

Corticostriatal circuitry in regulating diseases characterized by intrusive thinking

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Intrusive thinking triggers clinical symptoms in many neuropsychiatric disorders. Using drug addiction as an exemplar disorder sustained in part by intrusive thinking, we explore studies demonstrating that impairments in corticostriatal circuitry strongly contribute to intrusive thinking. Neuroimaging studies have long implicated this projection in cue-induced craving to use drugs, and preclinical models show that marked changes are produced at corticostriatal synapses in the nucleus accumbens during a relapse episode. We delineate an accumbens microcircuit that mediates cue-induced drug seeking becoming an intrusive event. This microcircuit harbors many potential therapeutic targets. We focus on preclinical and clinical studies, showing that administering N-acetylcysteine restores uptake of synaptic glutamate by astroglial glutamate transporters and thereby inhibits intrusive thinking. We posit that because intrusive thinking is a shared endophenotype in many disorders, N-acetylcysteine has positive effects in clinical trials for a variety of neuropsychiatric disorders, including drug addiction, gambling, trichotillomania, and depression.

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Dialogues Clin Neurosci. 2016;18:65-76.

Introduction

Intrusive thoughts are characteristic of a number of neuropsychiatric disorders, such as obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), depression, schizophrenia, body dysmorphic disorder, eating disorders, and drug addiction.¹ Such thoughts are involuntary images, ideas, or thoughts that can be difficult to manage or eliminate. For example, the intrusive desire in drug addicts to use drugs cannot be easily controlled and thereby causes behaviors that can lead to relapsing to drug use.² In depression, unwelcome rumination on negative or sad events can precipitate a state of depression, and stress-associated cues can initiate difficult-to-manage thoughts that lead to a state of anxiety in PTSD.³ Paranoid delusions can be a particularly troubling phenomenon, disrupting thought processing in patients with schizophrenia.^{4,5} Finally, intrusive thinking has been best characterized in OCD, where it is a primary initiator of repetitive behavior that has a significant negative impact on a patient's life.⁶

Keywords: addiction; corticostriatal; glutamate; intrusive thinking; synaptic plasticity; N-acetylcysteine

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Selected abbreviations and acronyms

GLT-1	<i>glutamate type 1 transporter</i>
mGluR2/3	<i>group II metabotropic glutamate receptor</i>
mGluR5	<i>group I metabotropic glutamate receptor 5</i>
MMP	<i>matrix metalloproteinase</i>
NAC	<i>N-acetylcysteine</i>
NACore	<i>nucleus accumbens, core subcompartment</i>
NAshell	<i>nucleus accumbens, shell subcompartment</i>
OCD	<i>obsessive-compulsive disorder</i>
PFC	<i>prefrontal cortex</i>
PTSD	<i>posttraumatic stress disorder</i>
t-SP	<i>transient synaptic potentiation</i>

Thus, intrusive thoughts act as triggers that initiate relapsing to undesired behaviors or internal states of mind that we characterize as one or another type of neuropsychiatric disorder.⁷ By considering that intrusive thoughts are a shared endophenotype of many neuropsychiatric disorders, it is clear that discovering the neurobiological underpinnings of how a thought becomes intrusive and can initiate maladaptive behaviors could have far-reaching therapeutic impact on a number of disorders. While not likely to cure any of the disorders, a treatment rendering intrusive thoughts more controllable and less likely to trigger unwanted behaviors would broadly support current pharmacological and psychosocial therapies in many neuropsychiatric disorders.

In this review, we explore questions pertaining to the neurobiology of intrusive thoughts, and how we might use this neurobiology to facilitate treatment of a number of neuropsychiatric diseases that are characterized in part by intrusive thinking.

- Is intrusive thinking adaptive in some situations where highly motivating stimulus demands a restricted focus on a single behavioral response?
- Why do people with neuropsychiatric disorders have difficulty controlling intrusive thoughts that trigger undesirable behaviors?
- How can the neurobiology of intrusive thinking be used to identify molecular targets for treating neuropsychiatric disorders characterized in part by intrusive thoughts?

Because of recent neurobiological advances in animal models of addiction, this review will utilize drug addiction as an exemplar neuropsychiatric disorder for understanding the biological basis and pharmacological treatment of intrusive thoughts.

Intrusive thoughts can be adaptive

Before delving deeply into the neurobiology of maladaptive intrusive thoughts, we first consider that thoughts becoming transiently intrusive can contribute to the execution of a normal, adaptive behavior.¹

This viewpoint has proven very useful in conceptualizing drug addiction, where it is an axiom in the field that “drugs usurp normal reward brain circuits.” For example, this perspective has contributed to the rise of our current understanding of the critical role dopamine transmission plays in both normal reward learning and developing drug addiction.⁸⁻¹⁰ Accordingly, it may prove equally worthwhile exploring whether the circuitry underpinning the intrusive thoughts that trigger neuropsychiatric symptoms may have evolved to serve a biological purpose.

When might the biology of intrusive thinking be used to generate an adaptive behavioral response? Consider that you encounter mortal danger, and the adaptive response is to run as far and as fast as possible from the source of danger. It could be argued that the thought of escape becomes intrusive since this thought will be prepotent in guiding your behavior until you escape. Thus, in the process of escaping, you will be unaware of other competing stimuli that might normally capture your attention and guide your behavior. Such competing stimuli might range from relatively minor stimuli, such as rain getting your clothes wet, to major stimuli, such as stepping on a nail while running. In this example, to support the likelihood of successful escape, the high motivational value of mortal danger cancels conscious perception of other less motivating, but also biologically relevant, stimuli. Importantly, for the intrusive nature of the thought of escape to be adaptive, the thought will be terminated, or at least adaptively modified once the goal of escape is achieved, and you then attend to the competing stimuli of wet clothes and a wound in your foot. In contrast, this pattern of thinking becomes pathological when the intrusive thought is not discontinued. For example, if you have an anxiety disorder, the life-threatening experience may trigger a pathological intrusion that you would have difficulty suppressing in order to focus on important competing stimuli and thoughts.

Through this example of a prepotent thought generating a highly focused, adaptive behavior, we recognize that adaptive intrusive thinking consists of three

components that we can dissect to determine neurobiological underpinnings. First, the thought itself is highly motivating of behavior. Second, competing thoughts or stimuli do not readily disrupt the intrusive thought. Third, the thought ceases to be intrusive when it is no longer adaptive. It is possible that the pathology of intrusive thinking leading to maladaptive behavior could arise from impairment in any of the three components. For example, the motivational value of the thought could be excessive, the motivational value of competing thoughts may be reduced, or the ability to adaptively devalue or suppress the intrusive thought may be weakened. Although the third component is most often evoked in clinical settings as a definition of intrusive thinking,^{1,2} next we will overview literature suggesting that all three components of an intrusive thought are harbored at least in part within corticostriatal glutamatergic projections from the prefrontal cortex (PFC) and allocortical regions (eg, amygdala and hippocampus) to the ventral striatum.

Clinical neuroimaging, intrusive thinking, and corticostriatal projections

Maladaptive intrusive thoughts initiating neuropsychiatric behavioral disorders have been characterized as an impairment in “top-down” control that is identified in neuroimaging studies by functional and morphological changes within corticostriatal projections.¹¹ Clinical neuroimaging studies employing cognitive probes that might evoke intrusive thinking consistently indicate activation of PFC and amygdala. Imaging studies using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) in addictive disorders, including drug addiction, gambling, and overeating, reveal that presenting cues associated with the addictive behavior increases activity in the anterior cingulate, amygdala, and ventral striatum (nucleus accumbens).^{12,13} Similarly, evoking sad thoughts in major depression or intrusive urges in OCD are associated with activation of anterior cingulate, orbital frontal cortex, amygdala, and ventral striatum.¹³⁻¹⁵ In the case of depression and OCD, there is also consistently reduced activity and morphometric volume in dorsolateral PFC, which has been particularly influential in characterizing these disorders as a loss of top-down control. Finally, evoking stress in subjects diagnosed with PTSD also reveals marked activation of anterior cingulate and amyg-

dala, with less activation in ventral PFC, perhaps indicative of impaired extinction.¹⁶⁻¹⁸ Next, we will explore general theories of how the striatum is topographically organized to compute motivationally relevant information arriving from cortex and to translate this information into adaptive behavioral responses.

Overview of the role of the striatum in regulating how motivationally relevant stimuli translate into behavior

The striatum harbors procedural memories, such as riding a bike, as well as habitual and stimulus-response behaviors, which makes this brain structure a likely site for the pathological intrusion of thoughts that lead to difficulty in controlling habitual behavior in disorders, such as OCD and addiction.^{19,20} Accordingly, there is a research focus on the striatum as a potential site of pathological impairment. Animal models of perseverative disorders, in particular models of addiction, have been used to examine in great detail the synaptic changes in the striatum produced by addictive drugs²¹⁻²³ and to use this knowledge to uncover potential molecular pharmacotherapeutic targets for treating drug use and relapse.²⁴ While these studies have not yet been overwhelmingly successful in bringing forth effective treatments for addiction, they have resulted in a deep understanding of how the striatum is organized to generate behaviors and how drugs of abuse and other experiences, such as stress, produce striatal cellular adaptations that are beginning to explain how motivationally relevant thoughts can become intrusive and difficult to control.

The striatum can be divided into four functional regions that receive topographically organized inputs from the frontal cortex (*Figure 1*).^{25,26} The divisions are not absolute, and all the compartments share functions and work in a coordinated manner to guide an organized, adaptive behavior. Given this caveat, work with experimental animals and, to a lesser extent, human imaging studies have assigned specific functions to each compartment. In the dorsal striatum, learned behaviors are initiated. The dorsolateral striatum most strongly regulates habitual behavior and harbors classic procedural memories, while the dorsomedial striatum is critical for action-outcome learning of goal-directed behavior. In the ventral striatum, the shell subcompartment of the nucleus accumbens (NAshell) is generally considered

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to play the largest role in predicting reward and reward learning, while the core subcompartment (NAcore) is important for evaluating reward associations.

The different functions of the striatal quadrants (*Figure 1*) can perhaps be best illustrated through the pre-clinical addiction literature. When an animal is learning an action-outcome relationship for obtaining an addictive drug—for example, learning to lever press for an intravenous infusion of cocaine—the drug-induced release of dopamine into the NAshell, and to a lesser extent NAcore, is detected as motivationally relevant, thereby reinforcing lever pressing for the drug.^{27,28} In many experiments, a pavlovian cue, such as light and tone, is paired with the infusion of drug, and the animal learns to further associate lever pressing and drug infusion with the light/tone-conditioned cue. This pavlovian association strong-

ly involves amygdala projections to the NAshell and NAcore. Similarly, the animal makes an association between the drug and the environment in which the drug is delivered, and in the case of our example, the contextual association would be with the operant chamber.²⁹ Importantly, once these associations (action-outcome, pavlovian, contextual) are learned, the motor pattern generator whereby the drug cue or context initiates the behavior (lever pressing) is in the dorsomedial striatum.³⁰ With continued training, the stimulus-response relationship (cue triggering a lever press) becomes habitual and this relationship is ultimately stored as a procedural memory in the dorsolateral striatum.^{27,31} Importantly, reward learning in the NAshell is relatively friable and easy to modify by changing environmental contingencies. However, as training continues, the stimulus-response associations with the reward gradually transfer to the dorsolateral striatum, where they become relatively stable procedural memories.³²

While it is important to understand how drug associations are made and solidified as stimulus-response habits in the striatum, in the clinical setting, these habits are already formed by the time a person seeks treatment for a substance use disorder. Accordingly, it is a therapeutically more relevant question to ask: How does the striatum suppress or modify habits that no longer serve an adaptive purpose? Although a behavioral response that is repetitively experienced and is repeatedly associated with the desired outcome (eg, a drug infusion) becomes stored as a habit in the dorsolateral striatum, the behavior remains initiated by prefrontal and allocortical (amygdala and hippocampal) glutamatergic inputs to the nucleus accumbens, in particular the NAcore (*Figure 1*). This ongoing transfer of environmental information from the ventral to dorsal striatal quadrants reflects the hierarchical organization of the four divisions, with the NAcore acting as a portal whereby motivationally relevant stimuli enter basal ganglia circuitry, and the dorsal striatum coordinating the appropriate behavioral response.^{25,33} For example, in an animal model of addiction where a rodent learns to press a lever for cocaine over many days, the response is well learned and can be initiated by presenting a cue that has been previously associated with cocaine delivery.³⁰ To initiate a cue-induced lever press, the cue presentation is processed in the PFC and amygdala, communicated to the NAcore, and then communicated to the dorsal striatum to access previously stored stimulus-response procedures coding the lever

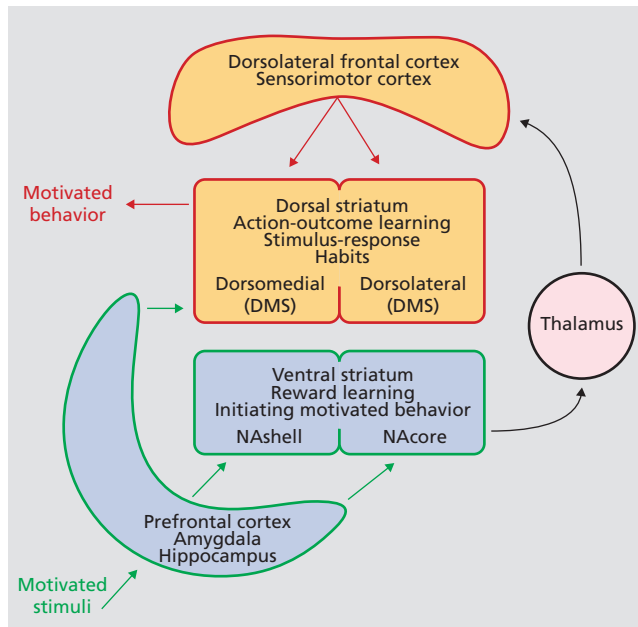


Figure 1. Corticostriatal circuitry responsible for translating motivationally relevant stimuli into adaptive behavioral responses. Information that will motivate behavior arrives from the prefrontal cortex, amygdala, and hippocampus into the ventral striatum. This information activates specific ensembles of neurons that project to the dorsal striatum via hierarchically organized basal ganglia circuitry through the thalamus. In the dorsal striatum, specific behaviors are stored as stimulus-response associations, habits, or procedural memories, and the appropriate behavior initiated to achieve the most adaptive outcome for the organism. DLS, dorsolateral striatum; DMS, dorsomedial striatum; NAcore, core subcompartment of the nucleus accumbens; NAshell, shell subcompartment of the nucleus accumbens

press response. Communication between the ventral and dorsal striatum is largely via well-characterized, topographically organized thalamo-cortico-striatal circuitry that processes information arriving to the accumbens and then engaging dorsal striatal motor pattern generators to elicit the desired behavior.³³ Given the hierarchical organization of the striatum in processing stimuli that can elicit or modify a learned stimulus response, the NAcore is positioned as the site where new information processed in PFC and allocortical brain regions arrives into the striatum to disrupt or suppress an intrusive thought.

To illustrate the role of the NAcore in how a stimulus response or habitual behavior can be disrupted by stimuli that require a behavior to change in order to remain adaptive, we again turn to the addiction literature. If the lever press for a drug is associated with an electric foot shock, the addicted animal will sustain substantially more foot shock than an animal trained to press for food. Indeed, how difficult it is for the electric shock to disrupt a drug-seeking behavior can be viewed as an estimate of the extent to which the stimulus (light/tone/context) is intrusive and is commandeering the animal to maintain a maladaptive behavior (pressing for drug) in spite of a competing motivationally relevant stimulus (shock).³⁴⁻³⁷ This indicates that chronic drug use has produced changes in how the striatum processes competing stimuli, thereby making the drug-associated stimulus-response behaviors more intrusive and difficult to disrupt. Thus, the capacity of the addicted animal to keep responding in the presence of foot shock is similar to the person in mortal danger described above who is having an intrusive thought of escape and does not notice a foot injury sustained by stepping on a nail. In contrast, the food-responding animal pressing for food is not experiencing intrusive motivation to seek reward and responds appropriately to the foot shock pairing by inhibiting lever pressing.

Through the knowledge outlined above of how cortico-striatal projections translate environmental stimuli and thoughts into behavior, we have identified the NAcore as a portal for how motivationally relevant information is processed to guide behavior and to modify stimulus-response habits. Accordingly, the NAcore has become a site in the brain for focusing reductionist technologies to more mechanistically understand how enduring molecular and cellular changes are permitting maladaptive thoughts to become intrusive and trigger symptoms of neuropsychiatric disorders.

Addictive drugs and stress alter cue processing at cortical synapses in the accumbens, causing thoughts to be intrusive

A recent animal study nicely illustrates that PFC synapses in the NAcore are important in how competing, motivationally relevant information can disrupt an intrusive behavioral response, such as lever pressing, for an addictive drug. In this study, maladaptive intrusive thoughts related to addiction were modeled in rats trained to use cocaine, and a subpopulation of the rats was identified that sustained relatively large foot shocks and continued to seek drug delivery triggered by a conditioned cue.³⁴ By optically stimulating PFC inputs to the nucleus accumbens, these investigators effectively increased the capacity of foot shock to disrupt cocaine seeking. In other words, the stimulated rats demonstrated improved top-down control and were able to attend to the foot shock and update their lever pressing behavior in an adaptive manner (in the case of this particular study, stop pressing for cocaine).

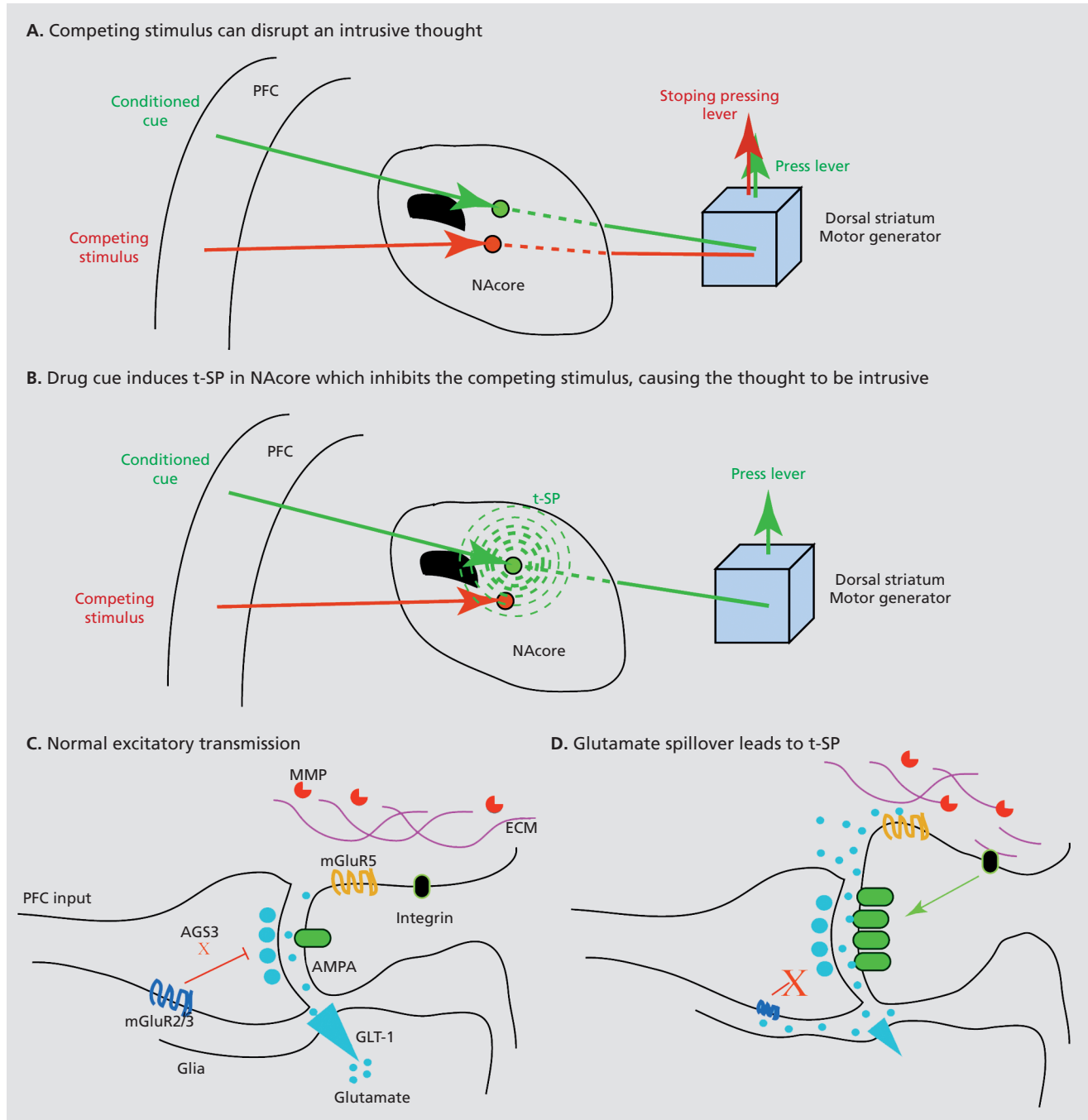
The recent optogenetic study above was built upon nearly 20 years of previous animal research showing that enduring changes are produced in cortico-accumbens synapses by repeated administration of addictive drugs.^{21-23,38} The list of changes identified is prodigious and in some instances contradictory depending on the drug treatment protocol and the class of addictive drug the animal is using. For example, a very well-studied enduring synaptic effect of cocaine use is an increase in accumbens neuron dendritic spine density and size, but use of morphine or heroin produces the opposite effect on spine density and size.³⁹⁻⁴² Since by definition addiction disorders with all drug classes share an endophenotype of the motivation to take drugs becoming intrusive, the long list of drug-induced synaptic adaptations can be simplified by considering only molecular adaptations that are shared between classes of drugs and that endure during drug withdrawal. This rationale is similar to how dopamine release in the accumbens was identified as an obligatory mediator of reward learning.¹⁰ Also, with these exclusion criteria, drug- and stress-induced adaptations at glutamatergic synapses have emerged as strong candidates for how a cue initiates a perseverative drug-seeking response.^{43,44} Importantly, in many experiments, it has been shown that these adaptations are not produced in animals trained to self-administer a biological reward such as sucrose,

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indicating that they are potentially pathological markers of substance use disorders.

Figure 2 illustrates the primary adaptations elicited by presenting a drug-conditioned pavlovian cue to an animal withdrawn from training to self-administer an

addictive drug, including rats and mice trained to use cocaine, heroin, nicotine, alcohol, or methamphetamine. When presentation of the drug-associated cue is processed in the PFC and allocortical regions, their glutamatergic projections to the NAc core are activated to



communicate the presence of a stimulus that will ultimately trigger a behavioral response (eg, lever pressing for drug). Since this is the same circuit for processing cues that achieve biological rewards, why do drug-associated cues elicit a more intrusive, perseverative behavior? One characteristic shared between addictive drugs, but not food training, is that in the NAc, the drug cues elicit glutamate spillover from the synaptic cleft.⁴⁵⁻⁴⁹ Spillover occurs due to two separate enduring changes at glutamatergic synapses produced by repeated drug exposure. All drugs examined to date reduce the capacity of release-regulating presynaptic group II metabotropic glutamate receptors (mGluR2/3) to negatively regulate synaptic glutamate release. This is accomplished by a drug-induced, enduring, downregulation of mGluR2/3 protein or by upregulating AGS3 (activator of G-protein signaling 3), a G-protein-binding protein that inhibits mGluR2/3 intracellular signaling by sequestering and thereby functionally inactivating G α .⁵⁰ Simultaneously, chronic use of drugs or acute stress downregulates astroglial glutamate transporters (eg, glutamate type 1 transporter [GLT-1]) in NAc.^{45,48,51-57} Because the glial glutamate transporters are densely distributed adjacent to the synaptic cleft, synaptic glutamate more effectively escapes uptake and enters the extrasynaptic space when GLT-1 is downregulated.⁵⁸ Regardless of the combination of enduring changes produced by addictive drugs or stress, once in the extrasynaptic space, glutamate stimulation of group I metabotropic glutamate receptor 5 (mGluR5) appears to be critical in regulating cue-induced drug seek-

ing, since mGluR5 antagonists administered systemically or directly into the NAc or NAc shell inhibit cued reinstatement of seeking for all drugs tested to date.⁵⁹⁻⁶¹ In addition, for at least some drugs (eg, heroin and nicotine), extrasynaptic stimulation of GluN2B-containing N-methyl-D-aspartate (NMDA) glutamate receptors contributes to cue-induced reinstatement of drug seeking.^{42,48} Activation of mGluR5 or GluN2B stimulates the catabolism and sculpting of the extracellular matrix (ECM) by activating gelatin-specific matrix metalloproteinase (MMP2, MMP9) activity in NAc.⁶² The mechanism for how these glutamate receptors stimulate MMPs may involve synthesis of nitric oxide and N-nitrosylation of MMPs (unpublished observations).^{63,64} Regardless, ECM digestion creates peptide ligands that bind to receptors on medium spiny neurons in the NAc, causing glutamatergic synapses to undergo transient synaptic potentiation (t-SP).^{48,62,65-67} How the ECM signals t-SP is under investigation, but signaling through integrin receptors is a likely mechanism.^{68,69}

Three characteristics of cue-induced t-SP in the NAc make it a likely candidate mechanism for how a motivating environmental stimulus translates into an intrusive thought and maladaptive behavior. First, the transient nature of the potentiation means that it is eventually disrupted, and in animal models of cue-induced drug seeking, the termination of synaptic potentiation parallels the animal no longer lever pressing for the cue. Second, when the drug goal is achieved (ie, the cue correctly predicts drug delivery), t-SP is terminated. This is akin to attending to your wounded foot

Figure 2. Circuit and cellular adaptations leading to intrusive thinking. **(A)** A stimulus that initiates a behavior is processed through the NAc into the striatum. This behavioral response can be disrupted by a subsequent competing stimulus that indicates that continuing the behavior is maladaptive. **(B)** After drug use, a conditioned cue leads to a response, but induces t-SP in the NAc that attenuates the capacity of a motivationally relevant competing stimulus from changing the behavioral output. Thus, the cue-induced lever pressing is maladaptively maintained as an intrusive thought. **(C)** Normal glutamate transmission in the NAc corresponding to **panel A**. Information coding the cue is communicated through an ensemble of excitatory synapses (estimated to be roughly 2% of NAc neurons⁹⁹), and the fidelity of communication is maintained by the rapid elimination of glutamate by glial transporters (GLT-1) and by presynaptic inhibition of glutamate release via mGluR2/3. In this case, activation of an adjacent ensemble coding for a competing stimulus can be processed with high fidelity through the NAc into the dorsal striatum to inhibit the behavioral response initiated by the cue. **(D)** With chronic drug use there is a downregulation of GLT-1 and a reduction in mGluR2/3 signaling via increased AGS3. This causes synaptic glutamate to spillover into the extracellular space where stimulation of mGluR5 activates MMP catabolism of the ECM. Digested peptides from the ECM signal to the postsynaptic dendritic spine via binding to integrin receptors that initiate t-SP (measured by insertion of AMPA receptors and spine head enlargement). It is hypothesized that the spread of t-SP (indicated by progressively larger green circles in **panel B**) to adjacent neurons via glutamate spillover from the ensemble of synapses coding the conditioned cue inhibits the capacity of a competing stimulus to communicate through the NAc to the dorsal striatum and inhibit the cue-induced behavior. Accordingly, the drug-associated cue-behavior stimulus-response becomes an intrusive thought. Larger or smaller symbols between **panels C and D** indicate up- or downregulation of protein and/or function. AGS3, activator of G-protein signaling 3; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid class of glutamate receptor; ECM, extracellular matrix; GLT-1, glutamate type 1 transporter; mGluR2/3, group II metabotropic glutamate receptor; mGluR5, group I metabotropic glutamate receptor 5; MMP, matrix metalloproteinase; NAc, core subcompartment of the nucleus accumbens; PFC, prefrontal cortex; t-SP, transient synaptic potentiation

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after successful escape in the example above. Third, the extent of t-SP is correlated with the intensity of drug seeking (lever pressing) and does not occur in cue-induced sucrose seeking.⁶⁵ Considering these three characteristics, we hypothesize that the transient potentiation of the majority of glutamatergic synapses in the NAcore by the drug cue reduces the capacity of medium spiny neurons to process motivationally relevant stimuli arriving after the cue that would normally adaptively change the animal's behavior. In other words, because the PFC-NAcore synapses normally coding a competing stimulus (as a shock would compete for the drug-conditioned cue) are already potentiated, these synapses will not properly code and transmit the information to dorsal striatal motor pattern circuits and will therefore not disrupt the ongoing behavior (lever pressing). Although the drug-associated cue is properly processed to initiate adaptive lever pressing, lever pressing becomes perseverative because competing stimuli cannot effectively modulate NAcore neurons and disrupt the ongoing behavior. Thus, the already processed cue-induced lever pressing persists, and the drug cue becomes intrusive causing the animal to persistently relapse to drug seeking.

Evidence from clinical trials supporting a PFC-NAcore pathology in intrusive thoughts

Figure 2 provides a number of sites for pharmacological intervention to clinically evaluate in treating neuropsychiatric diseases characterized in part by intrusive thoughts. Indeed, every potential molecular target in Figure 2 (GLT-1, mGluR2/3, mGluR5, MMP, and integrins) has been examined pharmacologically in animal models and shown to reduce cue-induced drug seeking, and MMP inhibitors simultaneously prevent the induction of t-SP (none of the other targets have yet been examined in this regard).^{52,62,69-73} While many of these targets have generated compounds that have entered clinical trials for various disorders (eg, mGluR2/3 agonist for schizophrenia,⁷⁴ mGluR5 antagonist for fragile X,⁷⁵ and MMP inhibitors in cancer⁷⁶), only GLT-1 has been studied in neuropsychiatric disorders characterized by intrusive thinking. Specifically, N-acetylcysteine (NAC) restores GLT-1 activity in the NAcore in animal models of addiction^{77,78} and has been examined in clinical trials for treating drug addiction,⁷⁹⁻⁸² gambling,⁸³ trichotillomania,⁸⁴ depression,⁸⁵ PTSD (Back SE, unpublished data, 2016), and OCD.⁸⁶ While NAC reduced

drug use in most of the studies, even when NAC did not successfully reduce drug use or relapse, there was a positive reduction in the desire to use the drug (ie, intrusive thoughts related to drug use). Similarly, in a trial for comorbid PTSD and substance use disorder, NAC reduced drug craving and PTSD, and was particularly effective at reducing the PTSD symptom domain of intrusive thoughts (Back SE, unpublished data, 2016). Thus, while a few trials with NAC did not achieve the primary outcome of reducing or ameliorating the psychiatric disorder(s) being examined, when a measure of intrusive thinking is evaluated, such as drug craving in addiction, this endophenotype is consistently reduced by NAC.

The fact that NAC does not appear to be curative in treating neuropsychiatric disorders, but rather ameliorates the domain of intrusive thinking, speaks to the design of future clinical trials evaluating NAC or other compounds that restore GLT-1 (see below). Thus, by reducing intrusive thoughts, patients will have greater opportunity to cognitively regulate the emergence of neuropsychiatric symptoms. However, other cognitive impairments specific for a given disorder may impede this opportunity. For this reason, it seems logical to use NAC in combination with other compounds with proven effectiveness in ameliorating a given disorder. For example, varenicline is the lead US Food and Drug Administration–approved drug for treating cigarette addiction, and increases amygdala-accumbens resting state functional connectivity (rsFC), while NAC increases PFC-accumbens connectivity, supporting a view that combining varenicline and NAC may be especially beneficial in treating addiction to cigarettes.^{87,88} Similarly, antidepressants normalize amygdala hyperactivity in treating depression, pointing to the possibility that antidepressant treatment of elevated amygdala activity combined with PFC-accumbens normalization by NAC might be beneficial.⁸⁹

Although NAC has a long history of clinical use as a mucolytic agent and in restoring glutathione after an acetaminophen overdose,⁹⁰ and was therefore a convenient prototype for pilot clinical trials, it is not necessarily the ideal agent for treating intrusive thinking. NAC has a relatively short half-life, necessitating it be taken twice a day and thereby decreasing compliance in neuropsychiatric diseases such as addiction.⁹¹ Oral NAC has relatively poor bioavailability to the brain, resulting in typical daily doses of 2 to 4 grams. Finally, NAC has off-target

effects, for example, as an antioxidant by promoting glutathione synthesis or as an activator of cystine-glutamate exchange.⁹² While no clinical trials to date indicate that these actions or the desired affect on GLT-1 produce significant side effects compared with placebo, it is preferable to have a more specifically targeted action. Efforts are underway to improve NAC itself and/or its delivery. Also, two other chemical scaffolds have been identified that produce compounds capable of activating GLT-1 that can also be explored. β -Lactam antibiotics promote GLT-1 in animal models of addiction or excitotoxic disease, such as amyotrophic lateral sclerosis,^{93,94} and in animal models have been shown effective at reducing drug seeking.^{77,95-97} The other class of compounds restoring GLT-1 are xanthine derivatives; notably, propentofylline reduced cue-induced cocaine seeking in an animal model of relapse.⁹⁸

Conclusions

Intrusive thinking is a cardinal symptom of many neuropsychiatric disorders. The capacity of thoughts to be-

come intrusive has a biological substrate within the nucleus accumbens that is engaged by synaptic glutamate spillover and the widespread induction of t-SP at glutamatergic synapses. It is hypothesized that through this mechanism the accumbens becomes less responsive to stimuli that would normally compete with an intrusive thought and produce adaptive changes in thinking and behavior. Based on animal models of addiction, a key molecule that can be targeted to ameliorate cued drug seeking is the astroglial glutamate transporter GLT-1. Restoring glutamate transport inhibits reinstated drug seeking, and one compound capable of restoring glutamate transport, NAC, has proven successful in many pilot double-blind clinical trials for treating neuropsychiatric disorders where intrusive thinking is an endophenotype that can trigger symptoms of the disorder. Thus, by targeting intrusive thinking, it may be possible to facilitate treatment for a number of neuropsychiatric disorders where intrusive thinking is a significant pathogenic characteristic, including drug addiction, stress disorders, eating disorders, gambling, OCD, and depression. \square

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Los circuitos corticoestriatales en la regulación de las enfermedades caracterizadas por pensamientos invasores

Los pensamientos invasores activan síntomas clínicos en muchos trastornos neuropsiquiátricos. Se recurre a la adicción a drogas, como modelo de trastorno que se sustenta en parte por pensamientos invasores, para explorar estudios que demuestran que los deterioros en los circuitos corticoestriatales contribuyen de manera importante a los pensamientos invasores. Los estudios de neuroimágenes han vinculado hace tiempo esta proyección con la apetencia imperiosa para emplear drogas inducidas por señales, y los modelos preclínicos muestran que durante un episodio de recaída los cambios importantes son producidos en las sinapsis corticoestriatales en el núcleo accumbens. Se describe un micro circuito del núcleo accumbens que media la búsqueda de droga inducida por una señal, la que llega a constituirse en un acontecimiento invasor. Este micro circuito contiene muchas dianas potencialmente terapéuticas. Este artículo se enfoca en estudios preclínicos y clínicos que muestran que la administración de N-acetilcisteína restaura la captación de glutamato sináptico por los transportadores de glutamato astroglial y de ese modo inhibe los pensamientos invasores. Se postula que debido a que los pensamientos invasores constituyen un endofenotipo que es compartido por muchos trastornos, la N-acetilcisteína tiene efectos positivos en ensayos clínicos para una variedad de trastornos neuropsiquiátricos incluyendo la adicción a drogas, el juego patológico, la tricotilomanía y la depresión.

Les circuits corticaux-striataux dans la régulation des maladies caractérisées par des pensées intrusives

Les pensées intrusives déclenchent des symptômes cliniques dans de nombreux troubles neuropsychiatriques. En utilisant la toxicomanie comme modèle de trouble maintenu en partie par des pensées intrusives, nous analysons des études démontrant que des troubles des circuits corticaux-striataux contribuent fortement aux pensées intrusives. Des études de neuro-imagerie ont longtemps impliqué cette projection dans les envies irrésistibles de drogue induites par un signal. Des modèles précliniques montrent que des modifications notables sont générées au niveau des synapses cortico-striatales dans les noyaux accumbens pendant un épisode de rechute. Nous décrivons un microcircuit des noyaux accumbens, qui joue un rôle de médiateur dans la recherche de la drogue provoquée par un signal, devenant alors un événement intrusif. Ce microcircuit héberge de nombreuses cibles thérapeutiques potentielles. Nous analysons des études précliniques et cliniques montrant que la N-acétylcystéine rétablit la capture du glutamate synaptique par des transporteurs du glutamate astroglial, inhibant ainsi les pensées intrusives. Selon ces études cliniques, les pensées intrusives étant un endophénotype partagé dans de nombreux troubles, la N-acétylcystéine a des effets positifs pour de multiples troubles neuropsychiatriques, dont la toxicomanie, l'addiction aux jeux, la trichotillomanie et la dépression.

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