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ADDICTIONS (J GRANT, SECTION EDITOR)

Neurocognitive Function as a Treatment Target for Tobacco Use Disorder

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Abstract
Purpose of Review Novel approaches are needed to improve the treatment of tobacco use disorder (TUD). Two distinct literatures have examined the impact of cognitive function in the maintenance of TUD. One approach has focused on automatic cognitive processes, and the second approach has addressed the role of executive cognitive processes. This review focuses on interventions that target automatic and cognitive processes for TUD.
Recent Findings There appears to be evidence that attention retraining (AR) reduces automatic cognitions, but the effect on smoking requires further research. Several medications including varenicline, bupropion, and galantamine can improve executive processes and potentially reduce craving and smoking. However, whether the beneficial effects of these medications are mediated by cognitive improvement remains to be determined. Other strategies including the approach-avoidance task, transcranial direct current stimulation, and exercise require further study.
Summary Most research focuses on targeting automatic and controlled cognitive processes, separately in relatively small samples. Future research should consider targeting both processes simultaneously.

This article is part of the Topical Collection on *Addictions*

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Introduction

Cigarette smoking or tobacco use disorder (TUD) is responsible for over 430,000 preventable deaths in the USA per year [1]. There are several evidence-based treatments recommended in clinical practice guidelines to aid smoking cessation. However, despite many smokers being interested in quitting, most quit attempts are unsuccessful with 80% of smokers relapsing within 1year [2–4]. TUD is especially difficult to treat in smokers with psychiatric disorders, who smoke twice more commonly than those without psychiatric disorders [5]. Further, in the USA, the smoking rates remain unchanged for those with psychiatric disorders although smoking rates in the general population declined significantly over the past decade [6]. TUD likely contributes to shortened life expectancy in people with severe mental illness [7]. Therefore, there is a need to identify novel treatments for individuals with TUD, especially for smokers with comorbid psychiatric disorders.

TUD is associated with deficits in executive processes as well as changes in automatic processing resulting in enhanced attention-capturing properties of tobacco-related stimuli. These changes seem to be associated with greater rates of relapse following a quit attempt [8, 9]. Cognitive deficits are also common across many psychiatric disorders including addictions and correlate with individuals' daily functioning and predict treatment outcomes across many psychiatric disorders [10–13]. Thus, for individuals with TUD with or without psychiatric disorders, these deficits may serve as potential transdiagnostic treatment targets. This transdiagnostic treatment strategy is in line with the

Research Domain Criteria (RDoC) initiative [14]. The RDoC approach includes several domains such as negative and positive valences, cognitive systems, systems for social processes, and arousal and regulatory systems. Deficits in cognitive function is a potential transdiagnostic treatment target to be considered [15].

The goal of this review is to present an overview of cognitive enhancement approaches for TUD. We first summarize the background and rationale for cognitive enhancement approaches in TUD. Next, we review the behavioral and pharmacological cognitive-enhancement strategies for TUD. We conclude with a discussion of research gaps and areas of for future research using this approach.

Rationale for Cognitive Enhancement Approaches for TUD

Multiple studies have shown that abstinence from smoking impairs cognitive function as documented by decrements in performance on tasks of sustained attention, and these deficits are ameliorated by smoking or nicotine administration [16, 17]. Additionally, there is growing evidence supporting that chronic smoking is associated with impaired cognitive function. For example, smokers performed worse than nonsmokers on several domains of cognitive function including auditory–verbal and visuospatial learning, cognitive efficiency, visuospatial memory, executive skills, general intelligence, and processing speed [18]. These findings are consistent with those reported in other studies that included smokers and matched controls [19–22]. However, it is not possible to draw strong causal inferences from these cross-sectional and prospective observational studies on the effect of chronic smoking on cognitive performance. It is possible that preexisting cognitive deficits (e.g., working memory or sustained attention) may facilitate initiation of smoking and dependence [23], and this may in part be due to cognitive-enhancing effects of nicotine [24].

Irrespective of their cause, it is clear that cognitive function may be an important predictor of smoking relapse. One study reported that abstinence-induced working memory deficits predicted shorter time to relapse in smokers [9]. Another study reported that response inhibition and motor impulsivity predicted relapse at 1-week post-quit and motor impulsivity predicted relapse at 1 and 3 months post-quit [25]. Further, studies have also reported that attentional biases to smoking cues, an index of automatic cognitive processes, predict relapse in smokers who are attempting to stop smoking [8, 25, 26]. These findings suggest that cognitive-enhancement strategies targeting automatic or executive functions may be an effective strategy for enabling people with TUD to quit smoking.

Dual Process as a Cognitive Model of Addiction

From the perspective of cognitive psychology, addiction can be viewed as a conflict between "automatic" (or "implicit") processes, which generally enhance risk of drug taking/relapse, and "controlled" (or "explicit") processes, which generally inhibit automatic processes or the output of those processes (see review in [27]). Drug use or relapse is expected to occur if automatic processes dominate. This framework has been termed "dual process theory" due to the presence of two process types (e.g., [28, 27]).

Automatic Processes

Attentional bias is an automatic cognitive process in which a smoker attends to a smoking-related cue without making the conscious decision to attend to the cue [29]. Attentional bias can be assessed using reaction time tasks such as the visual probe task as well as self-report and eye movements [17, 30, 31].

"Approach bias" is the second commonly assessed automatic process and refers to the tendency to approach drug cues [32]. Approach biases are measured with computerized tasks involving motor movements such as the approach-avoidance task [33]. There is evidence that approach bias is present in heavy smokers but not in ex-smokers [33]. Additionally, approach biases in smokers are correlated with craving [33].

Theoretically, attentional and approach biases are thought to capture the incentive salience of tobacco-related cues, which becomes sensitized in some individuals [34]. Tobacco use is maintained by the ability of conditioned stimuli (i.e., smoking cues) to trigger motivation for tobacco use [34].

Executive Processes

Controlled cognitions, also known as executive processes include working memory, sustained attention, problem solving, decision making, response inhibition, and cognitive flexibility [35]. The executive processes that are particularly relevant for TUD include sustained attention, response inhibition, and working memory functions.

Response inhibition is defined as the ability to inhibit a dominant pre-potent response or automatic response voluntarily [35]. Working memory is the ability to store short-term memories about a recent event or to retrieve and process information from long-term memory storage in order to regulate behavior [36]. Working memory function is linked to inhibitory control such that under high working memory demand or reduced working memory capacity may provoke drug craving or relapse [37].

Both top-down and bottom-up processes control sustained attention function [38]. Top-down processes (the executive or endogenous attention) are controlled by the neural circuitry of prefrontal cortex and is closely linked to other executive functions including response inhibition and working memory [39].

Bottom-up processes (stimulus-driven or exogenous or attention) is primarily driven by external stimuli such as drug cues. These functions can be assessed by separate cognitive tasks and are potential treatment targets for cognitive-enhancement strategies.

Methods

The author conducted a search of studies in which researchers attempted to manipulate attentional and approach bias in smokers. Studies were included in Table 1 if they were an intervention that attempted to reduce attentional or approach bias, included an assessment of attentional or approach bias after the intervention, assessed craving, and/or smoking after the intervention. A search of studies published through August 2016 on PubMed and Web of Science were included. Search terms included "cognitive bias modification" and "smoking," "attentional retraining" and "smoking," "attentional bias modification" and "smoking," and "approach bias modification" and "smoking," "transcranial direct current stimulation" and "smoking," and "exercise and cognition." Additional manuscripts were identified by examining reference lists.

The authors conducted a literature search of research papers that assessed the effect of pharmacotherapy and behavioral interventions on executive processes to target smoking (Table 2). In order to be included in the table, the study had to be designed to manipulate an executive process (e.g., working memory), include an assessment of an executive process following the intervention, and include an assessment of smoking behavior or craving after the intervention. A search of studies published through August 2016 on PubMed and Web of Science were included. Search terms included "cognitive enhancers" and "smoking," "varenicline" and "smoking," "galantamine" and "smoking," "acetylcholine" and "smoking," and "bupropion" and "smoking." Pharmacotherapy studies involving participants with schizophrenia were excluded. Research suggests that the mechanisms of smoking initiation and cessation are different among individuals with schizophrenia compared to the general population and individuals with other mental health disorders (see Fonder et al., 2004 for review) [62].

Treatment Approaches Targeting Cognitive Functions

Interventions Targeting Automatic Cognition in Smokers

We identified ten studies that manipulated attentional bias and three studies that manipulated approach bias [40–51, 52•]. Eight of the studies that manipulated attentional bias used attentional retraining (AR) [40–47]. AR involves using modified cognitive tasks to change attentional bias. The most widely used task has been a modified visual probe (VP) task [63]. In this task, participants are simultaneously presented with smoking and neutral pictures. On AR tasks, the dot always replaces the neutral picture [40]. There is a perfect association between picture type and dot location. On control tasks, the dot is equally likely to replace the smoking picture and the neutral picture [41]. There is no association between picture type and dot location (although some studies use attend-smoking control groups [40]). Through training, participants learn to attend away from motivationally salient stimuli (e.g., drug-related stimuli) and toward neutral stimuli.

AR reduced bias to smoking cues in five of the studies in Table 1 [40, 41, 43–45]. AR reduced craving in one study and reduced smoking in two of the studies [43, 45, 47]. Three of these studies assess the generalization of AR to new pictures, other cognitive tasks, or self-report measures [41, 44, 45]. Two studies reported that the effect of AR generalized to new pictures [44, 45].

Table 1 also includes three studies that attempted to manipulate approach bias [48–50]. All of these studies used the approach-avoidance task. Typically during the approach-avoidance task (AAT), participants push smoking stimuli away using a joystick and pull neutral stimuli toward them (although in some studies the proportion of smoking/neutral associated with pushing or pulling may vary [49, 50]). Pulling leads to enlarged pictures while pushing reduces the picture size.

Only one study in Table 1 reported an effect of the AAT on cognition [48]. Moreover, the significant effect in this study was only among participants with no college education and plans to quit. In Machulska et al. [50] both the control and AAT training led to reductions in approach bias. Only one study assessed craving, and in this study, there was no effect of the AAT on craving [50]. In the two studies that assessed the effect of the AAT on smoking reduction, one reported a significant effect. Machulska et al. [50] reported an effect of the AAT on self-reported smoking at 3 months. In this study, both groups had reductions in self-reported smoking behavior after the five training sessions [50] but only smokers trained with the AAT reported reduced smoking at 3 months.

Additionally, one study in Table 1 used exercise to manipulate attentional bias [51]. In this study, the authors assessed the effect of active vs. passive exercise on attentional bias in smokers. Active exercise was conceptualized as 15 min of subjective light to moderate exercise on a Monarch cycle ergometer. The passive condition required participants to sit in a laboratory for 15 min with no access to reading material, phone, or other entertainment. The authors assessed attentional bias with an eye tracker at baseline and after the exercise intervention. Participants in the exercise condition exhibited reduced dwell time on smoking images compared to those in the passive control condition, and they were also less likely to initially fixate the smoking images.

Table 1 Studies examining the effect of interventions on automatic cognitions and smoking-related variables among smokers

Study	Study type	Number	No. of trainings	Training task	Control condition	Assessment
Attwood et al. (2008) [40]	AR	27 AR 27 attend-smoking	Single session	AR (attend-neutral)	Modified VP (attend-smoking)	VP task
Field et al. (2009) [41]	AR	24 AR 24 attend-smoking 24 control	Single session	AR (attend-neutral)	Modified VP (attend-smoking and 50/50)	VP task Stroop
McHugh et al. (2010) [42]	AR	25 AR 26 control	Single session	AR (attend-neutral)	Modified VP (50/50)	VP task
Kerst And Waters (2014) [43]	AR	30 AR 30 control	~15 over 1 week	AR (attend-neutral)	Modified VP task (50/50)	VP task
Lopes et al. (2014) [44]	AR	22 AR 3 22 AR 1 22 control	3 trainings over 2 weeks	AR (attend-neutral)	Modified VP task (50/50)	VP task
Robinson (2015) [45]	AR	31 AR 33 control	~30 trainings over 2 weeks	AR (attend-neutral)	Modified VP task (50/50)	VP task Stroop
Begh et al. (2015) [46••]	AR	60 AR 58 control	5 weekly trainings	AR (attend-neutral)	Modified VP task (50/50)	VP task
Elfeddali et al. (2016) [47]	AR	210 control 224 AR	6 trainings over 2 weeks	AR (attend-neutral)	Modified VP task (50/50)	VP task AAT Manikin Task
Macy et al. (2014) [48]	AAT	AAT 154 Control 130	Single session	AAT	Side-to-side control task[a]	Smoking IAT
Kong et al. (2015) [49]	AAT	29 AAT 31 Control	4 weekly sessions	AAT[b]	Sham AAT (50% avoidance/50% approach smoking and neutral stimuli)	AAT (same as sham)
Machulska et al. (2016) [50]	AAT	73 AAT 66 control	4 consecutive sessions	AAT	Sham AAT	AAT (same as sham)
Van Rensburg et al. (2009) [51]	Exercise	20 (crossover)	1 session	15-min moderate exercise	Passive sitting	Eye movement assessment of attentional bias
Meng et al. (2014) [52•]	tDCS	30	1 session	tDCS 1. Cathodal over both sides of FPT 2. Cathodal over right FPT	Sham stimulation	Eye movement task of AB

Study	Treatment status	Effect on cognition	Effect on craving	Effect on smoking	Generalization
Attwood et al. (2008) [40]	Not treatment Seeking	AR decreased bias in attend neutral group and increased bias in attend smoking group	AR increased cued-craving for males for attend smoking group	No effect on smoking topography	Not assessed
Field et al. (2009) [41]	Not treatment seeking	AB reduced in AR group after training session	No effect on QSU-brief or urge to smoke scale	No effect on motivation to smoke within 30 min or smoking diary	No effect on new pictures or smoking Stroop
McHugh et al. (2010) [42]	Not treatment seeking	No effect of AR on bias	No effect on QSU-brief	Not assessed	Not assessed
Kerst And Waters (2014) [43]	Not treatment seeking	AR reduced bias over time	AR reduced craving following smoking cues	No effect of AR on smoking diary or CO	Not assessed
Lopes et al. (2014) [44]	Smoking cessation program	AR reduced bias 24 h. and 1 month after training (AR 3 vs. Control)	No effect on single item measure of craving	No effect of AR on smoking diary or CO	Effect on new pictures and avoid 3 group negative bias at 6 months
Robinson (2015) [45]	Not treatment seeking	Averaged across sessions/days, AB lower in AR group	No effect on cued craving, non-cued craving, or QSU-brief	AR reduced cigarettes smoked on PDA over time. No effect	Generalized to new pictures, no effect on self-reported bias/ads or Stroop

Table 1 (continued)

Study	Treatment status	Effect on cognition	Effect on craving	Effect on smoking	Generalization
				on CO or cotinine, or smoking diary	
Begh et al. (2015) [46••]	Nicotine patch and behavioral treatment	No effect of AR on AB	No effect of AR on mood and Physical Symptom-Scale Craving	No effect of AR on CO or time to lapse	Not assessed
Elfeddali et al. (2016) [47]	Treatment seeking	No effect of AR on AB	Craving used as covariate only	Effect on self-reported abstinence at 6 months in heavy smokers	No effect on approach-avoidance Manikin Task
Macy et al. (2014) [48]	Not treatment seeking	IAT more negative in AAT group among those with no college education and plans to quit	Not assessed	AAT group with more education who viewed anti-smoking PSA spent more time reading quit materials	Not assessed
Kong et al. (2015) [49]	Cognitive behavioral therapy	No effect of AAT on approach bias	Not assessed	Trend toward higher biochemically confirmed abstinence rates for AAT compared to control at 4-week follow-up	Not assessed
Machulska et al. (2016) [50]	Psychoeducation and motivational interviewing	Both training versions led to a reduced approach bias for nicotine cues	No effect of AAT on craving	Reduced self-report smoking behavior for both groups post-test Effect of AAT-on self-reported smoking at 3-month follow-up	Not assessed
Van Rensburg et al. (2009) [51]	Not treatment seeking	Fewer fixations on smoking stimuli during exercise condition	Lower post-treatment desire to smoke during exercise condition	Not assessed	Not assessed
Meng et al. (2014) [52•]	Not treatment seeking	No effect of tDCS on attentional bias	Not assessed	Reduced self-report cigarette for bilateral cathodal only	Not assessed

AB attentional bias, *AAT* approach-avoidance task, *AR* attentional retraining, *CO* carbon monoxide, *QSU* Questionnaire for Smoking Urges, *PSA* public service announcement, *VP* visual probe, *tDCS* transcranial direct current stimulation

[a] Participants moved pictures of cigarettes with mouse

[b] AAT task consisted of 90% avoidance/10% approach for smoking stimuli and 10% avoidance/90% approach for neutral. AR 3 = three sessions of AR, AR 1 = one session of AR and two sessions of placebo (all neutral pictures), AR 0 = two placebo session and one session of standard VP

Another study examined the effect of transcranial direct current stimulation (tDCS) on attentional bias and self-reported smoking [52•]. In this study, the following three conditions were contrasted: (1) bilateral cathodal over both sides of FPT; (2) cathodal over right FPT; and (3) sham-tDCS. Attentional bias was assessed with an eye movement measure before and after tDCS. The authors reported no effect of tDCS on the eye movement task. The authors also found that bilateral cathodal over both sides of FPT reduced daily cigarette consumption.

Interventions Targeting Executive Functions

Behavioral Interventions

One study examined the effect of exercise on cognitive function [59••]. This study compared the effect of a 15-min exercise session to passive sitting on cognitive function assessed by the Stroop Color-Word interference task. The exercise session consisted of 15 min of brisk walking on a treadmill. The passive condition required participants to sit in a laboratory for a 15 min with no access to reading material, phone, or other entertainment. The Stroop Color-Word interference task and craving were assessed at baseline, immediately post-treatment, 5 min post-treatment, 10 min post-treatment, and 15 min post-treatment. The authors reported that there was no main effect of exercise on the Stroop task. However, those assigned to exercise had lower urges and desire to smoke after exercise than those assigned to the passive condition.

Pharmacological Interventions

Six of the articles included pharmacotherapy as the intervention [53–58]. In four of the studies, varenicline, a nicotinic acetylcholine receptor (nAChR) partial agonist, was used [53–55, 58]. Two studies used cholinesterase inhibitors, galantamine, and donepezil, respectively [56, 57]. Cholinesterase inhibitors are used to treat Alzheimer's disease and other neuropsychiatric disorders associated with cognitive decline [64]. One study used bupropion which is a weak inhibitor of dopamine and norepinephrine reuptake inhibitor with cognitive-enhancing actions [65]. Both varenicline and bupropion are approved as pharmacological treatments for TUD. The studies examined the effect of pharmacotherapy on a wide range of cognitive abilities including sustained attention, inhibitory control, and prospective memory.

All of the pharmacotherapy articles reported a significant effect on some aspect of cognitive function (see Table 2). Four of the studies in Table 2 assessed the effect of the pharmacotherapy on craving [53–55, 58]. Varenicline significantly reduced craving in all three studies that examined this relationship. Galantamine also significantly reduced craving in the one study that assessed this relationship. Three of the four studies that assessed the effect of pharmacotherapy on smoking behavior reported a significant effect [53, 55, 57, 58].

Transcranial Direct Current Stimulation

Two studies examined the effect of tDCS on executive processes [60, 61]. Xu and colleagues administered tDCS over the dorsolateral prefrontal cortex during one session. They found no effect of tDCS on an attention task or craving. Fecteau and colleagues administered tDCS over the dorsolateral prefrontal cortex during five sessions. They reported that tDCS improved performance on one of two decision-making tasks and reduced craving.

Discussion

Automatic Cognitive Processes

The results of studies summarized in Table 1 indicate that among interventions that target automatic cognitive processes, AR appears to be the most studied approach for targeting automatic cognitions in individuals with TUD. Although there is consistent evidence that AR reduces bias, there is still more research needed to determine if AR can affect smoking behavior. As described in Table 1, studies varied in methodology including the number of training sessions, participant engagement in other treatments, and the number of trials. Despite these differences, there appears to be consistent evidence that AR can reduce bias to smoking cues. This finding is consistent with meta-analyses that indicate that AR can reduce attentional bias across a range of psychopathologies [74]. There is little evidence supporting the potential of AR to impact clinically meaningful targets such as craving and smoking behavior [46••]. However, as noted in the table, few of these studies have investigated AR among treatment-seeking smokers. Therefore, additional research is needed to determine how AR affects smokers wishing to quit. Future research could also examine whether the effect of AR on study outcomes is moderated by baseline variables such as stage of change or readiness to quit.

Overall, there is limited research on the effect of the AAT. Although the findings in Table 1 suggest that there is little evidence for the AAT reducing approach bias or craving, it is too early to draw conclusions. It is possible that nonsignificant findings are due to small sample sizes. This review found some evidence that the AAT reduces smoking behavior, but the mechanism of this relationship is unclear. Given that the alcohol literature has demonstrated that the AAT can reduce relapse rates [32, 66], future study is warranted. Also, in the alcohol literature, there is evidence that reduction in approach bias mediates the effect of the intervention on relapse [66]. This finding suggests that the AAT may be a promising tool in the addictions.

Table 2 Studies examining the effect of interventions on controlled cognitions and smoking-related variables among smokers

Study	Study type	Number	Length of treatment	Treatment	Control	Cognitive assessments
Patterson et al. (2009) [53]	Pharmacotherapy	67 (crossover)	21 days	Varenicline	Placebo	Letter-N-back task, the Penn Continuous Performance Task (CPT), Conditional Exclusion Test (CET)
Ashare and McKee (2012) [54]	Pharmacotherapy	19 placebo 21 bupropion 18 varenicline	1 week	Varenicline[a] Bupropion[b]	Placebo	CPT, Digit Span, Delay Discounting
Rhodes et al. (2012) [55•]	Pharmacotherapy	31 varenicline 26 placebo	4 weeks pre-quit 1 week during quit	Varenicline[c]	Placebo	Stop Signal Task
Sofuoglu et al. (2012) [56]	Pharmacotherapy	12 (crossover)	4 days	Daily galantamine (GAL) 8 mg	Placebo	Go/No-Go task
Ashare et al. (2012) [57]	Pharmacotherapy	12 donepezil 6 placebo	4 weeks	Daily donepezil 5 mg	Placebo	Letter-N-back task Continuous Performance Task
Austin et al. (2014) [58]	Pharmacotherapy	80	1 session	Varenicline smoking condition 1 mg Varenicline abstinent condition 1 mg	Placebo smoking condition Placebo abstinent condition	Rapid Visual Information Processing (RVIP), Stop Signal, Prospective Memory (PM), and Cambridge Gambling
Van Rensburg and Taylor (2008) [59••]	Exercise	23 (crossover)	1 session	15-min moderate exercise	Passive sitting	Stroop Color-Word interference task
Xu et al. (2013) [60]	tDCS	24 (crossover)	1 session	tDCS over the DLPFC	Sham stimulation	Attention Task
Fecteau et al. (2014) [61]	tDCS	12 (crossover)	5 sessions	tDCS over the DLPFC	Sham stimulation	Decision-making tasks: Ultimatum Game and Risk Task

Study	Treatment seeking/other treatment	Effect on cognition	Effect on craving	Effect on smoking
Patterson et al. (2009) [53]	Treatment seeking (practice quit attempt)	Varenicline improved performance on the Letter-N-back task and the CPT task	Varenicline reduced craving	Varenicline increased days of biochemically verified abstinence
Ashare and McKee (2012) [54]	Not treatment seeking	Varenicline improved reaction time but reduced accuracy on CPT compared to placebo Bupropion enhanced working memory in females and negatively impacted delay discounting performance in females	Varenicline reduced craving compared to placebo	Not assessed
Rhodes et al. (2012) [55•]	Treatment seeking (but analysis of pre-quit period)	Varenicline improved lapses in attention	Not assessed	Trend toward lower smoking rate among Varenicline group
Sofuoglu et al. (2012) [56]	Not treatment seeking	GAL improved performance on Go/No-Go task	GAL reduced craving	Not assessed
Ashare et al. (2012) [57]	Not treatment seeking	Donepezil improved performance on Letter-N-back task No significant effect on CPT	Not assessed	Placebo group had greater reduction in self-reported smoking
Austin et al. (2014) [58]	Not treatment seeking	Varenicline improved performance on Stop Signal and Cambridge Gambling compared to placebo Varenicline improved speed of responding on PM task No effect of Varenicline on RVIP	Varenicline reduced craving	No effect of Varenicline on smoking inhalation behavior

Table 2 (continued)

Study	Treatment seeking/other treatment	Effect on cognition	Effect on craving	Effect on smoking
Van Rensburg and Taylor (2008) [59••]	Not treatment seeking—5 h of abstinence	No effect of exercise on Stroop-color word interface task	Lower post-treatment desire to smoke and QSU during exercise condition	Not assessed
Xu et al. (2013) [60]	Not treatment seeking	No effect of tDCS on attention task	No effect of tDCS on craving	Not assessed
Fecteau et al. (2014) [61]	Treatment seeking	Effect on Ultimatum Game No effect on Risk Task	tDCS reduced desire to smoke	tDCS reduced self-reported smoking

DLPF dorsolateral prefrontal cortex

[a] Varenicline was 5 mg daily for days 1 and 2, 0.5 mg twice daily for days 3–5, and 1.0 mg twice daily on days 6 and 7

[b] Bupropion was 150 mg daily for days 1–3, 300 mg daily on days 4–7

[c] Varenicline one 0.5-mg tablet daily for 3 days, followed by one 0.5-mg tablet twice daily for 4 days, then two 0.5-mg tablets twice daily; 0.5-mg pills were used during week 4 to maintain blinding

tCDS and exercise are also potential interventions that target automatic cognitive processes. The exercise and tDCS studies highlight novel and understudied areas for manipulating attentional bias to reduce smoking. Future studies should examine these interventions in smokers attempting to quit. Moreover, a mediation analysis should be conducted to determine if a change in automatic cognition mediates the relationship between the intervention and reduced smoking.

Controlled Cognitive Processes

The studies in Table 2 indicate that there are several medications that can improve cognitive function and potentially reduce craving and smoking. These include varenicline and bupropion, which have been approved as pharmacological aids for smoking cessation. In addition, two cholinesterase inhibitors, galantamine and donepezil, have improved cognitive function in smokers. However, many of these studies included multiple cognitive tasks and reported nonsignificant effects on some tasks. For example, Patterson et al. [53] reported a significant effect of varenicline on the Letter N-back task and Continuous Performance Task but the not the Conditional Exclusion Test. Additionally, it is difficult to interpret the results summarized in Table 2 because each cognitive task has multiple outcomes. For example, Rhodes et al. (2012) observed an effect of varenicline on sustained attention as assessed by the Stop Signal task. However, there was no effect on inhibitory control also measured by the Stop Signal task. Consistent with previous literature, varenicline reduced craving in all of the studies [67]. The effect of varenicline on smoking was inconsistent. This finding may be explained by the fact that some of the studies included nontreatment-seeking smokers and only provided varenicline for one session (e.g., [58]). There is also some evidence that galantamine can reduce craving [56].

Among other interventions, acute exercise did not change cognitive performance but reduced craving. Regarding tDCS, one study reported improved performance on a game task.

Future Directions

As discussed in our review, dual-process theories make a distinction between automatic/implicit processes and controlled/explicit processes [27]. The automatic cognitive process is rapid and parallel whereas the controlled cognitive process is slow and serial [28]. Most research to date focuses on targeting automatic or controlled cognitive processes; however, there is empirical and theoretical support for targeting both processes [27]. Dual-process theories indicate that automatic and controlled cognitive processes interact to promote drug use [68]. Specifically, dual-process models indicate that when controlled cognitions are intact, automatic cognitions do not predict smoking; however, when controlled cognitions are compromised, automatic

cognitions are not inhibited by controlled cognitions and therefore predict drug use (e.g., Stacy and Wiers 2010).

Empirically, there is evidence that controlled cognitive processes (e.g., executive function) moderate automatic cognitions [69–71]. For instance, in a study of adolescents, working memory capacity moderated the relationship between implicit drug-related word associations and cigarette smoking and alcohol use [71]. In this study, participants with smaller working memory capabilities exhibited stronger drug-related associations that predicted drug use while the same was not true for individuals with larger working memory capacities.

Evidence also suggests that working memory influences automatic cognitions directly. Researchers have manipulated controlled cognitive processes as an independent variable and observed the effect on automatic cognitions [72]. For example, in one study, the authors varied the difficulty of a working memory task. As the level of difficulty of the task increased, accuracy in detecting smoking words decreased, suggesting that working memory capacity may be required for the effective control of attentional bias. The interrelationship between automatic and controlled cognitive processes could also be examined by the manipulation of automatic cognitive processes as an independent variable and observing the effect on executive function. However, to the author's knowledge, this type of study has not been investigated.

Overall, these studies suggest that interventions that address both automatic and controlled cognitive processes may have promise. Furthermore, interventions could be customized to the needs of the individuals. Individuals with intact controlled cognitive processes but strong automatic biases to smoking stimuli could be offered AR. Alternatively, an individual with impaired controlled cognitive processes and strong automatic biases toward smoking cues could be offered AR plus cognitive enhancement intervention (behavioral or pharmacological). As mentioned before, smokers with mental illnesses have deficits in executive cognitive functions and may potentially benefit from combination treatment interventions targeting both processes. This personalized or tailored treatment approach remains to be tested in future controlled studies.

Lastly, lack of uniformity for the cognitive tasks that have been used across studies makes it difficult to compare the results of studies included in our review. In addition, the length of treatment and duration of smoking abstinence also varied across these studies. Employment of a uniform cognitive assessment battery that will assess cognitive functions that are sensitive to smoking abstinence and medication would help the field to move forward [73].

Compliance with Ethics Guidelines

Conflict of Interest Dr. Cendrine D. Robinson, Dr. Andrew J. Waters, Dr. Nicole Kang, and Dr. Mehmet Sofuoglu declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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