Depression, anhedonia, and psychomotor symptoms: the role of dopaminergic neurocircuitry

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CNS Spectr

Depression, Anhedonia, and Psychomotor Symptoms: *The Role of Dopaminergic Neurocircuitry*

By Dan J. Stein, MD, PhD

ABSTRACT

The heterogeneity of major depression suggests that multiple neurocircuits and neurochemicals are involved in its pathogenesis. Anhedonia and psychomotor symptoms are, however, particularly characteristic features of major depression and may provide insights into its underlying psychobiology. Importantly, these symptoms appear to be mediated by dopaminergic mesolimbic and mesostriatal projections, the function of which is, in turn, influenced by key gene variants and environment stressors. Indeed, there is growing evidence of the way in which the dopaminergic system is associated with cognitive-affective disturbances in depression, and provides a useful target for therapeutic interventions. At the same time, a range of other systems are likely to contribute to the psychobiology of this condition.

CASE REPORT

Rachel is a 43-year-old woman who presented for treatment to her primary care physician. She complained of depressed mood, not finding pleasure in her life, and of feeling slower and slower. She had a range of other classical symptoms of depression, including poor concentration, decreased appetite, and insomnia. On mental status examination, her speech was slowed, and there was evidence of psychomotor retardation. Her primary care physician initiated bupropion, increasing the dosage to 100 mg TID. After several weeks of treatment, she demonstrated a good response to treatment. Rachel was particularly delighted to report that she was enjoying life again, and had the sense that she was moving around more quickly and more responsively.

COGNITIVE-AFFECTIVE NEUROSCIENCE

Depression is a heterogenous condition characterized by multiple symptoms and subtypes. Different symptoms (eg, poor concentration, disturbed sleep) and subtypes (eg, melancholic, seasonal) are likely mediated by different neurocircuitry and neurochemistry,[1-3] and may or may not be present, in any particular individual with depression. Depression may be characterized by an increase or a decrease in certain of its symptoms (eg, hyperphagia, hypophagia), further complicating attempts to explore its psychobiology.

Nevertheless, anhedonia—or loss of pleasure—appears to be a particularly central feature of major depression.[4-6] Reward is mediated by dopaminergic projections to the nucleus accum-

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bens, suggesting that mesolimbic neurocircuitry plays a crucial role in the pathogenesis of depression.[7,8] Furthermore, other dopaminergic projections (ie, mesostriatal, mesocortical) may play a role in mediating additional symptoms of depression that appear to lie at the core of this disorder (eg, psychomotor symptoms, loss of motivation)[9,10] and its melancholic subtype.[11]

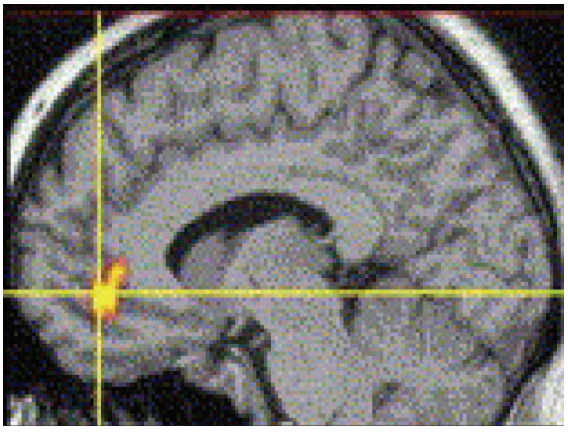
Neuroanatomy/Neurochemistry

Basic research on the brain reward and motivation systems and animal models of anhedonia and psychomotor symptoms[12-15] have provided a foundation for investigating the role of dopaminergic and associated neurocircuitry in the pathogenesis of depression. Complementary work[16,17] has shown that neurological lesions in this circuitry can result in anhedonia or psychomotor symptoms. Finally, neuroimaging studies[9,10,18-22] of anhedonic and psychomotor symptoms in depression have contributed to delineating the neurocircuitry and neurochemistry of this disorder.

Anhedonia, for example, was positively correlated with ventromedial prefrontal cortex and negatively correlated with amygdala/ventral striatal activity in response to happy stimuli (Figure 1).[19] In another study,[20] trait anhedonia was positively correlated to ventromedial prefrontal cortex activity during the processing of positive information, and inversely correlated with anterior caudate volume (Figure 2). Psychomotor symptoms have also been associated with frontal and caudate abnormalities in depression,[9,10,23] and fatigue may involve related regions.[2,24]

Molecular imaging studies[8,25,26] provide partial support for the role of the dopaminergic system in mediating depression, particularly depression with psychomotor symptoms.[27-29] Functional brain imaging during a dopaminergic challenge has emphasized that dopaminergic circuitry is involved in altered reward processing in anhedonia (Figure 3).[30] Electroconvulsive therapy and prefrontal transcranial magnetic stimulation result in increased dopamine release,[8,31] and deep brain stimulation to the reward circuitry is able to relieve anhedonia in treatment-resistant depression.[32]

FIGURE 1.
fMRI showing positive correlations between anhedonia and VMPFC responses which were greater to happy than neutral stimuli[19]



fMRI=functional magnetic resonance imaging; VMPFC=ventromedial prefrontal cortex.

Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. *Biol Psychiatry*, 2005;58:843-853. Adapted with permission.

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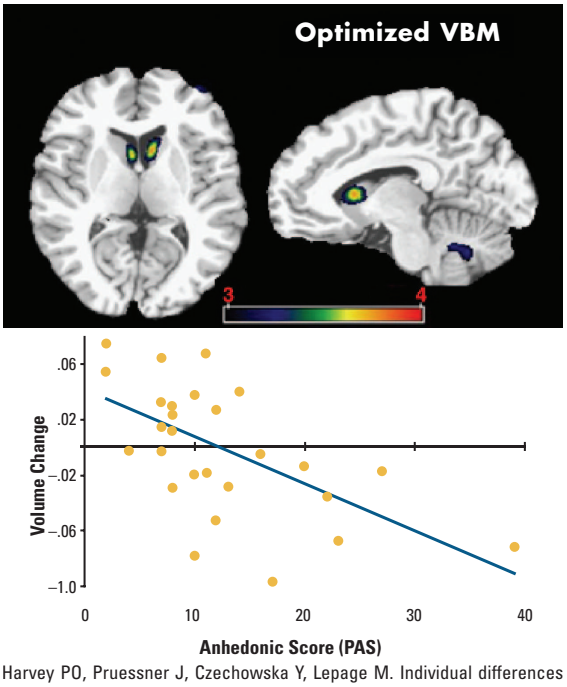
FIGURE 2.
Significant negative correlation between severity of trait anhedonia and absolute volume of the anterior caudate on MRI[20]



Harvey PO, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. *Mol Psychiatry*, 2007;12:767-775. Adapted with permission.

MRI=magnetic resonance imaging; VBM=voxel-based morphometry; PAS=Revised Chapman Physical Anhedonia Scale.

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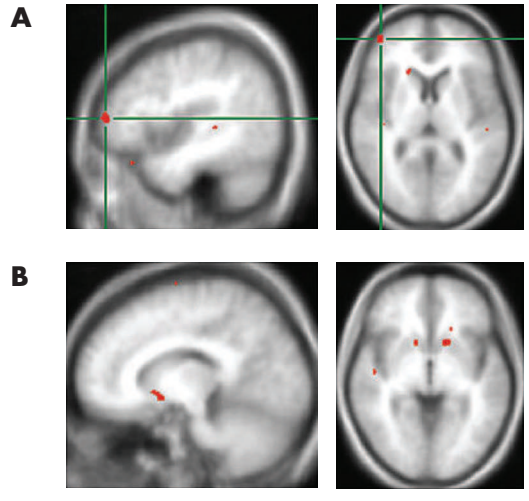
Depression involves a range of other circuits and chemicals, and the extent to which anhedonia, psychomotor symptoms, and other features associated with reduced positive affect are specifically linked to dopaminergic dysfunction is debatable.[33,34] Several other systems and molecules that play an important role in mediating depression intersect closely with the dopaminergic system; these include serotonin,[35] glutamate,[36] opioids,[37] the hypothalamic-pituitary-adrenal axis,[38] and neurotrophic factors.[39,40] However, certain depressive symptoms may be more specifically linked to one of these systems.[2,41]

Gene/Environment

The heritability of anhedonia and psychomotor symptoms deserves further study.[42,43] Response to early maternal separation and to other stressors is mediated in part by dopaminergic circuitry,[15,44] and dopaminergic gene variants and their interactions with environmental stressors play a role in the pathogenesis of depression.[45,46] Still, a range of other gene-environment mechanisms are also likely to play a role in this condition.[47,48] Research on the relationship between dopaminergic receptor variants, cortico-striatal activation, and responsivity to reinforcers,[49] may ultimately be relevant to understanding the pathogenesis of depression.

FIGURE 3.
Reward scores (eg, euphoria, increased energy) in response to a dopaminergic challenge correlated with changes in activity in dopamine-rich areas (ie, [A] ventrolateral PFC and [B] caudate/putamen) on fMRI[30]



Tremblay LK, Naranjo CA, Graham SJ, et al. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. *Arch Gen Psychiatry*. 2005;62:1228-1236. Adapted with permission.

PFC=prefrontal cortex; fMRI=functional magnetic resonance imaging.

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Evolutionary Approaches

A range of evolutionary theories have been put forward to explain anhedonia and psychomotor symptoms in depression.[50,51] Nesse,[50] for example, notes that low mood increases ability to cope with situations in which effort to pursue a major goal will likely result in danger, loss, bodily damage, or wasted effort. Similarly, others[51] have argued that depression represents an adaptive response to the perceived threat of exclusion from important social relationships. Some evolutionary theories have focused specifically on the importance of anhedonia.[52]

CLINICAL IMPLICATIONS

DSM-IV-TR *Diagnosis*

Anhedonia and psychomotor symptoms seem to be particularly core features of major depression, and also characterize its melancholic subtype.[5,9,53] Other important symptoms of depression may also fall under the rubric of reduced positive affect (eg, lack of energy).[33] Nevertheless, it is important to emphasize that symptoms such as anhedonia and psychomotor symptoms occur in a broad range of other medical conditions, including psychotic disorders, Parkinson's disease, and cocaine withdrawal.

Assessment/Evaluation

There are a number of scales of anhedonia including the Snaith-Hamilton Pleasure Scale, the Fawcett-Clark Pleasure Capacity Scale, and the Revised Chapman Physical Anhedonia Scale, and these do not completely overlap.[54] The Salpêtrière retardation rating scale, the CORE Assessment of Psychomotor Change, and the Motor Agitation and Retardation Scale, are observer-rated measures to assess psychomotor abnormalities, and a range of more sensitive experimental performance measures is also available.[10,55]

Pharmacotherapy/Psychotherapy

Dopaminergic agents have a useful role to play in the treatment of depression and treatment-resistant depression.[8,56,57] Both dopamine agonists and low-dose atypical antipsychotics

(which increase extracellular levels of dopamine and norepinephrine, but not serotonin, in the prefrontal cortex) appear effective in the pharmacotherapy of treatment-resistant depression.[2] Although effective antidepressants tend to be useful across the range of depressive symptoms, there is some evidence[10,33] that dopaminergic agents are particularly useful for reduced positive affect and for psychomotor symptoms.

CONCLUSION

Depression is universally described as a "down" rather than an "up" feeling. Similarly, there is a common association between depression, anhedonia (feeling down), and psychomotor retardation (slowing down). There is growing evidence that dopaminergic mesolimbic and mesostriatal projections play an important role in mediating these symptoms. Functioning of the dopamine system is impacted on by particular gene variants as well as environmental stressors, and also by its interactions with a range of other systems. As always, researchers hope that a better understanding of these mechanisms will ultimately lead to better treatments. ***CNS***

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