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N-Acetylcysteine as a Treatment for Addiction

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1. Introduction

Drug addiction is a chronic relapsing disorder characterized by compulsive use despite negative consequences and relapses even after years of abstinence (Leshner, 1997). Criteria put forth by the American Psychiatric Association (2000) for diagnosing drug addiction require at least three of the following symptoms associated with drug use: tolerance; withdrawal; a loss of control over drug intake; unsuccessful attempts to reduce intake; a significant amount of time spent acquiring, using, or recovering from the substance; reduced interest in social or work activities; and continued use despite awareness of adverse physical and psychological consequences (American Psychiatric Association, 2000). In the United States, 22.5 million people, or 8.9% of the population meets the criteria for substance dependence or abuse (Substance Abuse and Mental Health Services Administration, 2010), and in Europe, drug, and especially cocaine, use has been increasing over the last ten years in the general population, with a more pronounced trend in young individuals (EMCDDA, 2009), suggesting that cocaine addiction may continue to spread in western countries. Worldwide estimates suggest more than 8% of the population have an alcohol use disorder and more than 2% have an illicit drug use disorder (World Health Organization, 2010).

The prevalence of drug use despite obvious health and financial consequences is a testament to the tenacity of addiction as a brain disease affecting cognition, motivation and memory (Leshner, 1997). At the psychobiological level, addiction has been hypothesised to reflect the development of loss of executive control over aberrant incentive habits (Belin et al., 2009a, Belin & Everitt, 2010), resulting from drug-induced neuroplasticity processes in vulnerable subjects. These plasticity processes have been suggested to stem from the impact of drug action on the mesolimbic dopamine system, through which drug use can induce a host of changes in the brain resulting in significant neural reorganization (see Lüscher & Malenka, 2011; Russo et al., 2010). Much of this reorganization is due to long term potentiation, or strengthening, of excitatory synapses as a result of drug use. As recently reviewed, the

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dopamine signals from neurons originating in the ventral tegmental area (VTA) targeting the nucleus accumbens (NAc) in the ventral striatum modulate glutamate synaptic plasticity and are believed to be critically involved in the pathophysiology of addiction (Chen et al., 2010).

In animal models using passive drug exposure, these neurons show an N-methyl-D-aspartate (NMDA) receptor-dependent strengthening of excitatory synapses (long term potentiation) 24 hrs following an acute experimenter-administered injection of cocaine, amphetamine, nicotine, ethanol, and morphine (Saal et al., 2003; Ungless et al., 2001). Interestingly, this strengthening was not found with the non-abused psychoactive drugs, fluoxetine or carbamazepine, suggesting the role this plasticity may play in determining whether a drug is abused or not.

Although of interest, these data capture neither the volitional aspect of drug use nor the instrumental nature of drug seeking and taking, thereby greatly limiting their translation to the pathophysiology of addiction (Belin et al., 2009b, Belin & Dalley, 2012). Therefore, in preclinical models, a more valid approach to the human drug administration situation is the self-administration paradigm in which – akin to the human experience – an animal, rather than the experimenter, voluntarily administers the drug through instrumental conditioning (see later).

Following two weeks of cocaine self-administration, long term potentiation of glutamate function in DAergic VTA neurons is maintained even after 90 days of abstinence – an effect not found in a yoked, non-contingent control group receiving the same cocaine exposure (Chen et al., 2008). Similarly, measurements in the core of the NAc (NAcC) – where VTA projections are now known to co-release glutamate along with DA (Stuber et al., 2010) – following at least two weeks of cocaine self-administration, showed long-lasting resistance to the induction of long-term synaptic depression compared to yoked controls or controls lever pressing for food reinforcement. Finally, cocaine self-administration followed by either a 3-week abstinence period or 3 weeks of extinction training induced a state of long-term potentiation of glutamate synapses that was resistant to further potentiation (Moussawi et al., 2009). The resistance to further potentiation has been attributed to the prolonged expression of AMPA receptors that had been trafficked to the cell membranes during the drug exposure (Chen et al., 2010) and is indicative of long-lasting neural reorganization brought about by drug abuse. Combined, these data indicate that volitional administration of cocaine results in prolonged changes in NMDA receptor-dependent synaptic plasticity within the nucleus accumbens (Martin et al., 2006).

This long-term strengthening of glutamatergic synapses within the brain reward circuitry as a result of chronic voluntary drug use is also related to dysregulation of glutamate homeostasis (for a review see Kalivas, 2009). Glutamate homeostasis refers to the balance between synaptic glutamate levels and extracellular, extrasynaptic glutamate levels that regulate stable neurotransmission (see Figure 1). If synaptic glutamate release is the key component of glutamate-induced excitatory synaptic transmission, extrasynaptic glutamate is vital for the negative feedback of glutamatergic transmission. This negative feedback is necessary for modulating and inhibiting further excitatory stimulation. Such feedback is supported by activation of extrasynaptically-localized Group II metabotropic glutamate autoreceptors (mGluR2/3 receptors) which results in a regulated reduction of vesicular neurotransmitter release whereby synaptic glutamate concentration is greatly decreased (Dietrich et al, 2002; Manzoni et al., 1997).

Extrasynaptic glutamate availability is primarily provided by the cystine/glutamate exchanger antiporter (system xc-) found on brain glial cell membranes (Baker et al., 2002). System xc- transports the extracellular cystine dimer into the astrocytes and intracellular glutamate out of the astrocytes and into the extracellular space in a 1:1 ratio, thereby enhancing extrasynaptic glutamate levels (Bannai, 1986). Glutamate availability inside the astrocytes is provided by the primary glial glutamate transporter, GLT-1 (Haugeto et al., 1996), and these two systems work in concert to maintain homeostatic glutamate levels. Seven days of cocaine exposure (experimenter administered 15-30 mg/kg daily) followed by three weeks of abstinence, or self-administration (0.25 mg/kg in 2-hr sessions until responding stabilized to <10% variation) followed by extinction (until active lever pressing declined to at least 10% of self-administration levels) decrease basal levels of extracellular glutamate by ~50% within the NAc. Extracellular glutamate levels are then elevated again into a range between about 160-600% of the withdrawal baseline following cocaine re-exposure (e.g., Baker et al., 2003a; Baker et al., 2003b; McFarland et al., 2003; Pierce et al., 1996). This dysregulation of glutamate homeostasis as a result of drug withdrawal has been suggested to be caused by an overall downregulation of system xc- and is in fact mimicked by blocking system xc- in the NAc (Baker et al., 2003b). Indeed, following chronic cocaine or nicotine self-administration, there is reduced NAc expression of both xCT, the light chain and catalytic subunit of the system xc- antiporter heterodimers, and GLT-1 (Knackstedt et al., 2009; 2010a), indicating these mechanisms are involved in the dysregulation of glutamate homeostasis and may impact the development and trajectory of addiction.

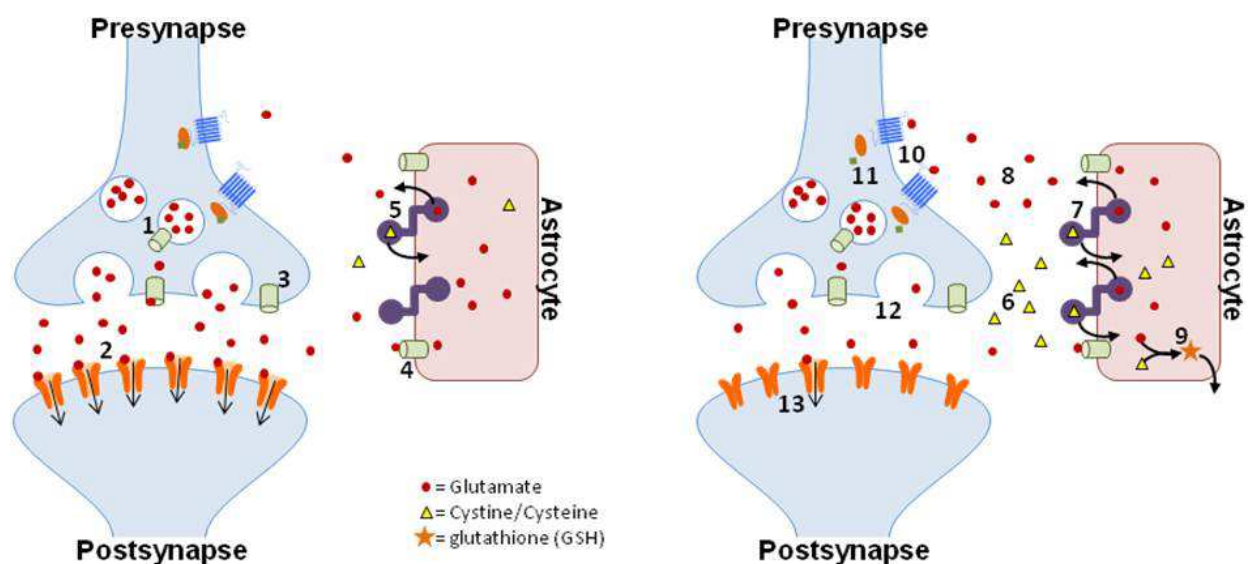


Fig. 1. Actions of N-acetylcysteine on the cystine/ glutamate exchanger (system xc-). Glutamate is packaged into presynaptic vesicles by vesicular glutamate transporters (vGluTs) [1]. Following release of glutamate into the synaptic cleft, glutamate binds to postsynaptic localized ionotropic receptors (iGluRs) such as the α -amino-3-hydroxy-5-methylisoxazole-4 propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate receptors [2]. Excitatory amino acid transporters (EAATs) clear extracellular glutamate by taking it back up into cells. These transporters are localized on the presynaptic terminal [3] protecting extrasynaptic receptors from synaptic glutamate and synaptic receptors from extrasynaptic glutamate, and allow for re-packaging glutamate into vesicles. These transporters are also localized on astrocytes [4]. Once in the glial cell, glutamate can be transported into the extrasynaptic

environment by the cystine/ glutamate exchanger (system xc-) in a 1:1 ratio [5]. Administration of NAC provides extra synaptic cysteine that is oxidized extracellularly into the cystine [6] required to enhance activation of the cystine/ glutamate exchanger [7]. The enhanced xc-activation results in increased glutamate concentration in the extracellular space [8]. Intracellular cystine is rapidly reduced to cysteine where it is combined with intracellular glutamate (and glycine) in the synthesis of glutathione (GSH) which is then released from the astrocyte [9]. Extrasynaptic glutamate binds to and activates mGluR2/3 receptors [10] which negatively regulate adenylyl cyclase [11] thereby suppressing presynaptic glutamate release [12] and reducing postsynaptic iGluR activation [13].

2. Mechanisms of N-acetylcysteine action

The cysteine prodrug and antioxidant precursor, N-acetylcysteine (NAC), has been in use in humans for many years, primarily as a treatment for acetaminophen/paracetamol overdose (Prescott et al., 1977; Scalley & Conner, 1978) and more recently as a mucolytic agent effective in chronic obstructive pulmonary disease (Decramer & Janssens, 2010; Kory et al., 1968) and cystic fibrosis (Dauletbaev et al., 2009; Stamm & Docter, 1965). Further, an evaluation of the potential therapeutic use of NAC in a variety of psychiatric disorders has been recently reviewed (Dean et al., 2011). The aforementioned nature of the neurophysiological changes induced by drug use has also indicated a potential use for NAC treatment in addictions, prompting the initiation of thorough research into NAC as a treatment for addiction in both preclinical models of addiction and drug addicts

In preclinical models of addiction, NAC appears to regulate the systems involved in glutamate homeostasis in the brain. Following 7 days of cocaine exposure and 21 subsequent days of withdrawal, decreased basal extracellular glutamate levels in the NAc are recovered following an IP injection of NAC in rats (Baker et al., 2003a). Notably, inhibition of system xc- prevented the NAC-induced recovery of extracellular glutamate levels in this region, implicating the xc- system in the neurobiological mechanisms whereby NAC normalises cocaine-induced extracellular glutamate dysregulation (Baker et al., 2003a). Thus, NAC may induce a recovery of the downregulated xCT and GLT-1 function (Knackstedt et al., 2009; 2010a). Indeed, the recovery of an altered GLT-1 function allows for increased transport of glutamate into the astrocyte while the recovery of altered system xc- function by xCT recovery allows for increased export of glutamate back into the extrasynaptic space (see Figure 1). The resulting increase in extracellular glutamate then facilitates activation of extrasynaptic mGluR2/3 autoreceptors, ultimately reducing evoked synaptic glutamate release (Moran et al., 2005). This decrease in synaptic glutamate release as a downstream result of NAC administration is the mechanism by which NAC also restores the capacity to induce further long-term potentiation, since blockade of mGluR2/3 receptors prevented this restoration (Moussawi et al., 2009).

NAC is also a known precursor of the endogenous antioxidant, glutathione (GSH), the synthesis of which depends upon the rate-limiting activity of the xc- system. GSH is primarily produced within astrocytes using glutamate and cystine as substrates to generate γ -glutamylcysteine, which is then combined with glycine to create GSH (see Dringen & Hirrlinger, 2003). GSH is released from astrocytes into the extracellular space, where it is broken down by γ -glutamyltranspeptidase into glutamate and a cysteine-glycine dipeptide that is further hydrolyzed into the individual peptides. This reaction is the mechanism by

which astrocytes provide the precursors necessary for neuronal GSH production (Dringen & Hirrlinger, 2003). In addition to protecting brain cells from the oxidative stress, GSH has been shown to enhance responsivity of NMDA receptors to glutamatergic stimulation (see Janáky et al., 1999), suggesting some direct modulation of glutamatergic signalling as a result of NAC administration. The role of GSH in addiction has yet to be determined, and thus far, the effects of NAC as a pharmacotherapy for drug dependence appear to be primarily mediated via its actions on system xc- and GLT-1 (Knackstedt et al., 2009; Knackstedt et al., 2010a).

3. N-acetylcysteine in animal models of self-administration, reinstatement, and relapse

The study of the addictive properties of drugs in animals is largely based on variations of the self-administration procedure developed in rats by Weeks (1962; see Belin & Dalley 2012; Panlilio & Goldberg, 2007). Although now conducted with many species, in its simplest and most common form, rats (or mice) are prepared with indwelling intravenous catheters that exit through a backmount to be attached to a tether hanging within a conditioning chamber. Tubing connecting the catheter to a syringe outside the chamber runs through the tether and provides the route by which drugs can be administered directly into the blood stream (see Figure 2).

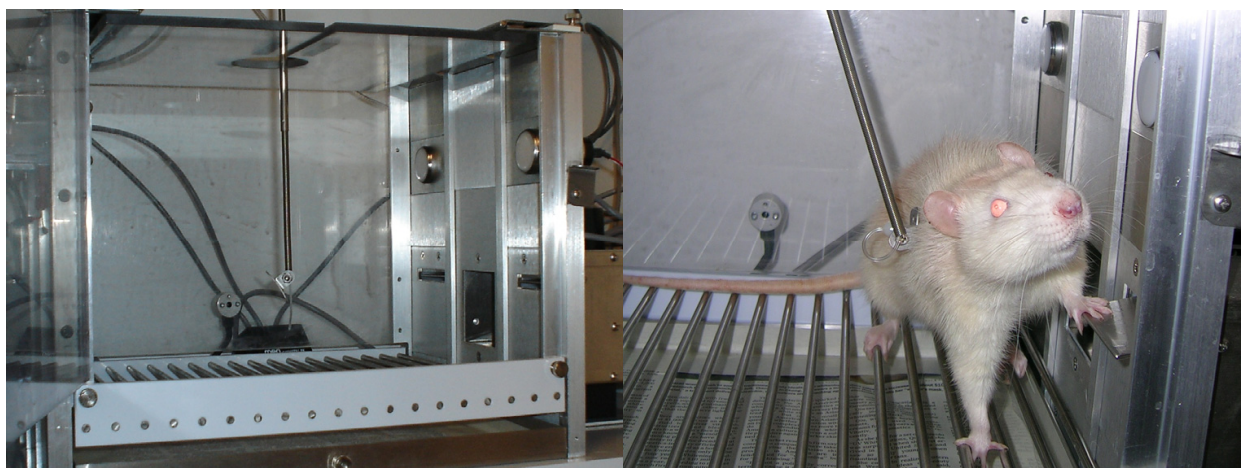


Fig. 2. Operant drug self-administration chamber and procedure. Operant chambers are typically equipped with two retractable levers (assigned as either 'active' or 'inactive') with a cue light above each. When a rat presses the active lever under an FR1 schedule, the resulting drug infusion is accompanied by the onset of the cue light associated with the active lever.

When in the self-administration chamber, two levers are typically available – an 'active' and an 'inactive' lever. Under the most basic Fixed Ratio 1 (FR1) schedule of reinforcement, also called continuous reinforcement, a single press on the active lever results in a drug infusion often paired with a non-drug stimulus, such as a brief presentation of a light. The drug delivery reinforces the behavior, making it more likely the rat will press the active lever again (cf. Hall, 2002). Presses on the inactive lever have no consequence and are used as an index of general activity. This self-administration procedure is particularly useful in determining the abuse liability of psychoactive substances (for a review see O'Connor et al.,

2011). The ability to self administer drugs for short periods of time daily (1-2 hrs per session) results in a stable drug intake over time, a so-called titration process that is suggested to reflect individual control of intake responding to optimal dosing (Wilson et al., 1971; Zimmer et al., 2011) around which blood levels fluctuate in the course of the self-administration session.

Pharmacological challenges during ongoing self-administration, following extinction or abstinence, or before relapse or reinstatement of self-administration (see later) have been useful in identifying potential targets for the development of pharmacotherapies for various forms of addictions (e.g., Schindler et al., 2011; Steensland et al., 2007). Such an approach is based on the common psychodynamic view of the addiction process of which the stages, namely development, maintenance, and relapse/reinstatement, are modelled in Figure 3.

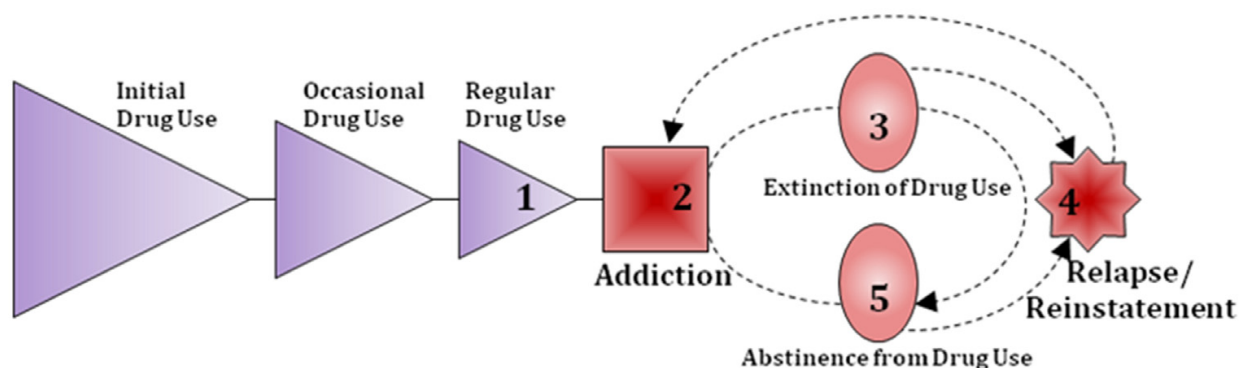


Fig. 3. Stages of the development and maintenance of addiction in humans and animal models. Stages of the addiction cycle that have been targeted with NAC treatment are regular drug use before the development of addiction as defined by the DSM-IV [1], thereby aiming at preventing the transition from controlled to compulsive drug use, the addiction stage (in animal models, when intake has escalated or become habitual) [2], following behavioral extinction of drug seeking predominately seen in animal models – human addicts rarely engage in extinction [3], at the time drug or a drug-associated cue is re-introduced causing reinstatement [4], following short- or long-term abstinence from drug more typical for human addicts and increasingly modelled in animals [5], and at the return to the drug-seeking/taking context, resulting in relapse [4].

A reasonable time point for targeting addiction is when the individual is still regularly engaged in drug use with the intended outcome of reducing intake and eventually stopping use altogether. Therefore, it is of interest to assess potential pharmacotherapies during the self-administration phase. In a standard self-administration task, that is thought to model the stage in which humans engage in regular use but are not necessarily addicted (Figure 3, Stage 1), rats that had access to cocaine for 2 hrs under an FR1 schedule of reinforcement, and administered 60 mg/kg NAC before each daily training session displayed no differential intake as compared with vehicle-treated controls (Amen et al., 2011; Madayag et al., 2007).

The efficacy of NAC on ongoing cocaine intake changes however, with increasing access to cocaine. Indeed, with long (e.g., ≥ 6 hrs) rather than short (e.g., 2 hrs) daily access to cocaine self-administration, rats no longer titrate intake, but instead tend to increase, or escalate, their intake across days (cf. Ahmed & Koob, 1998). This escalation of drug intake over time, associated with dysregulation of neural networks governing reward (for a review see Koob

& Kreek, 2007), has been suggested to reflect the loss of control over intake that characterises human drug addicts (Figure 3, Stage 2). In an experiment assessing the effects of NAC on cocaine escalation (Madayag et al., 2007), rats initially acquired cocaine (0.5 mg/kg) self-administration in 2-hr sessions under an FR1 schedule of reinforcement until intake stabilized (<10% variation across ≥ 3 sessions). They were then shifted to 6-hr daily sessions for 11 days in which they were able to self-administer a higher dose of cocaine (1.0 mg/kg) and subsequently given either 60 mg/kg NAC or vehicle pre-treatment. Whereas saline-pretreated rats displayed typical escalation of their cocaine intake across sessions, NAC-pretreated rats maintained a stable drug intake across days (Madayag et al., 2007). In a similar study, daily pretreatment with the higher dose of 90 mg/kg NAC appeared to reduce cocaine intake across the 12 sessions of long-access cocaine self-administration compared to saline pretreatment (Kau et al., 2008). Combined, the findings that NAC impacts escalation without affecting typical short-access drug self-administration suggests that loss of control over drug intake may be better reflective of dysregulated glutamate homeostasis.

3.1 Treatment during reinstatement of drug seeking

The ultimate goal of any addiction therapy is to achieve and maintain drug abstinence. This therapeutic goal is especially challenging due to the strong associations formed between the interoceptive drug experience and surrounding cues. Re-experiencing a drug or drug cue following a successful quit attempt can evoke and enhance drug craving (e.g., Niaura et al., 1988; O'Brien et al., 1992), thus increasing the likelihood of reinstatement of drug use, often resulting in relapse. As such, finding effective techniques that target the motivational impact of a 'lapse' in drug use (drug-induced reinstatement) or drug-related paraphernalia (cue-induced reinstatement) is of high therapeutic value for maintaining drug abstinence.

From an experimental standpoint, when operant behavior no longer results in the delivery of the reinforcing outcome, extinction occurs, so that instrumental performance declines (Figure 3, Stage 3). Extinction of a behavior is a new learning process that exists alongside the old, previously learned, association (for a review see Bouton, 2002). This new learning is largely dependent on continued absence of the primary reinforcer while the manipulanda (i.e., levers) are still available to press. In humans, these sort of explicit extinction sessions are generally only provided within the context of cue-exposure therapy which aims at presenting inpatients with drug use paraphernalia in the absence of the drug (see Monti & MacKillop, 2007; Siegel & Ramos, 2002). Reinstatement of the previously extinguished behavior can therefore be evoked by presentation of the reinforcer (i.e., drug-induced reinstatement) or a conditioned stimulus (CS) associated with the reinforcer that had not presented during the extinction phase (i.e., cue-induced reinstatement; Figure 3, Stage 4; de Wit & Stewart, 1981).

When an addict 'lapses', or uses once, following abstinence, he is at a much higher risk for re-engaging in regular use. Attenuating the effects of this drug-induced reinstatement may help prevent a 'lapse' in drug abstinence from turning into a full-blown relapse of addiction (e.g., Shadel et al., 2011; Witkiewitz & Masyn, 2008). In rats, cocaine exposure following extinction of self-administration is associated with a glutamate release from prefrontal projections into the NAcC (McFarland et al., 2003), and this release may provide the

mechanism that triggers reinstatement of drug seeking. Acute treatment with NAC has been shown to attenuate drug-induced reinstatement. In some of these experiments, rats were trained to self-administer cocaine in 2-hr or 6-hr daily sessions. During the subsequent extinction phase, instrumental responses were reinforced only with contingent presentations of the drug-associated light, and no cocaine was infused, so lever pressing progressively declined. For the drug-induced reinstatement test, rats were injected with a priming dose of cocaine, this pharmacological challenge resulted in a marked increase in the previously extinguished instrumental response, i.e., lever pressing. Pretreatment with 30, 60, or 600 mg/kg NAC before cocaine re-exposure prevented reinstatement of cocaine-seeking behavior (Baker et al., 2003a; Baker et al., 2003b; Kau et al., 2008; Moran et al., 2005). Concurrent blockade of system xc⁻ using (S)-4-carboxyphenylglycine (CPG) during the reinstatement test blocked the reinstatement-attenuating effects of NAC (Kau et al., 2008), thereby suggesting that NAC effects on cocaine-induced reinstatement are mediated through system xc⁻. Additionally, as measured by *in vivo* microdialysis during the reinstatement test, NAC administration restored the reduced extracellular glutamate levels that resulted from cocaine self-administration and withdrawal (Baker et al., 2003b). Further, concurrent blockade of mGluR2/3 autoreceptors also prevented the attenuating effects of NAC on cocaine-induced reinstatement (Moran et al., 2005) demonstrating that the effect of NAC restoration of extracellular glutamate on reinstatement may depend upon activation of the mGluR2/3 autoreceptors.

The effects of NAC on drug-induced reinstatement have also been shown when NAC is administered prior to, but not explicitly during, the reinstatement test. In one such experiment, rats were trained to self-administer cocaine under short-access conditions and then underwent extinction followed by cocaine-primed reinstatement (Amen et al., 2011). Following the first test in which cocaine seeking was reinstated, rats were treated with 60 mg/kg NAC for 7 days. The day following the seventh NAC treatment, rats were subjected to a second cocaine-primed reinstatement test. Rats that had received NAC treatment showed significantly reduced cocaine seeking compared to the rats that had received saline treatment during those 7 days (Amen et al., 2011). Although daily treatment with 60 mg/kg NAC before 2-hr cocaine self-administration sessions (see above) had no effect on amount of cocaine taken or subsequent extinction (without NAC pretreatment), cocaine-primed reinstatement was significantly reduced, even though it had been 2-3 weeks since last NAC treatment (Madayag et al., 2007). Similarly, 90 mg/kg NAC pretreatment throughout long-access cocaine self-administration resulted in attenuated cocaine-primed reinstatement that was reversed by inhibition of system xc⁻ following an extinction phase without NAC (Kau et al., 2008). These effects are indicative of the long-lasting protection of glutamate homeostasis as a result of NAC treatment. Indeed, concurrent microdialysis in the NAc immediately prior to the reinstatement test showed that there were lower extracellular basal glutamate levels in rats that had been pretreated with saline during the self-administration stage than in those that had been pretreated with NAC (Madayag et al., 2007). Once cocaine had been administered to induce reinstatement, the saline-pretreated group reached the level of extracellular glutamate that was shown at baseline by the NAC-pretreated group. These findings suggest that NAC administration during self-administration provided protection against the withdrawal-induced downregulation of extracellular glutamate in the NAc and subsequent cocaine-induced reinstatement.

3.2 Treatment during extinction and reinstatement

The effect of chronic NAC treatment during both extinction and subsequent reinstatement tests has also been evaluated (Figure 3, Stages 3 and 4). In one such study (Reichel et al., 2011), rats were trained to self-administer cocaine (50 µg/infusion) under an FR1 schedule until they reached >10 infusions in two hours for twelve consecutive sessions. During the following twelve sessions, lever presses had no programmed consequences (i.e., extinction), and rats were given daily injections of 0, 60 or 100 mg/kg NAC. There was no effect of the lower 60 mg/kg dose of NAC on extinction responding. However, there was a significant enhancement of extinction (i.e., less active lever pressing) when rats were treated daily with 100 mg/kg NAC (Moussawi et al., 2011; Reichel et al., 2011). This effect was also found during extinction of heroin self-administration for which daily administration of 100 mg/kg NAC resulted in enhanced extinction rate (Zhou & Kalivas, 2008). Although NAC treatment was ineffective when applied during acquisition of self-administration, it enhanced extinction learning.

In each of these studies, two tests of reinstatement were then conducted: cue-induced reinstatement and cue+drug- or drug-induced reinstatement. Human addicts are particularly sensitive to cues that had previously been associated with drug use, and exposure to these cues following drug abstinence can reinstate drug seeking and taking behavior, resulting in relapse (see O'Brien et al., 1992; Taylor et al., 2009). Similarly, rats are also quite sensitive to the effects of re-presentation of these drug-associated CSs. As such, the impact of NAC treatment on cue-induced reinstatement of instrumental responding has recently begun to be assessed. For the cocaine self-administration group treated with the lower, 60 mg/kg, dose of NAC, there was a significant reduction in cue-induced reinstatement compared to saline controls, but no effect on cue+drug-induced reinstatement (Reichel et al., 2011). However, when NAC (100 mg/kg) was administered during extinction following either cocaine or heroin self administration, there was a significant reduction in both cue- and cue+drug- or drug-induced reinstatement. These results suggest that, compared to a conditioned stimulus, a higher treatment dose was necessary to disrupt the ability of an unconditioned drug stimulus+drug-associated CS compound to reinstate drug-taking behavior (Moussawi et al., 2011; Reichel et al., 2011; Zhou & Kalivas, 2008). Notably, these effects on reinstatement lasted from two weeks (Moussawi et al., 2011; Reichel et al., 2011) to 40 days (Zhou & Kalivas, 2008) following the last 100 mg/kg NAC treatment, indicating a long-term restoration of glutamate homeostasis in the NAcC brought about by the re-regulation induced by chronic NAC exposure (Moussawi et al., 2011). At the neurophysiological level, rats trained to self-administer cocaine that received saline (rather than NAC) during extinction showed reduced extrasynaptic glutamate levels in the NAcC compared to saline-yoked controls. In rats that received NAC during extinction, there was full recovery of the extrasynaptic glutamate levels two weeks following the last NAC injection - a time period corresponding to the behavioral effect on cue- and cue+drug-induced reinstatement (Moussawi et al., 2011). Furthermore, administration of the mGluR2/3 antagonist, LY341495, into the NAcC prevented the attenuating effects of NAC on cue- and cue+drug-induced reinstatement of cocaine-seeking, again indicating the importance of presynaptic autoreceptors in maintaining glutamate homeostasis (Moussawi et al., 2011).

3.3 Treatment during abstinence

A key concern with the translational potential of the extinction-reinstatement model of drug dependence is that human users are not typically subjected to extinction of responding during presentation of drug-related cues unless they are patients in an explicit cue-exposure therapy session (cf. Monti & MacKillop, 2007). Rather, addicts undergo abstinence – a period in which they either voluntarily (i.e., independently, or by checking into a rehabilitation clinic) or forcibly (e.g., incarceration) abstain from drug use outside the drug-taking environment (Figure 3, Stage 5; Reichel & Bevins, 2009). Following the abstinence period, a person returns home where the associative strength of all the drug-associated cues is still fully intact, and no behavior has been extinguished, and ‘relapse’ of the addictive behavior often resumes.

A rat model of ‘forced abstinence’ operationally uses the same drug self-administration protocols as the extinction-reinstatement model, but rather than undergoing an extinction phase in which responding diminishes with repeated non-reinforced lever pressing, the animal is typically left in its home cage for a specified period of time (e.g., 2 weeks) where it can undergo a treatment protocol before returning to the drug-associated conditioning chamber. Notably, extinction and abstinence following cocaine self-administration produce different patterns of protein expression in the NAc (Knackstedt et al., 2010b), warranting further investigation into the efficacy of potential pharmacotherapies in each model of addiction.

The abstinence model has recently been used to assess the efficacy of NAC treatment following cocaine self-administration (Reichel et al., 2011). Rats were trained to self-administer cocaine under an FR1 schedule until they reached >10 infusions in two hours for twelve consecutive sessions. During the subsequent two-week abstinence period, rats were given daily injections of 60 or 100 mg/kg NAC or saline. They were then tested for relapse to cocaine seeking by returning them to the self-administration environment and recording non-reinforced lever presses. Treatment with the lower, 60 mg/kg, dose of NAC during abstinence had no effect on relapse compared to saline, however, treatment with the higher 100 mg/kg dose of NAC during abstinence significantly reduced cocaine-seeking during the relapse test (Reichel et al., 2011). During subsequent tests in which the drug-paired cue, and then the drug+cue, was presented, 100 mg/kg NAC treatment during abstinence maintained a significant effect on drug seeking. Finally, following a second phase of abstinence in which no NAC was administered, there was still a significant attenuation of drug seeking when rats were presented with the drug+cue in the self-administration chamber, again indicative of the long-term re-regulation of glutamate homeostasis provided by NAC administration.

3.4 Treatment during habitual drug seeking

Regular daily drug use is not limited to the taking of the drug. Rather, addicted individuals can invest countless hours ‘foraging’ for their next high. This foraging takes a person through multiple exposures to stimuli that are predictive of the impending drug experience. As such, not only can these drug-associated CSs reinstate drug-seeking behavior when presented following behavioral extinction but they can also serve as powerful conditioned

reinforcers that drive and maintain continued drug foraging over long periods of time when presented contingently. This foraging can continue to persist even after the explicit drug-taking behavior has been extinguished (Olmstead et al., 2001; Zapata et al., 2010), indicating a habitization of the drug-seeking behavior which may be a key characteristic in the transition from casual drug use to addiction (e.g., O'Brien et al., 1998, Everitt & Robbins 2005, Belin et al., 2009a).

Cocaine seeking (see Chapter 2) as opposed to mere cocaine taking, or self-administration, has been operationalized in primates (Goldberg, 1973) and then in rats (Arroyo et al., 1998) and humans (Panlilio et al., 2005) in the so-called second-order schedule of reinforcement. In this specialized model of self-administration, drug seeking is separated from the unconditioned effects of the drug. Cues associated with drug reinforcement function as conditioned reinforcers that maintain persistent, habitual, seeking responses across protracted periods of time without primary drug reinforcement (Everitt & Robbins, 2000; Schindler et al., 2002).

In this procedure, rats are initially trained to self-administer drug under the FR1 schedule of reinforcement with a single lever press resulting in a drug infusion associated contingently with a 20-second cue light presentation. Following stabilization of responding, the response requirement is shifted across days to gradually move the behavior of the rat to what is known as a second-order schedule of reinforcement. There are several ways of increasing the response requirement (cf. Economidou et al., 2011; Vanderschuren et al., 2005, Belin & Everitt 2008), either by introducing ratio / ratio increments or fixed interval schedules with increasing interval durations across days. In the experiment in which NAC effect was measured on early and well-established cue-controlled cocaine seeking (Murray et al., 2012), rats were moved up through the following schedules: FR3; FR5(FR2:S); FR10(FR2:S); FR10(FR4:S); FR10(FR6:S); FR10(FR10:S); FI15(FR10:S). Under each of these schedules of cocaine reinforcement, completion of each unit schedule (given within the parentheses) resulted in a 1-second cue light presentation; cocaine infusions were delivered only upon completion of the first unit schedule according to the schedule outside the parentheses. Therefore, during the final second-order training schedule [i.e., FI15(FR10:S)], cocaine and the 20-second cue light were given on completion of the first FR10:S unit after the Fixed Interval 15-minute period had timed out. In these conditions instrumental responding is no longer under the control of the goal, from which it is now temporally distal, but instead becomes highly dependent upon contingent presentations of conditioned CSs, acting as conditioned reinforcers (cf. Arroyo et al., 1998). As shown in Figure 4, following acquisition of the second-order schedule, removal of CSs (i.e., 1-second light presentations provided under a FR10 schedule of reinforcement are removed, returning the animal to a strict FI15 schedule of reinforcement) results in a decline in lever pressing across sessions in the first 15-minute interval that is reversed when the unit schedule is returned (i.e., 1-second light presentations under FR10). By the time behavior has reached this stage of training, drug seeking during the first 15-min drug-free interval is maintained at very high rates and is thought to reflect cue-controlled habitual cocaine seeking which, at the neurobiological level, has been hypothesised to result of a gradual recruitment of dorsolateral striatal dopamine circuitry (Belin & Everitt, 2008; Ito et al., 2002; Murray et al., in press; Vanderschuren et al., 2005).

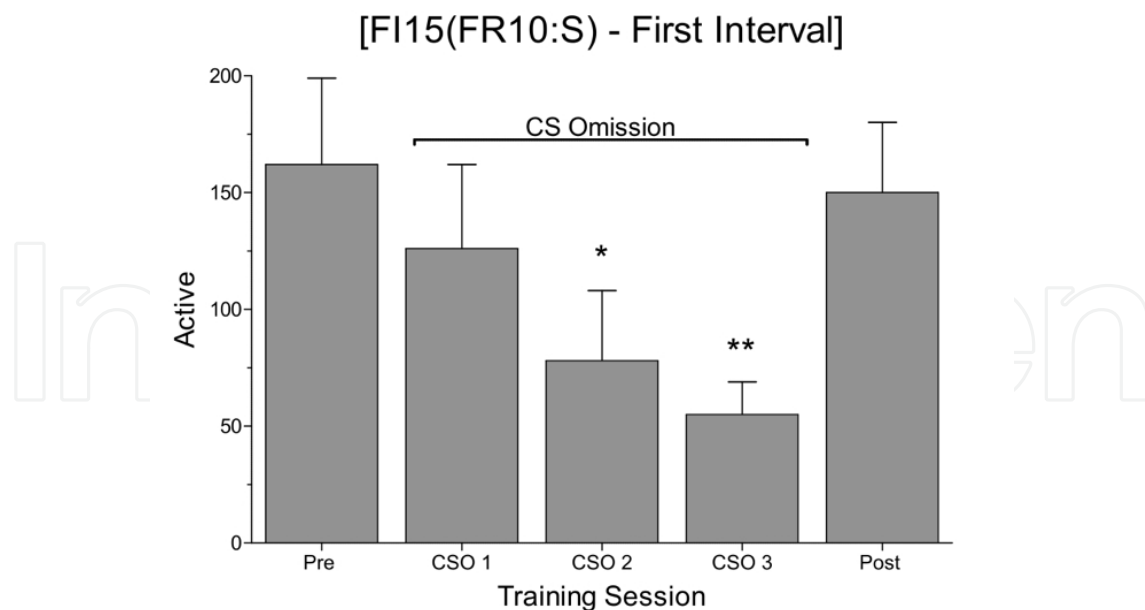


Fig. 4. Control of cocaine seeking by contingent presentations of conditioned reinforcers. Three consecutive days of conditioned reinforcer (1-s cocaine-associated light presentations) omission (CSO 1-3) are compared with performance on the session before conditioned reinforcer omission (Pre) and performance on the session when the reinforcer is returned (Post). * indicates significant difference from Pre, $p < .05$, ** $p < .01$. Adapted from Arroyo et al (1998) with permission from Springer.

Assessment of drug seeking before actual drug reinforcement can be conducted at both an early stage of acquisition and at a later, well-established stage. To assess drug seeking in the early stage when the behavior had only ever been reinforced under an FR1 schedule of reinforcement by the unconditioned drug stimulus with concurrent CS presentations, a switch in the contingency was instituted for a 15-min test session. This testing procedure allowed for measurement of drug seeking now reinforced by 1-sec cue light presentations. Cocaine was delivered only on the first lever press following the 15-min interval, and each test was immediately followed by an FR1 training session. The effects of acute NAC treatment on cocaine seeking during the early-stage tests are shown in Figure 5A. Drug seeking before the experience of unconditioned cocaine effects was reduced with 60 and 90 mg/kg NAC treatment.

After increasing the response requirements and at least 15 sessions of FI15(FR10:S) training, so that cocaine seeking maintained by regular contingent presentations of the drug-associated conditioned reinforcer was well-established, conditions known to be associated with a shift in the locus of control over behavior from the ventral to the dorsolateral striatum (Vanderschuren et al., 2005; Belin & Everitt, 2008), the effect of NAC pre-treatment on cocaine seeking was measured once again (Figure 5B). At this stage, drug seeking was more sensitive to NAC treatment, with 30, 60, and 90 mg/kg disrupting the conditioned reinforcing effects of the cocaine-associated stimulus. The results of this experiment demonstrate that acute NAC treatment dose-dependently reduced cocaine seeking maintained by conditioned reinforcers both at an early stage of acquisition when drug seeking is considered to be goal-directed and following extensive training on the second-order schedule, when drug seeking is considered to be habitual (Murray et al., 2012). These

findings demonstrate that NAC pretreatment may be an aid to establish abstinence by reducing cocaine seeking in individuals that actively seek cocaine on a daily basis, rather than only during relapse following an extinction or abstinence period.

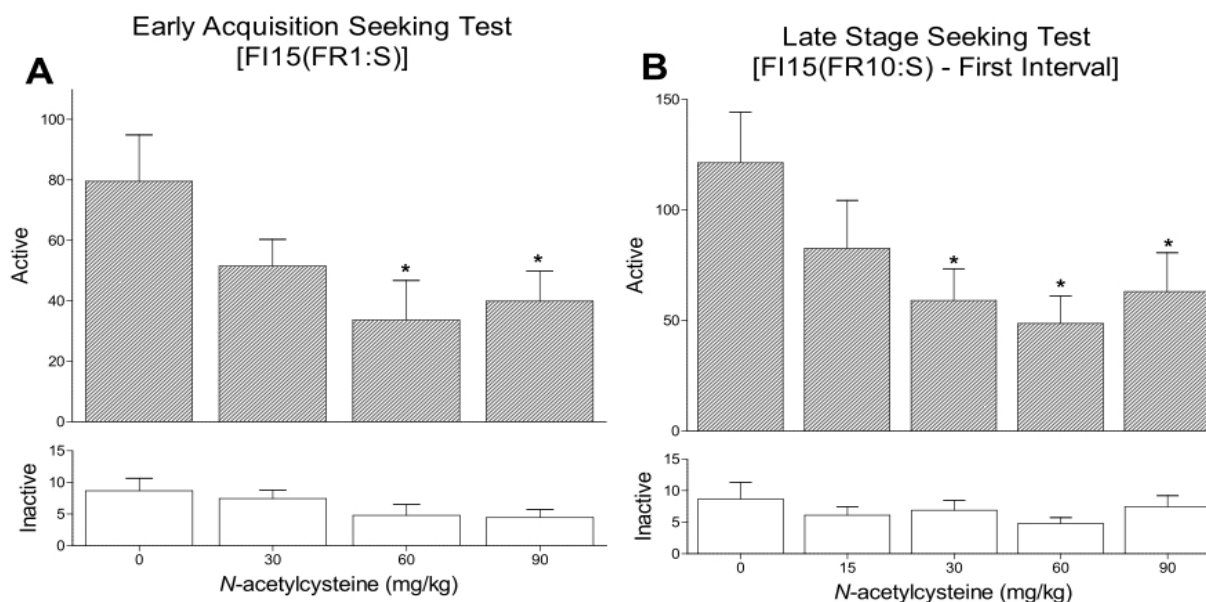


Fig. 5. Effects of NAC on cocaine seeking. Panel A depicts active (top) and inactive (bottom) lever presses during acute NAC treatment in the 15-min cocaine seeking test with contingent conditioned reinforcer presentations (FR1) at an early stage of self-administration. Panel B depicts active (top) and inactive (bottom) lever presses during acute NAC treatment in the first 15-min cocaine seeking interval with contingent conditioned reinforcer presentations (FR10) during the late stage of cocaine self-administration. For both panels, * indicates significant difference from 0 mg/kg NAC, $p < .05$. Adapted from Murray et al. (2012) with permission from Wiley.

4. N-acetylcysteine in humans: From acetaminophen overdose antidote to addictive and impulsive-compulsive spectrum disorders

NAC, as an antioxidant and glutathione precursor, has been used for more than 30 years in intravenous or oral protocols as an acetaminophen poisoning antidote. Within this framework, NAC has been shown to have low rates of adverse reactions which nevertheless include nausea, vomiting, as well as cutaneous and systemic anaphylactoid reactions. ECG abnormalities, status epilepticus and fatal reaction due to NAC overdose are rare, the latter having been observed only at doses 10 times greater than the recommended antidote dose (for review see Sandilands & Bateman, 2009). Atopy and asthma are major risk factors for developing adverse and anaphylactoid reactions to NAC (Schmidt & Dalhoff, 2001).

Thanks to its antioxidant effect, NAC has dose-dependent protective effects against contrast-induced nephrotoxicity (Briguori et al., 2011). NAC can also be used as both a chelating agent for methylmercury (for review see Dodd et al., 2008) and a mucolytic and anti-inflammatory agent, with controversial efficacy in patients with exacerbations of chronic

obstructive pulmonary disease (Decramer et al., 2005). Unlike orally-administered glutathione and L-cysteine, NAC successfully crosses the blood-brain barrier, and permits restoration of glial and neuronal glutathione levels, playing a role in the oxidative homeostasis in the brain, protecting neurons against oxidative stress. In addition, NAC treatment reduces levels of some pro-inflammatory cytokines (IL-6, IL-1 β , and TNF- α) shown to be implicated in several psychiatric disorders, notably in depressive and bipolar disorders as well as in schizophrenia. NAC has been used to target the prefrontal glutamatergic dysfunction implicated in schizophrenia and impulsive-compulsive behaviors (for reviews see Dean et al., 2011; Sansone & Sansone, 2011). One of the first uses of NAC in psychiatry was a case-report of the amelioration of self-injurious behaviors and craving in a female patient suffering from Post-traumatic Stress Disorder and borderline personality disorder (Pittenger et al., 2005). There are to date very few rigorous studies assessing the efficacy of NAC in the treatment of addiction and impulsive-compulsive spectrum disorders (including behavioral addictions, impulse-control disorders and obsessive-compulsive and related disorders). Those available, despite limited statistical evidence (randomized studies with small size samples, non-randomized cohorts, or case reports), have provided consistent results, in that NAC was always reported to reduce drug use, craving or withdrawal symptoms during the treatment period, sometimes even resulting in a persistent effect on relapse after the end of the trials (Olive et al., 2012).

4.1 NAC and cocaine dependence

NAC treatment for addiction has been primarily studied in cocaine dependent patients, alongside the aforementioned publication of preclinical studies initiated by Kalivas' team (Baker et al., 2003a; Baker et al., 2003b). In one such study, the safety and tolerability of NAC have been assessed in 13 otherwise-healthy, non-treatment-seeking, cocaine-dependent patients with a mean age of 37.1 ± 7.6 . During the first hospitalization of the experiment, patients received either four treatments of NAC (600 mg per treatment; 2400 mg total) or placebo spaced 12 h apart. In a cross-over design, the opposite treatment (i.e., NAC or placebo) was given during a hospitalization during the second week. NAC treatment resulted in a significant reduction of withdrawal symptoms (assessed with the Cocaine Selective Severity Assessment, CSSA, a measure of cocaine abstinence signs and symptoms; Kampman et al., 1998) while placebo had no effect. The effect of NAC treatment was not restricted to withdrawal symptoms since it was also accompanied by an overall reduction in self-reported craving (five items, including desire to use, level of craving and other similar constructs, rated on ten-point Likert scales). In this study NAC was well tolerated during the treatment periods, with neither significant adverse effects nor with effects on primary biological parameters (renal and liver functions, complete blood count) between groups. In addition, at completion of the two-week follow-up period patients displayed a marked decrease both in days of cocaine use from $41\% \pm 7$ (in the ninety days before study) to $27\% \pm 7$, and average daily dollar expenditure for cocaine from $\$30.31 \pm 3.44$ (in the ninety days before study) to $\$8.77 \pm 2.52$, suggesting that a brief NAC treatment, perhaps through promotion of reduced withdrawal symptoms and subjective craving, may have a prolonged efficacy even weeks after the end of the treatment (LaRowe et al., 2006).

In addition to this clinical evaluation, at the end of the treatment period, the same patients were exposed to a cue-reactivity procedure to assess cocaine desire. During two sessions,

patients were semi-randomly presented cocaine-related, neutral, and affective (pleasant and unpleasant) slides. Cocaine-related slides produced greater skin conductance than either neutral or pleasant slides. NAC treatment did not modify physiological reactions to any of the slides viewed (i.e., skin conductance and heart rate measures). Cocaine slides evoked higher ratings of craving for, desire to use, and interest in, cocaine, as well as longer viewing times relative to neutral slides. NAC treatment resulted in lower motivation to use cocaine in comparison with placebo when viewing cocaine slides, characterized by a reduced desire to use, a reduced interest in cocaine, and less time viewing cocaine slides. Craving for cocaine was also reported to be lower in NAC- than in placebo-treated participants even though this difference did not reach statistical significance (LaRowe et al., 2007).

In an independent laboratory study in 6 cocaine-dependent patients, with a mean age of 41.8 ± 7.4 and a mean age of drug-use onset of 18.3 ± 4.0 , subjective 'high', 'rush', and craving for cocaine were assessed using a computerized version of a ten-point Likert scale. The patient had to use a joystick and move a tab along a horizontal bar with the anchors 'Least Ever' and 'Most Ever' at each extreme end, then push a button at the desired rating after viewing either a neutral or a cocaine video and after a 20 mg/kg IV cocaine infusion. This assessment was conducted the day before and after 3 days of NAC treatment (1200 mg or 2400 mg daily, TID). NAC treatment significantly reduced subjective craving induced by cocaine infusion, as measured before and after treatment. By contrast, NAC affected none of the subjective measures induced by cocaine videos, nor did it affect subjective feelings of high and rush induced by the cocaine infusion (Amen et al., 2011).

Finally, in an open-label study, 23 cocaine-dependent patients, with a mean age of 40 ± 1.4 and a mean lifetime of cocaine use of 13.3 ± 1.5 years, were treated for 4 weeks with three different doses of NAC (1200, 2400 or 3600 mg/day). In a subjective evaluation, the three doses of NAC decreased the mean number of days of use (from 8.3 ± 1.3 to 1.1 ± 1.4) and the dollar amount spent (from $\$1292.8 \pm 508.6$ to $\$52.2 \pm 25.9$) across the 28 days of treatment. This was in agreement with an objective evaluation revealing that urine drug screens were negative in two-thirds of the sample during treatment (without comparison with baseline due to a lack of significant sampling during this period). Cocaine abstinence symptoms (assessed with the CSSA) decreased during the treatment period. Retention in treatment was significantly better in the 2400 mg and the 3600 mg groups than in the 1200 mg group (88.9% and 83% respectively, vs. 37.5%). Adverse events were mild to moderate, including headache, pruritus and elevated blood pressure, but did not significantly differ among the treatment groups (Mardikian et al., 2007).

These results indicate that administration of NAC (at daily doses of 2400 and 3600 mg) can be an effective treatment for relapse prevention in cocaine-dependent patients, due to its ability to decrease withdrawal symptoms and craving severity. The severity of the cocaine withdrawal symptomatology at treatment entry is negatively correlated with the treatment outcome and the duration of continuous abstinence from cocaine (Kampman et al., 2002). Furthermore, subjective and objective feelings of craving, even during experimental cue-induced and cocaine-infusion procedures, which are predictors of early drug-use outcomes and rapid treatment attrition (Rohsenow et al., 2007), are reduced by NAC, a treatment that results in few mild-to-moderate side effects. Further studies with high-level evidence (i.e., randomized, double-blind, placebo-controlled, long-term studies) must be conducted in cocaine-dependent patients to determine the effective dosing ranges, the optimal duration of

treatment, and the indications of NAC as a treatment for cocaine withdrawal or as an anti-addiction drug (used as an adjunct to psychotherapy to help patients in maintain abstinence).

4.2 NAC and marijuana dependence

In an open-label study, 24 cannabis-dependent subjects aged 18-21 were treated for 4 weeks with 1200 mg NAC twice daily (Gray et al., 2010). During the trial, the medication adherence was good (82.6% of scheduled doses), and adverse events were mild-to-moderate - none leading to discontinuation of the treatment. In a subjective evaluation at the fourth week of treatment, NAC significantly decreased the number of days per week cannabis was used, and showed a tendency to reduce the quantity of self-reported marijuana used per day (15.9 ± 2.4 vs. 11.9 ± 2.1 potency-adjusted 'hits'). In an objective evaluation, the cannabinoid content of urine samples was not affected, but craving for marijuana, measured by the Marijuana Craving Questionnaire, was significantly reduced. These results show the potential promise for NAC treatment of cannabis abuse and dependence, especially provided that no effective treatments are available for this particularly vulnerable population. A double-blind placebo-controlled study evaluating the efficacy of NAC (1200 mg twice daily for 8 weeks) combined with Contingency Management on marijuana use in a younger population (ages 13-21) is currently recruiting (NCT01005810).

4.3 NAC and methamphetamine dependence

In a small double-blind placebo-controlled study (Grant et al., 2010), 31 methamphetamine-dependent patients, with a mean age of 36.8 ± 7.12 and a mean age of onset of drug use of 24.3, were treated during 8 weeks with NAC (increased dose from 600 mg daily to 2400 mg daily every 2 weeks) and naltrexone (increased dose from 50 mg daily to 200 mg daily every 2 weeks) or placebo. In a subjective evaluation, at the end of the study, NAC+naltrexone treatment decreased the mean number of days of use every two weeks from 8.1 ± 4.9 to 1.9 ± 1.8 days in comparison with placebo (from 6.3 ± 4.6 to 2.3 ± 3.5 days). In an objective evaluation given at the end of the study however, positive urine drug screens did not differ between groups (46.2% vs. 35.3%). Concerning methamphetamine craving (assessed with the Penn Craving Scale: a self-report measure of frequency, intensity, and duration of craving, ability to resist taking drug, and an overall rating of craving for methamphetamine), NAC+naltrexone treatment did not result in significant improvement since there was no difference between the two groups in their decrease in total score at the end of the study (-43.6% vs. -37.7% for treated and placebo patients, respectively). Rates of adverse events (including nausea and lethargy) did not significantly differ between groups (57.1% vs. 41.2%). This preliminary 8-week study suggested that NAC+naltrexone treatment effectively reduced reported frequency of methamphetamine use even without affecting overall craving for the drug.

4.4 NAC and nicotine dependence

In a double-blind placebo-controlled study, 26 nicotine-dependent patients, with a mean age of 50, who had been smoking for an average of 33 years, were treated for 4 weeks with NAC (2400 mg daily) or placebo (Knackstedt et al., 2009). NAC treatment did not affect the objective measures related to nicotine dependence including carbon monoxide levels, or

craving for cigarettes (assessed with the Questionnaire for Smoking Urges-Brief), nor did it affect withdrawal symptoms (assessed with the Minnesota Nicotine Withdrawal Scale). In a subjective evaluation, there was a trend towards an overall reduction in cigarette use during the study (main effect of time), but no group effect, indicating a lack of efficacy of that dose of NAC on tobacco use. In a separate double-blind placebo-controlled study, 22 students at least twenty years old smoking for an average of 6 years, received NAC (1800 mg twice daily) or placebo for 4 days (Schmaal et al., 2011). None of the subjects reported smoking during the 4 days of treatment. At the end of the experiment, NAC did not affect craving for cigarettes (assessed with the Questionnaire for Smoking Urges-Brief) or withdrawal symptoms (assessed with the Minnesota Nicotine Withdrawal Scale). However, compared to placebo, NAC reduced the subjective rewarding effect of a cigarette smoked at the end of the experiment, suggesting a potential preventative impact of the treatment on relapse.

4.5 NAC and alcohol dependence

NAC has just been evaluated for an 8-week treatment of alcohol dependence, but the results are not yet published (NCT00568087). NAC has only been fully assessed in humans for its antioxidant properties, with some results in combination with corticosteroids and enteral nutrition in the treatment of severe acute alcoholic hepatitis (for review see Reep and Soloway, 2011), while a recent study shows minimal benefits of the combination therapy by prednisolone plus NAC in terms of survival among patients with this indication (Nguyen-Khac et al., 2011). Finally, preliminary findings in rats suggest NAC may also be helpful in the prevention of alcohol-induced heart disease (Seiva et al., 2009). Clearly, further work regarding the potential of NAC treatment for alcohol dependence needs to be conducted.

4.6 NAC and opiates dependence

To our knowledge, NAC has not yet been evaluated in the treatment of opiate dependence in humans.

4.7 NAC and pathological gambling

NAC treatment has been shown to reduce pathological gambling. In an open-label study (Grant et al., 2007), 27 subjects who engaged in pathological gambling, with a mean age of 50.8 ± 12.1 and a mean age of onset of problem gambling of 37.1 ± 12.8 , were treated for 8 weeks with NAC (increased dose from 600 mg daily to 1800 mg daily every 2 weeks). Twenty-three patients (85.2%) completed the study for which the primary outcome was the effect of NAC treatment on the pathological gambling score, an adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS), measuring the severity and change in severity of pathological gambling symptoms (Pallanti et al., 2005). Of those that completed the study, 16 patients (69.6%) were responders on the PG-YBOCS, showing a 30% or greater reduction in total score at end-point compared with baseline. Ten patients reported total abstinence from gambling. The total score on the PG-YBOCS decreased during the treatment phase from 20.3 ± 4.1 to 11.8 ± 9.8 . On the overall severity and change in clinical symptoms (assessed by the Clinical Global Impression-Improvement scale, a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention), 59.3% of patients were 'much' or 'very much' improved at the end of the study. Urge, thought, and self-reported gambling

symptoms were improved after NAC treatment. In a second phase, 13 of the patients who completed the open-label study and were considered responders were included in a double-blind placebo-controlled study with NAC treatment at the highest dose or placebo for another 6 weeks. At the end of the 6 weeks, 83.3% of active treatment patients vs. 28.6% of placebo patients still met responder criteria on the PG-YBOCS.

4.8 NAC and impulsive-compulsive spectrum disorders

Finally, NAC has been assessed in several impulsive-compulsive spectrum disorders other than addictions, including trichotillomania, obsessive-compulsive disorder (OCD), and nail-biting in patients suffering from bipolar disorder. In a double-blind placebo-controlled study (Grant et al., 2009), 50 patients with trichotillomania (compulsive hair-pulling), with a mean age of 34.3 ± 12.1 and a mean age of onset of 12.1 ± 5.0 years, were treated for 12 weeks with NAC (1200 mg daily for 6 weeks, then 2400 mg daily) or placebo. Eighty-eight percent of all patients completed the study regardless the group assignment. In a subjective evaluation, NAC-treated patients, as compared to those treated with placebo, displayed significant reductions in the severity of trichotillomania symptoms according to the patient self-rating (using the Massachusetts General Hospital Hair Pulling Scale) and the physician-assessment (with the Psychiatric Institute Trichotillomania Scale), associated with a significant improvement of the severity and the resistance and control dimensions of the disorder. On the severity and change in global clinical symptoms (assessed by the CGI-improvement scale), 56% of NAC patients were 'much' or 'very much' improved at the end of the study compared with 16% of those taking placebo. In a report series, NAC used as an add-on therapy in the treatment of bipolar disorder was associated with a dramatic reduction in nail-biting behavior in three cases (Berk et al., 2009). NAC efficacy on this behavior may be due either to an anti-impulsive action of NAC or to an effect on anxiety or stress. In a case report, NAC has been used in conjunction with fluvoxamine (a serotonin-reuptake inhibitor agent) treatment in a refractory OCD patient. During a total period of 12 weeks, including 7 weeks at the total daily dose of 3000 mg, Y-BOCS scores decreased dramatically and the patient was able to resist her compulsive symptoms during the treatment period (Lafleur et al., 2006).

These findings attest to the promise NAC treatment has for treating the behavioral symptoms of impulsive/compulsive disorders. Three double-blind placebo-controlled studies are currently being carried out, demonstrating the recent interest for NAC in the treatment of impulsive-compulsive spectrum disorders. The first one is evaluating the efficacy of NAC (3000 mg twice daily for 12 weeks) in adult Serotonin Reuptake Inhibitor-refractory obsessive-compulsive disorder and depression (NCT00539513). The second one is evaluating the efficacy of NAC (1600 mg twice daily for 2 weeks then 2600 mg capsules twice daily for the remaining 10 weeks) for the treatment of pediatric obsessive-compulsive disorder (NCT01172275), and the third one is assessing the efficacy of NAC (from 1200 mg daily to 3000 mg daily, during 12 weeks) in pathologic skin picking (repetitive, ritualistic, or impulsive picking of otherwise normal skin leading to tissue damage, personal distress, and impaired functioning; NCT01063348). Moreover, NAC is currently being evaluated in a double-blind placebo-controlled study for children with Tourette syndrome (childhood-onset neuropsychiatric disorder characterised by multiple and chronic motor and vocal tics; NCT01172288).

5. Conclusion

In laboratory studies, NAC has been shown to prevent escalation of cocaine use during long access (6h/day) to the drug (an animal model of loss of control over drug intake, a hallmark feature of addiction) without affecting drug use during short access (1h and 2h/day). NAC also prevents relapse behaviors, reducing drug-associated cues-, cocaine-, and heroin-priming-induced reinstatement after extinction and abstinence protocols (animal models of relapse, when a drug-addicted individual is exposed to different triggers of drug craving and relapse after a period of abstinence). Finally, NAC reduces cocaine seeking, when drug seeking has become habitual (an animal model of the daily behavior of drug foraging, as it can be seen in individuals who spend great deal of time in activities necessary to obtain and prepare the substance, rather than only during relapse following an extinction or abstinence period). These preclinical data resonate well with the human literature which shows overall promising results from clinical trials on drug addiction and impulsive-compulsive spectrum disorders. More specifically, the efficacy of NAC treatment for cocaine addiction appears relevant, with improvement of withdrawal symptoms, attenuation of subjective and objective craving for the drug (during laboratory experiments, NAC attenuates environmental and cocaine-induced urges to use), and persistent reduction in cocaine use even after the end of the treatment. Results in cannabis addiction are less marked but also hold promise, notably due to the absence of available treatment for addicted young adults, who are particularly vulnerable to the development of other, stronger, addictions and psychotic comorbid disorders (Gray et al., 2010). Promising but mitigated results in methamphetamine and nicotine addiction should make us remember that the pathology of addiction may be quite different across drugs of abuse and that a single pharmacotherapy may not be sufficient for all drugs (cf. Badiani et al., 2011). Even if the small sample size of these studies may have precluded the identification of statistically significant differences between groups, negative results may also be attributable to the implication of other biological and psychological factors in methamphetamine and nicotine dependence and craving. In particular, learned contextual associations and context-induced relapse (Crombag et al., 2008) may not be affected by NAC treatment. Indeed, interesting preliminary results in other behavioral disorders including pathological gambling and impulsive-compulsive disorders, which appear alleviated with NAC treatment, may suggest that NAC is not necessarily working to treat these behavioral disorders at the same level of the drug of abuse.

At the neurobiological level this suggests that NAC-induced re-regulation of the homeostatic extrasynaptic glutamate levels in the brain may be affecting the behavioral component of 'seeking' - whether that be drug, a poker game, or the anxiety-alleviation provided by compulsive hair pulling. Preclinical studies using models in rats that specifically address the development of habitual drug seeking behavior, compulsive seeking and taking behavior, or addiction-like behavior (Belin et al., 2011) may help to elucidate the main psychological and associated neural substrate whereby NAC exerts its action and so in the different addictions, as it has been shown, for example, that opiate and stimulants addiction are behaviorally and neurobiologically distinct (for review see Badiani et al., 2011). Studies evaluating the efficacy of NAC on neuropsychological processes that contribute to the development of drug addiction, (e.g., decision-making or impulsivity) may also prove useful. In humans, clinical studies should take interest in assessing efficacy of NAC as a cognitive enhancer (Brady et al., 2011), as it has been shown that improvement of

inhibitory control, attentional and decision-making processes may help individuals perform better in face of stressful and complex environmental situations.

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