Anhedonia After a Selective Bilateral Lesion of the Globus Pallidus

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Case Presentation

Mr. A, a 34-year-old man, came to our outpatient clinic for treatment of a major depressive episode. His history was also notable for polysubstance abuse and dependence in sustained remission, with prior abuse of alcohol, LSD, and other hallucinogens and prior dependence on marijuana, cocaine, opiates, and Ecstasy (MDMA [3,4-methylenedioxymethamphetamine]). He began using alcohol at age 9, marijuana at age 12, cocaine at age 13, opiates at age 20, and Ecstasy at age 21. He had a history of depressive symptoms 6 years earlier in the context of active substance dependence and chronic back pain but had no other prior psychiatric diagnosis or treatment. One year before presentation to our clinic, he had been smoking cocaine daily, using Ecstasy several days a week, and consuming two to 10 alcoholic drinks daily but reported no depressive symptoms. After consuming cocaine, Ecstasy, oxycodone, and methadone at a party, he became aggressive and was brought to an emergency room. There, he ingested all of his remaining methadone to prevent it from being discovered. He reported no suicidal intentions surrounding this ingestion. He became unresponsive, hypoxic, and hypotensive. Mr. A was resuscitated and then stabilized in an intensive care unit over 4 days.

After this overdose, Mr. A became acutely depressed. He endorsed a depressed mood, anhedonia, low energy, difficulties concentrating and remembering, feelings of hopelessness and guilt, poor self-esteem, social isolation, increased sleep, and a 20-lb weight gain over the ensuing year. He reported the disappearance of drug cravings and remained abstinent from all recreational drugs other than an occasional glass of wine with dinner. He reported that he no longer experienced pleasure from drinking alcohol. Four serial urine toxicology screens were negative over 6 months.

Mr. A developed a resting tremor of his left hand, slight rigidity of his right arm and left leg, and slowing of rapid alternating movements of his left hand, all of which were still present 16 months after the overdose, as assessed by a movement disorders specialist. He had no prior history of neurological problems. A magnetic resonance imaging (MRI) scan of his brain revealed a selective bilateral lesion of the globus pallidus (Figure 1), with clear involvement of the internal globus pallidus on the right and both internal and external globus pallidus on the left. The bilateral lesion was small, selective, and restricted to the globus pallidus. There were no other lesions or findings on the MRI. Comprehensive neuropsychological tests revealed intact cognitive functions, including attention, working memory, and executive function, and an indicated absence of a frontal-subcortical syndrome (Table 1).

Basic blood tests, including a CBC, a basic metabolic panel, liver function tests, and thyroid function tests, were all within normal limits at the time Mr. A came to our clinic. There was no known family history of affective disorders or substance abuse.

"The patient's social isolation and diminished pleasure in social situations may have been related to impaired encoding of social rewards through the globus pallidus."

Discussion

In summary, we describe the case of a 34-year-old man with a history of polysubstance abuse and one prior episode of depressive symptoms who developed a severe depressive episode, a loss of drug cravings, a diminished pleasurable response to alcohol, and extrapyramidal motor symptoms after a hypoxic episode. Testing was notable for bilateral lesions of the globus pallidus on his MRI and intact cognitive functioning on extensive neuropsychological tests.

The globus pallidus is a "watershed area" that is highly sensitive to hypoxic damage (1). Cerebrovascular ischemic damage (stroke) of the globus pallidus after hypoxemia secondary to opiate overdose has been described (2). Although depression is common after a stroke, poststroke depression has been most highly correlated with lesions of the globus pallidus (3).

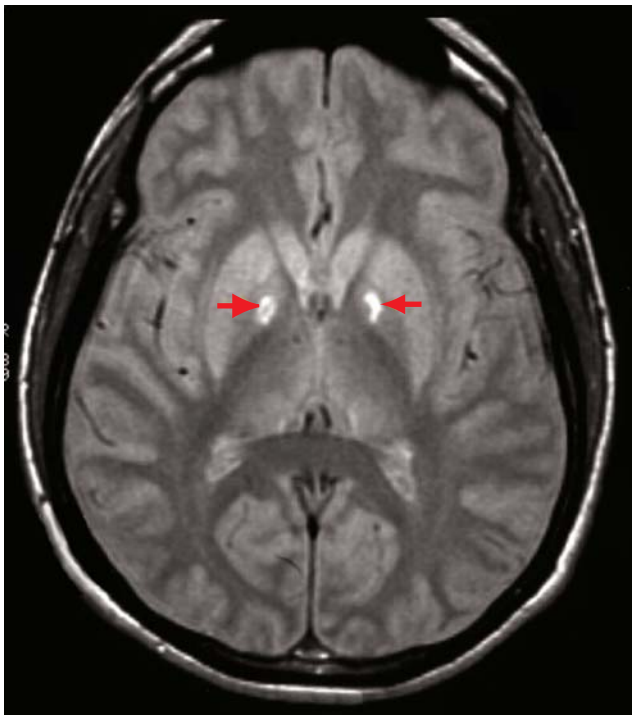
The clinical presentation of anhedonia in response to drugs, as well as to naturally occurring pleasurable stimuli, is consistent with the involvement of the globus pallidus in reward. The brain reward circuit (Figure 2; see also references 4–8) includes the ventral tegmental area, which

TABLE 1. Comprehensive Neuropsychological Test Results of Mr. A[a]

Variable	Score	Interpretation
Full-scale IQ	103	average
Attention		
Trail Making Test A (seconds)	36	average
Language		
Boston Naming Test (maximum of 60)	53	within normal limits
Controlled Oral Word Test, list generation subtest (FAS)	48	average
Memory		
California Verbal Learning Test–2 total	42	average
Wechsler Memory Scale III, logical memory scale I subtest	10	average
Wechsler Memory Scale III, logical memory scale II subtest	11	average
Rey-Osterrieth Complex Figure Test, 30-second delay subtest	23.5	average
Visuospatial function		
Rey-Osterrieth Complex Figure Test, copy subtest (maximum of 36)	36	within normal limits (perfect score)
Executive function		
Trail Making Test B (seconds)	60	average
Wisconsin Card Sorting Test categories subtest (maximum of 6)	6	within normal limits
Wisconsin Card Sorting Test peserveration errors subtest	6	high average
Wisconsin Card Sorting Test percent peserveration errors subtest	7.4	high average
Wisconsin Card Sorting Test failure to maintain set subtest	1	within normal limits
Stroop Word Test	100	average
Stroop Color Test	86	average
Stroop Color and Word Test	50	average

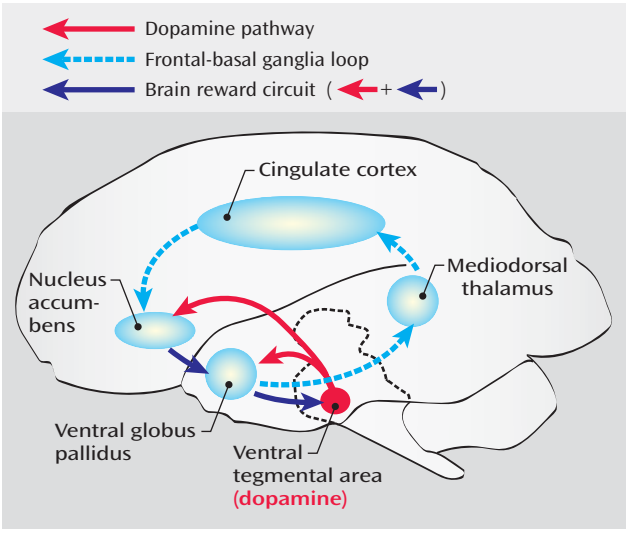
[a] Testing revealed sparing of several areas of cognitive functioning, particularly attention, working memory, and executive function. The neuropsychological profile argued against a "frontal-subcortical syndrome."

FIGURE 1. An Axial Proton Density Magnetic Resonance Imaging Scan of Mr. A at the Level of the Basal Ganglia, Demonstrating Signal Hyperintensities in the Globus Pallidus Bilaterally[a]



[a] See arrows.

FIGURE 2. The Brain Reward Circuit[a]



[a] Dopaminergic neurons project from the ventral tegmental area to the nucleus accumbens and the ventral globus pallidus. Neurons from the nucleus accumbens project to the ventral globus pallidus, which, in turn, projects to the ventral tegmental area. In addition, the ventral globus pallidus gains access to the prefrontal cortex through projections to the mediodorsal thalamus, which projects to the anterior cingulate.

projects dopaminergic fibers to the nucleus accumbens as well as to the globus pallidus (6). The nucleus accumbens projects fibers to the ventral globus pallidus, which, in turn, projects to the ventral tegmental area (4, 6, 8).

The defining characteristic of this circuit is its ability to sustain brain stimulation reward (9). That is, laboratory animals can be easily trained to perform an operant response (e.g., lever pressing) that results in delivery of rewarding electrical stimulations through an electrode implanted into any site of the brain reward circuit. Indeed, rats will perform electrical self-stimulation of the ventral globus pallidus at a high rate.

Presentation of rewards and stimuli predictive of future rewards trigger the firing of ventral globus pallidus neurons (10). Blockade of the ventral globus pallidus has been shown to impair intravenous drug self-administration in

laboratory animals (11) as well as to impair relapse to drug- and stress-triggered drug-seeking behavior (12, 13). These findings are consistent with the patient's loss of drug cravings and alcohol-induced euphoria. In animal studies, disruption of the ventral globus pallidus interferes with partner bonding and partner preference (14). The patient's social isolation and diminished pleasure in social situations may have been related to impaired encoding of social rewards through the globus pallidus. Finally, lesion of the dorsal portion of the globus pallidus, which is involved with motor behavior through extrapyramidal motor circuits (15), is consistent with the patient's tremor, rigidity, and bradykinesia.

In conclusion, this case suggests an association between bilateral lesions of the globus pallidus and a syndrome of anhedonia, loss of drug cravings, and extrapyramidal signs that are consistent with the participation of this brain structure in both reward circuitry and movement. We describe a clinical correlation between damage of the globus pallidus and diminished rewarding effects of drugs of abuse, which has been previously observed in animal models. Cases such as this may occur with increased frequency in the future, given the significant increase in emergency room visits related to heroin use and narcotic analgesics from 1995 to 2002 (35% and 163%, respectively) (16) and the fivefold increase in the purity of street heroin from 1981 to 2000 (17). Indeed, 48% of heroin users report a history of at least one nonfatal overdose (18). We hope that this individual case may lead to future controlled studies in both animals and humans to further elucidate the role of the globus pallidus.

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