations providing indirect evidence for reduced central dopaminergic transmission in depression. However, some of the differences observed between controls and depressed patients in dopamine function seem to be specific to a subsample of patients, and influenced by the methods chosen. Studies that investigated the neural bases of some MDD behavioural symptoms showed that anhedonia, loss of motivation and the diminished ability to concentrate or make decisions could be associated with a blunted reaction to positive reinforcers and rewards on one side, and with a bias towards negative feedback on the other side. Only a few studies have investigated the neural basis of anhedonia and the responses to rewards in MDD subjects, mostly evidencing a blunted response to reward signals that was associated with reduced brain activation in regions associated with the brain reward system. In conclusion, there is evidence for a dysfunction of the dopamine system in depression and for blunted response to reward signals. However, the exact nature of this dysfunction is not yet clear and needs to be investigated in further studies.

Introduction

MDD (major depressive disorder) was ranked among the top ten causes of worldwide disability in 1996 and is expected to rise to the second cause of disability in the world by 2020 [1]. According to the Diagnostic Statistical Manual of Mental Disorders [2], MDD is characterized by the presence of at least five of the following symptoms during the same 2-week period: (i) depressed mood most of the day, nearly every day; (ii) diminished interest or pleasure in all, or almost all, activities (anhedonia); (iii) significant weight gain or weight loss or a decrease or increase of appetite; (iv) insomnia or hypersomnia nearly every day; (v) psychomotor agitation or retardation; (vi) fatigue or loss of energy; (vii) feelings of worthlessness or excessive or inappropriate guilt; (viii) diminished ability to think or concentrate; and (ix) recurrent thoughts of death and/or suicidal ideation.

The neural substrates of MDD are complex and are not yet fully understood. For instance, the results obtained with neuroimaging studies in depressed patients are in part contradictory and suggest that the pathophysiology of MDD involves several neuroanatomical substrates and neurotransmitter systems [3]. Willner [4] postulated that a functional impairment of the mesolimbic DA (dopamine) pathway underlies the core MDD symptoms of anhedonia and loss of motivation. This hypothesis is consistent with findings showing that euphoria is correlated with amphetamine-induced DA release in the human ventral striatum [5] and that cerebral blood flow differences between depressed patients and controls were identified in regions associated with the mesolimbic DA system, including amygdala, striatum, ACC (anterior cingulate gyrus) and prefrontal cortex [3,6]. The mesolimbic DA pathway is also involved in the processing of reward information in the brain (see [7,8] for reviews). Reward is, in turn, an important determinant of motivated behaviour, and obtaining reward is associated with pleasant feelings.

In the present paper, I provide a short review of the findings supporting the hypothesis of a dysfunctional DA system in the pathophysiology of depression. First, I explain the relationship between the mesolimbic DA system and the cerebral reward system. Then, I give an overview of the results suggesting that these systems could be dysfunctional in depressed patients.

Reward and the DA system

The search for the neural substrates of reward began with the discovery of ICSS (intracranial self-stimulation) by Olds and Milner [9], who observed that rats with electrodes implanted in certain brain sites, such as the lateral hypothalamus, would press a lever to discharge electrical stimulation through the electrodes. Crow and Deakin [10] showed that ICSS could...
be obtained in a range of sites extending through the lateral hypothalamus into the ventral tegmentum of the midbrain.

Major advances in the understanding of ICSS results were made with the discovery of a chemical specificity for ICSS. Pharmacological investigations showed that ICSS was influenced by psychotropic drugs, which act on catecholamine neurons, including chlorpromazine, an antipsychotic drug, reserpine, an antidepressive drug [11], as well as amphetamine [12] and cocaine [13], both acting on DA transmission. These findings led to the hypothesis that the ascending catecholamine systems constituted a catecholamine reward pathway. Much data pointed to contribution of mesolimbic and mesocortical DA systems in brain reward mechanisms [10].

This hypothesis was supported by neurophysiological studies in awake primates, which showed that neurons located in regions associated with the DA system, including the striatum, the amygdala and the OFC (orbitofrontal cortex), as well as DA midbrain neurons, were activated by food and liquid rewards (see [14] for a review). More specifically, DA neurons have been shown to be involved in reward-related learning. Therefore, in procedures involving Pavlovian conditioning, DA neurons that responded initially to a food or liquid reward, the unconditioned stimulus, acquire a response to the cues associated with the delivery of reward, the conditioned stimuli, after repeated pairings [15]. Such neuronal responses are strongly diminished after extinction [16,17], and are modulated by DA [18]. Additionally, DA neurons and some OFC neurons exhibit firing related to the coding of prediction errors, i.e. higher firing rate to unpredicted than to predicted rewards, and no response when rewards are omitted [19].

Finally, human studies using neuroimaging methods also provided evidence for an implication of the mesolimbic and mesocortical DA systems in the processing of reward. Thus the ventral striatum was shown to be activated in response to a broad range of reinforcers [20–22], as well as during the expectation of monetary reward [23]. Activation in response to reward and behavioural reinforcement was also found in other brain regions associated with the mesolimbic DA system, including the ACC and OFC [24–27]. In addition, the dorsal striatum, including putamen and caudate nucleus, and the ventral striatum, mostly the Nacc (nucleus accumbens) as well as the OFC were activated in procedures testing reward-related learning [28–30]. From those regions, the ventral putamen and the OFC were shown to be activated during appetitive Pavlovian conditioning in a way that was compatible with the predictions obtained with the temporal difference model [31–33]. At last, some studies investigated the direct implication of DA in response to rewards using the [11C]raclopride PET (positron-emission tomography) method. [11C]Raclopride is a radioligand that is sensitive to changes in intrasynaptic DA concentrations and a decrease of [11C]raclopride binding is thought to reflect endogeneous DA release [34]. Using this method, Pappata et al. [35] showed that [11C]raclopride binding decreased in the ventral striatum in response to large monetary rewards compared with large monetary losses, and Zald et al. [36] found that [11C]raclopride binding decreased in the putamen and caudate in response to unpredictable compared with predictable rewards. However, further studies suggested that active behavioural engagement was essential to induce a change in striatal raclopride binding in response to unpredictable rewards [37].

Taken together, these results point to an involvement of the mesocorticolimbic and mesostriatal DA systems in the processing of reward information. Brain regions associated with these neurotransmitter systems are activated in response to rewarding stimuli, suggesting that the cerebral reward circuitry comprised at least the following regions: ventral and dorsal striatum, OFC and ACC. An implication of the amygdala was also evident in some human neuroimaging studies and in the formation of stimulus–reward associations in animals [26,38]. However, the function of DA in the processing of reward remains unclear. Even if many studies suggest that DA mediates some aspects of reward-related learning (see above), there is some evidence that DA could transmit the hedonic value of rewarding stimuli. For instance, Wise et al. [39] demonstrated that DA blockade impaired primary reinforcement. More recently, the findings from PET studies of amphetamine- or methylphenidate-induced DA release showing that the euphoria associated with these agents correlated with DA release in the anteroventral striatum and the ventral putamen [5,40,41], yielded new support for the hypothesis that DA could be involved in the mediation of the hedonic feelings related to rewards.

**Dopamine function in MDD**

The role of the mesocorticolimbic DA system in reward processing and in the mediation of the hedonic value of stimuli led to the hypothesis that a reduced function of this system could underlie the anhedonia, amotivation and psychomotor slowing associated with depression [4,42,43]. This hypothesis is supported by several observations providing indirect evidence for reduced central dopaminergic transmission in depression (reviewed in [44]). First, in depressed patients, concentrations of the DA metabolite, homovanillic acid, are consistently reduced in the CSF (cerebrospinal fluid) and jugular vein plasma in vivo [45–47]. Secondly, DA receptor agonists (e.g. pramipexole) exert antidepressant effects in placebo-controlled studies [4,48]. Thirdly, catecholamine depletions induces depression in susceptible individuals [49,50]. Finally, neuroreceptor imaging studies of MDD showed a reduced l-[^11C]dopaa uptake across the blood–brain barrier [51] and loss of the normal asymmetry in striatal D2 receptor binding [52]. Increased striatal binding to D2/D3 receptors was evident in depressives with psychomotor slowing [53], but studies whose samples were not predominantly composed of psychomotor-slowed cases found no difference in D2/D3 receptor levels during depression [54–57]. Similarly, a reduced striatal DAT (DA transporter) binding in MDD compared with controls was found in some [58,59], but not all [60–62], studies of striatal DAT of MDD.

In summary, most of the findings reviewed point to a dysfunction of the central DA function in MDD. However,
the exact nature of this dysfunction is difficult to understand since some of the differences observed between controls and depressed patients in DA function seem to be specific to a subsample of patients and influenced by the methods chosen. These differences among the studies make any attempt at generalization difficult. One way to get past this problem is to investigate DA function during behavioural activation that is associated with MDD symptoms. In the next section, I provide an overview on the studies that tried to elucidate the brain mechanisms of MDD behavioural symptoms, mainly those of anhedonia and loss of motivation.

**Processing of reward information in MDD**

Some MDD behavioural symptoms, including anhedonia, loss of motivation and the diminished ability to concentrate or make decisions, could be associated with a blunted reaction to positive reinforcers and rewards on one side, and with a bias towards negative feedback on the other. The hypothesis that depressed patients manifest an abnormal response to negative feedback is consistent with the findings that depressed patients respond catastrophically to error feedback on memory or planning tasks, in that they are disproportionately likely to commit an error on a trial that follows negative feedback [63, 64]. Abnormal response to negative feedback was also reported on a probabilistic reversal learning task where subjects were requested to ignore misleading negative feedback to correct responses on 20% of trials. MDD patients reversed in response to the misleading task feedback, while showing intact rule acquisition, and normal levels of response perseveration when the rule actually reversed [65]. These cognitive effects are specific to depression [63], and were also evident in remitted depressed patients [66], suggesting that abnormal reactions to negative feedback may extend to samples with increased risk of depression, even in the absence of current symptoms. An fMRI (functional magnetic resonance imaging) study investigating the neural correlates of the sensitivity to negative feedback in MDD [67] suggested that a disrupted control by the prefrontal cortex of the amygdala may underlie these abnormal responses to negative feedback.

Testing the hypothesis that MDD patients show a blunted reaction to positive reinforcers [68] revealed that currently depressed subjects, but not remitted depressed subjects, express a diminished responsiveness to anticipated reward. An fMRI study [69] investigating the neural responses to monetary incentives in MDD showed that depressed individuals did not differ from control participants in their behavioural responses, and recruited the Nacc during gain anticipation. However, MDD subjects showed an increased activity of the ACC in response to increasing gains, a region that was activated in response to increasing losses in the controls. Together with the fact that MDD showed a reduced discrimination of gain compared with non-gain outcomes, these results support the idea of an increased conflict during anticipation of gains. On the basis of the temporal difference model of DA (see above), a further fMRI study [70] showed that long-term-medicated MDD patients exhibited a reduced reaction to reward-learning signals among others in the ventral striatum and ACC. Finally, preliminary results from an fMRI study of appetitive conditioning show dysfunctional learning in both appetitive and aversive learning conditions associated with a pattern of dysfunction of amygdala, lateral OFC, striatum (caudate nucleus) and ACC in unmedicated MDD patients [71].

Using a dopaminergic probe consisting of the oral administration of dextroamphetamine sulfate [72] showed that severity of depression correlated highly with the rewarding effects of dextroamphetamine in a group of unmedicated depressed patients, and that MDD subjects with severe symptoms reported significantly greater rewarding effects than controls. These results evidence a hypersensitive response of the brain reward system that could be related to a DA hypofunction. In a further study [73], these authors demonstrated that this hypersensitive response to the rewarding effects of dextroamphetamine in MDD was associated with a reduction of the brain activation in the ventromedial prefrontal cortex, the OFC and the ventral striatum.

**Conclusion and future directions**

The present paper provides a brief overview of the findings suggesting that a dysfunction of the cerebral reward system could contribute to the pathophysiology of MDD. The role of the mesocorticlimbic DA system in reward processing and in the mediation of the hedonic value of stimuli led to the hypothesis that a reduced function of this system could underlie the anhedonia, amotivation and psychomotor slowing associated with depression. This hypothesis is supported by several observations providing indirect evidence for reduced central dopaminergic transmission in depression. However, the exact nature of this dysfunction is difficult to understand since some of the differences observed between controls and depressed patients in DA function seem to be specific to a subsample of patients and influenced by the methods chosen. These differences among the studies make any attempt for generalization difficult. One way to get past this problem is to investigate DA function during behavioural activation that is associated with MDD symptoms. However, only a few studies have investigated the neural basis of anhedonia and the neural responses to reward in MDD subjects, mostly finding a blunted response to reward signals that was associated with a reduced brain activation in regions associated with the brain reward system. However, the exact nature of these impairments is still unclear.

In conclusion, there is some evidence that a dysfunction of the mesolimbic DA system could contribute to the pathophysiology of MDD and could underlie the anhedonia symptoms associated with depression. However, only a few studies investigated the neural correlates of anhedonia in depressed patients and there is a need for more investigations in this field of research.

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