Dual dopamine–5-HT releasers: potential treatment agents for cocaine addiction

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Biogenic amine transporters (BATs) are integral membrane proteins that translocate biogenic amine neurotransmitters [norepinephrine, dopamine (DA) and 5-hydroxytryptamine (5-HT)] across cell membranes. BATs are the principal sites of action for many psychotropic drugs, including abused stimulants such as cocaine and methamphetamine. Preclinical and human data demonstrate that withdrawal from long-term cocaine administration produces a dual deficit of synaptic DA and 5-HT in the brain, indicating the advantage of developing medications that normalize impairments in both neurotransmitter systems. In this article, we review data supporting the notion that stimulant effects normally produced by increased levels of extracellular DA can be antagonized by concurrent increases in levels of extracellular 5-HT. Accordingly, nonselective BAT substrates that can release both DA and 5-HT, such as the novel compound PAL287, have low abuse potential while maintaining the ability to suppress drug-seeking behavior. The collective findings indicate that such drugs will provide neurochemical normalization therapy for cocaine addiction and might also be useful for treating depression, obsessive–compulsive disorder, attention deficit disorder and obesity.

Introduction

The acute administration of abused stimulants such as cocaine and methamphetamine produces a ‘high’ or ‘rush’ that is mediated by increases in synaptic dopamine (DA) levels in mesolimbic reward circuits, although some evidence also implicates elevations in synaptic norepinephrine (NE) levels [1]. Episodic use of stimulants, especially when self-administered via smoked or intravenous (i.v.) routes, can lead to addiction in susceptible individuals. The persistent abuse of stimulants causes long-term changes in brain neurochemistry and circuitry via synaptic plasticity [2,3]. Preclinical and clinical findings show that withdrawal from chronic cocaine is associated with impairments in 5-hydroxytryptamine (5-HT) neuronal function, in addition to the well-accepted deficits in DA function [4]. Perhaps the most compelling evidence of 5-HT deficits in cocaine addiction is the occurrence of a psychiatric syndrome resembling major depression that follows abstinence from binge cocaine use [4,5], coupled with the increased prevalence of suicidal ideation and suicide attempts among cocaine addicts [6]. The established role of 5-HT dysfunction in mediating depression and suicide [7] indicates that decreased synaptic 5-HT levels could have a role in cocaine withdrawal states [8].

Biogenic amine neurotransmitters – NE, DA and 5-HT – are crucially involved in the pathogenesis and treatment of various psychiatric disorders. Nerve cells that synthesize, store and release biogenic amines have membrane-bound transporter proteins that terminate transmitter action by translocating previously released transmitter molecules back into the nerve terminal from the extracellular space [9]. The three biogenic amine transporters (BATs) are principal sites of action for cocaine and amphetamines, and it is useful to divide BAT ligands into two categories based on their molecular mechanism of action: uptake inhibitors and substrates (Box 1). Cocaine binds to BATs and inhibits neurotransmitter uptake, leading to increases in synaptic transmitter levels. The cocaine-induced increase in extracellular neurotransmitter concentration is dependent on impulse-driven exocytosis and is sensitive to negative-feedback loops. Amphetamine-like compounds are BAT substrates that release transmitters via carrier-mediated exchange, a process that is not dependent on impulse-driven exocytosis and is not sensitive to negative-feedback loops. As a result, the administration of BAT substrates tends to produce larger increases in levels of extracellular neurotransmitters than does administration of uptake inhibitors [10].

A major aim of drug abuse research is to characterize the neurobiological changes produced by chronic stimulant exposure. Using this information, researchers hope to develop medications that can ameliorate the symptoms of stimulant withdrawal and, thereby, facilitate abstinence. Considerable evidence indicates that negative affective states associated with withdrawal are predisposing factors in the maintenance of continued drug-seeking behavior and must be treated to prevent relapse [11]. The many possible strategies for tackling this problem are being investigated by various research groups. In the early 1990s, we focused our efforts on dual DA- and 5-HT-releasing agents for several reasons. First, preliminary
Box 1. BATs and stimulant addiction

- BATs (Figure I) are integral membrane proteins that transport biogenic amine neurotransmitters (DA, 5-HT and NE) across cell membranes in a Na+-dependent manner.
- The physiological role of BATs is to terminate neurotransmitter action by translocating previously released neurotransmitter molecules into the nerve terminal from the extracellular space.
- BATs are targets for medications used to treat depression, anxiety and other psychiatric disorders.

- BATs are the principal site of action for abused stimulants such as cocaine and amphetamine.
- Acute administration of stimulants produces an increase in extracellular levels of DA in various brain regions. Such stimulant-induced increases are thought to underlie reinforcing effects in the nucleus accumbens.
- Chronic use of stimulants eventually leads to a dual deficit in synaptic DA and 5-HT, in addition to alterations in gene regulation and protein expression, all of which contribute to the development of addiction.

Figure I. Classification of BAT ligands: reuptake inhibitors versus substrate-type releasers. (a) Reuptake inhibitors such as cocaine and 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine [GBR12909 (GBR); red triangles] bind to BATs but are not transported. These drugs increase extracellular concentrations of DA (black circles) by blocking the transporter-mediated uptake of transmitters from the synapse. Abbreviation: VMAT, vesicular monoamine transporter. (b) Substrate-type releasers such as amphetamine and methamphetamine (METH; red diamonds) bind to BATs and are transported into the cytoplasm of nerve terminals. Releasers increase extracellular DA concentrations using a two-pronged mechanism. First, they increase cytoplasmic levels of transmitter by disrupting its storage in vesicles; second, they evoke non-exocytotic transmitter release by reversing the direction of transporter flux. (c) The increase in extracellular DA levels produced by GBR is dependent on impulse-driven exocytosis and is sensitive to negative-feedback loops. Thus, such increases tend to be lower than those produced by substrates. (d) The increase in extracellular DA levels produced by METH is not dependent on impulse-driven exocytosis and is not sensitive to negative-feedback loops. Thus, such increases tend to be greater than those produced by reuptake inhibitors.
Table 1. 5-HT dysfunction during cocaine withdrawal in rats is similar to depressive disorders in humans\textsuperscript{a,b}\textsuperscript{.}

<table>
<thead>
<tr>
<th>5-HT site</th>
<th>Cocaine withdrawal in rats</th>
<th>Major depression in humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT nerve terminals</td>
<td>Extracellular 5-HT levels in nucleus accumbens</td>
<td>CSF 5-HIAA levels</td>
</tr>
<tr>
<td></td>
<td>ACTH and corticosterone response to fenfluramine\textsuperscript{c}</td>
<td>Prolactin and cortisol response to fenfluramine</td>
</tr>
<tr>
<td>Presynaptic 5-HT\textsubscript{1A} somatodendritic autoreceptors</td>
<td>ACTH and corticosterone response to PCA\textsuperscript{c}</td>
<td>Electrophysiological response to 5-HT agonists after chronic SSRI and MAOI administration\textsuperscript{d}</td>
</tr>
<tr>
<td>Postsynaptic 5-HT\textsubscript{1A} receptors</td>
<td>ACTH and prolactin response to 8-OH-DPAT\textsuperscript{c}</td>
<td>Electrophysiological response to 8-OH-DPAT after chronic administration of tricyclics\textsuperscript{d}</td>
</tr>
<tr>
<td>Postsynaptic 5-HT\textsubscript{2} receptors</td>
<td>ACTH and prolactin response to DOI\textsuperscript{e}</td>
<td>5-HT\textsubscript{2} receptor B\textsubscript{max} in frontal cortex of individuals who committed suicide</td>
</tr>
<tr>
<td></td>
<td>Head shake response to DOI in rats and mice\textsuperscript{e}</td>
<td>5-HT\textsubscript{2} receptor B\textsubscript{max} after chronic antidepressant administration in rodents\textsuperscript{e}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Abbreviations: ACTH, adrenocorticotrophin; B\textsubscript{max}, receptor binding density; DOI, (6)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride; 8-OH-DPAT, (6)-8-hydroxy-2-(di-2-propylamino)tetraline; MAOI, monoamine oxidase inhibitor; PCA, parachloroamphetamine; SSRI, 5-HT-selective-reuptake inhibitor; 5-HIAA, 5-hydroxyindoleacetic acid; \textsuperscript{b}increased or enhanced response; \textsuperscript{c}decreased or blunted response. 

Table summarizes data showing that cocaine withdrawal produces a 5-HT deficit syndrome similar to that observed in major depression. At the level of the 5-HT nerve terminals, cocaine withdrawal in rats decreases extracellular 5-HT levels and produces blunted neuroendocrine responses to challenge with 5-HT-releasing agents, fenfluramine and PCA. Patients with major depression have low 5-HIAA levels and blunted neuroendocrine responses to 5-HT challenge. Cocaine withdrawal sensitizes presynaptic somatodendritic 5-HT\textsubscript{1A} receptors, whereas treatment of rats with antidepressants has the opposite effect. Cocaine withdrawal desensitizes the neuroendocrine effects of postsynaptic 5-HT\textsubscript{1A} receptors, and patients with major depression show a desensitized response to the 5-HT\textsubscript{1A} partial agonist ipsapirone. Finally, cocaine withdrawal sensitizes postsynaptic 5-HT\textsubscript{2A} receptors, and patients who commit suicide display an increased 5-HT\textsubscript{2A} receptor B\textsubscript{max}. Reproduced, with permission, from Ref. [8].

\textsuperscript{b}Work from our laboratory.

\textsuperscript{c}Preclinical findings relevant to depression.

sites, rather than highly selective drugs that target a single receptor [14].

In the following sections of this article, we review findings demonstrating that: (i) withdrawal from abused stimulants produces a 5-HT deficit that resembles major depressive disorder in humans; (ii) administration of DA- and 5-HT-releasing agents alone or together decreases drug-seeking behavior; (iii) increases in extracellular levels of 5-HT in brain can antagonize psychomotor stimulant actions of DA releasers; and (iv) a single molecule that can release both DA and 5-HT suppresses cocaine self-administration behavior yet has minimal abuse liability.

**Stimulant withdrawal produces a 5-HT deficit**

*In vivo* microdialysis experiments reveal that rats withdrawn from i.v. cocaine self-administration have decreased extracellular levels of DA and 5-HT in the nucleus accumbens [15,16], which is a brain region implicated in mediating the rewarding effects of abused drugs [17]. A feasible mechanism to explain this finding is the enhanced uptake of DA and 5-HT; indeed, chronic cocaine administration can increase the density of DA transporters (DATs) and 5-HT transporters (SERTs) in rats [18,19] and humans [20,21]. Researchers have used neuroendocrine challenge paradigms to test the hypothesis that cocaine withdrawal causes 5-HT dysfunction. In preclinical studies, rats received repeated injections of cocaine–HCl (15 mg/kg intraperitoneally (i.p.)) for seven days and were tested two days later by measuring hormonal responses evoked by the 5-HT releaser fenfluramine. Rats withdrawn from cocaine exhibited reductions in fenfluramine-induced secretion of the stress hormones adrenocorticotrophin and corticosterone [22,23], a finding that has been replicated in cocaine-dependent human subjects [24,25]. Thus, animal and human data confirm that chronic stimulant exposure alters regulation of the hypothalamic–pituitary–adrenal axis [26]. Behavioral investigations in rodents consistently demonstrate that psychostimulant withdrawal produces negative affective states, as measured by changes in intracranial self-stimulation (ICSS) thresholds and operant responding for natural reinforcers [27]. Additional findings show that cocaine withdrawal renders specific subpopulations of postsynaptic 5-HT\textsubscript{1A} receptors subsensitive, and 5-HT\textsubscript{2A} and 5-HT\textsubscript{2C} receptors supersensitive [28]. The collective evidence [29] supports the hypothesis that chronic stimulant exposure produces 5-HT dysfunction that mirrors some of the neurobiological abnormalities seen in major depression [8] (for review, see Ref. [27]) (Table 1). Unlike patients with endogenous depression, however, cocaine addicts also exhibit prominent DA dysfunction [2]. These findings imply that stimulant addicts suffer from a dual deficit of synaptic DA and 5-HT (Figure 1), and successful pharmacological interventions should attempt to normalize deficits in both transmitters.

**Administration of DA- and 5-HT-releasing agents alone or together reduces drug-seeking behavior**

Administration of the DA releaser phentermine decreases the rate of responding for cocaine in rhesus monkeys without affecting responding for food [30]. This suppressive effect occurs across a broad range of training doses of cocaine and can be sustained by daily administration of phentermine. It has recently been reported that chronic infusions of (+)-amphetamine decrease cocaine self-administration in monkeys without affecting food-reinforced behavior [31]. These results provide a rationale for using DA-releasing agents as agonist medications for the treatment of cocaine addiction [13,32]. The 5-HT releaser fenfluramine also suppresses responding for cocaine in rhesus monkeys, and combined administration of phentermine and fenfluramine produces ~75% reduction in cocaine self-administration [33]. Studies in rats demonstrate that a mixture of d-fenfluramine and phentermine reduces cocaine self-administration by ~80%, yet the combination is not self-administered [34]. Importantly, 5-HT-releasing agents attenuate cue-elicited cocaine-seeking behavior in rats [35] and reduce cocaine craving in abstinent cocaine-dependent patients [36]. These findings indicate
that combined treatment with DA- and 5-HT-releasing agents could have therapeutic value in reducing both drug-seeking behavior and the ability of drug-associated cues to induce relapse.

**Increased levels of extracellular 5-HT can antagonize psychomotor stimulant actions of DA releasers**

A chief limitation of using amphetamines as medications is their high abuse potential—an effect probably related to increases in mesolimbic DA levels. In this regard, accumulating evidence indicates that increases in synaptic 5-HT levels can counteract the stimulant and reinforcing effects mediated by increased synaptic DA concentration [37,38]. For example, pretreatment with 5-HT-reuptake inhibitors reduces intravenous cocaine self-administration in rats [39] and squirrel monkeys [40]. Similarly, cocaine analogs with high affinity for SERTs [41] support reduced self-administration behavior than do analogs with low affinity for these sites. Agents that broadly activate brain 5-HT systems can reduce self-administration of stimulants [42]. The ‘anti-stimulant’ effect of increasing extracellular levels of 5-HT is readily observed following administration of 5-HT releasers in combination with DA releasers, or administration of single agents that release both neurotransmitters. Drugs that release DA more potently than they release 5-HT (e.g. amphetamine, phentermine and m-fluoroamphetamine) are strong locomotor stimulants and support self-administration behavior (Table 2). Drugs that release 5-HT more potently than they release DA (e.g. fenfluramine, chlorphentermine and p-methylamphetamine) do not stimulate motor activity and are not self-administered. Importantly, fenfluramine administration reduces stimulant effects produced by phentermine under different conditions in diverse species. Specifically, concurrent fenfluramine administration reduces the locomotor effects of phentermine in mice [43], positive rewarding effects of phentermine in rats [44] and subjective effects of phentermine in humans [45]. Such findings support the hypothesis that a single molecule that can release DA and 5-HT would decrease stimulant self-administration yet have minimal abuse liability.

**Potential adverse effects of SERT substrates**

Unfortunately, the use of 5-HT-releasing agents as medications can be limited by side-effects. Based primarily on experience with fenfluramine, three adverse effects must be considered with respect to SERT substrates: cardiac valve disease, primary pulmonary hypertension (PPH) and 5-HT neurotoxicity [10]. The association of fenfluramine with an increased incidence of cardiac valve disease led to its withdrawal from the market in 1997 [46]. Subsequent investigations revealed that the cardiotoxic effects of fenfluramine are probably due to stimulation of mitogenic 5-HT2B receptors by the N-de-ethylated metabolite norfenfluramine [47–49]. The activation of 5-HT2B sites leads to the deposition of a plaque-like encasement of the valve with proliferative myofibroblasts in an abundant extracellular matrix [46]. Other evidence indicates that SERTs are involved in the mechanism, whereby fenfluramine increases the risk of developing PPH (for review, see Ref. [10]). Medications linked to the occurrence of PPH share the common feature of SERT substrate activity. By contrast, not all SERT substrates are associated with PPH. The antidepressant trazodone is not associated with PPH, yet its major metabolite – m-chlorophenylpiperazine (mCPP) – is a potent SERT substrate [50]. The term ‘5-HT neurotoxicity’, when used in the present context, refers to the fact that high-dose administration of 5-HT releasers...
often causes persistent depletion of brain tissue 5-HT and reductions in SERT binding. A key observation is that not all SERT substrates deplete 5-HT. For example, repeated administration of mCPP fails to deplete brain 5-HT, despite producing SERT-mediated increases in extracellular levels of 5-HT that are comparable to those caused by fenfluramine. These data indicate that SERT substrate activity is necessary, but not sufficient, to produce long-term depletion of brain 5-HT. Our investigations support the possibility of developing dual DA–5-HT releasers that lack fenfluramine-like adverse effects. In particular, lead drug molecules should be chemically distinct from the phenylethylamine structure shared by amphetamine-like agents and should lack major agonist activity at 5-HT2B receptors.

**Studies with PAL287: a dual DA–5-HT releaser**

Based on the information discussed, we evaluated the pharmacological activity of >350 BAT substrates to search for candidate medications. The goal was to identify a non-amphetamine molecule that would potently release DA and 5-HT, but not NE. Although it was not possible to separate NE- and DA-releasing properties, we chose the novel BAT substrate PAL287 (1-naphthyl-2-aminopropane; Table 2) as a lead compound for further evaluation. PAL287 is a nonselective biogenic amine releaser whose most potent actions are on 5-HT release. Doses of i.v. PAL287 ranging from 0.3 to 3.0 mg/kg increase extracellular DA and 5-HT levels in a dose-dependent manner, with larger effects on 5-HT.

### Table 2. Summary of 5-HT-mediated and DA-mediated effects of selected releasing agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>[3H]-5-HT release EC50 (nM)</th>
<th>[3H]-DA release EC50 (nM)</th>
<th>Locomotor activation</th>
<th>Self-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td><img src="image" alt="Amphetamine structure" /></td>
<td>1756 ± 94</td>
<td>24.8 ± 3.5</td>
<td>Strong</td>
<td>Yes</td>
</tr>
<tr>
<td>Phentermine</td>
<td><img src="image" alt="Phentermine structure" /></td>
<td>3511 ± 253</td>
<td>262 ± 21</td>
<td>Strong</td>
<td>Yes</td>
</tr>
<tr>
<td>m-fluoroamphetamine</td>
<td><img src="image" alt="m-fluoroamphetamine structure" /></td>
<td>1937 ± 202</td>
<td>24.2 ± 1.1</td>
<td>Strong</td>
<td>Yes</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td><img src="image" alt="Fenfluramine structure" /></td>
<td>79.3 ± 11.5</td>
<td>&gt;10000</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Chlorphentermine</td>
<td><img src="image" alt="Chlorphentermine structure" /></td>
<td>30.9 ± 5.4</td>
<td>2650 ± 273</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Phentermine + fenfluramine</td>
<td>N/A</td>
<td>N/A</td>
<td>Weak</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>p-methylamphetamine</td>
<td><img src="image" alt="p-methylamphetamine structure" /></td>
<td>53.4 ± 4.1</td>
<td>44.1 ± 2.6</td>
<td>Weak</td>
<td>Minimal</td>
</tr>
<tr>
<td>PAL287</td>
<td><img src="image" alt="PAL287 structure" /></td>
<td>3.4 ± 0.2</td>
<td>12.6 ± 0.4</td>
<td>Weak</td>
<td>No</td>
</tr>
</tbody>
</table>

*Summary of data showing that increased 5-HT-releasing activity reduces psychomotor and rewarding effects mediated by increased DA release.

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Reproduced, with permission, from Ref. [52].

Reproduced, with permission, from Ref. [61].
(three doses at 6.0 mg/kg i.p.) and (+)-MDMA (3,4-methylenedioxymethamphetamine; three doses at 7.5 mg/kg i.p.).

A 3 mg/kg i.v. dose of PAL287 produces increases in extracellular DA concentration that are similar to those elicited by 1 mg/kg of (+)-amphetamine, yet PAL287 produces nearly five times less ambulation than does (+)-amphetamine. Both drugs evoke repetitive movements (i.e. stereotypy) to a similar extent, indicating that the decreased ambulation caused by PAL287 is not due to heightened stereotypy. However, the stereotypy caused by PAL287 is qualitatively different from that caused by (+)-amphetamine. The latter (which includes head bobbing, sniffing and rearing) occurs mostly in the vertical plane. By contrast, the stereotypy produced by PAL287 consists of elements of the 5-HT behavioral syndrome (forepaw treading and head weaving) and occurs mostly in the horizontal plane, consistent with PAL287-induced 5-HT release. It should be mentioned that the stereotypic effects evoked by high i.v. doses of these drugs in rats do not occur after administration of therapeutic oral doses of DA- and 5-HT-releasing agents (e.g. amphetamine and fenfluramine, respectively) to patients in a clinical setting.

Importantly, PAL287 does not support self-administration behavior and suppresses ongoing cocaine self-administration in rhesus monkeys. A dose of 1.0 mg/kg/h of PAL287 significantly reduces both cocaine- and food-maintained responding; however, the suppression of cocaine self-administration is greater than is the reduction in food-maintained responding. The latter is unlikely to be of clinical relevance because fenfluramine, a well-tolerated medication, also suppresses food-maintained responding in this model system [55].

Concluding remarks
The results obtained with PAL287 support the hypothesis that a non-amphetamine substrate for DATs and SERKTs releases DA and 5-HT from neurons in vivo, is minimally reinforcing and suppresses ongoing cocaine self-administration [52]. PAL287 has several desirable qualities for a candidate medication, including lack of 5-HT neurotoxicity and low abuse liability. Future studies should evaluate the potential of PAL287 for increasing the risk of PPH, perhaps by determining its potency at human voltage-gated K⁺ channels [56]. Evidence reviewed here supports the use of monoamine releasers as agonist-substitution medications for the treatment of stimulant addictions [52]. A dose of 1.0 mg/kg/h of PAL287 had virtually eliminated cocaine self-administration in rhesus monkeys by the end of the seven-day treatment, although this effect was not fully selective. Future studies should examine the effect of PAL287 on other unit doses of cocaine. The role of NE in the actions of PAL287 is an important issue that awaits additional study [1].

Our findings using PAL287 in monkeys are reminiscent of the previously reported suppression of cocaine self-administration produced by (+)-amphetamine, although amphetamine has greater selectivity than does PAL287 in reducing this self-administration rather than food-maintained responding [57]. Clinical studies support these findings: a slow-release formulation of (+)-amphetamine is effective at maintaining cocaine addicts in treatment and reducing illicit cocaine use [58,59]. We predict that agents such as PAL287, which have mixed DA–5-HT-releasing activity, will provide the therapeutic effects of amphetamine-type monoamine releasers while minimizing the adverse effects associated with the phenylethylamine structure. Although further work must be done to refine PAL287, in particular to reduce its potency at 5-HT₂B receptors, we believe that this compound represents the prototype for a new generation of drugs that enhance biogenic amine release by acting as substrates at BATs. It is possible that a PAL287-like compound with greater reinforcing effects will be required to optimize compliance in the clinic, but this awaits investigation.

While PAL287-like compounds move slowly from the preclinical arena towards clinical development, it should be possible to test dual DA–5-HT releasers in humans using clinically available compounds. For example, the use of DA–5-HT releasers as treatments for addictive disorders can be tested by the administration of (+)-amphetamine (to increase extracellular DA levels) and the 5-HT precursor 5-hydroxytryptophan (5-HTP) co-administered with the peripheral decarboxylase inhibitor carbidopa (to increase extracellular 5-HT levels) [60]. Moreover, the use of DA–5-HT releasers as a treatment for obesity can be tested using phentermine (to increase extracellular NE levels) and 5-HTP–carbidopa. In summary, we suggest that drugs with a mode of action similar to that of PAL287 will provide neurochemical normalization therapy for cocaine addiction and be useful for treating depression, obsessive–compulsive disorder, attention deficit disorder and obesity. Ultimately, it will be of interest to determine whether this type of treatment can restore the brain to its pre-addicted state.

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