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Cognitive Function During Nicotine Withdrawal: Implications for Nicotine Dependence Treatment

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Abstract

Nicotine withdrawal is associated with deficits in neurocognitive function including sustained attention, working memory, and response inhibition. Several convergent lines of evidence suggest that these deficits may represent a core dependence phenotype and a target for treatment development efforts. A better understanding of the mechanisms underlying withdrawal-related cognitive deficits may lead to improve nicotine dependence treatment. We begin with an overview of the neurocognitive effects of withdrawal in rodent and human models, followed by discussion of the neurobehavioral mechanisms that are thought to underlie these effects. We then review individual differences in withdrawal-related neurocognitive effects including genetics, gender, and psychiatric comorbidity. We conclude with a discussion of the implications of this research for developing improved therapies, both pharmacotherapy and behavioral treatments, that target cognitive symptoms of nicotine withdrawal.

Keywords

nicotine; withdrawal; cognition; attention; working memory; smoking cessation

1. Introduction

Despite public health gains in recent decades, cigarette smoking continues to be the greatest preventable cause of morbidity and mortality in the U.S. and worldwide. Yet quitting smoking is difficult, even with FDA approved pharmacotherapies (Ray et al., 2009b). In chronic cigarette smokers, cessation of use produces unpleasant physiological, affective, and cognitive withdrawal symptoms that peak within the first few days of nicotine deprivation (Hughes, 2007; Teneggi et al., 2005) and predict relapse (Killen and Fortmann, 1997; Rukstalis et al., 2005; Strasser et al., 2005). Indeed, as many as 50–75% of smokers relapse within the first week following a quit attempt (Garvey et al., 1992; Hughes, 1992).

Although nicotine withdrawal is associated with a variety of symptoms, withdrawal-related cognitive deficits are gaining attention as a core dependence phenotype and a target for medication development efforts (Lerman et al., 2007; Sofuoglu, 2010). These withdrawal-related cognitive impairments can be measured objectively in animals and humans, and data

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across species support the reversal of these effects following nicotine re-exposure or administration of medications efficacious for smoking cessation (Davis et al., 2005; Patterson et al., 2009; Portugal and Gould, 2007). The clinical relevance of these symptoms is supported by the high prevalence in treatment seeking smokers (Covey et al., 2008; Hughes, 2007; Rukstalis et al., 2005) and the predictive validity for smoking relapse (Culhane et al., 2008; Krishnan-Sarin et al., 2007; Patterson et al., 2010; Powell et al., 2004). Evidence supporting the importance of higher order cognitive control in maintaining goal-directed behavior (Hare et al., 2009; Kounieher et al., 2009) may provide a theoretical framework for explaining why cognitive deficits may be associated with relapse. That is, the deficits in prefrontal executive function observed during nicotine withdrawal may disrupt the motivation necessary to maintain abstinence, may make it difficult to adjust behavior once an error (i.e., a lapse) occurs, or may decrease the ability to sustain the cognitive control necessary to maintain abstinence in the face of cravings to smoke. However, empirical studies are necessary to test these hypotheses.

These convergent lines of evidence provide an impetus to better understand the mechanisms underlying withdrawal-related cognitive deficits in order to improve nicotine dependence treatment. Indeed, one approach to accelerate progress in treatment development is to dissect this complex behavior into its component symptoms and to target translational research on more focused core phenotypes (Conn and Roth, 2008; Lerman et al., 2007; Markou et al., 2009). Toward that end, in this paper we review the emerging evidence base supporting withdrawal-related cognitive deficits as a target for nicotine dependence treatment development. We begin with an overview of the neurocognitive effects of withdrawal in rodent and human models, followed by discussion of the neurobehavioral mechanisms that are thought to underlie these effects and individual differences. We conclude with a discussion of the implications of this research for developing improved therapies, both pharmacotherapy and behavioral treatments, that target cognitive symptoms of nicotine withdrawal. This review focuses on early nicotine withdrawal effects because of the relevance to nicotine dependence treatment (Lerman et al., 2007); for reviews of acute nicotine effects on cognition, we direct the reader to Heishman and colleagues (2010) and Evans and Drobos (2009).

2. Nicotine Withdrawal and Cognitive Performance

2.1 Rodent models

Preclinical models provide valuable tools for evaluating cognitive deficits during nicotine withdrawal. In rodent models, animals are chronically treated by implanting osmotic mini-pumps that deliver infusions of nicotine for some period of time (e.g., 14 days). The effects of nicotine withdrawal are observed by either removing the mini-pumps (i.e., spontaneous withdrawal) or by precipitating withdrawal through infusions of nicotinic antagonists, such as dihydro-beta-erythroidine (DH β E) or methyllycaconitine (MLA) (Bancroft and Levin, 2000; Davis and Gould, 2006; Levin and Rezvani, 2002). Behavioral paradigms assessing attention, learning and memory, and response inhibition in animals have been developed to model the cognitive deficits observed in humans. Attention is typically modeled using an operant signal detection task (SDT) or the five-choice serial reaction time task (5-CSRTT) both of which require animals to respond to a particular stimulus and are analogous to the Continuous Performance Task in humans (Robbins, 2002). Associative learning is often measured with fear conditioning paradigms, during which animals are trained by pairing an auditory conditioned stimulus (CS) with an aversive unconditioned stimulus (US) (e.g., footshock). Contextual fear conditioning is a measure of the association between the training context and is hippocampal dependent, whereas cued fear conditioning is a measure of the association between the CS and US and does not require the hippocampus (Davis and Gould, 2008). Animal models of memory typically employ maze tasks, such as the radial-

arm maze, Morris water maze, and elevated-plus maze, which require animals to use visuospatial cues to learn the location of food or some other desirable object. These tasks are generally thought to reflect spatial memory, but there is substantial overlap with working memory processes (Hodges, 1996). Animal models of response inhibition measure the ability to inhibit a pre-potent response and utilize go/no-go tasks, stop signal reaction time tasks, and measures derived from the 5-CSRTT (e.g., premature responses). We restrict our review to tasks that require suppressing a response and thus do not include measures of impulsive choice (e.g., delay discounting). Further, the focus of this review is on the cognitive effects of *nicotine withdrawal*; for discussions of the acute effects of nicotine on cognition in animals see Levin and colleagues (2006) and Floresco and Jentsch (2011).

2.1.1 Attention—Rodent models have demonstrated deficits in tasks designed to measure attention following nicotine withdrawal. Following spontaneous withdrawal from nicotine, rats showed an increase in percentage of omissions in the 5-CSRTT, but no change in the percentage of correct responses or response time (Shoaib and Bizarro, 2005). In another study using the 5-CSRTT, nicotine withdrawal decreased the number of correct responses and increased omissions, but had no effect on incorrect responses (Semenova et al., 2007). The evidence with respect to the effects of nicotinic antagonists on attention is similarly mixed. For instance, withdrawal precipitated by DH β E, an $\alpha 4\beta 2$ nAChR antagonist, resulted in impairments similar to those caused by spontaneous withdrawal in rats (Shoaib and Bizarro, 2005), but this effect was not replicated in a subsequent study (Hahn et al., 2011). Methyllcaconitine (MLA), an $\alpha 7$ nAChR antagonist, impaired performance on the 5-CSRTT in nicotine treated rats in one study (Hahn et al., 2011), but had no effect in another (Blondel et al., 2000). Although varenicline has been shown to improve signal detection, particularly under challenging conditions (Rollema et al., 2009), we are not aware of research testing whether varenicline ameliorates withdrawal-induced attentional deficits.

2.1.2 Learning and memory—Withdrawal from chronic nicotine has detrimental effects on performance on a variety of learning and memory tasks. Following withdrawal from chronic nicotine, mice demonstrate impaired contextual and trace fear conditioning, but not cued fear conditioning (Davis et al., 2005; Raybuck and Gould, 2009). Incidental learning, measured by a spatial object recognition task, was also impaired following nicotine withdrawal, but no changes were observed in the novel object recognition task (Kenney et al., 2011). Withdrawal precipitated by the $\alpha 4\beta 2$ nAChR antagonist DH β E, but not MLA, disrupted contextual fear conditioning (Davis and Gould, 2006). It is important to note that the learning and memory tasks affected by nicotine withdrawal are hippocampus-dependent tasks (Davis and Gould, 2008). Furthermore, the withdrawal-induced deficits in contextual and trace fear condition and spatial object recognition observed in rodents are not universal; many of these effects are strain-dependent (Portugal et al., 2012a), age-dependent (Portugal et al., 2012b), and time-dependent (Gould et al., 2012). Importantly, effective treatments for smoking cessation (e.g., bupropion and varenicline) ameliorate withdrawal-induced deficits in contextual fear conditioning suggesting one mechanism by which these medications may promote abstinence (Portugal and Gould, 2007; Raybuck et al., 2008).

Similarly, rats withdrawn from nicotine exhibit deficits in performance on Morris water maze and radial-arm maze tasks, which are analogues of working memory tasks in humans (Levin et al., 1990; Levin et al., 2006). However, others have found that the beneficial effects of nicotine on choice accuracy in a radial arm maze task persisted for two weeks following withdrawal from nicotine (Levin 1990). Nicotine has been shown to reverse memory impairments induced by the nonspecific nicotinic antagonist mecamylamine (Levin et al., 1993) and DH β E, but not MLA (Bancroft and Levin, 2000; Bettany and Levin, 2001). Similar to fear conditioning, nicotine's effects on memory in rodents may be region-specific. Infusions of mecamylamine to the ventral hippocampus, substantia nigra, and ventral

tegmental area, but not to the nucleus accumbens, impaired choice accuracy on a radial arm maze task (Kim and Levin, 1996; Levin et al., 1994). Likewise, infusions of DH β E to the hippocampus impaired working memory (Bancroft and Levin, 2000; Bettany and Levin, 2001), but infusions to the medial thalamic nucleus improved performance on a radial arm maze task (Cannady et al., 2009). Although few studies have examined the effects of nicotine dependence treatments on memory impairment following nicotine withdrawal in rodents, both bupropion and varenicline ameliorated deficits in performance on the elevated-plus maze induced by scopolamine, a muscarinic cholinergic antagonist (Kruk-Słomka et al., 2012; Kruk et al., 2011). However, it should be noted that nicotine-induced improvement in memory was attenuated by both bupropion and varenicline (Biała and Kruk, 2009; Kruk-Słomka et al., 2012; Kruk et al., 2011).

2.1.3 Response inhibition—There is relatively weaker evidence regarding the effects of nicotine withdrawal on response inhibition in rodents. For example, spontaneous and DH β E-precipitated withdrawal increased premature responding during a 5-CSRTT (Shoaib and Bizarro 2005), but in another study acute nicotine withdrawal (i.e., 24 hours) was associated with *improved* response inhibition (Kolokotroni et al., 2012). In contrast, deficits in response inhibition (e.g., decreased accuracy during no-go trials and increased premature responding during a go/no-go task) emerged following nine days of nicotine withdrawal (Kolokotroni et al., 2012). Although the finding that acute withdrawal enhanced response inhibition may seem counterintuitive, it fits with data suggesting that chronic exposure to nicotine (Blondel et al., 2000; Semenova et al., 2007) and varenicline, an α 4 β 2 partial agonist (Wouda et al., 2011), impairs response inhibition. However, no study that we know of has examined the effects of nicotine dependence treatments on response inhibition during nicotine withdrawal. Of relevance to human models of relapse, animals previously exposed to chronic nicotine may be hypersensitive to the effects of a nicotine challenge on a range of response inhibition measures (Day et al., 2007; Kirshenbaum et al., 2011; Kolokotroni et al., 2012). This suggests that during a quit attempt, a smoking lapse may promote failures of inhibition leading to an increased risk of full blown relapse.

2.2 Human models

Sustained attention, working memory, and response inhibition are considered three key domains comprising executive cognitive function (Alvarez and Emory, 2006; Lezak, 2004). Briefly, sustained attention, or vigilance, refers to a basic executive function that facilitates the ability to discriminate between targets and distractors (Sarter et al., 2001; Sarter and Paolone, 2011). Working memory is a multi-component process responsible for the active maintenance and manipulation of information critical for learning, decision-making, and sustaining goal-directed behavior (Baddeley, 2003, 2007). Response inhibition refers to the ability to inhibit pre-potent responses (de Wit, 2009; Perry and Carroll, 2008; Sarter and Paolone, 2011). For the purpose of this review, measures of “inhibitory control”, “response inhibition”, and “behavioral control” are referred to as response inhibition. Although typically discussed as separate components of cognition, there is some overlap in the assessment of performance domains and the underlying neurocircuitry. For example, the active maintenance and manipulation of information required during working memory tasks also requires vigilance and the ability to discriminate relevant from irrelevant stimuli (i.e., attention). Likewise, the ability to inhibit a prepotent response depends, in part, on the ability to discriminate a target from a distractor. Neuroimaging studies have also shown that these tasks activate similar brain regions (Cabeza et al., 2011; Hutchinson et al., 2009). Other cognitive domains such as cognitive flexibility may also be impaired during nicotine withdrawal in animals (Allison and Shoaib, 2013; Ortega et al., 2013), but few studies have tested this hypothesis. Thus, we focus on sustained attention, working memory, and response inhibition.

2.2.1 Sustained attention—Smokers often report “difficulty concentrating” during withdrawal (Hughes, 2007), suggesting that measures of sustained attention may represent an index of cognitive control that may contribute to difficulty refraining from smoking. The most widely used behavioral assessment of sustained attention is the Continuous Performance Test (CPT). However, many versions of this task exist and variability in task parameters and requirements may contribute to inconsistencies in the observed effects of nicotine withdrawal. For example, some tasks require participants to press a key for any letter except “X” (Conners, 2000), whereas others, such as the CPT identical pairs version (CPT-IP), require participants to respond only to an infrequent target stimulus (Cornblatt et al., 1988). Some suggest that withholding a response to an infrequent target reflects response inhibition rather than sustained attention (Ballard, 2001). Other tasks thought to reflect sustained attention, such as the Rapid Visual Information Processing (RVIP) task, include a working memory component as they require maintaining and updating information about the previous two stimuli (e.g., Coull et al., 1996; Lawrence et al., 2003). For example, smokers abstinent for 17, but not 5 hours, had more omission errors and slower reaction times on the Connors CPT (Harrison et al., 2009). Others have reported no changes in performance during two versions of a CPT following 24 hours of abstinence (Jacobsen et al., 2005) or following overnight abstinence (Ashare and Hawk, 2012). However, one study observed decrements in performance (i.e., slower reaction time) on the RVIP as soon as 30 minutes post cessation (Hendricks et al., 2006). Thus, differences in the duration of abstinence as well as specific task parameters may contribute to inconsistencies in the literature.

To the extent that deficits in sustained attention are an important component of nicotine withdrawal, they should be related the ability to quit smoking. Although baseline deficits in sustained attention predict relapse to smoking among individuals with schizophrenia and attention-deficit/hyperactivity disorder (ADHD) (Culhane et al., 2008; Humfleet et al., 2005; Pomerleau et al., 2003), no study that we know of has demonstrated a link between *withdrawal-related* deficits in attention and relapse. Thus, it is unclear whether sustained attention represents a core process of cognitive control underlying smoking relapse in the general population of smokers.

Despite the relatively scarce literature linking attentional deficits with relapse, several studies have demonstrated that efficacious treatments for nicotine dependence attenuate withdrawal-induced deficits in attention. Following overnight abstinence, nicotine replacement therapy (i.e., nicotine spray and lozenge), compared with placebo, improved the number of correct responses on the Connors’ CPT and a RVIP task (Atzori et al., 2008; Myers et al., 2008), but not on a CPT-IP task (Dawkins et al., 2007). Varenicline, compared with placebo, increased the number of correct responses and reduced reaction times following 72 hours of abstinence (Patterson et al., 2009). In another study, varenicline, but not bupropion, improved reaction time during the Connors’ CPT following overnight abstinence (Ashare and McKee, 2012). However, the effect sizes for abstinence effects on attention are generally small (Dawkins et al., 2007; Myers et al., 2008; Patterson et al., 2009).

2.2.2 Working memory—Working memory in humans is often assessed via an n-back task, during which participants are instructed to respond whenever a stimulus is presented that is the same as the one presented n trials previously (i.e., 1-, 2-, or 3-back) (Green et al., 2005; Owen et al., 2005). Following overnight abstinence, smokers were less accurate (i.e., more errors, fewer correct responses) and had slower reaction times on an n-back task (Jacobsen et al., 2005; Mendrek et al., 2006). However, some have only reported decreased accuracy (Jacobsen et al., 2007) or longer response latencies (Xu et al., 2005) while others have found no effect of withdrawal on n-back performance (Greenstein and Kassel, 2009; Sweet et al., 2010). Indeed, effect sizes can range from small (Patterson et al., 2009) to large

(Myers et al., 2008). Importantly, many of these effects are strongest, or only evident, at higher working memory loads (e.g., 2- or 3-back level; Jacobsen et al., 2007; Loughhead et al., 2010; Loughhead et al., 2009; Mendrek et al., 2006), though these findings are not universal (Xu et al., 2005; Xu et al., 2006).

Of relevance to nicotine dependence, working memory may subserve the top-down control of self-regulatory behaviors and contribute to the down-regulation of cravings (Hofmann et al., 2012). Indeed, emerging evidence suggests that withdrawal-related deficits in working memory predict relapse to smoking (Patterson et al., 2010), suggesting that a failure to maintain a representation of goal-related information may underlie relapse to smoking. Evidence also suggests these withdrawal-related cognitive impairments may be reversed by efficacious treatments for nicotine dependence. Following overnight abstinence, a nicotine lozenge, compared to placebo, reduced reaction time during the Sternberg Short-term Memory Scanning task (Atzori et al., 2008). In abstinent smokers, varenicline has been shown to decrease reaction time during a working memory task compared to placebo (Atzori et al., 2008; Loughhead et al., 2010; Patterson et al., 2009). During a digit span task performed during nicotine abstinence, bupropion, but not varenicline, was found to improve working memory, although this effect appeared to be specific to females (Ashare and McKee, 2012).

2.2.3 Response inhibition—In the context of smoking cessation, impairment in response inhibition may contribute to difficulty refraining from smoking. Measures of response inhibition typically involve two processes: the “go” process which is established as the default response and the “stop” or “no-go” process which requires effortful control to inhibit, stop, or modify the pre-potent response (Logan, 1994; Logan et al., 1997). Following overnight abstinence, nicotine withdrawal impairs response inhibition across a variety of tasks, including the stop task (Ashare and Hawk, 2012), go/no-go (Harrison et al., 2009), and commission errors on a CPT (Ashare and Hawk, 2012; Harrison et al., 2009; Kozink et al., 2010a) with effect sizes in the small to medium range (Dawkins et al., 2007; Kozink et al., 2010a).

Importantly, deficits in response inhibition predict relapse to smoking. For example, inhibitory control assessed following overnight abstinence, as measured by CPT commission errors, predicted relapse at one and three months post-quit (Powell et al., 2010). Similarly, in a sample of adolescents, those who remained abstinent after 4 weeks of treatment exhibited better response inhibition at baseline (i.e., fewer CPT errors of commission) (Krishnan-Sarin et al., 2007). In addition, nicotine reverses withdrawal-induced deficits in response inhibition (Bekker et al., 2005; Dawkins et al., 2007). To our knowledge, there have been no studies of the effects of non-nicotine treatments for smoking cessation on withdrawal-related impairment in response inhibition. Nevertheless, the ability to suppress automatic responses, such as habitual smoking, may represent a core process of cognitive control underlying nicotine dependence and smoking relapse.

2.3 Neurobehavioral Mechanisms

Nicotine is the primary addictive chemical in tobacco, exerting its effects via stimulation of neuronal nicotinic acetylcholine receptors (nAChRs). The most abundant subtypes in the brain are the $\alpha 7$ and the high affinity $\alpha 4\beta 2^*$ receptors. Because the majority of nAChRs are located on presynaptic terminals, the primary action of nAChRs is the modulation of neurotransmitter release (Wonnacott, 1997). Nicotine binds to nAChRs, which then stimulates the release of dopamine, GABA, and glutamate (for reviews, see Paolini and De Biasi, 2011; Tuesta et al., 2011). Stimulation of $\alpha 4\beta 2$ nAChRs in the ventral tegmental area (VTA) increases dopamine release in the nucleus accumbens (David et al., 2006; Ikemoto et

al., 2006) and prefrontal cortex (Livingstone et al., 2009), areas important in nicotine's rewarding and cognitive enhancing effects, respectively. Although dopamine release is likely the main source of nicotine's addictive properties, nicotine's effects on multiple neurotransmitters are thought to contribute to cognitive performance (Levin et al., 2006).

Chronic exposure to nicotine produces neuroadaptive changes that make quitting difficult. For example, upregulation of nAChRs following chronic exposure has been demonstrated in rodents (Turner et al., 2011) and in post-mortem human brain (Breese et al., 1997). Further, following cessation of smoking, unbound nAChRs are present at a higher level for as long as one week, and nAChR binding availability has been associated with self-reported withdrawal and craving (Cosgrove et al., 2009; Staley et al., 2006). As described above, in rodents exposed to chronic nicotine, nAChR antagonists (e.g., MLA and DH β E) produce cognitive deficits (Bettany and Levin, 2001; Cannady et al., 2009; Davis and Gould, 2006), supporting a role for nAChR regulation in withdrawal-related cognitive function. Although there is strong evidence of the cognitive enhancing effects of nAChR stimulation (Poorthuis et al., 2009; Sarter et al., 2009), to date, studies of nAChR availability or regulation during nicotine withdrawal and corresponding changes in cognition has only been conducted in animals. For example, the duration of nAChR upregulation following nicotine withdrawal corresponds to the duration of withdrawal-related deficits in contextual fear conditioning (Gould et al., 2012) and the β 2 subunits play a role in withdrawal-related disruption of fear conditioning (Raybuck and Gould, 2009). In humans, individuals with mild cognitive impairment and Alzheimer's disease exhibit reductions in α 4 β 2 nAChR availability in both the hippocampus and frontal cortex which are associated with the severity of cognitive impairment (Kendziorra et al., 2011; Sabri et al., 2008). Thus, these studies support the notion that nAChR availability may be associated with deficits in cognitive function and represent a potentially fruitful avenue for exploring neurochemical mechanisms underlying withdrawal-related cognitive deficits.

Studies using blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) have begun to elucidate the neural correlates of sustained attention. Sustained attention tasks activate the right fronto-parietal-thalamic network, which includes prefrontal regions, the anterior cingulate cortex (ACC), and the thalamus (Lawrence et al., 2003; Sarter et al., 2001). Although several studies have examined the neural correlates of acute nicotinic effects on sustained attention following minimal or a few hours of nicotine deprivation, there is mixed evidence regarding the direction of these effects (Beaver et al., 2011; Hahn et al., 2009; Hahn et al., 2007; Lawrence et al., 2002). However, little is known regarding abstinence effects on the neural substrates of sustained attention. To our knowledge, only one fMRI study has examined directly the effects of abstinence on brain function and behavior during performance of a sustained attention task. Kozink and colleagues (2010b) reported that 24 hours of smoking abstinence decreased activation in right frontal regions during a sustained attention task, and increased activation in several cortical regions during responses to targets. This finding is consistent with evidence that nicotine replacement reversed abstinence-induced decreases in the fronto-parietal-thalamic network (Beaver et al., 2011). However, these studies were relatively small (15–20 smokers) and assessed attention with the rapid visual information processing (RVIP) task, which has a strong working memory component.

In contrast to sustained attention, the neural substrates of working memory function during nicotine withdrawal have been examined in several studies. Initial studies show that nicotine withdrawal alters working memory-related brain activation in a neural circuit including the bilateral dorsolateral prefrontal cortex (DLPFC) and medial/frontal cingulate gyrus (MF/CG) or ACC (Loughead et al., 2010; Xu et al., 2005; Xu et al., 2006). However, the direction and interpretation of abstinence-induced alterations has not been consistent across

studies. Some studies have reported no difference in working memory performance in abstinence versus smoking, but with increases in BOLD signal (activation) in abstinence; this has been interpreted as decreased processing efficiency in abstinence (Jacobsen et al., 2007; Xu et al., 2005; Xu et al., 2006). In contrast, significant abstinence-induced decreases in BOLD signal in working memory-related brain regions (i.e., MF/CG and DLPFC) were observed at the highest task loads during an N-back task (i.e., 3-back level) (Loughead et al., 2010). In highly dependent smokers, decreased BOLD signal in abstinence correlated with poorer performance (Loughead et al., 2010). Reduced recruitment of the brain's working memory circuit in abstinence versus smoking was reproduced in a much larger study of treatment-seeking smokers, with evidence for greater effects of abstinence on working memory-related brain activity in smokers under age 50 compared to older smokers (Falcone et al., 2013). In addition to age-related differences, an effect that may be due to changes in cholinergic and dopaminergic function in older adults (De Biasi and Dani, 2011; Mitsis et al., 2009), differences across studies may be attributed to several factors. These include smaller sample sizes in earlier work, treatment-seeking status of smokers, and task difficulty (i.e., some tasks do not include a 3-back condition). Although withdrawal-related deficits in working memory may be the result of a failure to recruit sufficient resources, rather than inefficient processing, the relationship between fMRI-based markers and smoking relapse requires further investigation.

In healthy subjects, fMRI studies of the neural substrates of response inhibition include the right inferior frontal gyrus (rIFG), insula, and dorsomedial regions such as the anterior cingulate cortex (ACC) and pre-supplementary motor area (pre-SMA) (Chambers et al., 2009; Swick et al., 2011). Although several studies have examined the direct effects of nicotine, only a few have tested the effects of nicotine withdrawal on brain activation during response inhibition. Kozink and colleagues (2010a) studied two regions of interest (rIFC and pre-SMA), and observed an increase in failed inhibitions during abstinence vs. smoking with a corresponding increase in activation in the right inferior frontal cortex. However, regional activation patterns in fMRI studies vary between different response inhibition tasks (Swick et al., 2011).

Suppression of activation in task-independent regions in the "default mode network" (DMN) also appears to be necessary for performance of difficult cognitive tasks (Raichle et al., 2001). There is mounting evidence suggesting that while smokers are engaged in cognitive control tasks, these regions, which include the posterior cingulate cortex (PCC) and ventromedial PFC (vmPFC), tend to be less deactivated during nicotine withdrawal (Cole et al., 2010; Falcone et al., 2013; Loughead et al., 2010). Recent work has also begun to examine patterns of spontaneous fluctuations in activity in brain networks at rest, known as resting state functional connectivity (Fox et al., 2005). In general, there is an inverse correlation between the executive control network (ECN), which includes fronto-parietal regions, and the DMN (Menon and Uddin, 2010; Sridharan et al., 2008). Nicotine administration activates the ECN and deactivates the DMN (Newhouse et al., 2011) and the suppression of DMN activity following administration of transdermal nicotine may be associated with enhanced attentional processing (Hahn et al., 2007). When overnight abstinent smokers were administered a nicotine lozenge, the strength of the negative correlation between the ECN and the DMN increased and this was correlated with the beneficial effects of nicotine on cognitive symptoms (Cole et al., 2010).

3 Individual differences in withdrawal effects on cognition

3.1 Genetic effects

Smoking cessation has a strong heritable component (Broms et al., 2006; Xian et al., 2003) and the heritability of self-reported nicotine withdrawal symptoms, including difficulty

concentrating, has been estimated to be between 26 and 53% (Pergadia et al., 2006). Further, strain differences in nicotine withdrawal deficits in contextual fear conditioning in mice suggest that genetics play a role in withdrawal-related cognitive deficits (Portugal et al., 2012a; Wilkinson et al., 2012). There is some support for the role of nAChR, dopamine, and serotonin-related genes in the cognitive effects of nicotine (for a review, see Herman and Sofuoglu, 2010), but the few studies that have examined genetic moderators of withdrawal-related cognitive deficits have focused on genes involved in dopamine regulation, including the *ANKK1* Taq1A and the *COMT* val¹⁵⁸met polymorphisms. There is some evidence that the A1 allele of the Taq1A polymorphism is associated with reduced dopamine D2 receptor density and that these individuals may use nicotine as a means for self-medicating their hypodopaminergic state (Jonsson et al., 1999; Stapleton et al., 2011). Compared to smokers with the A2A2 genotype, those carrying the A1 allele of the Taq1A polymorphism showed attentional deficits during smoking abstinence, but enhanced attentional processing when smoking as usual (Evans et al., 2009) or with nicotine patch (Gilbert et al., 2005). The *COMT* gene has a common functional polymorphism at codon 158 (val¹⁵⁸met); the val allele is associated with a 3- to 4-fold increase in COMT enzyme activity, which inactivates dopamine in the PFC resulting in decreased prefrontal dopamine levels (Chen et al., 2004; Lachman et al., 1996). Consistent with the role of dopamine in nicotine addiction, the *COMT* val allele is associated with increased susceptibility to nicotine dependence, and greater risk for smoking relapse (Beuten et al., 2006; Colilla et al., 2005; Johnstone et al., 2007; Munafo et al., 2008). Smokers with the val/val genotype exhibited reduced brain activation during a working memory task following overnight abstinence compared to met allele carriers (Loughead et al., 2009). The T allele of the *DRD2* C957T SNP, a synonymous polymorphism in the *DRD2* gene, has been associated with increased receptor binding (Hirvonen et al., 2004) and increased odds of quitting smoking with nicotine patch treatment (Lerman et al., 2006). Following overnight abstinence, T allele carriers performed more poorly and exhibited increased brain activation during an n-back working memory task during nicotine patch compared to placebo (Jacobsen et al., 2006). Results from these studies should be considered with the caveat that sample sizes tend to be very small and populations may be nonrepresentative (e.g., smokers of European ancestry only). Thus, although there is some support for a role of genetics in the expression of withdrawal-related cognitive deficits, independent replication of these findings is needed.

3.2 Gender

Gender differences in withdrawal-related cognitive deficits are biologically plausible given evidence that hormonal fluctuations contribute to changes in cognitive functioning and there are sex differences in the regulation of nicotinic receptors and rates of nicotine metabolism (Benowitz et al., 2006; Biegon et al., 2010; Cosgrove et al., 2012; Dluzen and Anderson, 1997; Farage et al., 2008). For instance, females with attention problems report greater smoking-induced improvement in concentration and greater withdrawal-induced deficits in response inhibition than males (McClernon et al., 2008; McClernon et al., 2011). Others have shown that males experience greater cognitive deficits following smoking abstinence compared to females (Jacobsen et al., 2005; Merritt et al., 2012), though these differences may be domain-specific (Ashare and Hawk, 2012; Trimmel and Wittberger, 2004). There is also evidence that males and females may differ in their response to smoking cessation medication on cognitive tasks (Ashare and McKee, 2012) and that these effects may even be dose-specific (Poltavski et al., 2012). This work is limited by the fact that many studies do not report gender effects or examine them post-hoc, are limited by small sample sizes, and do not control for menstrual phase. Thus, future work should address this question with studies specifically designed to test gender as a moderator of nicotine withdrawal-induced cognitive deficits.

3.3 Psychiatric Comorbidity

3.3.1 Schizophrenia—There is a wide body of literature supporting the association of schizophrenia with increased smoking rates and greater difficulty quitting smoking (George, 2007; Kumari and Postma, 2005). Consistent with a self-medication hypothesis, the neurocognitive deficits observed in patients with schizophrenia may be ameliorated by nicotine (Barr et al., 2008; George et al., 2002). Although these cognitive deficits are qualitatively similar to those observed in healthy smokers during abstinence, patients with schizophrenia may experience greater withdrawal-related deficits in working memory (George et al., 2002; Sacco et al., 2005) and attention (AhnAllen et al., 2008). In contrast, some have found that smokers with schizophrenia do not exhibit deficits in attention accuracy during abstinence, but tended to show more variability in response time, which may reflect lapses in attention (Evins et al., 2005). Importantly, withdrawal-related decrements in performance predict relapse to smoking among patients with schizophrenia (Dolan et al., 2004; Moss et al., 2009) and treatments for smoking cessation, such as varenicline (Liu et al., 2011) and bupropion (Evins et al., 2005), may reduce these cognitive deficits.

3.3.2 Attention Deficit Hyperactivity Disorder—A diagnosis of attention deficit hyperactivity disorder (ADHD) or higher levels of ADHD symptoms is a well-known risk factor for nicotine dependence (Fuemmeler et al., 2007; Kollins et al., 2005; Wilens et al., 2008) and reduced ability to quit (Covey et al., 2008; Humfleet et al., 2005). One hypothesis to explain this association is that the cognitive enhancing effects of nicotine ameliorate the symptoms of ADHD (Evans and Drobles, 2009; McClernon and Kollins, 2008). Indeed, compared to controls, adult smokers with ADHD exhibited greater deficits in attention and inhibitory control following smoking abstinence (Kollins et al., 2009; McClernon et al., 2008). However, in a follow-up study, there was no difference between smokers with ADHD and controls in withdrawal-related cognitive deficits (Kollins et al., 2012). One direction for future research is to explore whether measures of cognitive task-related neural activation is more sensitive to group differences in abstinence effects than the behavioral measures described above.

3.3.3 Depression—Individuals with depressive disorders, including major depressive disorder (MDD) and dysthymia, smoke at higher rates and are more nicotine dependent (Weinberger et al., 2012, 2013), and have more difficulty quitting (Japuntich et al., 2007; Sonne et al., 2010). At the neurobiological level, nAChR activation may exacerbate depressive symptoms and nAChR antagonists may attenuate these effects, while agonists may lead to desensitization (Andreassen et al., 2009; Picciotto et al., 2008; Rabenstein et al., 2005). Several studies have also demonstrated impairments in attention, working memory, and response inhibition in depressed individuals (for reviews, see Bora et al., 2012; Murrough et al., 2011). Despite these connections, no study that we know of has specifically tested depression as a moderator of the effects of abstinence on cognitive function. More broadly, incorporating assessments of affective state to examine withdrawal-induced cognitive deficits in the context of mood regulation could be helpful. For example, cognitive deficits may exacerbate negative mood symptoms of withdrawal which, in turn, increase relapse risk.

4 Implications for treatment development

The evidence reviewed above points to a role for withdrawal-related cognitive deficits, particularly working memory, in maintaining smoking behavior. Thus, cognitive enhancing treatments represent plausible therapeutics for smoking cessation. Indeed, nicotine replacement therapy, varenicline, and bupropion have cognitive enhancing effects across a

range of populations (Gualtieri and Johnson, 2007; Hong et al., 2011; Newhouse et al., 2012; Potter and Newhouse, 2007). Cognitive remediation strategies that target cognitive symptoms of nicotine withdrawal, combined with these existing treatments, may also improve quit rates. Cognitive remediation treatment reduces the cognitive symptoms of ADHD and schizophrenia, and may be particularly effective when combined with existing pharmacotherapy (Stevenson et al., 2002; Wykes et al., 2011). Further, there is evidence that working memory training reduces impulsive decision-making among stimulant dependent individuals (Bickel et al., 2011). Another promising approach in this regard is the repurposing of medications used to treat cognitive deficits associated with other neuropsychiatric or neurodegenerative conditions.

Alzheimer's disease, a disorder characterized by deficits in cognition, is marked by a significant loss of cholinergic neurons and decreased ACh levels (Terry and Buccafusco, 2003), as well as other pathologic markers. Pharmacological modulation of the endogenous cholinergic system occurs through the use of acetylcholinesterase inhibitors (ACHEIs). ACHEIs increase available ACh in the synapse through inhibition of the catabolic enzyme, acetylcholinesterase (AChE) (Delrieu et al., 2011). All three of the currently FDA-approved ACHEIs (donepezil, galantamine, and rivastigmine), appear equally effective at reducing cognitive deficits (Birks, 2006; Delrieu et al., 2011). Specifically, ACHEIs target the cognitive symptoms of AD including attention, working memory, and overall global functioning (Foldi et al., 2005; Koontz and Baskys, 2005). In addition to inhibiting AChE, galantamine (unlike other ACHEIs) also acts as a positive allosteric modulator (PAM) of the $\alpha 4\beta 2$ and $\alpha 7$ nAChRs, and this dual action may contribute to its cognitive enhancing effects (Ago et al., 2011; Chuah and Chee, 2008; Gron et al., 2005; Kuryatov et al., 2008; Pandya and Yakel, 2011). Preclinical studies show that galantamine reverses withdrawal-related deficits in contextual fear conditioning (Wilkinson and Gould, 2011) and that donepezil and galantamine reduce nicotine self-administration and reinstatement (Hopkins et al., 2012; Kimmey et al., 2012). We have shown that donepezil may improve working memory in non-treatment-seeking smokers (Ashare et al., 2012). Galantamine has some beneficial effects on cognition and drug use in stimulant abusers (Sofuoglu and Carroll, 2011; Sofuoglu and Mooney, 2009; Sofuoglu et al., 2011) and may improve inhibitory control in abstinent smokers (Sofuoglu et al., 2012). Preliminary studies with cholinesterase inhibitors in alcoholic, methamphetamine-dependent, and schizophrenic smokers show that they are well tolerated but provide mixed results for efficacy with respect to reducing smoking behavior (De la Garza and Yoon, 2011; Diehl et al., 2006; Diehl et al., 2009; Kelly et al., 2008).

Atomoxetine, a selective norepinephrine reuptake inhibitor, is an approved non-stimulant treatment for ADHD. Its attention-enhancing effects suggest that it may be an effective treatment for withdrawal-induced cognitive deficits. Although it showed promise in a mouse model of nicotine withdrawal-induced deficits in contextual fear conditioning (Davis and Gould, 2007), it failed to alleviate withdrawal-related attentional deficits or to alter smoking behavior in a placebo-controlled human laboratory study of smokers following overnight abstinence (Ray et al., 2009a). Stimulant treatments for ADHD, such as methylphenidate and mixed amphetamine salts, may be viable treatments for attenuating withdrawal-induced cognitive deficits, but methylphenidate may actually increase cigarette consumption (Rush et al., 2005; Vansickel et al., 2011; Vansickel et al., 2007) and both have potential for abuse (Bright, 2008). The $\alpha 2$ adrenergic receptors are thought to mediate the cognitive enhancing effects of norepinephrine (Ramos and Arnsten, 2007). Indeed, the $\alpha 2$ adrenergic agonist guanfacine is an efficacious treatment for the symptoms of ADHD. However, no study that we know of has examined whether guanfacine ameliorates nicotine withdrawal-induced cognitive deficits.

5 Limitations

Despite emerging evidence supporting the role of cognitive deficits during nicotine withdrawal in rodents and humans, this work is limited by several factors. First, the cognitive domains reviewed here are broadly defined, have substantial overlap, and are measured with a variety of tasks. For example, some versions of the CPT require participants to *respond* only to an infrequent target (Conners, 2000), whereas others require *withholding* a response to an infrequent target (Cornblatt et al., 1988). The latter may reflect response inhibition, rather than sustained attention (Ballard, 2001). To add further variability, the RVIP is thought to have a strong working memory component (Coull et al., 1996; Lawrence et al., 2003). Furthermore, response inhibition is sometimes referred to as “inhibitory control” or “behavioral control” and the two most common tasks used to assess response inhibition, the go/no-go and the stop signal task, may recruit different neural substrates suggesting that they are not measuring identical processes (Swick et al., 2011). Even when studies utilize the same task, different outcomes may be reported (e.g., accuracy, signal detection indices, etc.), making it difficult to compare results across studies. Standardized batteries have been developed for the assessment of other neuropsychiatric disorders including ADHD, Alzheimer’s disease, and schizophrenia (Nuechterlein et al., 2008; Wild et al., 2008). However, these tasks may require less effort from an otherwise cognitively healthy population of smokers, resulting in ceiling effects. Although the recently released NIH Toolbox for Assessment of Neurological and Behavioral Function (<http://www.nihtoolbox.org>) may provide an additional resource to reduce measurement variability, it could be beneficial for an NIH working group to consider a specific subset of tasks that will be sensitive to the deficits observed in smokers or other substance abusers. Nevertheless, even the most comprehensive battery of behavioral measures may be unable to assess all aspects of cognitive function important during nicotine withdrawal. The use of multiple methods (e.g., subjective, behavioral, imaging, psychophysiological) may address this issue to facilitate a better understanding of the underlying mechanisms driving behavior. Second, neuroimaging studies incorporating genetics tend to have smaller sample sizes, likely due the cost and time associated with running these experiments. Therefore, these studies may be more likely to yield false positive results which may contribute to difficulty replicating findings. Third, motivation to quit smoking may be an important factor in the sensitivity of paradigms for testing abstinence effects, particularly with respect to treatment effects on quitting smoking (Perkins et al., 2010; Perkins et al., 2008). The majority of laboratory studies reviewed above included smokers who were not currently interested in quitting, with a few exceptions (Culhane et al., 2008; Dolan et al., 2004; Krishnan-Sarin et al., 2007; Patterson et al., 2009). Thus, the effects of nicotine withdrawal on cognitive deficits described here may not generalize to the population of smokers with high motivation to quit and may explain variability in these effects and difficulty relating them to relapse.

6 What do we know and where are the gaps?

We have reviewed evidence supporting the notion that withdrawal-related cognitive deficits represent a core nicotine dependence phenotype and may contribute to difficulty maintaining goal-directed behavior during a quit attempt. We conclude that: 1) withdrawal-related deficits in sustained attention appear to be more robust in humans than in animals, but these effects vary according to the assessment used; 2) withdrawal-related deficits in working memory performance are relatively consistent in rodents, but may depend on the outcome measure (i.e., reaction time vs. accuracy) in humans; and 3) nicotine withdrawal may improve response inhibition in rodents, but the impairments observed in humans appear to be related to the ability to quit smoking. What is clear from our review is that the effects of nicotine withdrawal on cognitive function are more complex than initially theorized. First, these deficits likely depend on a variety of factors including the duration of withdrawal and

the population being studied. A better understanding of these individual differences will enable treatment strategies designed to target specific risk factors for relapse. Second, the heterogeneity across behavioral measures of cognition contributes to difficulty replicating findings. Finally, behavioral assessments of cognitive function should be included clinical trials or in early medication screening paradigms to better characterize the association of withdrawal-related deficits with relapse. No treatment will be effective for all smokers. Therefore, identifying the factors that contribute to relapse and increasing the number of available treatments will help more smokers successfully quit smoking.

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