SHORT REPORT

Panic and fear induced by deep brain stimulation

N A Shapira, M S Okun, D Wint, K D Foote, J A Byars, D Bowers, U S Springer, P J Lang, B D Greenberg, S N Haber, W K Goodman

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Background: Mood, cognitive, and behavioural changes have been reported with deep brain stimulation (DBS) in the thalamus, globus pallidus interna, and anterior limb of the internal capsule/nucleus accumbens region.

Objective: To investigate panic and fear resulting from DBS.

Methods: Intraoperative DBS in the region of the right and then left anterior limb of the internal capsule and nucleus accumbens region was undertaken to treat a 52 year old man with treatment refractory obsessive-compulsive disorder (OCD). Mood, anxiety, OCD, alertness, heart rate, and subjective feelings were recorded during intraoperative test stimulation and at follow up programming sessions.

Results: DBS at the distal (0) contact (cathode 0–, anode 2+, pulse width 210 ms, rate 135 Hz, at 6 volts) elicited a panic attack (only seen at the (0) contact). The patient felt flushed, hot, fearful, and described himself as having a “panic attack.” His heart rate increased from 53 to 111. The effect (present with either device) was witnessed immediately after turning the device on, and abruptly ceased in the off condition.

Conclusions: DBS of the anterior limb of the internal capsule and nucleus accumbens region caused severe “panic.” This response may result from activation of limbic and autonomic networks.

The neural circuitry underlying panic and fear is a topic of active investigation.^{1–5} Some proposed mechanisms have focused on the amygdala, believed to carry out emotional processing; the frontal cortex, which may modulate or inhibit panic; and the hypothalamus, which may mediate the relation between subjective panic and the autonomic system.^{1–5} There is a paucity of data examining the role of circuits involving the nucleus accumbens region in producing panic. In this report we discuss the phenomenon of de novo panic induced by both right and left deep brain stimulation (DBS) in the region of nucleus accumbens.

CASE REPORT

A 52 year old right handed man with a 32 year history of severe treatment refractory and crippling obsessive-compulsive disorder (OCD) presented for a surgical evaluation. He had obsessions (symmetry and exactness) and compulsions (ritualised handwashing and checking). He also suffered from symptoms of “incompletion” which compelled him to repeat behaviours until they felt “right”. He did not meet criteria for other anxiety disorders and had never experienced a panic attack. He had poor responses to multiple appropriate drugs and three courses of intensive behavioural therapy. At initial presentation, he also met DSM-IV diagnostic criteria for moderate recurrent major depressive disorder with melancholic features and was on escitalopram 30 mg daily. Neurological examination was normal.

The patient understood the risks and benefits of DBS and signed informed consent to participate in a DBS protocol for treatment refractory OCD (NIMH R21-MH64161). Using MRI/CT fusion based stereotactic guidance, DBS electrodes were inserted bilaterally through the anterior limb of the internal capsule into the nucleus accumbens near the anterior commissure (fig 1). Computed tomographic/magnetic resonance imaging (CT/MRI) fusion was undertaken for electrode localisation using a method previously published by us.⁶

Brief stimulation paradigms were used to evaluate effects of right and left DBS in the region of nucleus accumbens and internal capsule. The intraoperative evaluation of the DBS electrodes was carried out using bipolar stimulation at each contact. Pulse width and stimulation frequency were fixed at 210 μ s and 135 Hz, respectively. Voltage was varied between 0, 2, 4, 6, and 8 volts. The patient was blind to parameter changes, and the voltage was returned to 0 before testing at each contact. Testing occurred for approximately two to four minutes at each setting.

The results of intraoperative macrostimulation on the right are summarised in table 1. Most notably, the patient experienced reproducible sensations of flushing, fear, and “panic” when the most ventral contact (0) was stimulated (with bipolar stimulation). He described the sensation as feeling hot, flushed, fearful, and “panicky.” He could feel palpitations in his chest, and when asked indicated he had an impending sense of doom. The feelings were coincident and continuous with the stimulator “on” setting and they rapidly dissipated when switched off. With stimulation on the right, the feeling of panic was accompanied by tachycardia (heart rate increase from 53 to 119 beats/min when “on”, returning to 74 beats/min after stimulation was discontinued). The patient experienced a similar transient increase in his pulse (from 69 to 82 beats/min, subsequently returning to 67 beats/min) when contact 0 was activated on the left side, despite administration of a β blocker one hour before stimulation (three doses of 20 mg labetalol intravenously over 30 minutes). The β blocker was given by the anaesthesia team following right DBS as prophylaxis against tachycardia during intraoperative stimulation on the left side.

Approximately one month after implantation, the patient underwent sham testing of his DBS. He was asked to describe changes in emotional state in response to the DBS; no current was applied to any electrodes during this session. The patient was blinded to DBS settings by a curtain that separated the patient and examiner from the DBS programming nurse. The examiner communicated with the programmer by displaying written instructions. The patient was asked at regular intervals how he felt, regardless of whether stimulation parameters had changed. During this sham testing, the patient denied any anxiety or other significant

Abbreviations: DBS, deep brain stimulation; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; OCD, obsessive-compulsive disorder

Table 1 Results of right intraoperative deep brain stimulation testing							
DBS parameters			Vital signs			Results	
Anode	Cathode	Potential (V)	Pulse (beats/min)	BP (mm Hg)	Anxiety (0–10)	Alertness	Patient comments
Preoperative*			59	131/78	5	4	
Collision†			53		5	4	
0	2	4	53		4	4	A
0	2	6	119	145/84	8	–2	B (Feeling hot, flushed, panicky)
Off			74		5	0	C (Cooler, clearer, not panicky)
1	3	6	68	156/88	2	5	D (Giddy, like he wants to laugh)
Off			61		3	–2	
2	3	2	57	168/88	3	1	
2	3	6	63		2	3	High, giddy, trouble thinking
2	3	8	69	154/88	4	–5	Concentration poor, little high and euphoric
Off			49		2	0	
3	2	6	60	164/84	2	–5	Elevated mood, euphoric, slight haze

Anxiety was measured on a 0–10 subjective scale: 0, no anxiety; 10, maximum anxiety.
*Preoperative, before the procedure.
†Collision, after impact of the electrodes but in the “off” position.

changes in his emotional state. A planned second outpatient testing session confirmed the panic/fear response at the ventral contact.

The patient's current stimulator settings are with contacts 1, 2, and 3 (anode), case (cathode), pulse width 210 μ s, 130 Hz, 3.5 volts (18 months post-implantation). He has not had any panic with chronic DBS. He is currently taking 10 mg of escitalopram daily.

DISCUSSION

The findings in this case report show that stimulation of a circumscribed area in the region of the nucleus accumbens in an OCD patient can result in panic. This response may provide a glimpse of the potential brain circuitry underlying this phenomenon. The finding that the ventral contact elicited the strongest response may provide useful information about the potential circuits responsible for fear and panic. It is likely that within that circuitry the hypothalamic or autonomic fibres, or both, in this region may mediate the increase in heart rate, flushing, and heat sensation. The region of the anterior hypothalamus is very close to the active contact. Further, the main inputs to the accumbens (or ventral striatum) are the anterior cingulate and orbitofrontal cortices, the amygdala, and the midbrain dopamine neurones.⁷⁻⁹ The findings in this paper should be interpreted with caution as the patient involved in the study had OCD, and therefore we cannot be certain if they are generalisable. Additionally, an important consideration is that response of panic could have been secondary to physiological changes induced by stimulation, and this point will need to be clarified in future studies.

Amygdalofugal and hypothalamic pathways, as well as amygdalar connections with the locus ceruleus, and the periaqueductal grey matter, thalamus, and frontal cortex, may produce hormonal, autonomic, and behavioural changes characteristic of panic, although this circuitry also awaits further elucidation.¹⁰ Other triggers that can activate the panic response include fear provoking memories from the hippocampus¹ and projections from the noradrenergic locus ceruleus.^{11,12} The locus ceruleus, the periaqueductal grey matter, and the nucleus paragigantocellularis project to the amygdala and may produce panic, possibly when stimulated by autonomic disturbances.¹ The amygdala, orbitofrontal, and anterior cingulate circuit has been shown to be involved in the fear response. Interestingly, there is a recent report of panic with autonomic disturbances occurring in a patient who was receiving hypothalamic DBS for cluster headaches,¹³ and also for DBS in the subthalamic nucleus region.¹⁴

We believe it plausible that in this case DBS activated accumbens region outflow and that this led to the dramatic clinical effect of panic. This region has many potential structures that may play a role in this response, including accumbens, internal capsule, amygdala/stria terminalis, anterior hypothalamus, and medial olfactory stria. We have now observed this response in three patients implanted at this target. The mechanisms of DBS are complex^{15,16} and it is likely that both inhibition and excitation of cells and fibre bundles may play a role in the panic response.

Recent data indicate that subthalamic nucleus (STN) DBS can both impair fear recognition¹⁷ and induce fear and panic.¹⁴ Although in this case we stimulated in the nucleus accumbens circuitry, we may have activated the amygdala. The activation may have occurred in a manner similar to STN region DBS, suggesting that the panic response is the result of efferent fibres that may emanate from many different regions

of brain, but that all connect to amygdala and ultimately frontal cortex.

The finding that stimulation of the nucleus accumbens/hypothalamic region can provoke panic may reveal a new aspect of the underlying neural circuitry of fear and panic. These observations will need to be followed with functional imaging to assist in clarifying our understanding of the neural circuitry underlying panic.

Authors' affiliations

N A Shapira, J A Byars, W K Goodman, Department of Psychiatry, University of Florida, Gainesville, Florida, USA

M S Okun, Departments of Neurology and Neurosurgery and Psychiatry, University of Florida, Gainesville

K D Foote, Department of Neurosurgery, University of Florida, Gainesville

D Bowers, U S Springer, P J Lang, Department of Clinical and Health Psychology, University of Florida, Gainesville

D Wint, Section on Integrative Neuroimaging, National Institute of Mental Health, Bethesda, Maryland, USA

B D Greenberg, Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, USA

S N Haber, Department of Pharmacology and Physiology, University of Rochester, New York, USA

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Correspondence to: Dr Michael S Okun, University of Florida Brain Institute, Department of Neurology, 100 S Newell Drive, Room L3-100, Gainesville, FL 32610, USA; okun@neurology.ufl.edu

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