Impulsive and Reflective Processes in Chronic Tobacco Dependence

Empirical Research on Assessment and Modification

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GENERAL ABSTRACT

Tobacco smoking remains a major public health concern, with substantial economic costs. Although evidence-based treatments are available, relapse rates remain high. Dual-process models explain the development and maintenance of tobacco dependence by an imbalance between strong impulsive processes (e.g., appetitive responses toward smoking-related stimuli, such as involuntary approach tendencies) and weak reflective processes (e.g., deficits in inhibitory control). From a neurobiological perspective, the Incentive-Sensitization Theory (IST) posits that appetitive responses are driven by the incentive sensitization of the mesocorticolimbic reward circuit (including, e.g., amygdala, striatum), which attributes incentive-motivational value to drug-related cues. Computerized training interventions targeting these processes have shown promise in reducing alcohol relapse rates and unhealthy eating behaviors. However, evidence on assessing and modifying these processes in tobacco dependence is limited and inconsistent, possibly due to methodological shortcomings, such as small sample sizes and poor measurement reliability. This dissertation aimed to address previous limitations and methodological shortcomings to advance the field by pursuing two objectives.

The **first objective** was to test key assumptions of dual-process models and the IST in chronic tobacco dependence within two cross-sectional studies. **Study I** assessed responses toward smoking-related stimuli in a large sample of chronically smoking individuals ($N = 362$) employing a multi-method approach, including self-report, cognitive-behavioral (reaction time tasks), psychophysiological (facial electromyography), and neural (functional magnetic resonance imaging) measures. **Study II** compared a smoking sample ($N = 122$) to healthy controls ($N = 69$), investigating general and smoking-specific inhibitory deficits using Go/No-Go Tasks. Results suggest that chronic tobacco dependence is associated with both deficits in reflective processes (i.e., inhibitory control) *and* strong impulsive processes toward smoking-

related stimuli. However, contrary to the assumptions of the IST, these impulsive processes appeared to reflect automatized, habitual action patterns rather than appetitive responses (e.g., approach tendencies) driven by the incentive-motivational value of these stimuli. Nevertheless, incentive-driven appetitive responses appeared to emerge when individuals experience heightened craving.

The **second objective** was to examine the efficacy and working mechanisms of training interventions targeting dysfunctional impulsive and reflective processes in two randomized-controlled trials. **Study III** investigated the effects of Approach Bias Modification (ApBM) as an add-on to regular smoking cessation treatment (TAU) on neural reactivity toward smoking-related versus neutral stimuli (smoking cue-reactivity). Contrary to findings in alcohol research, TAU+ApBM did not significantly reduce smoking cue-reactivity in reward-related brain regions compared to control conditions. **Study IV** evaluated the efficacy and working mechanisms of general and smoking-specific Go/No-Go Task-based inhibitory control training as a stand-alone intervention for smoking reduction. Results suggest that Go/No-Go training may yield short-term reductions in tobacco dependence and craving, though its long-term efficacy and underlying mechanisms remain uncertain.

In sum, this dissertation provides novel insights into impulsive and reflective processes in chronic tobacco dependence and their targeted modification. The findings challenge the IST assumption that chronic smoking is primarily driven by incentive-motivated appetitive responses toward smoking-related stimuli, instead highlighting the significant role of automatized, habitual action patterns. This has important implications for training interventions, suggesting that disrupting habit-driven impulsive processes may be a promising target. The results also underscore the role of inhibitory deficits and provide empirical support for Go/No-Go Task-based inhibitory control training. Key directions for future research include a more detailed investigation of habitual response patterns toward smoking-related stimuli, the

use of ecologically valid methods to capture the dynamic nature of impulsive processes in real-life settings, and further research on the efficacy and underlying mechanisms of inhibitory control training in smoking cessation.

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CHAPTER I:

GENERAL INTRODUCTION

"The tobacco epidemic is one of the biggest public health threats the world has ever faced, killing more than 8 million people a year around the world."

(World Health Organization [WHO], 2023, p. 1)

Tobacco smoking is a leading risk factor for preventable diseases, premature deaths, and substantial economic costs (Reitsma et al., 2021). In 2025, its global 12-month prevalence among individuals aged 15 and older was estimated at approximately 15% (WHO, 2021). Consequently, tobacco smoking and other forms of tobacco consumption are considered an epidemic and one of the greatest public health threats in history (WHO, 2021, 2023).

Given its severe negative consequences, tobacco smoking, like other substance use disorders (SUDs), is characterized by a striking paradox (Stacy & Wiers, 2010): *Why do individuals continue smoking despite knowing its harms and being motivated to quit?* Although evidence-based treatments (e.g., behavioral therapy) are available, relapse rates remain high (Mottillo et al., 2009; Rigotti et al., 2022). This underscores the urgent need for improved intervention strategies, leading to an important second question: *How can we improve the current treatment of tobacco smoking?* The present dissertation aims to address these questions by advancing the understanding of dysfunctional processes that are thought to underlie the development and maintenance of tobacco smoking, and by contributing to the development of more effective treatment approaches.

1.1. Impulsive and Reflective Processes in Smoking

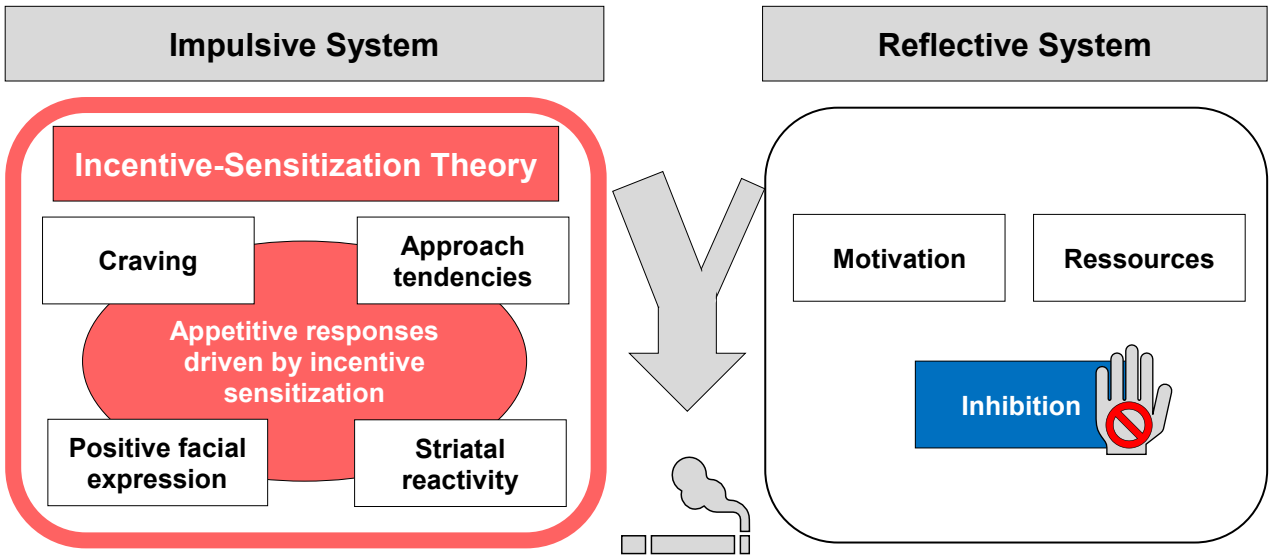
Why do individuals continue smoking despite knowing its harms and being motivated to quit?

One influential framework for understanding the paradox of tobacco smoking is provided by dual-process models of SUDs (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007; for a critical discussion, see Keren & Schul, 2009; Melnikoff & Bargh, 2018). These models propose that problematic drug use arises from an imbalance between two interacting

systems: a dominant impulsive system, driving automatic (impulsive) responses toward drug-related cues, and a weaker reflective system, which supports more deliberate, goal-directed behavior. For example, individuals who smoke may automatically reach for a cigarette (impulsive process), even after having decided to quit smoking (reflective process)—showing how automatic impulses can override conscious intentions (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007). See Figure 1 for an illustration of the dual-process model framework.

Figure 1

Impulsive and Reflective Processes in Tobacco Dependence: Dual-Process Models and the IST



Note. The illustration is based on publications of dual-process models of substance use disorders (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007) and the Incentive-Sensitization Theory (Robinson & Berridge, 1993, 2025). Incentive sensitization mediates the attribution of incentive salience to smoking-related stimuli. Incentive salience refers to a motivational process in which such stimuli acquire incentive-motivational value. This can be reflected in the conscious experience of craving, but also in unconscious and involuntary appetitive responses toward drug-related stimuli (drug-"wanting"), such as approach tendencies, positive facial expressions, and neural reactivity in the striatum as part of the mesocorticolimbic reward circuit (Robinson & Berridge, 2025).

The impulsive and reflective systems are assumed to function in fundamentally different ways. The impulsive system is thought to operate fast, guiding behavior through learned associations (e.g., smoking while having a coffee). In contrast, the reflective system operates more slowly and requires more mental resources. It draws on inhibitory control and explicit knowledge, enabling individuals to align their behavior with long-term goals (e.g., quitting smoking for health reasons). According to dual-process models, chronic drug use further impairs reflective processes, particularly inhibitory control, allowing impulsive processes to increasingly dominate behavior (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007). Consistent with this view, various models on SUDs similarly emphasize the central role of inhibitory deficits in the development and maintenance of problematic drug use (e.g., Feil et al., 2010; Goldstein & Volkow, 2002; Robinson & Berridge, 2003).

Complementing the dual-process perspective, the Incentive-Sensitization Theory (IST; Robinson & Berridge, 1993, 2025) provides further neurobiological insights into how impulsive processes may develop and are maintained (see Figure 1). Specifically, the IST suggests that repeated drug use leads to persistent sensitization (i.e., hypersensitivity) of the mesocorticolimbic reward circuit (involving, e.g., striatum, amygdala). This neuroadaptation is thought to enhance dopamine release and attribute incentive salience to drug-related cues. Incentive salience refers to a motivational process through which drug-related cues acquire incentive-motivational value. This makes them “wanted”, which can be reflected in the conscious experience of craving, as well as in unconscious and involuntary appetitive responses toward drug-related cues (drug-“wanting”), such as automatic attentional engagement, involuntary approach tendencies, neural reactivity in the striatum, and positive facial expressions (Robinson & Berridge, 1993, 2025).

Based on the integrated framework combining dual-process models (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007) and the IST (Robinson & Berridge, 1993,

2025) in the context of tobacco smoking, the following assumptions can be derived: Within the domain of *impulsive processes*, it is assumed that individuals who smoke exhibit appetitive responses toward smoking-related cues *(Assumption I)*. These responses are expected to vary systematically with smoking-related characteristics: higher tobacco dependence severity and higher levels of craving are expected to be associated with stronger appetitive responses toward smoking-related cues *(Assumptions IIa and IIb)*. Finally, appetitive responses are presumed to be driven by a shared underlying mechanism—incentive sensitization *(Assumption III)*. With regard to *reflective processes*, it is assumed that individuals who smoke exhibit deficits in inhibitory control *(Assumption IV)*. These deficits are expected to be more pronounced in individuals with higher tobacco dependence severity and higher levels of craving *(Assumptions Va and Vb)*.

1.1.1 Task Paradigms and Assessments

Various experimental paradigms have been developed to assess impulsive and reflective processes in SUDs. According to the taxonomy proposed by R. W. Wiers (2018)[1], these paradigms can be categorized based on whether they include drug-related stimuli. Paradigms involving drug-related stimuli are regarded as assessments of impulsive processes (e.g., involuntary approach tendencies), whereas tasks using neutral, non-drug-related stimuli are considered to assess reflective processes (e.g., deficits in inhibitory control; R. W. Wiers, 2018). It is important to acknowledge that disentangling impulsive from reflective processes remains challenging. For instance, involuntary approach tendencies toward smoking-related stimuli may reflect strong impulsive-associative responses, deficient inhibitory control, or a combination of both (Stacy & Wiers, 2010). For the sake of conceptual clarity and consistency, this dissertation follows R. W. Wiers' taxonomy.

[1] R. W. Wiers (2018) classified training procedures that target dysfunctional impulsive and reflective processes based on their inclusion of drug-related stimuli (see page 10). In this dissertation, R.W. Wiers' classification was adapted to refer to task paradigms as well.

In addition to stimulus content, task paradigms can also be classified according to their level of measurement. These include cognitive-behavioral assessments (e.g., reaction times [RTs], error rates), psychophysiological assessments (e.g., facial electromyography [EMG]), and neural assessments (e.g., functional magnetic resonance imaging [fMRI]). Given that impulsive processes are thought to operate outside conscious awareness and control (at least to some extent), the task paradigms aim to assess them implicitly. Accordingly, cognitive-behavioral tasks typically require individuals to respond as quickly as possible to stimuli (Stacy & Wiers, 2010), while psychophysiological and neural assessments capture responses regulated by the autonomic nervous system (Carter & Tiffany, 1999). Most outcome measures of task paradigms are calculated as difference scores, comparing responses toward drug-related stimuli with responses in a control condition (e.g., toward neutral stimuli). Thus, difference scores reflect the extent of altered processing in response to drug-related stimuli. Including a healthy control group allows for between-group comparisons, such as identifying potential deficits in inhibitory control in smoking compared to non-smoking individuals.

1.1.2 Empirical Findings of Previous Studies

Numerous studies have examined the theoretical assumptions of dual-process models and the IST in smoking. When reviewing the literature, substantial inconsistencies emerge. On the one hand, there is evidence supporting the notion that individuals who smoke exhibit appetitive responses toward smoking-related stimuli *(Assumption I)*. Specifically, empirical research has demonstrated reaction time-based cognitive (i.e., strong smoking-approach associations) and behavioral (i.e., faster pulling than pushing smoking-related stimuli) approach biases (e.g., De Houwer et al., 2006; Machulska et al., 2015; C. E. Wiers et al., 2013), as well as exacerbated behavioral responsivity toward smoking-related stimuli (i.e., preparedness to respond; e.g., Li et al., 2021; Tsegaye et al., 2021). Further, psychophysiological studies utilizing EMG showed that smoking-related stimuli elicit facial muscle responses reflecting their appetitive-

motivational value (e.g., via increased activity of the zygomaticus ["smiling"] muscle; Drobes & Tiffany, 1997; Geier et al., 2000). Lastly, fMRI studies demonstrated increased reactivity toward smoking-related versus neutral stimuli in reward-related brain regions (e.g., striatum [David et al., 2005] and anterior cingulate cortex [ACC; Allenby et al., 2020]).

However, despite these supporting results, null findings are common across all levels of measurement (see the review articles on cognitive-behavioral measures: Kakoschke et al., 2019; psychophysiological measures: Boecker & Pauli, 2019; neural measures: Jasinska et al., 2014). Similarly, evidence for deficits in inhibitory control among individuals who smoke *(Assumption IV)* is inconsistent and varies depending on the task and the specific component of inhibitory control assessed (Smith et al., 2014).

In examining appetitive responses and deficits in inhibitory control, many studies have also explored their association with smoking-related variables, such as tobacco dependence severity and craving *(Assumptions II and V)*. Again, the same pattern of results emerged: some studies report significant associations, but findings remain inconclusive (cognitive-behavioral measures: see C. E. Wiers et al., 2013; Wittekind et al., 2023; Woud et al., 2016; psychophysiological measures: Boecker & Pauli, 2019; neural measures: Jasinska et al., 2014; X. Lin et al., 2020). Finally, a few studies have explored the interrelations among appetitive response measures to explore a potential shared underlying mechanism *(Assumption III)*. However, this research is confined to cognitive-behavioral assessments (i.e., attentional, behavioral, and associative approach biases), which have yielded mixed results (see Mogg et al., 2003; Mogg et al., 2005; Wittekind et al., 2023; Woud et al., 2016). Potential associations with psychophysiological and neural measures remain unexplored.

1.1.3 Limitations and Research Gaps of Previous Studies

To advance our understanding of tobacco dependence, it is crucial to explore the reasons behind inconsistent findings and to identify limitations in the existing literature. The following sections outline key issues that merit further investigation:

First, inconsistencies may arise from small sample sizes in many earlier studies, increasing the risk of both false positive (Type I errors) and false negative results (Type II errors; Button et al., 2013). This issue is evident across all levels of measurement (studies with $N < 30$: cognitive-behavioral measures: e.g., Kräplin et al., 2019; C. E. Wiers et al., 2013; and see Table 2 in Smith et al., 2014; psychophysiological measures: e.g., Dempsey et al., 2007; Lechner et al., 2014; Mucha et al., 2008; neural measures: see supplementary Table S1 in X. Lin et al., 2020). Of note, small sample sizes are not only an issue in primary research, but can also bias meta-analytical findings (L. Lin, 2018). Thus, larger, well-powered studies are needed to systematically test the key assumptions of dual-process models and the IST.

Second, the assumptions of dual-process models and the IST may not generalize to all individuals who smoke. For instance, it remains unclear whether the assumptions apply to specific subgroups, such as individuals with chronic smoking behavior. In fact, the role of incentive salience processes toward drug-related stimuli across different stages of SUDs remains a topic of debate (Vanderschuren, Louk J. M. J. & Pierce, 2010). Further, the extent of inhibitory deficits may vary depending on how individuals balance speed and accuracy in cognitive tasks (speed-accuracy trade-off; Smith et al., 2014; Wright et al., 2014). Task performance has been shown to differ based on age- and sex-related response strategies (Bianco et al., 2020; Fortenbaugh et al., 2015), as well as compensatory factors like cognitive ability (Milioni et al., 2017). These individual differences have largely been neglected; they were often not included as control variables, nor have their potential moderating effects been systematically investigated.

Third, most studies used a single-method approach (e.g., cognitive-behavioral measures). However, to capture the complexity of appetitive responses, multi-method approaches are recommended (see Research Domain Criteria [RDoC]; Insel et al., 2010). By doing so, multiple units of analysis can be integrated to provide a more comprehensive and valid understanding of the association between appetitive responses and smoking behavior (Morris et al., 2015). Moreover, a multi-method approach is crucial for testing the IST's assumption of a shared underlying mechanism—incentive sensitization (Robinson & Berridge, 2025).

Finally, inconsistent findings may arise from the use of unreliable measures characterized by high measurement error, which can either generate spurious findings or obscure true effects (Loken & Gelman, 2017; Parsons et al., 2019). If no association between measures is found, it remains unclear whether this reflects a true absence of an association or whether the association is merely obscured by high measurement error and low reliability. Poor measurement reliability thus limits the robustness of statistical inferences and impedes valid conclusions (Hedge et al., 2018; Parsons et al., 2019). Despite the central importance of this issue, reporting reliability estimates for experimental task measures has only recently become more common practice in the current research field. Evidence suggests that appetitive response measures have often been affected by low reliability (e.g., Bach et al., 2022; Kahveci et al., 2024). This is especially the case when difference scores were used, as they are particularly vulnerable to reliability issues (Hedge et al., 2018). Future research on impulsive and reflective processes in SUDs should optimize assessment procedures to improve the reliability of measures (e.g., by optimizing data preprocessing; Kahveci et al., 2024) or, at a minimum, report reliability estimates to support cautious interpretation of findings (Hedge et al., 2018; Parsons et al., 2019).

Taken together, previous research shows key methodological limitations that may explain the inconsistent findings on impulsive and reflective processes in smoking. These include small sample sizes, insufficient consideration of individual differences, and uncertainty about the

reliability of measures. Moreover, multi-method approaches are scarce. This emphasizes the need for well-powered, multi-method studies with reliable measures to systematically test the assumptions of dual-process models and the IST in the context of smoking.

1.2. Training Procedures Targeting Impulsive and Reflective Processes

How can we improve the current treatment of tobacco smoking?

Over the past two decades, cognitive task paradigms, initially designed to assess impulsive and reflective processes in SUDs, have been adapted into computerized training procedures. These training procedures aim to help individuals overcome SUDs by modifying dysfunctional impulsive and reflective processes (R. W. Wiers et al., 2013). According to the taxonomy proposed by R. W. Wiers (2018), the different procedures can be broadly classified based on whether they involve (re-)training a specific response toward appetitive[2] stimuli. The first category includes Cognitive Bias Modification (CBM; Koster et al., 2009) approaches, which seek to re-train dysfunctional impulsive-motivational processes (e.g., approach biases) toward appetitive stimuli. The second category comprises training procedures designed to enhance general cognitive functions (e.g., inhibitory control, working memory), typically involving neutral or non-appetitive stimuli.

One of the most widely studied CBM approaches is Approach Bias Modification (ApBM). It aims to re-train approach biases toward appetitive stimuli by requiring individuals to consistently avoid them: that is, pushing them away with a joystick, which causes them to shrink (Boffo et al., 2019; Kakoschke et al., 2017). Another widely studied training procedure is Inhibitory Control Training (ICT), which can be implemented either as a CBM tool (i.e., training inhibitory response toward appetitive stimuli) or as a general version targeting general cognitive functions (i.e., training inhibitory responses toward neutral or non-appetitive stimuli).

[2] The broader terms *appetitive stimuli* rather than *drug-related stimuli*, and *problematic consumption behavior* instead of *drug use* are used because Chapter 1.2 also refers to literature from the eating domain. Moreover, it should be noted that the training procedures are applied across a range of mental health conditions (e.g., depression, anxiety) and are not limited to SUDs (Vrijsen et al., 2024).

ICT typically involves training individuals to respond on frequent Go trials (prepotent response) and to withhold responses toward appetitive stimuli (stimulus-specific ICT as a CBM tool) or neutral/non-appetitive stimuli (general ICT) on infrequent No-Go trials (Iannazzo et al., 2025; Jones et al., 2016).

1.2.1 Efficacy of Approach Bias Modification and Inhibitory Control Training

Initial ApBM and stimulus-specific ICT studies were conducted in laboratory settings with heavy-drinking students (i.e., proof-of-principle studies). These studies demonstrated that appetitive responses toward alcohol-related stimuli can be experimentally modified. Moreover, changes were found to be associated with subsequent drinking behavior (ApBM: e.g., R. W. Wiers et al., 2010; ICT: e.g., Houben et al., 2011). These promising findings spurred research into their efficacy in clinical samples (Vrijsen et al., 2024).

Approach Bias Modification (ApBM)

In the context of alcohol use disorder (AUD), ApBM has been shown to significantly reduce both early (Manning et al., 2021; Manning et al., 2016) and long-term relapse rates (Eberl et al., 2013; Rinck et al., 2018; Salemink et al., 2022; R. W. Wiers et al., 2011) when added to standard clinical treatment (i.e., detoxification or abstinence-oriented multidisciplinary programs). As a result, ApBM has been incorporated into clinical guidelines for AUD treatment in Germany (Kiefer et al., 2021) and Australia (Haber, 2021). In contrast, evidence for ApBM in smoking remains mixed. Some studies reported reductions in daily cigarette consumption (Machulska et al., 2016; Wittekind et al., 2015) and higher abstinence rates at the 3-month follow-up (Smits et al., 2022). However, other trials failed to demonstrate significantly improved clinical outcomes compared to Sham training, either in terms of cigarette consumption or abstinence rates (Kong et al., 2015; Wittekind et al., 2019). Summarized, alcohol ApBM has shown promise and is already established as a treatment for AUD, whereas its efficacy in smoking remains debatable (Wittekind et al., 2025).

Inhibitory Control Training (ICT)

Meta-analytical findings suggest that stimulus-specific ICT procedures are efficacious in reducing problematic consumption behaviors such as unhealthy eating (Allom et al., 2016; Iannazzo et al., 2025; Jones et al., 2016). However, their efficacy in reducing cigarette consumption has so far been investigated in only three clinical trials (Iannazzo et al., 2025), with the available evidence offering only limited empirical support (Adams et al., 2017; Bos et al., 2019; Machulska et al., 2022).

Another question concerns whether stimulus-specific ICT outperforms general ICT. Since the former aims to improve inhibitory responses toward appetitive stimuli, it has been argued that its effects may better generalize to real-world situations (e.g., resisting a cigarette; R. W. Wiers, 2018). Indeed, meta-analytical findings suggest that only stimulus-specific ICT, but not general ICT, significantly reduces problematic consumption behavior. However, the limited number of included studies on general ICT constrains the ability to draw firm conclusions (Allom et al., 2016; Iannazzo et al., 2025).

1.2.2 Working Mechanisms of Approach Bias Modification and Inhibitory Control Training

A fundamental question of ICT and ApBM (or CBM more broadly) concerns their underlying working mechanisms (Ehring et al., 2022; Sheeran et al., 2017). Clarifying these mechanisms can help refine training procedures and tailor them to individual needs. In the context of SUDs, research into their precise working mechanisms is still in its infancy (Jones & Field, 2020; Vrijsen et al., 2024).

Approach Bias Modification (ApBM)

As previously described, ApBM aims to directly modify approach biases toward appetitive stimuli. Reductions in these biases are expected to mediate the positive effects on clinical outcomes (Boffo et al., 2019; Grafton et al., 2017). Evidence supporting approach bias changes as the working mechanism of ApBM remains limited. Specifically, there is no clear

dose-response relationship between bias change and clinical outcome, and evidence for the association between ApBM and bias change is scarce (Vrijsen et al., 2024). However, according to established criteria, all these conditions must be met for a process to be identified as a working mechanism (Kazdin, 2007).

Importantly, in the context of alcohol ApBM, research into its working mechanisms has extended beyond behavioral assessments to include neural processes. This line of research is based on the idea that directly targeting behavioral approach biases through ApBM may reduce drug-cue-induced incentive salience processes and neural reactivity in mesocorticolimbic regions (i.e., incentive sensitization; Robinson & Berridge, 2025; C. E. Wiers et al., 2015). Using fMRI, C. E. Wiers et al. (2015) found evidence supporting this idea: ApBM, compared to Sham training, reduced neural reactivity toward alcohol-related versus neutral stimuli in reward-related brain regions (e.g., amygdala) in abstinent inpatients with AUD. Moreover, these reductions were associated with decreased craving. This suggests that ApBM may reduce neural reactivity toward appetitive stimuli in regions involved in craving and motivational salience of cues (C. E. Wiers et al., 2015).

Inhibitory Control Training (ICT)

General and stimulus-specific ICT is based on partly distinct rationales (see Jones & Field, 2020, for an overview). The former aims to strengthen general inhibitory control, assuming that task-specific training effects transfer to other tasks measuring similar components of inhibitory control. While task-specific training effects have been observed, transfer effects were often lacking (e.g., Enge et al., 2014; Owen et al., 2010); a pattern also observed in studies on general ICT to reduce problematic alcohol consumption (Bartsch et al., 2016; Jones et al., 2018). These findings cast doubt on the ability of general ICT to improve general inhibitory control (Jones & Field, 2020).

In contrast, the rationale of stimulus-specific ICT relies on associative learning processes between appetitive stimuli and the performance of inhibition. Thus, in addition to potentially improving general inhibitory control (as for general ICT), two further mechanisms have been proposed (Jones & Field, 2020): first, the formation of automatic stimulus-stop associations through repeated pairing of inhibition with appetitive stimuli (automatic-inhibition hypothesis; Verbruggen & Logan, 2008); and second, reduced positive valence (devaluation) of appetitive cues via repeated inhibition of approach behavior toward appetitive stimuli (see Behavior Stimulus Interaction [BSI] theory; Veling et al., 2008). Although the mechanisms of stimulus-specific ICT are still under investigation (Jones & Field, 2020), current evidence provides preliminary support for the mechanism involving stimulus devaluation (Iannazzo et al., 2025)[3]. Of note, this conclusion is largely drawn from studies in the food and alcohol domains. None of the past three clinical trials on smoking-specific ICT has found evidence supporting any of the presumed working mechanisms (see Adams et al., 2017; Hughes et al., 2021; Machulska et al., 2022).

1.2.3 Limitations and Research Gaps of Previous Studies

Both ApBM and ICT show promise in reducing problematic consumption behavior. However, in the context of smoking, research regarding their efficacy and working mechanisms remains scarce and faces methodological limitations. The following outlines key shortcomings and important research gaps:

First, most ApBM and ICT research has targeted problematic alcohol and food consumption (Iannazzo et al., 2025; Kakoschke et al., 2017). For instance, Iannazzo et al.'s (2025) recent meta-analysis on ICT included only four studies on smoking, compared to 39 on

[3] Notably, the meta-analysis by Iannazzo et al. (2025) also reported significant improvements in inhibitory control task performance following ICT. However, most included studies used assessment tasks identical to the training procedure, limiting conclusions about generalization effects. Consequently, it remains unclear whether the observed improvements reflect enhanced general inhibitory control or merely task-specific training effects (Iannazzo et al., 2025).

food and 22 on alcohol. Given that nicotine engages different neurotransmitter systems than other substances (e.g., alcohol; Volkow et al., 2019), smoking behavior should rely on at least partially distinct mechanisms. Thus, simply generalizing findings from other domains to smoking is problematic and underscores the need for dedicated research in the context of tobacco dependence.

Second, previous smoking-specific ICT studies show notable methodological limitations. So far, only one study examined the effects of high-demand ICT (characterized by higher proportions of Go relative to No-Go trials, e.g., 75:25; see Adams et al., 2017). All other studies used lower-demand procedures (i.e., 50:50, see Bos et al., 2019; Hughes et al., 2021; Machulska et al., 2022). This distinction is crucial, as high-demand ICT has demonstrated positive effects on abstinence in the context of AUD, whereas lower-demand ICT has not (Stein et al., 2023; see also Wessel, 2018 for similar evidence). Further, all previous efficacy trials on smoking-specific ICT employed active control conditions, referring either to general ICT (i.e., involving neutral stimuli; see Bos et al., 2019; Hughes et al., 2021) or to ICT in which inhibition was performed in response to both smoking-related and neutral stimuli (see Adams et al., 2017; Machulska et al., 2022). As these ICT versions may also affect smoking behavior by improving general inhibitory control (Jones & Field, 2020), all previous studies compared two potential efficacious interventions. Thus, future research should include a "real" Sham condition, not aimed at improving inhibitory control, to isolate the specific effects of smoking-specific (and general) ICT.

Third, the working mechanisms underlying ApBM and ICT remain largely unclear (Jones & Field, 2020; Vrijsen et al., 2024). Research on alcohol ApBM has advanced by demonstrating its effects on neural reactivity toward alcohol-related versus neutral stimuli in reward-related brain regions; thereby highlighting these neural changes as a potential treatment target of ApBM (C. E. Wiers et al., 2015). Comparable investigations in smoking are currently lacking.

Regarding ICT, its potential working mechanisms remain to be investigated using study designs that include a high-demand training procedure and a non-ICT-based control condition.

Fourth, measurement reliability is a critical issue, not only in basic research but also when investigating working mechanisms. High measurement error can obscure true individual changes in target processes following ApBM and ICT (MacLeod et al., 2009; Vrijsen et al., 2024). As requested for basic research, intervention studies should optimize their analysis procedures to enhance the reliability of working mechanism measures (e.g., by optimizing data preprocessing; Kahveci et al., 2024). At a minimum, reliability estimates should be reported to evaluate whether findings on working mechanisms are robust or whether further replications with more reliable measures are needed (Hedge et al., 2018; Parsons et al., 2019).

Taken together, the limited research on ApBM and ICT in the context of smoking, combined with key methodological limitations, reveals important gaps in the field. Further research is needed to explore the potential neural mechanisms of smoking ApBM, to conduct well-designed ICT trials (i.e., by employing a high-demand ICT and including a non-ICT-based Sham condition), and finally, to consider measurement reliability when interpreting findings.

1.3. The Present Dissertation

1.3.1 General Aims and Methodology

Impulsive and reflective processes are thought to play a crucial role in the development and maintenance of SUDs (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007). Targeting these processes in training interventions has shown promise in reducing problematic consumption behavior (R. W. Wiers et al., 2013). However, in the context of smoking, research on the assessment and modification of impulsive and reflective processes remains inconsistent and is marked by important methodological gaps. This dissertation aims to address some of the aforementioned gaps and contribute to a better understanding of the observed inconsistencies,

whereby the focus is placed on adults with chronic[4], moderate-to-heavy tobacco dependence—a subgroup at particularly high risk for severe health consequences (Murray, 2014).

Across this dissertation project, appetitive responses toward smoking-related stimuli were assessed using a multi-method approach involving a range of experimental task paradigms. Table 1 provides an overview of the paradigms employed, specifying their respective level of measurement (cognitive-behavioral, psychophysiological, neural), the constructs and measures assessed (e.g., behavioral approach tendencies via RTs between conditions), and whether they are conceptualized as assessing impulsive or reflective processes based on the taxonomy by R. W. Wiers (2018).

Besides appetitive responses, inhibitory control as a reflective process was assessed using different cognitive-behavioral tasks. Notably, inhibitory control is a multifaceted construct with different tasks capturing distinct components (Bari & Robbins, 2013), such as action cancellation, action restraint (Schachar et al., 2007; Verbruggen & Logan, 2008), and interference inhibition (Scarpina & Tagini, 2017). For a detailed overview, see Table 1.

[4] Smoking for at least one year was an explicit inclusion criterion in Study I, but not in Study II. However, descriptive statistics revealed that all participants included in Study II had a smoking history of at least one year.

Table 1

Overview of Task Paradigms Utilized within this Dissertation Project

Task paradigm	Constructs and measures	Process
Cognitive-behavioral		
Stroop Color-Word Task (Stroop, 1935)	Higher error rates in incongruent (ink color–word meaning conflict) versus control trials indicate greater deficits in *interference inhibition* as a specific component of *inhibitory control* (Scarpina & Tagini, 2017).	Reflective
Stop-Signal Task (SST; Logan, 1994)	Reaction times (RTs) in Go and No-Go trials to calculate the stop-signal reaction time, a measure of *action cancellation* as a specific component of *inhibitory control* (Schachar et al., 2007; Verbruggen & Logan, 2008).	Reflective
General Go/No-Go Task (GNGT; Drewe, 1975; Luria, 1973)	Higher error rates in No-Go trials (commission error rate) indicate greater deficits in *action restraint* as a specific component of *inhibitory control* (Schachar et al., 2007; Verbruggen & Logan, 2008).	Reflective
Smoking-specific GNGT (Luijten et al., 2011)	Higher commission error rates and faster mean RTs in Go trials toward smoking-related versus neutral stimuli indicate *exacerbated responsivity* (Detandt et al., 2017).	Impulsive
Approach-Avoidance Task (AAT; Rinck & Becker, 2007)	Faster executions of $pull_{smoking}$ versus $push_{smoking}$ trials indicate stronger *behavioral approach tendencies* toward smoking-related stimuli (Kakoschke et al., 2019).	Impulsive
Implicit-Association Test (IAT; single-target: Wigboldus et al., 2004; dual-target: De Houwer et al., 2006; Greenwald et al., 1998)	Faster responses in congruent (smoking–approach/positive) versus incongruent trials (smoking–avoidance/negative) indicate stronger *associative (cognitive) biases* linking smoking with approach/positive valence (Kakoschke et al., 2019).	Impulsive
Psychophysiological		
Electromyography (EMG) during a passive picture viewing task (involving smoking-related and neutral stimuli; Geier et al., 2000)	Muscle activity of the corrugator supercilii (above the eyebrow, "angry muscle"; reflecting *negative valence*), zygomaticus major (cheek, "smiling muscle"; reflecting *positive valence*), and orbicularis oculi (below the eye) during startle probes (startle attenuation reflects *positive valence*; Lang et al., 1993).	Impulsive
Neural		
Functional magnetic resonance imaging (fMRI) during a passive picture viewing task (smoking-related versus neutral stimuli, termed as smoking cue-reactivity paradigm; Ekhtiari et al., 2022)	Blood-oxygen-level-dependent (BOLD) signal during blocks of smoking-related versus neutral stimuli. Depending on the brain region, higher activity during smoking-related versus neutral blocks reflects increased reward-related processing (e.g., anterior cingulate cortex [ACC], striatum; X. Lin et al., 2020) or the preparation of automatized, habitual motor responses (e.g., precuneus; Yalachkov et al., 2010).	Impulsive

Note. The column "Constructs and Measures" provides task paradigm details not essential to follow the general discussion.

Two cognitive-behavioral task paradigms are particularly relevant to this dissertation, as adapted versions were used as training procedures in efficacy trials: the Approach-Avoidance Task (AAT; Rinck & Becker, 2007) served as the basis for ApBM training, and the Go/No-Go Task (GNGT; Drewe, 1975; Luria, 1973) for ICT[5]. Both tasks are detailed below:

Approach-Avoidance Task (AAT)

The joystick-based AAT assesses behavioral approach tendencies toward drug-related stimuli. It is based on the assumption that individuals approach appetitive stimuli more quickly than non-appetitive ones (Loijen et al., 2020). During the task, individuals are presented with drug-related and control stimuli (e.g., neutral) and instructed to respond as quickly and accurately as possible to either a content-irrelevant feature (e.g., the color of a surrounding frame) or a content-relevant feature (e.g., the stimulus content category). Responses are executed by pushing the joystick away (avoid) or pulling it toward themselves (approach), with a zooming effect creating the impression of approaching (picture enlarges) or avoiding (picture shrinks; Kakoschke et al., 2019). The most commonly calculated outcome measure is the difference in RTs between trials that require pushing versus pulling drug-related stimuli ($push_{smoking}$ minus $pull_{smoking}$; Kahveci et al., 2024).

Go/No-Go Task (GNGT)

The GNGT evaluates inhibitory control by assessing the ability to withhold responses when a No-Go signal is presented (i.e., action restraint; Schachar et al., 2007; Verbruggen & Logan, 2008). During the task, individuals are presented with stimuli (e.g., digits, pictures) and required to respond as quickly and accurately as possible by pressing a button for Go stimuli (e.g., all digits except 3 and 6, yellow framed pictures), while withholding responses toward No-Go stimuli (e.g., the digits 3 and 6, blue framed pictures). The primary outcome measure is

[5] ICT can also be implemented using other tasks, such as the Stop-Signal Task (SST; Logan, 1994; see Table 1). However, GNGT-based ICT has been examined more frequently, and meta-analytic findings support its efficacy in reducing problematic consumption behavior, whereas such evidence is lacking for SST-based ICT (Iannazzo et al., 2025; Jones et al., 2016).

the commission error rate, which reflects failures to inhibit responses toward No-Go stimuli. Mean RTs in Go trials are also of interest, as they reflect individuals' readiness or preparedness to respond to the presented stimuli (Smith et al., 2014; Wright et al., 2014).

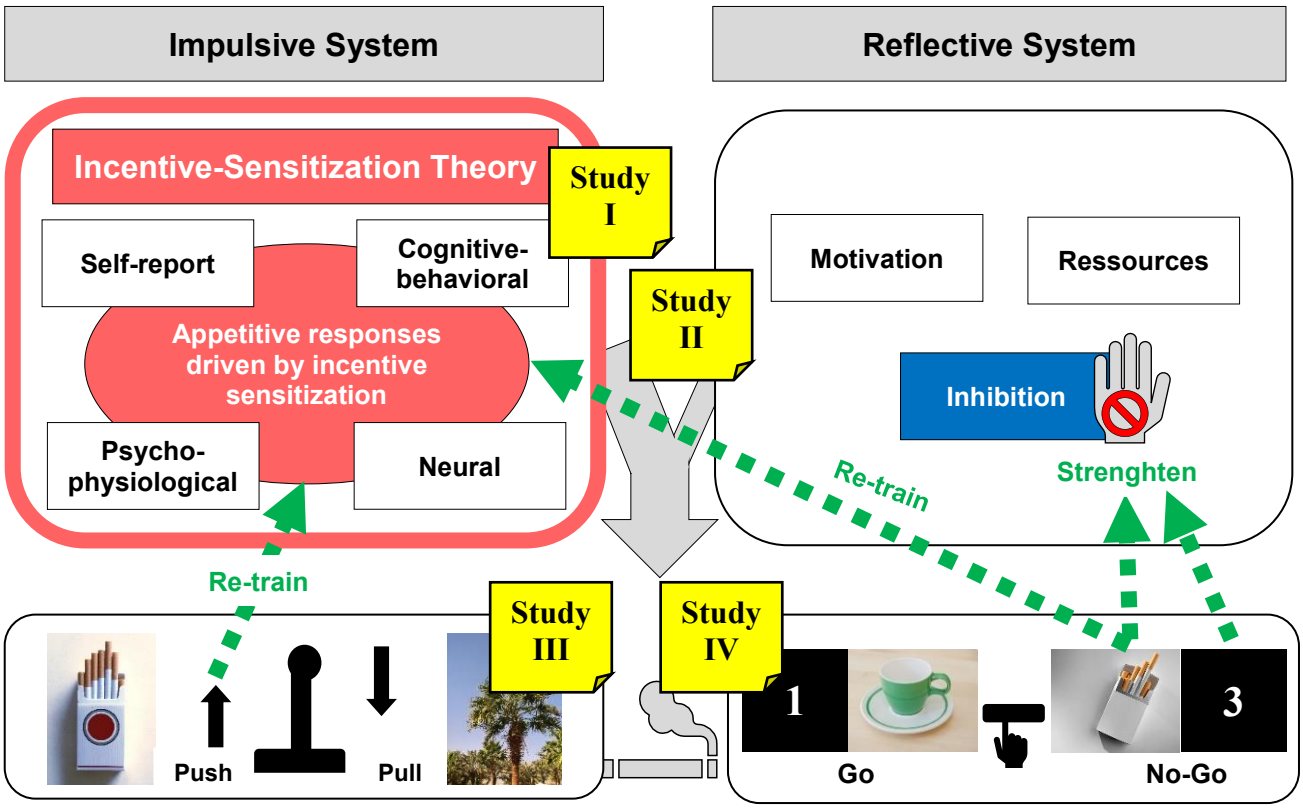
Two versions of the GNGT were employed within this dissertation project: a general and a smoking-specific version. The general version assessed inhibitory control toward digits, while the smoking-specific version differentiated commission error rates and mean RTs in Go trials toward neutral and smoking-related stimuli (Luijten et al., 2011). Although inhibitory control is considered a reflective process, inhibitory control deficits specifically toward drug-related stimuli, along with faster RTs in smoking-related Go trials, suggest exacerbated responsivity and can be interpreted as approach behavior (Detandt et al., 2017).

1.3.2 Study-Specific Aims and Methodology

Within the present dissertation project, four empirical studies were conducted: two cross-sectional investigations into impulsive and reflective processes related to chronic tobacco dependence (Studies I and II), and two randomized-controlled trials (RCTs) to evaluate the efficacy and working mechanisms of ApBM and ICT (Studies III and IV). Figure 2 provides an overview of the present dissertation project within the integrated theoretical framework of dual-process models (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007) and the IST (Robinson & Berridge, 1993, 2025). Each study is represented by a yellow pictogram, with its position indicating the type of study (basic or interventional) and its theoretical focus (impulsive or reflective system). For basic research (Studies I and II), positioning reflects the relative emphasis placed on hypotheses concerning the impulsive versus reflective system. For interventional research (Studies III and IV), positioning illustrates whether the training intervention primarily targeted impulsive or reflective processes, as further indicated by the green arrows. Of note, Study I used baseline data from Study III, and Study II from Study IV, resulting in overlapping samples of participants involved in smoking intervention studies.

Figure 2

Overview of the Current Dissertation Project



Note. The illustration is based on publications of dual-process models of substance use disorders (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007) and the Incentive-Sensitization Theory (Robinson & Berridge, 1993, 2025). Incentive sensitization mediates the attribution of incentive salience to smoking-related stimuli. Incentive salience refers to a motivational process in which such stimuli acquire incentive-motivational value. This can be reflected in the conscious experience of craving (as measured by self-report), but also in unconscious appetitive responses toward drug-related stimuli (drug-"wanting"), which may be evident at cognitive-behavioral, psychophysiological, and neural levels of assessment (Robinson & Berridge, 2025). Each study is represented by a yellow pictogram, with its position indicating the type of study (basic or interventional) and its theoretical focus (impulsive or reflective system). For basic research (Studies I and II), positioning reflects the relative emphasis placed on hypotheses concerning the impulsive versus the reflective system. For interventional research (Studies III and IV), positioning illustrates whether the training intervention primarily targeted impulsive or reflective processes, as further indicated by the green arrows.

The overall goal of the cross-sectional studies was to better understand *why individuals continue smoking despite knowing its harms and being motivated to quit.* Specifically, **Study I** aimed to test key assumptions derived from the integrated framework of dual-process models and the IST regarding appetitive responses toward smoking-related stimuli in a large sample of individuals with chronic tobacco dependence (N = 362). To this end, the study assessed responses toward smoking-related stimuli versus responses in control conditions (e.g., toward neutral stimuli) by employing a multi-method approach, including cognitive-behavioral (e.g., AAT), psychophysiological (facial EMG), and neural (fMRI) assessments. Additionally, interference inhibition was assessed as a measure of inhibitory control (via the Stroop task). Four hypotheses were tested: (1) individuals who smoke exhibit appetitive responses toward smoking-related stimuli, (2) higher scores on smoking-related variables (e.g., tobacco dependence severity, craving) are associated with stronger appetitive responses and lower inhibitory control (i.e., interference inhibition), and (3) appetitive responses are interrelated, reflecting a shared underlying mechanism—incentive sensitization.

Study II aimed to investigate general and smoking-specific inhibitory deficits in individuals who smoke (N = 122) compared to healthy controls (N = 69), using both a general and a smoking-specific GNGT. To address limitations in previous research, individual differences in inhibitory control related to age, sex, and intelligence were taken into account. Based on dual-process models, three hypotheses were tested: (1) the smoking sample exhibit greater inhibitory deficits reflected in higher commission error rates, which (2) remain robust when controlling for age, sex, and intelligence, and (3) among individuals who smoke, higher scores in smoking-related variables (e.g., tobacco dependence severity, craving) are associated with greater inhibitory deficits. Following the assumptions of the IST, it was further expected that individuals who smoke, compared to non-smoking controls, show greater deficits and faster mean RTs in Go trials toward smoking-related versus neutral stimuli (exacerbated

responsivity), and that the exacerbated responsivity would be more pronounced among individuals with higher scores in smoking-related variables. Additionally, potential moderating effects of age, sex, and intelligence on the association between smoking-related variables and GNGT performance were explored.

The overall goal of the RCTs was to advance research on *how the current treatment of tobacco smoking can be improved.* Specifically, **Study III** was the first to examine the effects of ApBM on neural reactivity toward smoking-related versus neutral stimuli (smoking cue-reactivity) as a potential working mechanism. Participants (N = 117) received a smoke-free course including a quit attempt (treatment-as-usual; TAU) and were then randomized to ApBM (TAU+ApBM), Sham training (TAU+Sham), or no additional training (TAU-only). Building on evidence that alcohol ApBM reduced cue-reactivity in reward-related brain regions (e.g., amygdala; C. E. Wiers et al., 2015), it was hypothesized that, compared to control conditions, ApBM would reduce smoking cue-reactivity in regions associated with reward processing. This reduction was expected to predict higher short- and long-term abstinence probability, and to be associated with reduced post-intervention craving and approach biases toward smoking-related stimuli.

Study IV aimed to investigate the efficacy and working mechanisms of high-demand (Go:No-Go trial ratio: 75:25) general and smoking-specific ICT based on the GNGT (GNG training), including a "real" non-ICT-based Sham condition. GNG training was delivered as a stand-alone intervention, with participants (N = 122) randomized to smoking-specific GNG training, general GNG training, Sham training (i.e., a categorization task), or a waitlist control condition. It was hypothesized that GNG training (smoking-specific and general), compared to control conditions, would lead to significantly greater reductions in smoking-related variables (including cigarettes per day [primary outcome], tobacco dependence severity, craving) post-intervention and at the 3-month follow-up. Further, smoking-specific GNG training was

expected to outperform general GNG training. Moreover, the study explored the three proposed working mechanisms of ICT: improved general inhibitory control, the formation of automatic stimulus-stop associations, and stimulus devaluation.

Importantly, across Studies I to IV, the reliability of all study measures was rigorously assessed and is transparently reported. In the general discussion of this dissertation, conclusions based on findings from measures with limited reliability are explicitly marked as tentative and should be interpreted with caution.

CHAPTER II:

CUMULATIVE PUBLICATIONS

STUDY I

Appetitive responses toward smoking-related stimuli in tobacco dependence: A multi-methodological investigation

This chapter is a pre-peer-review, pre-copyedit version of an article submitted for publication in *Addiction*.

Motka, F., Haoye, T., Levine, S. M., Vollstädt-Klein, S., Danböck, S. K., Bertsch, K., Winkler, M. H., & Wittekind, C. E. (under review). Appetitive responses toward smoking-related stimuli in tobacco dependence: A multi-methodological investigation.

Appetitive responses toward smoking-related stimuli in tobacco dependence: A multi-methodological investigation

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Author Note

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ABSTRACT

Background and aims: Appetitive responses, such as approach biases, are thought to play a crucial role in smoking. This study aimed to compare responses toward smoking-related stimuli with responses in control conditions (e.g., non-approach or neutral stimuli) using a multi-method approach. By examining associations between response measures and with smoking-related variables, the study sought to extend understanding of their role in chronic smoking.

Design and setting: Cross-sectional study conducted at a university laboratory and magnetic resonance imaging (MRI) scanner in Munich, Germany.

Participants: 362 chronically smoking individuals (51.38% female; data collection: November 2019 to March 2023) with moderate-to-severe tobacco dependence.

Measurements: Responses toward smoking-related stimuli were assessed using cognitive-behavioral (reaction-time-based approach biases), psychophysiological (electromyography: corrugator supercilii, zygomaticus major, and orbicularis oculi for acoustic startle reflex), and neural (functional MRI: regions relevant to smoking cue-reactivity) measures. Smoking-related variables were cigarettes per day, tobacco dependence severity, and craving. Split-half reliabilities were estimated for all measures.

Findings: Participants exhibited a significantly attenuated acoustic startle reflex toward smoking-related versus neutral stimuli ($p < .001$, Rosenthal's $r = 0.39$), while no significant differences emerged for other psychophysiological or cognitive-behavioral measures. Neural measures showed significantly heightened reactivity toward smoking-related versus neutral stimuli in sensory and motor regions (e.g., precuneus; $p < .001$, Rosenthal's $r = 0.44$) but reduced activity in reward-related regions (e.g., striatum; $p = .021$, Cohen's $d = 0.22$). Higher craving was significantly associated with stronger appetitive responses on some measures from all assessment methods ($ps \leq .041$), whereas greater tobacco dependence and smoking behavior were linked to reduced neural reactivity toward smoking-related stimuli ($ps \leq .036$). No

significant associations emerged between measures from different methods (factor loadings ≤ .145, *p*s ≥ .076). Differences scores between conditions (rel. = -.351 to .837) were generally less reliable than their individual components (rel. = .619 to .964; excluding one exception).

Conclusions: Appetitive responses toward smoking-related stimuli may play a limited role in chronic smoking, whereas habitual motor responses could be more crucial. Appetitive responses, however, may gain relevance during periods of heightened craving. Training interventions should prioritize disrupting habitual motor responses toward smoking-related stimuli, while interventions targeting appetitive responses may be more effective for individuals experiencing strong craving.

Keywords: Addiction, Smoking, Tobacco, EMG, fMRI, Approach Bias

INTRODUCTION

Tobacco smoking is a leading risk factor for preventable diseases and premature deaths [2]. Despite a strong desire to quit, most individuals who smoke experience repeated relapses [3]. The inability to quit, even among highly motivated individuals, is a core feature of tobacco dependence. Prominent theoretical frameworks suggest that smoking is driven by impaired inhibitory control and strong appetitive responses toward smoking-related cues [4]. Neurobiologically, the Incentive-Sensitization Theory (IST; [5]) hypothesizes that repeated drug use leads to a sensitization of the mesocorticolimbic brain circuitry, increasing the incentive-motivational value of drug-related cues (incentive salience). This sensitization is thought to underlie both conscious craving and unconscious motivational processes that direct attention to drug-related cues and elicit appetitive responses, such as strong behavioral approach tendencies [6]. Furthermore, dual-process models [7,8] postulate that problematic drug use is driven by an imbalance between weakened controlled and strong impulsive processes. Continued drug use is thought to exacerbate this imbalance so that impulsive processes (e.g., appetitive responses) are increasingly hard to regulate by the more controlled processes (e.g., abstinence motivation).

Overview of previous research

Various tasks have been developed to assess drug-induced appetitive responses. Cognitive-behavioral assessments include the joystick Approach-Avoidance Task (AAT; [9]), which measures behavioral approach tendencies, and (single-target) Implicit-Association Tests (ST-IAT; [10]), which capture associative (cognitive) biases (e.g., associations between smoking and approach-avoidance or valence). Evidence for cognitive-behavioral approach biases in smoking remains inconsistent [11]. Regarding valence associations, research has frequently shown that individuals who smoke hold negative attitudes toward smoking (e.g., [12–14]). This seemingly contradictory finding can be explained by the IST, stating that the

processes of drug-*liking* and drug-*wanting* diverge as dependence increases [6]. Appetitive responses have also been assessed psychophysiologically using facial electromyography (EMG). Empirical studies have shown that individuals who smoke exhibit attenuated acoustic startle responses [15] and facial muscle activity (zygomaticus and corrugator muscles) reflecting appetitive responses toward smoking-related stimuli [16,17]. Furthermore, meta-analyses have found heightened neural reactivity in regions involved in reward processing (e.g., anterior cingulate cortex [ACC], striatum) during exposure to smoking-related stimuli (termed cue-reactivity; [18,19]). Regarding impulsive processes, reduced performance in inhibitory control tasks has been linked to smoking behavior [20,21].

Appetitive responses toward smoking-related stimuli have attracted substantial research interest; however, several limitations persist. First, most studies used a single-method approach (e.g., cognitive-behavioral measures). However, to capture the complexity of appetitive responses, a multi-method approach is recommended, incorporating multiple units of analysis to provide a more comprehensive and valid understanding of the underlying mechanisms (see Research Domain Criteria [RDoC]; [22]). Second, associations between measures of appetitive responses remain largely unexplored, yet it is crucial for testing the IST's assumption of incentive sensitization as their shared mechanism. Findings from the few studies investigating correlations between cognitive-behavioral (i.e., attentional, approach, and associative) biases have been inconsistent (see [13,23–25]). Importantly, no research has yet examined associations using a multi-method approach, including psychophysiological and neural assessments. Third, drawing robust inferences and valid conclusions from statistical findings requires reliable measures, as reliability constrains the observable association between them [26,27]. To date, the reliability of measures assessing appetitive responses in smoking has only been investigated for cognitive-behavioral measures (e.g., [13]). Meanwhile, studies examining the reliability of psychophysiological and neural measures are still lacking.

The present study

This study examined appetitive responses toward smoking-related stimuli in a large sample (N = 362) of chronically smoking individuals with moderate-to-heavy tobacco dependence. Our multi-method approach included cognitive-behavioral (AAT, ST-IATs), psychophysiological (facial EMG), and neural assessments (functional magnetic resonance imaging [fMRI]). Based on dual-process models and the IST, we hypothesized that: (1) individuals who smoke exhibit appetitive responses toward smoking-related stimuli, (2) higher scores on smoking-related variables (i.e., cigarettes per day, tobacco dependence severity, current craving) are associated with stronger appetitive responses and lower inhibitory control performance (assessed via Stroop task; [28]), and (3) appetitive responses are interrelated based on incentive sensitization as their shared mechanism. Moreover, the reliability of all measures was evaluated.

METHODS

This cross-sectional investigation used baseline data from a preregistered intervention study (German Clinical Trials Register: DRKS00019221; 11/11/2019), including the preregistration of a cross-sectional analysis (see Wittekind et al. [1] for the study protocol). The data and analysis code of the present study will be available in OSF after peer-reviewed publication: https://osf.io/74ydh/ [dataset] [29].

Participants

Between November 2019 and March 2023, 362 non-deprived individuals who smoke participated in a preregistered intervention study on the efficacy of approach bias modification as an add-on to smoking cessation treatment. Participants completed the baseline assessment and were included in the present cross-sectional analysis. Inclusion criteria were: (1) age 18–70 years, (2) Fagerström Test for Nicotine Dependence (FTND; [30]) score ≥ 3[6], (3) exhaled

[6] A FTND score of 3 or higher indicates at least moderate dependence [31].

carbon monoxide (CO) ≥ 10 ppm, and (4) smoking ≥ 10 cigarettes per day within the past 12 months. Exclusion criteria were: (1) current/previous diagnosis of severe psychiatric disorders (bipolar disorder, psychosis), and (2) moderate or severe substance use disorder (≥ 4 DSM-5 criteria met, as assessed with the Mini International Neuropsychiatric Interview [MINI; [32]]) other than tobacco within the past 12 months. Full eligibility criteria are provided in Appendix A.1. Between March 2022 and March 2023, a subsample (n = 117) participated in an optional fMRI investigation (see Appendix A.1 for fMRI-specific exclusion criteria). The study was approved by the Ludwig-Maximilians-University Munich ethics committee. All individuals provided written informed consent.

Procedures, questionnaires, and experimental paradigms

Sociodemographic and drug-related information (e.g., cigarettes per day, time since last cigarette) were collected in a baseline interview, followed by experimental tasks, questionnaires, and a psychophysiological assessment (see Appendix A.2 for details and illustration). The fMRI investigation was arranged as a separate appointment. Tobacco dependence[7] was measured using the 12-item Cigarette Dependence Scale-12 (CDS-12; [33]; Cronbach's α = .75, 95% *CI* [.72–.79]), aligning with the DSM-IV and ICD-10 criteria. Craving was assessed using the Brief Questionnaire of Smoking Urges (QSU-brief; [34]; Cronbach's α = .90, 95% *CI* [.88–.91]) on a 7-item Likert-like scale.

Experimental tasks are described in detail in Appendix A.3. Cognitive-behavioral tasks included: a joystick-based AAT [9] to assess behavioral approach tendencies by comparing RTs for pushing versus pulling smoking-related stimuli; two ST-IATs [10] to evaluate implicit associations between smoking and approach/avoidance or positive/negative valence by comparing RTs in compatible (smoking paired with approach/positive words) versus

[7] The FTND was used for screening due to its efficiency but demonstrated unacceptable reliability in this study (Cronbach's α = .43, 95% *CI* [.34–.50]). Consequently, the CDS-12 score was used as a measure for dependence severity in all analyses.

incompatible trials (smoking paired with avoidance/negative words); and a color Stroop task [28] to assess inhibitory control by comparing RTs in incompatible (ink color–word meaning conflict) versus control trials (color naming). The psychophysiological assessment included facial EMG during the presentation of smoking-related, neutral, positive, and negative pictures [17] to assess muscle activity: *corrugator supercilii* (over eyebrow; contraction reflects negative valence), *zygomaticus major* (cheek; contraction reflects positive valence), and *orbicularis oculi* (under eye) responses during acoustic startle probes (startle attenuation reflects positive valence; [35]). The neural assessment involved an fMRI cue-reactivity paradigm (presentation of smoking-related and neutral pictures; [36]) to examine brain activity in response to smoking-related versus neutral stimuli.

Statistical analysis

Data preprocessing and measure extraction

Data preprocessings are described in Appendix A.4. The study collected four cognitive-behavioral (AAT, both ST-IATs, and Stroop task; Appendix A.4.1) and three psychophysiological measures (EMG: corrugator, zygomaticus, and orbicularis oculi; Appendix A.4.2). To identify brain regions involved in smoking cue-reactivity (contrast [smoking > neutral]), we combined a hypothesis-driven region of interest (ROI) and whole-brain analysis (Appendix A.4.3). ROIs we selected based on Lin et al.'s [18] meta-analysis, including the ACC, left angular gyrus, right thalamus, and right striatum. A whole-brain analysis identified clusters surviving a voxel-wise threshold of $p < .001$ and an extent threshold of FWEc = 336 voxels ($p_{FWE} < .05$) using SPM12. A one-sample *t*-test on the first-level contrast images [smoking > neutral], including age and sex as covariates, revealed three regions: right middle cingulate and paracingulate gyri (MCC), right precuneus, and right supramarginal gyrus. In total, seven regions relevant to smoking cue-reactivity were identified.

Condensed, the study included 13 measures assessing responses toward smoking-related stimuli and one assessing inhibitory control (Stroop task; see Table 1-I). Due to the unacceptable/lower split-half reliability[8] of difference scores (e.g., responses in smoking-related minus neutral trials; see Table 1-I notes), responses in target conditions were used as outcome measures (AAT: $pull_{smoking}$; ST-IATs: reaction times in compatible trials; Stroop task: incompatible trials; EMG/fMRI: activity during smoking-related trials) while controlling for the corresponding control conditions (AAT: $push_{smoking}$; ST-IATs: reaction times in incompatible trials; Stroop task: control trials; EMG/fMRI: activity during neutral trials). Preregistered difference scores (see [1]) are reported if they differ from target condition findings. For the zygomaticus activity, the difference score reliability (= .273) exceeded that of the target condition (= .113) and was therefore retained.

[8] Estimated using the R package *splithalfr* [37] with 5,000 random splits and corrected using the Spearman-Brown formula.

Table 1-I

Descriptive statistics, results of difference tests, and reliability of measures

Measures	Target condition			Control condition			
	n	*M* (*SD*)	Median	*M* (*SD*)	Median	Statistics	Reliability [95% *CI*][b]
Cognitive-behavioral							
AAT	357	725.76 (88.66)	719.00	720.54 (82.70)	713.00	$Z = 1.51$, $p = .130$	.964 [.957–.970]
Approach ST-IAT	353	888.54 (173.60)	860.80	884.95 (192.38)	846.36	$Z = 1.16$, $p = .248$	.923 [.887–.952]
Valence ST-IAT	353	866.81 (153.41)	839.71	802.98 (134.24)	778.99	$Z = 11.30$, $\mathbf{p < .001}$[a], $r = 0.60$	.905 [.883–.930]
Stroop	352	1388.80 (404.03)	1300.19	1116.01 (284.60)	1063.47	$Z = 15.30$, $\mathbf{p < .001}$[a], $r = 0.82$	.862 [.840–.890]
Psychophysiological							
EMGcor	300	0.14 (0.57)	0.06	0.12 (0.53)	0.07	$Z = 1.85$, $p = .064$	.771 [.588–.965]
EMGzyg	300	-0.005 (0.47)	-0.003	0.06 (0.58)	0.005	$Z = -1.10$, $p = .272$	.273 [-.001–.598]
EMGstartle	180	32.85 (28.96)	22.13	36.12 (30.90)	26.24	$Z = -5.16$, $\mathbf{p < .001}$[a], $r = 0.39$	.957 [.940–.970]
Neural							
ACC	113	-0.03 (0.21)	-0.04	-0.11 (0.22)	-0.14	$t(112) = 4.70$, $\mathbf{p < .001}$[a], $d = 0.44$	.619 [.507–.749]
Left angular gyrus	113	0.02 (0.21)	0.002	0.03 (0.24)	0.006	$t(112) = -0.65$, $p = .520$	.635 [.506–.768]
Right thalamus	113	0.09 (0.24)	0.09	0.14 (0.24)	0.13	$t(112) = -3.41$, $\mathbf{p < .001}$[a], $d = 0.32$	.694 [.591–.810]
Right striatum	113	0.01 (0.15)	-0.02	0.03 (0.16)	0.02	$t(112) = -2.35$, $\mathbf{p = .021}$[a], $d = 0.22$	.659 [.562–.756]
MCC	113	0.15 (0.34)	0.16	0.06 (0.36)	0.09	$Z = 4.76$, $\mathbf{p < .001}$[a], $r = 0.45$	.733 [.627–.853]
Right precuneus	113	-0.16 (0.32)	-0.14	-0.24 (0.33)	-0.20	$Z = 4.67$, $\mathbf{p < .001}$[a], $r = 0.44$	.817 [.763–.863]
Right supramarginal gyrus	113	-0.09 (0.24)	-0.08	-0.18 (0.25)	-0.18	$Z = 5.70$, $\mathbf{p < .001}$[a], $r = 0.54$	.672 [.531–.817]

Note. Split-half reliabilities apply to the target condition variable (EMGzyg: difference score). Effect sizes are reported as Cohen's *d* [38] for *t*-tests and Rosenthal's *r* [39] for Wilcoxon tests, with 0.20 to 0.50 indicating small to medium effects.

FTND = Fagerström Test for Nicotine Dependence; CDS-12 = 12-item Cigarette Dependence Scale; QSU-brief = Brief Questionnaire of Smoking Urges; AAT = Approach-Avoidance Task; ST-IAT = Single-Target Implicit-Association Test; EMGcor = Electromyography over the corrugator supercilii muscle; EMGzyg = Electromyography over the zygomaticus major muscle; EMGstartle = Electromyography over the orbicularis oculi muscle; ACC = left anterior cingulate and paracingulate gyri; MCC = right middle cingulate and paracingulate gyri; *CI* = Confidence interval.

[a] Significant after Benjamini-Hochberg correction.

[b] Reliability of difference scores: AAT: .837 [.799–.871]; approach ST-IAT: .684 [.636–.758]; valence ST-IAT: .654 [.593–.709]; Stroop task, EMG, and fMRI measures: -.351 to .345.

Data analysis strategy

Data were analyzed using R, version 4.3.0 [40]. For hypothesis 1, two-tailed paired non-parametric Wilcoxon signed-rank or parametric *t*-tests assessed response differences between target and control conditions (zygomaticus difference score: one-sample Wilcoxon signed-rank against zero). A power analysis using G*Power [41] determined that $N = 199$ participants are required to detect a small effect ($d = 0.2$) with $\alpha = .05$ and $1\text{-}\beta = .80$ in a two-tailed paired *t*-test. For hypothesis 2, linear regressions examined associations between smoking-related variables (cigarettes per day, FTND, QSU-brief) as predictors and responses in target conditions as outcomes, with age, sex, deprivation[9], and control condition responses as covariates. For hypothesis 3, confirmatory factor analyses (CFAs) tested whether target condition responses loaded onto a latent factor (incentive sensitization). The latent factor was regressed on age, sex, and deprivation, with control condition responses as covariates (see Appendix B for CFA model structure). Measures were *z*-standardized and reversed (if necessary) to ensure higher scores reflecting stronger appetitive responses. Analyses used the R package *lavaan* [43] with robust maximum likelihood estimation and full information maximum likelihood (FIML) for missing data. As fMRI data were available only for a subsample ($n = 113$), a second CFA was conducted using only cognitive-behavioral and psychophysiological measures. Additionally, non-parametric partial correlations examined associations between target condition measures, controlling for age, sex, deprivation, and control condition responses. The Benjamini-Hochberg correction [44] was applied to control the false discovery rate (FDR) at 5%, adjusting for the 14 tests performed due to the 14 outcome measures.

[9] Deprivation (i.e., time since last cigarette in min) was not included as control variable in analyses with fMRI measures because it was not assessed during the fMRI session. Additionally, deprivation was excluded from analyses involving the QSU-brief score, as craving has been shown to be associated with longer deprivation from smoking [42].

RESULTS

Sample characteristics

Participants were between 20 and 69 years old (M = 42.33 years, SD = 12.57), with 51.38% female[10]. Most were highly educated (63.97% held a German university entrance level qualification ["Abitur"]; *n* = 4 missing values[11]). On average, participants smoked 18.74 cigarettes daily (*SD* = 6.53; range: 10–60; *n* = 3 missing values) for 23.64 years (*SD* = 12.22, range: 1.5–54.5; *n* = 3 missing values) and showed moderate to high tobacco dependence severity (FTND: *M* = 5.35, *SD* = 1.60, range: 3–10, scale range: 0–10; CDS-12: *M* = 35.81, *SD* = 5.51, range: 19–48, scale range: 0–48). Craving at assessment start was low on average (QSU-brief: *M* = 16.66, *SD* = 10.88, range: 0–53, scale range: 0–70) with most participants smoking about 30 minutes prior (*M* = 32.63, *SD* = 54.97, range: 5–630[12]).

Stimulus ratings

Smoking-related stimuli used in the EMG, fMRI, and AAT assessments were rated to elicit moderate craving levels but significantly higher cravings compared to neutral stimuli (see Table 2-I). Additionally, smoking-related stimuli from the EMG assessment were rated as significantly more unpleasant and arousing than neutral stimuli.

[10] Data on race or ethnicity were not collected (see Limitations).

[11] Missing data on some variables resulted from test instructor errors during the sociodemographic interview.

[12] For participants who could not specify the time of their last cigarette on the day before the baseline assessment (*n* = 3), it was defaulted to 12:00 PM.

Table 2-I

Stimulus ratings

	Smoking-related stimuli/blocks	**Neutral stimuli/blocks**	
Ratings (scale)	*M* (*SD*)	*M* (*SD*)	Statistics
Psychophysiological			
Valence (pleasant [1] to unpleasant [9])	3.87 (1.73)	3.55 (1.51)	$Z = 3.09$, $\mathbf{p = .002}$
Arousal (relaxed [1] to aroused [9])	3.56 (1.69)	2.84 (1.47)	$Z = 7.84$, $\mathbf{p < .001}$
Craving (not at all [1] to very strongly [9])	4.60 (2.34)	2.59 (1.57)	$Z = 13.99$, $\mathbf{p < .001}$
Neural[a]			
Craving ("I want to smoke now": strongly disagree [0] to totally agree [100])	54.09 (26.14)	30.62 (20.44)	$Z = 7.84$, $\mathbf{p < .001}$

Note. Two-tailed paired Wilcoxon signed-rank tests investigated differences in ratings of smoking-related versus neutral stimuli/blocks.

[a] Smoking-related stimuli from the fMRI smoking cue-reactivity paradigm were also utilized in the cognitive-behavioral Approach-Avoidance Task (AAT).

Hypothesis 1: Appetitive responses toward smoking-related stimuli

Cognitive-behavioral measures

Participants did not exhibit significant cognitive (approach ST-IAT) and behavioral (AAT) approach biases toward smoking-related stimuli (see Table 1-I). Specifically, push and pull RTs for smoking-related stimuli in the AAT were not significantly different, nor did participants associate smoking more strongly with approach than avoidance in the ST-IAT. However, participants showed a significant negative association bias (valence ST-IAT), with faster responses when smoking and negative attributes shared a response key compared to smoking and positive attributes. As expected, participants were significantly slower in incompatible trials (ink color–word meaning conflict) compared to control trials (color naming).

Psychophysiological measures

Participants exhibited a significantly attenuated acoustic startle response (EMGstartle) during smoking-related compared to neutral trials (see Table 1-I). However, corrugator (EMGcor) and zygomaticus (EMGzyg) muscle responses did not differ significantly, indicating similar activity levels in smoking-related versus neutral trials.

Neural measures

Participants showed significantly higher brain activity during exposure to smoking-related compared to neutral stimuli in the ACC, MCC, right precuneus, and right supramarginal gyrus (see Table 1-I). Conversely, activity in the right thalamus and right striatum was significantly lower for smoking-related versus neutral stimuli. No significant difference was observed for the left angular gyrus.

Hypothesis 2: Associations between appetitive responses and inhibitory control with smoking-related variables

Cognitive-behavioral measures

Linear regression results (see Table 3-I) showed no significant associations between daily cigarette consumption, tobacco dependence severity, or craving and cognitive-behavioral measures of appetitive responses toward smoking-related stimuli (AAT, both ST-IATs) or inhibitory control performance (Stroop). This suggests that heavier smoking, greater dependence, and stronger craving were not linked to faster pull RTs for smoking-related stimuli (AAT), stronger smoking-approach or smoking-positive associations (ST-IATs), or slower responses in incompatible Stroop trials. However, stronger craving was significantly associated with stronger smoking-approach associations when using the approach ST-IAT difference score as the outcome (see Table 3-I notes).

Table 3-I

Linear regression results: Associations between appetitive responses, inhibitory control, and smoking-related variables

Measures	Cigarettes per day			Tobacco dependence (CDS-12)			Craving[b]		
	β	95% *CI*	*p*	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*
Cognitive-behavioral									
AAT	-0.396	-1.335–0.543	.408	-0.343	-1.470–0.785	.550	0.191	-0.356–0.739	.493
Approach ST-IAT	-0.827	-2.805–1.151	.412	-0.311	-2.679–2.058	.797	-0.897	-2.056–0.261	.128[c]
Valence ST-IAT	-0.671	-2.373–1.031	.439	-0.204	-2.244–1.836	.844	-0.742	-1.740–0.256	.145
Stroop	3.360	-0.566–7.285	.093	2.249	-2.448–6.946	.347	1.081	-1.185–3.346	.349
Psychophysiological									
EMGcor	-0.006	-0.014–0.003	.177	-0.004	-0.014–0.006	.480	-0.005	-0.010–0.0003	**.038**
EMGzyg	0.008	-0.005–0.022	.209	0.010	-0.005–0.026	.198	0.010	0.002–0.017	**.015**
EMGstartle	-0.021	-0.245–0.204	.857	0.030	-0.203–0.263	.798	0.059	-0.051–0.168	.293
Neural									
ACC	-0.003	-0.008–0.001	.160	0.001	-0.004–0.006	.757	0.001	0.0002–0.002	.113
Left angular gyrus	-0.004	-0.009–0.001	.085	-0.003	-0.007–0.002	.301	0.001	0.0004–0.002	.178
Right thalamus	-0.005	-0.009–-0.0003	**.036**	-0.003	-0.008–0.002	.203	0.001	0.0001–0.002	.070
Right striatum	-0.002	-0.005–0.001	.131	-0.001	-0.004–0.002	.445	0.001	0.00003–0.001	**.041**
MCC	-0.009	-0.015–-0.003	**.005**[a]	-0.009	-0.016–-0.002	**.009**	0.001	-0.001–0.002	.531
Right precuneus	-0.007	-0.012–-0.002	**.008**[a]	-0.008	-0.014–-0.002	**.006**	0.0003	-0.002–0.001	.632
Right supramarginal gyrus	-0.006	-0.011–-0.002	**.003**[a]	-0.005	-0.010–-0.0005	**.031**	0.00003	-0.001–0.001	.961

Note. Linear regressions were performed with age, sex, and deprivation (not applicable for neural measures and not included in models where craving was the main predictor) as covariates. Predictors, except for sex, were grand-mean centered.

CDS-12 = 12-item Cigarette Dependence Scale; QSU-brief = Brief Questionnaire of Smoking Urges; AAT = Approach-Avoidance Task; ST-IAT = Single-Target Implicit-Association Test; EMGcor = Electromyography over the corrugator supercilii muscle; EMGzyg = Electromyography over the zygomaticus major muscle; EMGstartle = Electromyography over the orbicularis oculi muscle; ACC = left anterior cingulate and paracingulate gyri; MCC = right middle cingulate and paracingulate gyri.

[a] Significant after Benjamini-Hochberg correction.

[b] For cognitive-behavioral and psychophysiological measures, the QSU-brief score was used as predictor. For neural measures, the mean craving rating after smoking-related blocks was used, as the QSU-brief was not administered during the fMRI session.

[c] Using the approach ST-IAT difference score, higher craving was significantly associated with a cognitive approach bias toward smoking-related stimuli (β = 0.004, 95% *CI* [0.0004–0.008], p = .030).

Psychophysiological measures

Higher craving was significantly associated with reduced corrugator (EMGcor) and increased zygomaticus activity (EMGzyg) in response to smoking-related stimuli (EMGzyg: versus neural stimuli), though both effects were non-significant after FDR-correction (see Table 3-I). This suggests that participants with stronger craving tended to exhibit lower corrugator and higher zygomaticus activity toward smoking-related stimuli. Craving was not significantly associated with the acoustic startle response (EMGstartle), indicating no relationship with the startle reflex during smoking-related trials. Additionally, no significant associations were found between facial muscle activity and daily cigarettes or dependence severity, suggesting that smoking heaviness and dependence were unrelated to zygomaticus and corrugator activity, and the acoustic startle reflex during smoking-related trials.

Neural measures

Higher daily cigarette consumption was significantly associated with reduced brain activity in the right thalamus (non-significant after FDR-correction), MCC, right precuneus, and right supramarginal gyrus in response to smoking-related stimuli (see Table 3-I). This suggests that participants with higher consumption exhibited lower activity in these regions when exposed to smoking-related stimuli compared to those with lower consumption. Similarly, greater dependence severity was significantly associated with reduced activity in the MCC, right precuneus, and right supramarginal gyrus (all non-significant after FDR-correction), indicating lower activity in these regions among participants with greater dependence. Lastly, higher craving was significantly associated with increased activity in the right striatum (non-significant after FDR-correction), indicating heightened striatal activity among participants with stronger craving. No significant associations were observed for other brain regions.

Hypothesis 3: Interrelations between measures of appetitive responses and inhibitory control

The CFAs showed that cognitive-behavioral and neural measures loaded significantly onto separate latent factors (see Table 4-I; note: AAT and ST-IAT difference scores did not load onto a shared latent factor). Importantly, no significant cross-loadings between measures from different assessment methods were observed. Moreover, model fit indices indicated misspecification, suggesting no shared latent factor across measures. Partial correlations supported the CFA results, showing no significant associations between measures from different assessment methods (with one exception; see Appendix C).

Table 4-I

Results of the confirmatory factor analyses

	CFA across cognitive-behavioral, psychophysiological, and neural measures[b]		**CFA across cognitive-behavioral and psychophysiological measures**[c,d]	
Measures	Loading (*SE*)	*p*	Loading (*SE*)	*p*
Cognitive-behavioral				
AAT	.145 (.082)	.076	.173 (.060)	**.004**[a]
Approach ST-IAT	.145 (.113)	.198	.336 (.085)	**<.001**[a]
Valence ST-IAT	.063 (.080)	.429	.277 (.067)	**<.001**[a]
Psychophysiological				
EMGcor	-.009 (.139)	.949	-.008 (.113)	.947
EMGzyg	-.069 (.156)	.660	.087 (.121)	.471
EMGstartle	-.043 (.051)	.406	.035 (.039)	.377
Neural				
ACC	-.522 (.110)	**<.001**[a]	–	–
Left angular gyrus	-.451 (.122)	**<.001**[a]	–	–
Right thalamus	-.524 (.071)	**<.001**[a]	–	–
Right striatum	-.497 (.062)	**<.001**[a]	–	–
MCC	-.350 (.087)	**<.001**[a]	–	–
Right precuneus	-.262 (.105)	**.013**[a]	–	–
Right supramarginal gyrus	-.452 (.082)	**<.001**[a]	–	–

Note. Model fit indices indicate a poor fit for both models (45; recommended cut-off criteria: comparative fit index [CFI] ≥ .95, Tucker-Lewin Index [TLI] ≥ .95, root-mean-square error of

approximation [RMSEA] ≤ .06, and standardized root-mean-square residual [SRMR] ≤ .08). CFA = Confirmatory Factor Analysis, SE = Standard Error.

[a] Significant after Benjamini-Hochberg correction.

[b] $\chi^2(347) = 1561.79$, $p < .001$; CFI = .63; TLI = .60; RMSEA = .17; SRMR = .26.

[c] $\chi^2(74) = 527.19$, $p < .001$; CFI = .80; TLI = .76; RMSEA = .14; SRMR = .18.

[d] No significant loadings were found when using the AAT and ST-IAT difference scores as outcome measures (all *p*s ≥ .084).

DISCUSSION

This study is the first to investigate appetitive responses toward smoking-related stimuli in a large sample of chronically smoking, moderate-to-heavy tobacco-dependent adults using a multi-method approach. All measures showed good to excellent reliability, except for the measure assessing zygomaticus muscle activity, for which results should be interpreted with caution [26]. Overall, findings from the experimental paradigms do not support the core assumptions of the IST regarding appetitive responses toward smoking-related stimuli in the present sample.

Summary of findings

Hypothesis 1: Appetitive responses toward smoking-related stimuli

A central tenet of the IST posits that individuals who smoke exhibit appetitive responses toward smoking-related stimuli; however, this is largely unsupported by our findings. Specifically, appetitive responses were not observed with cognitive-behavioral or psychophysiological measures, except for an attenuated acoustic startle reflex when exposed to smoking-related compared to neutral stimuli. This exceptional finding suggests that smoking cues hold positive significance for individuals who smoke—at least when assessed via the acoustic startle reflex. Regarding valence associations, our findings revealed strong negative

attitudes toward smoking, consistent with prior research (e.g., [12–14]). This aligns with the IST assumption that drug-*liking* and -*wanting* can be dissociated in individuals with chronic smoking behavior.

Consistent with meta-analytical findings [18,19], participants showed heightened brain activity in the ACC, MCC, right precuneus, and right supramarginal gyrus in response to smoking-related compared to neutral stimuli. The cingulate gyrus (encompassing the ACC and MCC), a key cortical region in smoking cue-reactivity [18], is involved in emotional processing, as well as motor coordination and control [46,47]. However, subcortical mesolimbic structures, such as the thalamus and striatum, showed reduced activity in response to smoking-related compared to neutral stimuli. This is significant, as the IST posits that incentive salience processes are mediated by heightened activity toward drug-related stimuli in subcortical mesolimbic structures [6]. The reduced activity suggests that smoking-related stimuli may not be processed as rewarding [48,49]. Instead, the observed increased activity in sensory and motor brain regions, such as the right precuneus and right supramarginal gyrus, rather reflects attentional bias and automatized, habitual motor responses toward smoking-related stimuli [50]. Summarized, our findings provide little evidence for appetitive responses but highlight the emotional salience of smoking-related stimuli and their link to heightened attentional and motor processes in chronically smoking individuals.

Hypothesis 2: Associations between appetitive responses and inhibitory control with smoking-related variables

Our findings challenge the assumption of the IST that heavier smoking and greater tobacco dependence are associated with stronger appetitive responses toward smoking-related stimuli. Instead, neural measures revealed the opposite: heavier smoking and greater dependence were associated with reduced activity in sensory and motor regions (MCC, precuneus, and supramarginal gyrus). This may indicate that individuals who smoke more

heavily and are more dependent consume cigarettes more automatically, relying less on external cues. In contrast, moderately dependent individuals might be more distracted and exhibit stronger motor responses toward smoking cues. The negative association between thalamic activity and heavier smoking (non-significant after FDR-correction) aligns with prior research linking greater dependence severity to reduced activation in subcortical mesolimbic structures (e.g., striatum, [18]; amygdala and putamen, [51]). This suggests that, with heavier smoking, mesolimbic structures may exhibit hypoactivity toward smoking cues, contrasting with the premise of the IST that ongoing drug use leads to a hyperactivation of the mesolimbic system. Consequently, heavy smoking behavior may involve less reliance on incentive-driven processing of smoking-related cues.

According to the IST, higher craving should correspond to stronger appetitive responses. Our findings partially support this (all effects non-significant after FDR-correction): higher craving was associated with stronger cognitive approach biases[13], increased zygomaticus activity (positive valence), reduced corrugator activity (reduced negative valence), and increased striatal activity (reward processing) in response to smoking-related stimuli. These findings support the notion of the IST that smoking-related stimuli hold greater incentive-motivational value for individuals experiencing higher craving. Summarized, consistent with the IST, individuals experiencing stronger craving appear to show stronger appetitive responses. However, our results suggest that individuals with heavier smoking and tobacco dependence do not exhibit stronger appetitive responses. Instead, neural findings indicate greater independence from external smoking cues in these individuals.

Regarding impulsive processes, dual-process models propose an association between lower inhibitory control and heavier smoking, tobacco dependence, and craving. However,

[13] Please note that this association emerged only when the approach ST-IAT difference score was used as the outcome measure.

Stroop task performance was not significantly associated with smoking-related variables. Nevertheless, as the Stroop task targets interference inhibition [52], future research should examine tasks addressing other facets of inhibitory control, such as action restraint (Go/No-Go Task) or action cancellation (Stop-Signal Task; [53]).

Hypothesis 3: Interrelations between measures of appetitive responses and inhibitory control

According to the IST, appetitive responses toward drug-related stimuli are driven by increased incentive sensitization as a shared mechanism. However, findings from CFAs and partial correlations do not support this. Measures from different assessment methods neither loaded significantly onto a shared latent factor (CFAs) nor correlated with each other (partial correlations; with one exception, see Appendix C). Instead, neural and cognitive-behavioral[14] measures clustered on separate latent factors or intercorrelated within the same assessment method. This may reflect shared response tendencies within methods—e.g., approach biases driving both cognitive and behavioral tendencies, or neural co-activation across regions—or shared measurement errors. Regardless, the multi-method approach suggests that appetitive responses across methods are not driven by a shared mechanism. However, this conclusion is limited by the lack of evidence for incentive salience processes in response to smoking-related stimuli in this sample.

Reliability of appetitive response measures

To our knowledge, this is the first study investigating the split-half reliability of psychophysiological and neural measures in smoking cue-reactivity paradigms. Consistent with psychometric research (e.g., [26]), difference scores showed low reliability, whereas their individual components exhibited much better reliability, aligning with findings on test-retest reliability in fMRI alcohol cue-reactivity paradigms [54]. Low reliability is critical, as it can

[14] Please note that cognitive-behavioral measures did not significantly load onto a latent factor when difference scores were used as the outcome measure.

generate spurious findings or obscure true effects [27,55]. Our results highlight the importance of assessing and reporting the reliability of measures in SUD research to validate statistical findings and improve measure reliability (e.g., through optimizing preprocessing procedures, see [56]).

Implications

Theoretical implications

Our results raise the question of whether alternative SUD models better explain our findings. Habit models [57,58], for instance, propose that incentive salience processes drive smoking in the early stages but diminish as smoking becomes habitual, with automatized motor responses toward smoking cues taking over. This may explain the lack of evidence for appetitive responses in our sample, the negative correlation between dependence severity and subcortical mesolimbic activity (i.e., thalamic regions), and heightened activity in motor regions. Notably, the negative association between dependence severity and activity in motor regions suggests reduced reliance on external cues for smoking behavior at high dependence levels. Future research should test this hypothesis and further examine habit model assumptions in smoking.

Another possibility is that the assumptions of the IST are not universally applicable to all individuals who smoke [6]. For example, reduced psychophysiological and neural cue-reactivity has been observed in those motivated to quit smoking [59–62]. As our sample came from a cessation intervention study, abstinence motivation is likely, though unmeasured. Further research should explore *when* appetitive responses toward smoking-related stimuli occur (e.g., in individuals not motivated to quit) and *which factors* influence their strength (e.g., craving levels). For this purpose, ecologically momentary assessment (EMA) studies could capture real-time fluctuations in craving, abstinence motivation, and appetitive responses in naturalistic settings.

Clinical implications

Our findings challenge the rationale behind approach-bias modification training, which aims to reduce appetitive responses toward drug-related stimuli [63]. Indeed, meta-analyses on the efficacy of cognitive bias modification, including approach-bias modification, report inconsistent and modest effects [64]. However, our results suggest that it may be worth exploring its efficacy in individuals experiencing heightened smoking desire. Furthermore, our neural findings point to strong automatized, motor responses rather than appetitive (incentive-driven) responses toward smoking-related stimuli. This highlights the potential of interventions targeting inhibitory deficits.

Limitations

Our results should be interpreted against important limitations. First, the smoking-related stimuli used in the EMG, fMRI, and AAT assessments elicited only moderate craving ratings, potentially leading to low appetitive responses. However, these stimuli were rated to have induced stronger craving than neutral ones and were selected from previous studies showing appetitive responses ([17,65,66]; see Appendix A.3 for picture selection). Moreover, appetitive responses were found even when craving ratings were moderate [67,68]. Second, the study lacked controls without a smoking history and a control condition with rewarding non-smoking stimuli (e.g., money). Thus, it remains unresolved whether findings are specific to individuals who smoke or smoking-related stimuli. Lastly, sampling bias cannot be excluded, as participants were recruited for a smoking cessation study. Additionally, data on race or ethnicity were not collected, and the sample's demographics (more females, higher education levels) differ from the broader German smoking population [69], limiting generalizability.

Conclusion

This study is the first to investigate appetitive responses in smoking using a multi-method approach. Overall, the results provide limited evidence to suggest that appetitive responses play

a significant role in chronic smoking behavior; rather, they suggest the importance of attentional and motor responses. Future research should further examine the assumptions of habit models and explore factors associated with the strength of appetitive responses (e.g., abstinence motivation, craving levels). Lastly, training interventions should focus on disrupting smoking cue-induced strong automatized (habitual) motor responses.

AUTHOR CONTRIBUTIONS

Authors	Contributions
Franziska Motka	Data curation, Formal analysis, Investigation, Project administration, Validation, Visualization, Writing (original draft)
Haoye Tan	Formal analysis (in terms of the fMRI data), Writing – review and editing
Seth M. Levine	Formal analysis (in terms of the fMRI data), Writing – review and editing
Sabine Vollstädt-Klein	Resources (providing the fMRI cue-reactivity paradigm with code), Software (adapting the code of the fMRI cue-reactivity paradigm), Writing – review and editing
Sarah K. Danböck	Writing – review and editing, Supervision
Katja Bertsch	Writing – review and editing, Resources, Supervision, Conceptualization, Funding acquisition
Markus H. Winkler	Methodology, Resources (in the sense of stimulus material), Software, Writing – review and editing
Charlotte E. Wittekind	Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review and editing

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STUDY II

Deficits in general and smoking-specific response inhibition in the Go/No-Go task in individuals who smoke: A cross-sectional analysis

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Deficits in general and smoking-specific response inhibition in the Go/No-Go task in individuals who smoke: A cross-sectional analysis

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ABSTRACT

Background and aims: Previous studies on response inhibition deficits in smoking have often been conducted in small, young, age-homogeneous samples, without controlling for covariates or testing moderating effects. The primary research question compared response inhibition between a large, age-diverse smoking sample and non-smoking controls, and examined whether deficits were exacerbated toward smoking-related stimuli. By accounting for key covariates and moderators, this study aimed to extend understanding of individual differences in response inhibition deficits in smoking.

Design and setting: Cross-sectional study conducted at a university laboratory in Munich, Germany.

Participants: The large (N = 122, 57% female), age-diverse (M_{age} = 41.4, range: 21-70 years), smoking group comprised individuals with moderate to severe tobacco dependence participating in a smoking reduction intervention study. Controls comprised N = 69 healthy individuals with no smoking history.

Measurements: Primary outcomes were Commission Error (CE) rates and mean Reaction Times in Go trials (Go-RT) in general and smoking-specific Go/No-Go Tasks (GNGTs). Covariates included age, sex, and IQ. Smoking-related variables were cigarettes per day (CPD), tobacco dependence severity, and craving.

Findings: General GNGT: The smoking group exhibited significantly higher CE rates (p < .001, medium effect, BF_{10} = 9.06) than the control group. Higher craving was associated with faster Go-RTs (β = -1.487, p = .041). Smoking-specific GNGT: CE rates were significantly higher in the smoking group only when controlling for covariates (β = 1.272, p = .040). Higher craving was associated with higher CE rates during smoking-related trials (β = 0.108, p = .010). The smoking group showed significantly faster Go-RTs in response to smoking-related compared with neutral stimuli, relative to the control group (β = -3.326, p = .027). Preliminary

evidence indicated that greater deficits were associated with higher scores in smoking-related variables, but only in older individuals.

Conclusions: Individuals who smoke appear to exhibit response inhibition deficits, although these are not uniform and seem to be exacerbated during higher reported craving or in response to smoking-related stimuli. Age may moderate the relationship between deficits and smoking-related variables.

Keywords: addiction, covariates, cross-sectional, Go/No-Go Task, moderators, response inhibition, smoking, tobacco dependence

INTRODUCTION

Dual-process models of addiction [1,2] underscore the significance of impaired executive functioning in the development and maintenance of problematic substance use. The Incentive-Sensitization Theory (IST; [3]) further suggests that these deficits are exacerbated following drug-induced neurobiological changes in the mesocorticolimbic reward system. Continued drug use results in sensitization to the incentive salience (i.e., "*wanting*") of drug-related cues, which manifests in heightened responsivity to these cues.

Response inhibition, a core executive function, is the ability to suppress prepotent behaviour in the presence of "stop" cues [4]. It has frequently been assessed using the Go/No-Go Task (GNGT; [5]), where participants respond quickly to frequent "Go" stimuli and inhibit responses to infrequent "No-Go" stimuli. Deficits in response inhibition are primarily evaluated by the rate of Commission Errors (CE), which refers to failures to inhibit responses during No-Go trials. Faster mean Reaction Times in Go trials (Go-RTs) indicate higher responsivity [4,6].

Meta-analytical results confirmed that individuals who smoke show higher CE rates in the GNGT [4]. So far, six cross-sectional studies (including [7–12]) employed the GNGT including smoking-related stimuli to test the assumptions of the IST (i.e., higher CE rates and faster Go-RTs toward smoking-related stimuli). The findings are mixed. Some studies confirmed that individuals who smoke exhibit higher CE rates [9,12][15] alongside shorter Go-RTs [12] in smoking-related compared to neutral trials. However, other studies did not observe higher CE rates [8,10][16] or only reported shorter Go-RTs [8]. Inconsistencies may result from variations in the implementation of smoking-related contexts: whereas Kräplin et al. [8] and

[15] In contrast, Detandt et al. [7] observed significantly reduced CE rates in individuals who smoke within smoking-related compared to neutral trials.

[16] Zhao and Chen [11] observed significantly higher CE rates only in trials with smoking-social compared to neutral contexts, but found no significant difference between trials with smoking-object versus neutral contexts.

Luijten et al. [10] used randomly interleaved smoking-related and neutral trials, Li et al. [9] and Tsegaye et al. [12] employed a block design.

Although several studies utilized GNGTs in smoking samples, previous research has significant limitations. First, most studies had small sample sizes, both in general GNGT studies ([4]; $n < 30$ individuals who smoke: e.g., [13,14]; but see [15]) and smoking-specific GNGT studies ($n < 30$ individuals who smoke, e.g., [7,8,10,11]), which increases the likelihood of Type-I and Type-II errors [16]. Second, most studies focused on young samples (general GNGT: see Tables 1 and 2 in [4], $M_{age} < 30$, e.g., [13,14], but see [15]; smoking-specific GNGT: $M_{age} < 30$, e.g., [7–12]), limiting the generalizability of findings to older individuals who smoke. Third, most GNGT studies did not control for important covariates, such as age, sex, or intelligence (e.g., [7–11,17]). However, these variables are known to be associated with both smoking-related variables (i.e., tobacco dependence severity, craving; [18,19][17]) and GNGT performance [20–22], and should be included as potential confounders in analyses [23]. Fourth, to our knowledge, no study has yet examined moderators on the relationship between smoking-related variables and GNGT performance. However, this is important because individuals can differ in their ability to compensate for deficits, and their strategy to balance speed and accuracy (speed-accuracy trade-off; [4,6]). Older adults and females may prioritize accuracy [24,25], whereas individuals with higher intelligence might better compensate for inhibitory deficits (e.g., [26]).

Given these limitations, the objective of the present study was to extend prior research on response inhibition deficits among individuals who smoke. Both a general and smoking-specific GNGT—the latter adapted from Luijten et al. [10] with interleaved design—were employed. The research questions were: (1) to examine group differences in GNGT performance (i.e., CE rates and Go-RTs) using *t*-tests and ANOVAs without accounting for

[17] Please note that Knott et al. [18] used the concept of gender rather than sex.

covariates to facilitate comparisons with prior GNGT studies, hypothesizing that the smoking group would show higher CE rates than the non-smoking group; (2) to assess the robustness of group differences by including age, sex, and intelligence as covariates in the regression models; and (3) to investigate associations between smoking-related variables (i.e., cigarettes per day [CPD], tobacco dependence severity, and craving) and GNGT performance in individuals who smoke, hypothesizing that higher scores in smoking-related variables would be associated with higher CE rates. Additionally, we exploratory investigated whether age, sex, and intelligence moderate the association between smoking-related variables and GNGT performance. Following the assumptions of the IST, we expected individuals who smoke to exhibit higher CE rates and faster Go-RTs toward smoking-related stimuli compared to non-smoking individuals, and within the smoking group, among those with higher scores in smoking-related variables.

METHOD

The data and analysis code are available in OSF: https://osf.io/rxu78/ [dataset] [27]. The analyses were pre-registered (see AsPredicted.org, #172127, 24/04/2024), except for the exploratory moderator analyses. For additional methodological information, see Appendix A.

Participants and design

A total of 122 non-deprived smoking adults with no substance use disorder other than moderate to severe tobacco dependence (i.e., ≥ 3 in the Fagerström Test for Nicotine Dependence [FTND; [28]]), who participated in an intervention study [29] aiming at reducing smoking behaviour completed the baseline assessment and were included in the present cross-sectional study (for more information, see Appendix A.1). After conducting an a-priori power analysis (see Appendix A.2), a total of 69 age-matched healthy individuals with no history of smoking (i.e., ≤ 10 cigarettes smoked in lifetime) or any other substance use disorder were recruited as controls. For full eligibility criteria and a critical discussion of our

inclusion/exclusion criteria, see Appendix A.1. The study was approved by the Ludwig-Maximilians-University Munich ethics committee (72_Wittekind_c). All participants provided written informed consent.

Procedure and measures

A series of interviews, questionnaires, and experimental tasks were conducted (see Appendix A.3). Basic drug-related information was collected during the initial interview (e.g., CPD or lifetime smoking). Tobacco dependency was evaluated using the 6-item FTND [28]. Craving was assessed through the Questionnaire of Smoking Urges, brief version (QSU-brief; [30]), a 10-item questionnaire on current smoking urges using a 7-item Likert-like scale. General intelligence was screened with a German vocabulary test (Wortschatztest [WST]; [31]), with raw scores converted to intelligence quotient (IQ) scores per the manual. To assess alcohol drinking behaviour, the 10-item Alcohol Use Disorder Identification Test (AUDIT; [32]) was used.

Two GNGTs were utilized: a general (stimuli: digits) and a smoking-specific (stimuli: smoking-related and neutral pictures) version. Both tasks were implemented with 320 test trials, a Go:No-Go trial ratio of 75:25, and a response window/stimulus presentation time of 1,000 ms (see Appendix A.3.1 for a detailed task description).

Statistical analysis

Data pre-processing, aggregation, and reliability

As pre-registered, CE rates (in %) and mean Go-RTs were calculated as primary outcomes. Because no participant reached an OE rate above 35%, all GNGT data were included in the analysis. Split-half reliabilities for CE rates and Go-RTs were estimated at $r \geq .609$ (see Appendix A.4.1 for details). Missing data were limited to QSU-brief scores relevant to research question 3 (3 missing values of 122 [~ 2.46%]). No imputation was performed for the main

analysis. The results remained consistent in a sensitivity analysis conducted after data imputation (see Appendix A.4.1).

Strategy of data analysis

Data were analysed using R, version 4.3.0 (R Core Team, 2023). As GNGT data violated conventional test and model assumptions (e.g., influential data points such as outliers and high leverage points, see Appendix A.4.2), robust statistical methods were employed following recommendations by Field and Wilcox [33]. These methods are less sensitive to influential data points and other data issues that could bias model parameter estimates. For more details on the analysis strategy (e.g., R packages, data trimming procedure), see Appendix A.4.2.

For research question 1, robust two-sample *t*-tests (general GNGT) and mixed-effects ANOVAs (smoking-specific GNGT) on trimmed means were performed to examine group differences in GNGT performance measures. Additionally, Bayes factors (BF_{10}) were calculated to complement the inference statistics by quantifying the relative evidence for both the null (e.g., no group effect) and the alternative (e.g., presence of a group effect) hypotheses [34]. For research question 2, robust multiple linear regressions were conducted to examine whether group (smoking/non-smoking) was associated with general GNGT performance while controlling for age, sex, and IQ (covariates). The smoking-specific GNGT data was analysed using robust linear mixed-effects models, with stimulus type (smoking-related/neutral) and stimulus type × group as additional predictors. For research question 3, the performance of the smoking group in the general GNGT was examined by conducting three robust multiple linear regressions with either CPD, the FTND, or QSU-brief score (smoking-related variables) as main predictor. Each model included age, sex, and IQ as covariates and their interactions with the respective main predictor (exploratory moderator analyses). For the smoking-specific GNGT, again, robust linear mixed-effects models were utilized, including stimulus type and its interaction with CPD, FTND, or QSU-brief as additional predictors (exploratory moderator

analyses). Additionally, analyses for research question 3 were conducted with smoking duration, rather than age, as predictor variable (see Appendix D).

Following dual-process models [1,2], smoking status and higher scores in smoking-related variables should be associated with greater deficits in response inhibition (i.e., higher CE rates). In line with the IST [3], smoking status and higher scores in smoking-related variables are expected to be associated with exacerbated responsivity (i.e., higher CE rates and faster Go-RTs) to smoking-related stimuli. Therefore, directional hypotheses with one-sided *p*-values for statistical inference were tested regarding the following effects: effects of group and smoking-related variables on CE rates, and effects of group × stimulus type and smoking-related variables × stimulus type on CE rates and Go-RTs. The Benjamini-Hochberg correction [35] was applied to control the false discovery rate (FDR) at 5% (see Appendix A.4.2).

RESULTS

For results on OE rates, see Table 2-II and Appendix C.

Description of study groups

The characteristics of both study groups are presented in Table 1-II. Participants who smoked consumed an average of 19.55 CPD (*SD* = 9.34; range: 7–60), for 22.28 years (*SD* = 13.20; range: 1–56), and exhibited moderate tobacco dependence (FTND: *M* = 5.23, *SD* = 1.85, range: 3–10). The smoking group demonstrated significantly lower IQ scores, a lower proportion of participants with a high school degree, and a higher[18], albeit still low-risk (AUDIT score < 8; [32]) alcohol consumption compared to the control group.

[18] The AUDIT score was not included as a control variable in the regression models because, according to dual-process models of addiction [1,2], deficits in response inhibition—similar to the severity of tobacco dependence—are expected to be associated with higher alcohol consumption.

Table 1-II

Demographic and smoking-related variables by study group

Variables	Smoking group (n = 122)			Control group (n = 69)			p
	M	*SD*	*range*	*M*	*SD*	*range*	
Demographic							
Age (years)	41.4	13.0	21–70	41.8	12.5	20–67	.834
Female[a] (n, %)	70, 57%			46, 67%			.268
High school degree (n, %)	78, 64%			62, 90%			**<.001**
WST-IQ	104.85	11.01	78–139	108.96	9.12	86–125	**.009**
AUDIT[b]	6.15[1]	4.58	0–21	2.45	1.95	0–7	**<.001**
Smoking-related							
Cigarettes lifetime	–	–	–	3.07	3.30	0–10	–
Cigarettes per day (n)	19.55	9.34	7–60	–	–	–	–
Smoking duration (years)	22.28	13.20	1–56	–	–	–	–
CO value	22.64	10.65	10–54	–	–	–	–
FTND[c]	5.23	1.85	3–10	–	–	–	–
QSU-brief[d]	18.68[2]	10.03	0–47	–	–	–	–

Note. Baseline differences of continuous and categorical variables were assessed using chi-square and two-sample *t*-tests. WST = Wortschatztest (German vocabulary test); AUDIT = Alcohol Use Disorders Identification Test; CO = Carbon Monoxide; FTND = Fagerström Test for Nicotine Dependence; QSU-brief = Questionnaire on Smoking Urges, brief version.

[1] n = 104 and [2] n = 119, due to missing values during data acquisition (see Appendix A.4.1).

[a] collected on the concept of sex.

total score ranges: [b] 0–40, [c] 0–10, [d] 0–60.

Research question 1: Group difference analyses: Smoking vs. control group

Effects of group and stimulus type on CE rates

In the general GNGT, the smoking group exhibited a significantly higher CE rate than the control group, T_y = -3.13, $p < .001$, $p_{FDR} = .002$, *95% CI* [-6.39; -1.66], $\xi = .33$[19] (see Table 2-II), supported by Bayesian analyses ($BF_{10} = 9.06$[20]) indicating substantial evidence for higher

[19] Robust explanatory effect size for *t*-tests on trimmed means: small: $\xi = .10$, medium: $\xi = .30$ [36].

[20] $3 < BF_{10} < 10$: indicates substantial evidence in favour of a difference between groups; $1 < BF_{10} < 3$: indicates weak evidence in favour of a difference between groups; $1/3 < BF_{10} < 1$: indicates weak evidence in favour of no difference between groups; $1/10 < BF_{10} < 1/3$: indicates substantial evidence in favour of no difference between groups [34].

CE rates in the smoking group. In the smoking-specific GNGT, the ANOVA did not show evidence for a group effect on CE rates, $Q(1,78.51) = 3.38$, $p = .070$, $p_{FDR} = .104$, $\xi = .24$. In contrast, Bayesian analyses ($BF_{10} = 1.88$) indicated weak evidence for higher CE rates in the smoking group, meaning no clear conclusion can be drawn. The main effect of stimulus type lacked statistical significance on CE rates, $Q(1,83.45) = 3.49$, $p = .065$, $\xi = .10$. There was no support for a significant interaction between group and stimulus type on CE rates, $Q(1,83.45) = 0.87$, $p = .354$, $p_{FDR} = .354$.

Table 2-II

Means, SDs, and medians of CE rates, OE rates, and Go-RTs in both GNGTs by study group

Variables	Smoking group (n = 122)			Control group (n = 69)		
	M	*SD*	*median*	*M*	*SD*	*median*
General GNGT						
CE rate	17.25	10.76	16.25	13.19	8.55	11.25
OE rate	1.08	3.09	0.42	0.60	1.14	0.00
Go-RT	472.67	51.93	463.06	464.66	40.55	456.42
Smoking-specific GNGT						
All trials						
CE rate	6.09	6.36	3.75	4.35	4.83	3.75
OE rate	0.20	0.63	0.00	0.17	0.32	0.00
Go-RT	416.17	59.65	396.52	393.39	38.49	394.50
Smoking-related trials						
CE rate	6.21	6.15	5.00	4.46	5.20	2.50
OE rate	0.19	0.60	0.00	0.16	0.46	0.00
Go-RT	415.53	59.75	399.11	394.74	39.23	395.32
Neutral trials						
CE rate	5.96	7.76	3.75	4.24	5.29	2.50
OE rate	0.22	0.74	0.00	0.18	0.37	0.00
Go-RT	416.80	60.07	395.33	392.04	38.40	391.30

Note. GNGT = Go/No-Go Task; CE = Commission Error; OE = Omission Error; Go-RT = mean Reaction Time in Go trials.

Effects of group and stimulus type on Go-RTs

In the general GNGT, the result of the *t*-test did not provide evidence for a difference in Go-RTs between groups, T_y = -1.05, p = .282, p_{FDR} = .282, *95% CI* [-23.52; 7.27], ξ = .12, supported by Bayesian analyses (BF_{10} = 0.29) indicating substantial evidence in favour of no group difference. Accordingly, Go-RTs were similar in both the smoking and non-smoking groups. In the smoking-specific GNGT, a significant main effect of group (non-significant after FDR-correction) was observed on Go-RTs, $Q(1,82.33)$ = 4.32, p = .041, p_{FDR} = .123, ξ = .26, indicating that the smoking group tended to show slower RTs across all Go trials. Bayesian analyses (BF_{10} = 6.79) provided substantial evidence for a group difference, supporting the finding of slower Go-RTs in the smoking group. The main effect of stimulus type lacked statistical significance on Go-RTs, $Q(1,83.43)$ = 0.61, p = .437, ξ = .02. There was no statistical support for a significant interaction between group and stimulus type on Go-RT, $Q(1,83.43)$ = 2.57, p = .113, p_{FDR} = .169.

Research question 2: Regression analyses with group and covariates as predictors

The results of research question 2 serve as a robustness check for those of research question 1, as the regression models controlled for important covariates, including age, sex, and IQ.

Effects of group and stimulus type on CE rates

The smoking group showed significantly higher CE rates in both GNGTs compared to the control group (see Table 3-II; smoking-specific GNGT: non-significant after FDR-correction). Notably, when the regression model for the smoking-specific GNGT was conducted without covariates, the group difference in CE rates was no longer significant. In the smoking-specific GNGT, no significant interaction between group and stimulus type on CE rates was observed.

Table 3-II

Results of regression models on CE rates and Go-RTs in both GNGTs

Predictors	CE rate			Go-RT		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*
			General GNGT			
Intercept	13.436	10.763 – 16.109	**<.001**	469.040	455.607 – 482.474	**<.001**
Group (1: smoking)	3.217	0.620 – 5.814	**.008**[*]	4.548	-8.504 – 17.599	.493
Age	-0.189	-0.289 – -0.088	**<.001**	1.473	0.969 – 1.978	**<.001**
Sex (1: female)	-1.301	-3.828 – 1.226	.311	-7.923	-20.623 – 4.776	.220
IQ	-0.072	-0.197 – 0.052	.253	-0.219	-0.845 – 0.407	.491
			Smoking-specific GNGT			
Intercept	3.254	1.857 – 4.651	**<.001**	391.031	375.883 – 406.178	**<.001**
Group (1: smoking)	1.272	-0.154 – 2.698	**.040**[1]	17.533	2.787 – 32.279	**.020**[*]
Age	-0.102	-0.151 – -0.054	**<.001**	1.680	1.113 – 2.247	**<.001**
Sex (1: female)	0.502	-0.709 – 1.713	.417	2.977	-11.299 – 17.254	.683
IQ	0.011	-0.048 – 0.071	.712	-0.840	-1.544 – -0.136	**.019**
Stimulus type (1: smoking)	0.333	-0.779 – 1.446	.557	2.443	0.093 – 4.792	**.042**
Stimulus type × Group	0.175	-1.217 – 1.567	.403	-3.326	-6.265 – -0.386	**.027**[*]

Note. For the effects of group and stimulus type × group on CE rates, one-sided *p*-values are reported, otherwise two-sided. All regression model predictors, except for sex, were grand-mean centered. GNGT = Go/No-Go Task; CE = Commission Error; Go-RT = mean Reaction Time in Go trials; *CI* = Confidence Interval.

[*] significant after Benjamini-Hochberg correction.

[1] no effect of group was observed in a regression model without covariates (i.e., age, sex, and IQ).

Effects of group and stimulus type on Go-RTs

In the general GNGT, the effect of group on Go-RTs was inconclusive. In the smoking-specific GNGT, the smoking group exhibited significantly slower Go-RTs compared to the control group. Also, there was a significant interaction between group and stimulus type on Go-RTs, indicating that the smoking group exhibited faster mean RTs in smoking-related compared to neutral Go trials, while the control group showed faster mean RTs in neutral Go trials (see Table 2-II).

Effects of covariates on CE rates and Go-RTs

Across both GNGTs, CE rates decreased with age, while Go-RTs increased significantly. There was no clear evidence indicating a relationship between sex and CE rates or Go-RTs. In the smoking-specific GNGT, a higher IQ was associated with faster Go-RTs, whereas no association was observed with Go-RTs in the general GNGT.

Research question 3: Regression analyses with smoking-related variables and covariates in individuals who smoke

Effects of smoking-related variables and stimulus type on CE rates and Go-RTs

Smoking-related variables (i.e., CPD, FTND, and QSU-brief) did not show conclusive evidence of a relationship with performance in the GNGTs (see Tables 4-II and 5-II), with one exception: higher QSU-brief scores were associated with faster Go-RTs in the general GNGT (non-significant after FDR-correction). Further, a significant interaction emerged between the QSU-brief score and stimulus type on CE rates in the smoking-specific GNGT (non-significant after FDR-correction). This effect indicates that higher craving was associated with a stronger tendency toward higher CE rates during smoking-related compared to neutral trials (see Figure 1-II).

Table 4-II

Results of regression models on CE rates and Go-RTs in the general GNGT

Predictors	CPD			FTND			QSU-brief[1]		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*
CE rate									
Intercept	15.785	13.252 – 18.318	**<.001**	16.169	13.446 – 18.892	**<.001**	16.232	13.637 – 18.826	**<.001**
Age	-0.209	-0.346 – -0.072	**.003**	-0.220	-0.366 – -0.074	**.003**	-0.185	-0.329 – -0.041	**.012**
Sex (1: female)	-0.210	-3.505 – 3.086	.900	-0.509	-4.075 – 3.058	.778	0.040	-3.427 – 3.508	.982
IQ	-0.102	-0.254 – 0.049	.184	-0.091	-0.257 – 0.075	.281	-0.026	-0.189 – 0.137	.753
Variable	-0.133	-0.409 – 0.142	.830	-0.246	-1.758 – 1.267	.626	-0.021	-0.302 – 0.260	.559
Variable × Age	0.024	0.009 – 0.039	**.002**[*]	0.072	-0.002 – 0.146	.060	0.016	0.001 – 0.030	**.040**
Variable × Sex	0.315	-0.037 – 0.667	.079	0.566	-1.376 – 2.509	.565	0.051	-0.297 – 0.399	.772
Variable × IQ	-0.002	-0.020 – 0.016	.831	-0.012	-0.106 – 0.081	.799	-0.010	-0.027 – 0.007	.261
Go-RT									
Intercept	478.303	465.424 – 491.183	**<.001**	477.138	463.679 – 490.598	**<.001**	476.473	463.316 – 489.630	**<.001**
Age	1.668	0.971 – 2.365	**<.001**	1.554	0.834 – 2.274	**<.001**	1.742	1.012 – 2.472	**<.001**
Sex (1: female)	-10.374	-27.130 – 6.383	.223	-9.418	-27.049 – 8.213	.292	-9.156	-26.743 – 8.430	.304
IQ	-0.362	-1.132 – 0.409	.355	-0.421	-1.243 – 0.401	.312	-0.553	-1.382 – 0.276	.189
Variable	0.028	-1.372 – 1.429	.968	4.436	-3.040 – 11.911	.242	-1.487	-2.912 – -0.062	**.041**
Variable × Age	-0.072	-0.148 – 0.004	.064	-0.263	-0.630 – 0.104	.158	-0.024	-0.099 – 0.052	.534
Variable × Sex	-0.228	-2.017 – 1.562	.801	-2.760	-12.362 – 6.842	.570	1.662	-0.101 – 3.425	.064
Variable × IQ	0.075	-0.017 – 0.167	.110	-0.092	-0.555 – 0.370	.693	0.061	-0.025 – 0.147	.164

Note. The predictor *Variable* refers to either CPD, FTND, or QSU-brief (smoking-related variables). For the effects of smoking-related variables on CE rates, one-sided *p*-values are reported, otherwise two-sided. All regression model predictors, except for sex, were grand-mean centered. CPD = Cigarettes Per Day; FTND = Fagerström Test for Nicotine Dependence; QSU-brief = Questionnaire on Smoking Urges, brief version; *CI* = Confidence Interval; CE = Commission Error; Go-RT = mean Reaction Time in Go trials.

[*] significant after Benjamini-Hochberg correction.

[1] $n = 119$, due to missing values during data acquisition (see Appendix A.4.1). After data imputation, the results remained unchanged.

Table 5-II

Results of regression models on CE rates and Go-RTs in the smoking-specific GNGT

Predictors	CPD			FTND			QSU-brief[1]		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*
CE rate									
Intercept	4.535	3.195 – 5.874	**<.001**	4.506	3.165 – 5.846	**<.001**	4.756	3.398 – 6.115	**<.001**
Age	-0.120	-0.188 – -0.052	**.001**	-0.133	-0.201 – -0.066	**<.001**	-0.137	-0.208 – -0.066	**<.001**
Sex (1: female)	0.360	-1.274 – 1.995	.666	0.376	-1.273 – 2.026	.655	-0.077	-1.790 – 1.636	.930
IQ	-0.024	-0.100 – 0.051	.523	-0.014	-0.090 – 0.063	.729	-0.024	-0.104 – 0.057	.564
Variable	-0.062	-0.208 – 0.083	.799	-0.110	-0.852 – 0.633	.614	-0.014	-0.160 – 0.132	.575
Variable × Age	0.009	0.002 – 0.017	**.015**	0.046	0.012 – 0.081	**.008**	-0.003	-0.010 – 0.004	.416
Variable × Sex	0.031	-0.144 – 0.205	.730	-0.492	-1.390 – 0.407	.283	-0.059	-0.230 – 0.113	.503
Variable × IQ	-0.008	-0.017 – 0.001	.067	-0.033	-0.076 – 0.010	.133	-0.006	-0.015 – 0.002	.150
Stimulus type (1: smoking)	0.516	-0.415 – 1.447	.277	0.490	-0.428 – 1.409	.296	0.440	-0.463 – 1.342	.340
Variable × Stimulus type	0.003	-0.097 – 0.103	.476	0.036	-0.463 – 0.535	.444	0.108	0.017 – 0.198	**.010**
Go-RT									
Intercept	413.749	398.828 – 428.670	**<.001**	410.501	395.795 – 425.207	**<.001**	409.127	394.056 – 424.198	**<.001**
Age	2.121	1.315 – 2.927	**<.001**	2.141	1.355 – 2.926	**<.001**	2.347	1.513 – 3.182	**<.001**
Sex (1: female)	7.991	-11.383 – 27.366	.419	9.575	-9.651 – 28.801	.329	6.029	-14.077 – 26.135	.557
IQ	-1.049	-1.940 – -0.158	**.021**	-1.032	-1.929 – -0.136	**.024**	-0.958	-1.906 – -0.011	**.047**
Variable	0.962	-0.660 – 2.584	.245	5.234	-2.933 – 13.402	.209	-0.560	-2.192 – 1.072	.501
Variable × Age	-0.128	-0.216 – -0.040	**.004**	-0.437	-0.837 – -0.037	**.032**	-0.033	-0.119 – 0.053	.456
Variable × Sex	-0.512	-2.581 – 1.557	.628	-1.961	-12.432 – 8.509	.714	0.901	-1.114 – 2.917	.381
Variable × IQ	0.037	-0.069 – 0.143	.495	-0.220	-0.724 – 0.285	.393	0.040	-0.059 – 0.139	.425
Stimulus type (1: smoking)	-0.949	-2.816 – 0.917	.319	-0.962	-2.830 – 0.906	.313	-1.095	-2.969 – 0.778	.252
Variable × Stimulus type	0.031	-0.170 – 0.232	.764	0.232	-0.782 – 1.247	.654	0.064	-0.123 – 0.252	.503

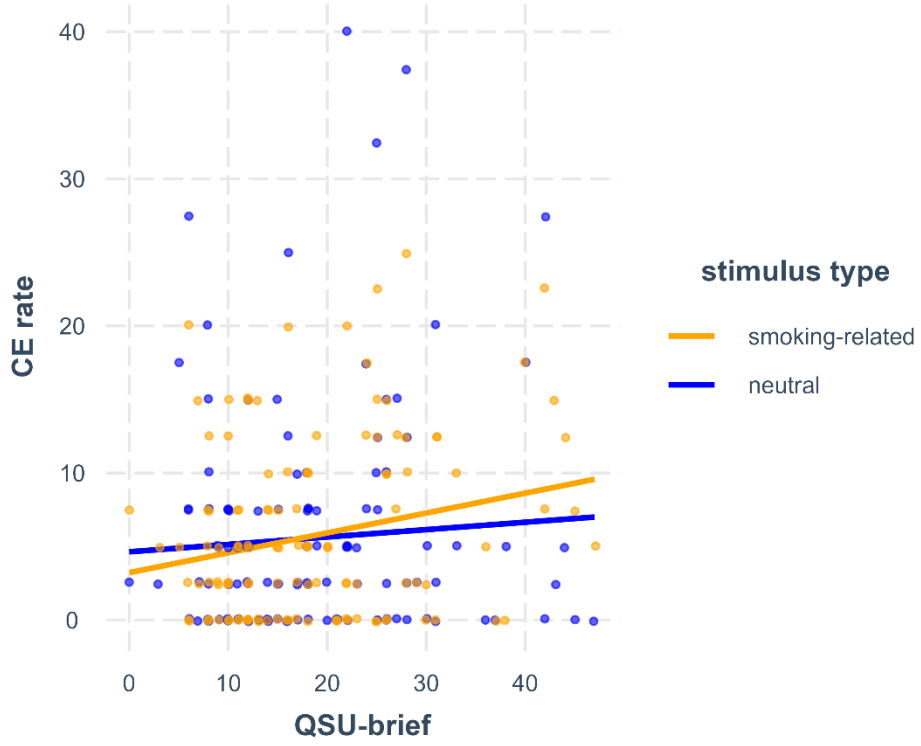
Note. The predictor *Variable* refers to either CPD, FTND, or QSU-brief (smoking-related variables). For the effects of smoking-related variable (× stimulus type) on CE rates, one-sided *p*-values are reported, otherwise two-sided. All regression model predictors, except for sex, were grand-mean centered. None of the effects of smoking-related variables (× stimulus type) or smoking-related variables (× covariates) on the CE rate or Go-RT were significant after Benjamini-Hochberg correction.

CPD = Cigarettes Per Day; FTND = Fagerström Test for Nicotine Dependence; QSU-brief = Questionnaire on Smoking Urges, brief version; *CI* = Confidence Interval; CE = Commission Error; Go-RT = mean Reaction Time in Go trials.

[1] n = 119, due to missing values during data acquisition (see Appendix A.4.1). After data imputation, the results remained unchanged.

Figure 1-II

QSU-brief score × stimulus type interaction on the CE rate in the smoking-specific GNGT



Note. QSU-brief = Questionnaire on Smoking Urges, brief version; CE = Commission Error. For better interpretability, the QSU-brief score was retained in its original scale (without grand-mean centering).

Effects of covariates on CE rates and Go-RTs

In both GNGTs, higher age was associated with significantly lower CE rates and slower Go-RTs. There was no clear evidence indicating a relationship between sex and CE rates or Go-RTs. In the smoking-specific GNGT, a higher IQ was associated with significantly faster Go-RTs, whereas no association was observed with Go-RTs in the general GNGT or CE rates.

Interactions between smoking-related variables and covariates on CE rates and Go-RTs

Since interaction analyses were not pre-registered, they are considered exploratory. Furthermore, none of the interaction effects were significant after FDR-correction (except for

the CPD × age effect on the CE rate in the general GNGT); therefore, results should be regarded as preliminary and confirmed in subsequent studies before firm conclusions can be drawn.

Some significant interactions between age and smoking-related variables on GNGT performance were observed (general GNGT: CE rate: CPD × age, QSU × age; smoking-specific GNGT: CE rate: CPD × age, FTND × age; Go-RT: CPD × age, FTND × age; for interaction plots see Appendix B, Figures B.1 and B.2). These effects indicate that, in older individuals (i.e., $M_{age}+1SD_{age}$ = 54 years), a greater number of CPD and a higher severity of tobacco dependence and craving were tendentially associated with higher CE rates and faster RTs in Go trials. Conversely, in younger individuals (i.e., $M_{age}-1SD_{age}$ = 28 years), a greater number of CPD and a higher severity of tobacco dependence and craving were tendentially associated with lower CE rates, but also slower Go-RTs. Simply put, older individuals who smoked more, had greater tobacco dependence, or reported stronger craving tended to respond faster in Go trials and tended to make more CEs by incorrectly responding in No-Go trials. In contrast, younger individuals who smoked more, had greater tobacco dependence, or reported stronger craving tended to respond more slowly in Go trials and tended to make fewer CEs by correctly withholding responses in No-Go trials. Overall, there was no clear evidence of significant interactions between smoking-related variables and sex or IQ.

Additional analyses

The main findings of the complementary analyses were: (1) no significant group differences in OE rates emerged (see Appendix C for results and Appendix E.1 for a discussion); (2) results of regression models with years of smoking as predictor were largely consistent with results of the main analyses (see Appendix D for results and Appendix E.2 for a discussion).

DISCUSSION

The present study aimed to extend previous research regarding deficits in response inhibition within the context of smoking by comparing a large, age-diverse smoking sample with healthy, non-smoking controls, while considering individual differences in age, sex, and intelligence (i.e., through the inclusion of those factors [covariates] and the examination of moderating effects). Both general and smoking-specific GNGTs were employed. All measures exhibited good to excellent reliability, except for the FTND score (tobacco dependence severity), whose results should be interpreted with caution [37].

Summary of findings

This study provides evidence that individuals who smoke demonstrate deficits in response inhibition compared to healthy, non-smoking individuals. We hypothesised that the smoking group would show higher CE rates in the general GNGT compared to the non-smoking group. This was confirmed by a significant group difference with medium effect size, which remained robust after accounting for individual differences in age, sex, and IQ. Furthermore, Bayesian analyses provided substantial evidence for higher CE rates in the smoking group. These findings align with previous meta-analytical research ([4]; included empirical studies supporting the finding, e.g., [10,14]) and more recent empirical evidence (e.g., [7,13]).

For the smoking-specific GNGT, results are more complex. A simple comparison of groups (i.e., ANOVA; research question 1) did not yield a significant difference in the CE rate, nor did the regression model without considering age, sex, and IQ differences in individuals. Importantly, after controlling for these variables, we observed a tendency (non-significant after FDR-correction) for higher CE rates in individuals who smoke (research question 2). This indicates that the manifestation of response inhibition deficits is not uniform, but rather varies

depending on individual differences in age, sex, and IQ. Their neglect may explain some of the non-significant findings reported in previous studies (e.g., [8,10]).

In terms of RTs, the smoking group responded significantly slower in Go trials of the smoking-specific GNGT than the control group, with Bayesian analyses providing substantial support for a group difference. No such effect was observed on Go-RTs in the general GNGT. These findings may indicate a generalized deficit in executive functioning in the smoking group [6], which became observable in the smoking-specific GNGT. This is plausible, as the smoking-specific GNGT likely required greater executive functioning (e.g., attentional control, working memory) due to the presentation of smoking-related and neutral content compared to digits in the general GNGT.

In line with the IST and previous smoking-specific GNGT studies [8,12], the smoking group exhibited exacerbated responsivity toward smoking-related stimuli, evidenced by shorter RTs in smoking-related compared to neutral Go trials relative to the control group. In contrast, no significant group difference was found in CE rates during smoking-related versus neutral trials. This contradicts the assumptions of the IST and previous studies reporting higher CE rates during smoking-related trials in individuals who smoke [9,12]. However, it aligns with the findings of Kräplin et al. [8], who only found group differences in Go-RTs. One possible explanation is that the former studies employed a contextual block design, whereas our study and Kräplin et al. used trial-wise random presentation of smoking-related and neutral stimuli. In interleaved designs, individuals may better compensate for deficits, whereas compensation is more difficult during smoking-specific blocks. Alternatively, the overall low CE rates observed in the smoking-specific GNGT (see Table 3-II and Kräplin et al [8], Table 2) may reflect a floor effect, limiting the detection of significant group differences.

In research question 3, we hypothesised that higher scores on smoking-related variables (i.e., CPD, tobacco dependence severity, and craving) would be associated with greater deficits

in response inhibition, particularly in response to smoking-related stimuli. All findings should be interpreted with caution, as they became non-significant after applying FDR-correction. Higher scores in smoking-related variables did not show a clear association with GNGT performance, with one exception: higher craving was associated with faster RTs in Go trials in the general GNGT, suggesting that the desire to smoke may accelerate reactions broadly, not just to smoking-related stimuli. Additionally, higher craving was associated with higher CE rates toward smoking-related compared to neutral stimuli in the smoking-specific GNGT. This aligns with the IST, suggesting that craving may exacerbate response inhibition deficits, particularly towards smoking-related stimuli.

In our exploratory examination of the moderating effects of age, sex, and IQ within research question 3, age emerged as a potential moderator in the relationship between smoking-related variables and GNGT performance. However, this effect was not consistently detectable and mostly not significant after FDR-correction (see also Appendix E.2 for a discussion on the effect of smoking duration). Older (i.e., ≥ 54 years), heavier-smoking individuals with greater severity of tobacco dependence and craving tended to show higher CE rates and faster RTs in Go trials. Conversely, younger individuals (i.e., ≤ 54 years) exhibited the tendency for a reversed pattern, with lower CE rates but slower Go-RTs. While the latter appears to contradict dual-process models, the combination of slower Go-RTs and reduced CE rates may reflect a strategic speed-accuracy trade-off to compensate for response inhibition deficits [6]. However, the moderating effect of age needs to be confirmed in studies with larger sample sizes, as our study was likely underpowered to detect interaction effects [38].

Clinical and theoretical implications

While our results support the significance of response inhibition in smoking, longitudinal studies are necessary to unravel their causal relationship. Moreover, ecological momentary assessment (EMA) studies are required to better understand state and trait associations between

response inhibition and smoking in everyday life. Clinically, our findings reinforce previous evidence that response inhibition training may effectively reduce smoking behaviour and craving [29]. Future research might investigate its efficacy in older, heavier-smoking populations. Moreover, smoking-specific inhibition training may be particularly effective in high-risk situations, such as during periods of heightened craving.

Limitations

Our results should be interpreted in light of several limitations. First, our covariates/moderators were not pre-registered, which may raise concerns about post-hoc adjustments, limiting credibility. However, age, sex, and intelligence are common covariates in cognitive task data analyses. Second, the GNGTs used a long response window, resulting in lower task difficulty. This may have reduced sensitivity in differentiating response inhibition, potentially contributing to non-significant findings. Third, exacerbated responsivity in individuals who smoke is likely not limited to smoking-related stimuli, as previous research shows deficits toward other reward-related stimuli, such as money [12]. Consequently, our findings should not be overinterpreted as specific to smoking-related stimuli. Fourth, our exclusion criteria for the non-smoking sample did not account for passive smoking. However, research indicates that non-smoking individuals passively exposed to smoking also exhibit executive functioning deficits [39]. Thus, it remains unclear to what extent passive smoking may have affected response inhibition in the non-smoking group. Lastly, we cannot exclude the possibility of sampling bias. This limitation arises from the lack of data on variables such as race or ethnicity. Also, participants were recruited for an intervention study aimed at reducing smoking behaviour, with a higher proportion of females and a predominance of highly educated individuals. In contrast, the smoking population in Germany is primarily male and less educated [40]. Therefore, the findings may not be generalisable to the general smoking population. However, we were able to recruit an older, more age-diverse sample (age: 21-29:

n = 29, 30-39: *n* = 30, 40-49: *n* = 25, 50-59: *n* = 27, 60-70: *n* = 11) with greater variation in smoking heaviness and/or duration compared to previous studies (e.g., [8–11,17]).

Conclusion

The findings of the present study substantiate the notion that response inhibition plays a crucial role in smoking. Furthermore, our results suggest that the extent of deficits is person-specific: greater deficits may be associated, first, with increased craving, second, during exposure to smoking-related cues, and third, with heavier smoking and greater severity of tobacco dependence and craving in older individuals. In light of these findings, it would be interesting to investigate whether trainings aimed at improving response inhibition might exert positive effects on smoking behaviour, particularly among older individuals who smoke heavily or experience high levels of craving.

AUTHOR CONTRIBUTIONS

Authors	Contributions
Franziska Motka	Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing
Simone Kühn	Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing
Charlotte E. Wittekind	Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Software, Supervision, Validation, Writing – Review & Editing

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STUDY III

The effects of approach bias modification on smoking cue-reactivity in individuals who smoke: A randomized-controlled fMRI study

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The effects of approach bias modification on smoking cue-reactivity in individuals who smoke: A randomized-controlled fMRI study

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Abstract

Background: Approach bias modification (ApBM) added to treatment-as-usual (TAU) has been shown to reduce relapse rates in alcohol use disorder, presumably by decreasing neural reactivity toward alcohol cues in reward-related brain regions. However, its efficacy and neural mechanisms in smoking cessation remain unclear. This randomized-controlled trial is the first to investigate the neural effects of ApBM on smoking cue-reactivity.

Methods: Individuals with chronic, moderate-to-heavy tobacco dependence (N = 117, M_{age} = 41.5, 45.3% female) received a one-day smoking cessation intervention (TAU). Then, participants were randomized to complete seven sessions of ApBM (TAU+ApBM), Sham training (TAU+Sham), or no training (TAU-only). Primary outcome was neural reactivity toward smoking-related versus neutral stimuli (smoking cue-reactivity) post-intervention. Associations with short- and long-term abstinence, smoking approach biases, and craving were explored.

Results: No significant group × time interactions on cue-reactivity were found, and ApBM did not enhance abstinence rates. Across the whole sample, cue-reactivity significantly decreased in motor-related regions, including the left anterior cingulate cortex (ACC), right middle cingulate cortex, right precuneus, and right supramarginal gyrus. Reductions in ACC cue-reactivity were significantly associated with reduced craving, while greater decreases in amygdala cue-reactivity predicted higher short-term abstinence probability. In the precuneus and supramarginal gyrus, increased cue-reactivity following ApBM was associated with a higher probability of long-term abstinence, while the control groups showed the opposite pattern.

Conclusions: ApBM did not reduce smoking cue-reactivity in reward-related brain regions, consistent with the lack of beneficial effects on clinical and behavioral outcomes. Alternative neural target processes and respective training procedures should be explored.

Keywords: ApBM, smoking, cue-reactivity, fMRI, approach bias, addiction

Introduction

Tobacco smoking remains a leading cause of morbidity and premature death worldwide, with substantial economic costs (Reitsma et al., 2021). Despite the availability of evidence-based treatments, relapse rates remain high (Mottillo et al., 2009; Rigotti et al., 2022), highlighting the urgent need for improved interventions. Novel approaches focus on modifying appetitive responses toward drug-related stimuli, such as approach biases—the automatic tendency to approach drug cues—observed in individuals who smoke (Machulska et al., 2015; C. E. Wiers et al., 2013). These responses are believed to play a key role in the development and maintenance of substance use disorders (SUD). Specifically, problematic drug use is thought to be driven by strong appetitive responses toward drug-related cues, which are insufficiently regulated by more controlled processes (Stacy & Wiers, 2010). Neurobiologically, these responses are believed to be associated with hyperactivation of mesocorticolimbic reward circuit after prolonged drug use, attributing incentive salience toward drug-related cues (Robinson & Berridge, 2025). Neuroimaging studies support this assumption, showing heightened activity in mesocorticolimbic regions (e.g., striatum, amygdala) in response to smoking-related versus neutral stimuli (smoking cue-reactivity; Engelmann et al., 2012; Lin et al., 2020). Importantly, smoking cue-reactivity has been shown to predict relapse (Allenby et al., 2020; Courtney et al., 2016), highlighting its clinical relevance for smoking cessation.

Approach bias modification (ApBM) aims to "re-train" approach biases by requiring individuals to consistently avoid drug-related stimuli in computerized training (Kakoschke et al., 2017). In alcohol use disorder (AUD), ApBM has significantly reduced both early (Manning et al., 2021; Manning et al., 2016) and long-term relapse rates (Rinck et al., 2018; Salemink et al., 2022) when added to treatment-as-usual (TAU), leading to its inclusion in AUD treatment guidelines in Germany (Kiefer et al., 2021) and Australia (Haber, 2021; see R. W.

Wiers et al., 2023 for a review). However, evidence that the effects of ApBM on clinical outcomes are mediated by reductions in behavioral approach biases remains limited (Vrijsen et al., 2024; R. W. Wiers et al., 2023). Beyond behavioral mechanisms, a functional magnetic resonance imaging (fMRI) study examined ApBM effects on neural activity in abstinent inpatients with AUD. Compared to Sham training, ApBM reduced amygdala reactivity during alcohol cue exposure, which correlated with decreased craving (C. E. Wiers et al., 2015). These findings suggest that ApBM reduces neural reactivity in brain regions associated with craving and motivational salience.

Compared to studies on alcohol, evidence for the efficacy of ApBM in smoking cessation is mixed. While some studies report reductions in daily cigarette consumption (Machulska et al., 2016; Wittekind et al., 2015) and higher 3-month abstinence rates (Smits et al., 2022), others found no significant effects (Kong et al., 2015; Wittekind et al., 2019; Wittekind et al., under review). Furthermore, findings challenge the assumption that the clinical effects of ApBM are mediated by changes in behavioral approach biases (Wittekind et al., 2022). To better understand its mechanisms, further research is needed to investigate *how* ApBM might influence appetitive responses toward smoking-related stimuli beyond behavioral approach biases. Notably, no study has yet examined its effects on neural smoking cue-reactivity—a gap the current fMRI study aims to address.

This study investigated the effects of ApBM when added to TAU on neural smoking cue-reactivity compared to Sham training and TAU-only in adults with chronic, moderate-to-heavy tobacco dependence. We hypothesized that: (1) ApBM would lead to greater reductions in neural reactivity toward smoking-related versus neutral stimuli (smoking cue-reactivity) in reward-related brain regions (e.g., striatum, amygdala); (2) reductions in cue-reactivity would predict a higher probability for short- (post-intervention) and long-term abstinence (6-month

follow-up); and (3) cue-reactivity would be associated with behavioral smoking approach biases and craving ratings.

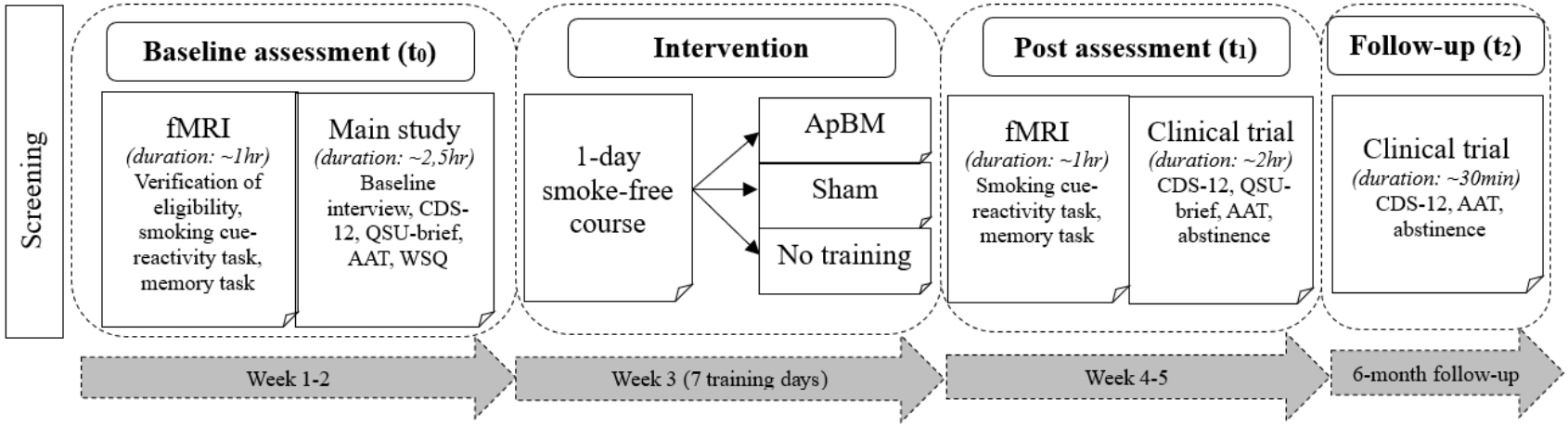
Methods and Materials

Study Overview

This fMRI study was part of a preregistered, randomized-controlled, double-blind, single-center, parallel-group superiority trial on the efficacy of ApBM as an add-on to smoking cessation treatment (German Clinical Trials Register: DRKS00019221, 11/11/2019). The clinical trial included participants from November 2019 to March 2023, with the fMRI study including participants who consented to the additional imaging study between March 2022 and March 2023. All participants completed a smoke-free course with a quit attempt (TAU) before randomization (1:1:1) to one of three arms: (1) TAU+ApBM, (2) TAU+Sham, or (3) TAU-only (see Figure 1-III). The study was approved by the Ludwig-Maximilians-University (LMU) Munich ethics committee (23_Wittekind_c_2019). All participants provided written informed consent.

Figure 1-III

Study Procedure



Note. This figure illustrates only the questionnaires and tasks relevant to the current functional magnetic resonance imaging (fMRI) investigation. For a complete overview of all assessments conducted in the main clinical trial, see Wittekind et al. (2022). CDS-12 = Cigarette Dependence Scale, 12-item version; QSU-brief = Questionnaire on Smoking Urges, brief version; AAT = Approach-Avoidance task; WSQ = Web Screening Questionnaire; ApBM = Approach bias modification.

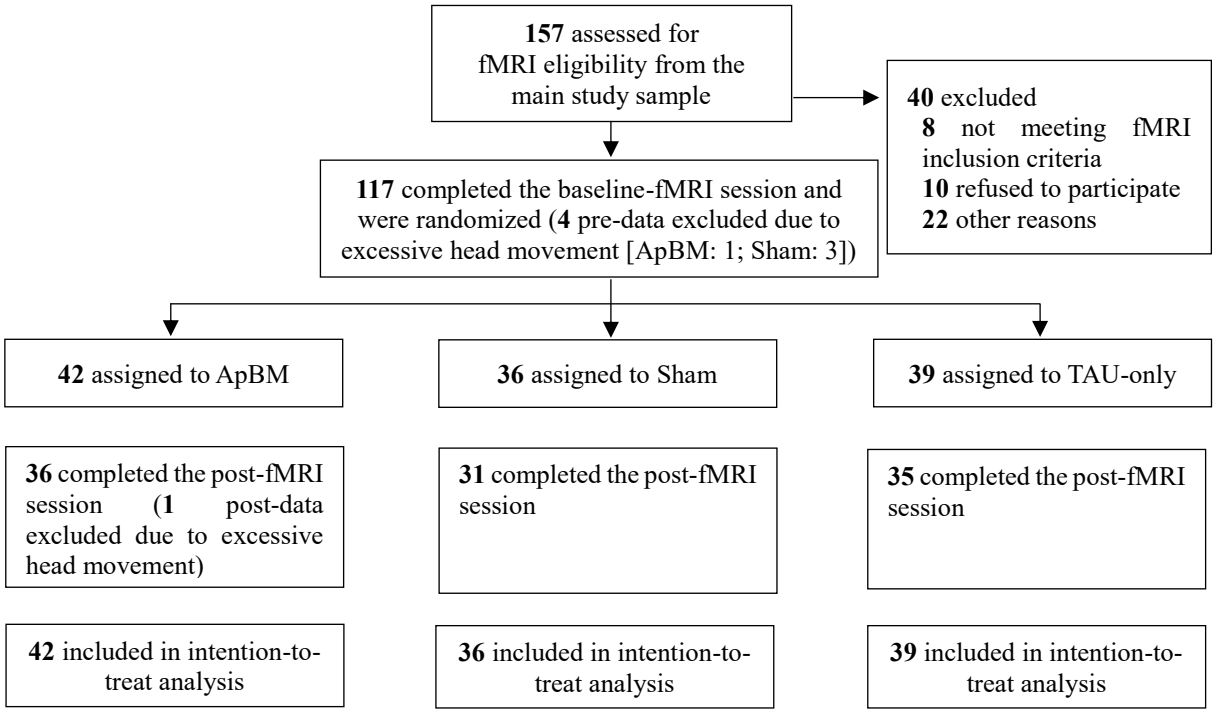
Participants and Power Analysis

Inclusion criteria of the clinical trial were: (1) age 18–70 years, (2) Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) score ≥ 3[21], (3) exhaled carbon monoxide (CO) ≥ 10ppm, (4) smoking ≥ 10 cigarettes per day within the past 12 months, (5) willingness to abstain from any smoking cessation interventions (e.g., e-cigarettes) during the study, and (6) motivation to participate in the smoking cessation intervention. Exclusion criteria included: (1) current/past diagnosis of severe psychiatric (bipolar disorder, psychosis) or major neurological disorders (multiple sclerosis, Parkinson's disease), and (2) moderate or severe substance use disorder (≥ 4 DSM-5 criteria, as assessed with the Mini International Neuropsychiatric Interview [MINI; Sheehan, 2016]) other than tobacco within the past 12 months. Additional exclusion criteria are detailed in Appendix A.1. Further fMRI-specific exclusion criteria were: (1) standard MRI contraindications (e.g., pacemaker), (2) psychotropic medication use, (3) head trauma history, and (4) uncorrectable visual impairments. The fMRI study included $N = 117$ individuals (see Figure 2-III for participant flow). This sample size was calculated to be sufficient to detect a between-group effect in smoking cue-reactivity changes based on findings from a comparable study in individuals with AUD (C. E. Wiers et al., 2015; see Appendix A.1 for details on the sensitivity analysis).

[21] A FTND score of 3 or higher indicates at least moderate dependence (AWMF, 2021).

Figure 2-III

Flow of Participants



Note. All individuals (n = 157) participating in the main study from March 2022 (when the fMRI assessments began) were invited to take part in the optional functional magnetic resonance imaging (fMRI) investigation until recruitment for the clinical trial concluded in March 2023. TAU = Treatment-as-usual; ApBM = Approach bias modification.

Study Procedure, Randomization, and Blinding

Individuals interested in the clinical trial completed a telephone screening to assess preliminary eligibility, explain study procedures, offer the optional fMRI investigation, and schedule appointments. Baseline (t_0) assessments for the fMRI study and clinical trial were conducted during separate appointments (fMRI: Neuroimaging Core Unit Munich [NICUM] of the LMU; clinical trial: laboratory of the Department of Psychology, LMU Munich) within two weeks before the smoke-free course, with the fMRI session always scheduled first (see Figure 1-III). Inclusion and exclusion criteria were verified before the fMRI session.

Participants were reassessed after the intervention phase (t_1: within a two-week timeframe) and at the 6-month follow-up (t_2; within a four-week timeframe).

The study used block-wise randomization, with all participants in the same smoke-free course assigned to the same study arm. The sequence was generated by an external center (Munich Centre of Clinical Trials). A staff member not involved in recruitment or assessments informed participants of their group assignment after the smoke-free course, conducted the first training session, monitored compliance, and sent reminders. Other staff (e.g., assessors, smoke-free trainers) remained blinded to group assignments. Participants in the ApBM and Sham training groups were blinded to their training condition, while blinding was not possible for the TAU-only group.

Interventions

Smoking Cessation Intervention (TAU)

The smoking cessation intervention included a one-day (total duration: 6 h), manualized cognitive-behavioral group intervention (smoke-free course), led by certified trainers. An optional 15-minute telephone counseling session was offered one week later. The course comprised four sections integrating psychoeducation, motivational interviewing, cognitive strategies, goal-oriented techniques, and a collective quit attempt (Wenig et al., 2013). For details, see Appendix A.2. Participants in the present fMRI study were recruited from 12 smoke-free courses, with an average of 13 participants per course.

Study Arms: Approach Bias Modification, Sham Training, and TAU-only

Participants in the ApBM and Sham training groups were instructed to complete seven daily sessions using a joystick on their home computer, with the first session conducted immediately after the smoke-free course. Each session began with ten practice trials, followed by 240 training trials, including 20 smoking-related pictures (simple, context-free, e.g., burning cigarettes; see Appendix A.3.1 for details on picture selection) and 20 positive pictures (e.g.,

men fishing). In each trial, participants were instructed to push or pull the joystick based on picture tilt (5° left/right), with instruction (pull vs. push right-tilted pictures) counterbalanced across participants. To simulate approach and avoidance, pictures increased in size when pulled and decreased when pushed. In the ApBM training, smoking-related pictures had to be pushed (avoidance), while positive pictures had to be pulled (approach). In the Sham training, smoking-related and positive pictures were equally assigned to pushing or pulling. Training sessions were implemented in Inquisit®. Participants in the TAU-only group received no additional training.

Data Collection

Interviews, Questionnaires, and Behavioral Tasks

Sociodemographic and smoking-related data (e.g., cigarettes per day, smoking duration) were collected during the clinical trial baseline assessment. Tobacco dependence severity was measured using the 12-item Cigarette Dependence Scale-12 (CDS-12; Etter et al., 2003), aligning with DSM-IV and ICD-10 criteria. Mental health disorders were screened with the Web Screening Questionnaire (WSQ; Donker et al., 2009). The primary clinical outcome, abstinence at t_2, was defined per the Russell Standard criteria[22] (West et al., 2005), with abstinence also assessed at t_1. Intervention effects on behavioral smoking approach biases were assessed using the joystick-based Approach-Avoidance Task (AAT; Rinck & Becker, 2007; see Appendix A.3.1 for task details). Half of the 40 smoking-related and 40 positive pictures used in the AAT were included in the ApBM and Sham trainings, while the other half were new (untrained) to examine generalization effects.

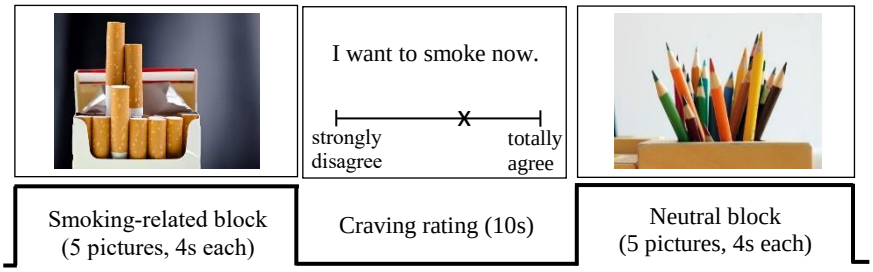
[22] Criteria: (1) a maximum of five cigarettes smoked until follow-up (t_2), (2) biochemical verification, (3) smoking status classified as smoking if not certifiably verified, (4) analysis of participants with protocol violations, and (5) blinded follow-up data collection.

Neural Smoking Cue-Reactivity Task

Neural reactivity toward smoking-related stimuli was assessed using an adapted version of the alcohol cue-reactivity paradigm (Vollstädt-Klein et al., 2011; see Figure 3-III for an illustration and task details). The stimuli comprised the same 40 smoking-related pictures from the AAT and 40 shape- and color-matched neutral pictures (e.g., pencils), presented in eight smoking-related and eight neutral blocks. Participants attended to the stimuli and rated their desire to smoke after each block. Details on fMRI data acquisition are provided in Appendix A.4.1. Post-scan, attention was assessed via an unannounced recognition task, requiring participants to classify 10 previously presented and 10 new pictures as "*known*" or "*unknown*".

Figure 3-III

Neural Smoking Cue-Reactivity Paradigm



Note. The smoking cue-reactivity paradigm comprised 40 smoking-related and 40 shape- and color-matched neutral stimuli, randomly presented in eight blocks per category, following a fixed order with no more than two consecutive blocks from the same category (s-s-n-s-n-s-s-n-s-n-s-n-n-s-n-n; s = smoking-related, n = neutral). Each block contained five stimuli, each displayed for 4 seconds. After each block, participants rated their current desire to smoke ("*I want to smoke now.*") on a visual analog scale from 0 ("*strongly disagree*") to 100 ("*totally agree*") within 10 seconds using a button press. A black fixation cross then appeared for at least 10 seconds, ensuring a total duration of 20 seconds for craving rating and fixation. The task lasted approximately 10 minutes (total scan duration: 30 minutes).

Data Analysis

Data Preprocessing and Measure Extraction

Behavioral Data

AAT data were preprocessed and analyzed using R (version 4.3.0; R Core Team, 2023). Details on the preprocessing procedure are provided in Appendix A.3.2. The AAT effect score was calculated by subtracting the median RT of the final push movements (RT from picture onset to full joystick extension) from that for pull movements in trials with untrained smoking-related stimuli ($push_{smoking}$–$pull_{smoking}$). Higher scores indicate a stronger approach bias towards smoking-related stimuli.

Neuroimaging Data

The fMRI data preprocessing and individual-level analysis are described in Appendix A.4.2. Data from five participants were excluded due to excessive head movement (see Figure 2-III). Both whole-brain and hypothesis-driven region of interest (ROI) analyses were employed at the group level using SPM12. To identify brain regions showing greater blood oxygenation level-dependence (BOLD) responses in smoking-related versus neutral blocks at t_0, whole-brain one-sample *t*-tests on the contrast [smoking–neutral] were performed. To examine changes in smoking cue-reactivity from t_0 to t_1 between groups, an ANOVA on the contrast (pre[smoking–neutral]–post[smoking–neutral]) was conducted with group as between-subject factor. Both analyses were controlled for age and sex. For the ROI analysis, the left anterior cingulate cortex (ACC), left angular gyrus, right thalamus, dorsal striatum, nucleus accumbens, amygdala, and medial prefrontal cortex were selected based on prior research on smoking cue-reactivity (Lin et al., 2020) and neural correlates of alcohol approach biases (C. E. Wiers et al., 2014) and alcohol ApBM (C. E. Wiers et al., 2015). See Appendix A.4.3 for details on ROI selection and mask generation. Mean values for the contrast [smoking–neutral] at t_0 and t_1 were extracted for each ROI, with the primary outcome defined as the

contrast at t_1. Visual attention during the cue-reactivity task can be considered high, with approximately 82% of stimuli at t_0 and t_1 correctly classified as "known" or "unknown".

Statistical Analysis

Analyses followed an intention-to-treat (ITT) approach in accordance with CONSORT guidelines (Moher et al., 2010). To assess neural smoking cue-reactivity at t_0, parametric *t*-tests or non-parametric Wilcoxon signed-rank test against zero were conducted on the mean activity for the contrast [smoking–neutral] in each ROI. Intervention effects on cue-reactivity in each ROI (Hypothesis 1) were examined using linear mixed-effects models (LMMs; Gueorguieva & Krystal, 2004) with the *lme4* package (Bates et al., 2015), incorporating all available data. Outcome measures were modeled with dummy-coded time, group, and their interaction as predictors, assuming participant-level random intercepts. Analyses were repeated for participants with high training adherence (≥ 5 sessions; preregistered criterion, see Wittekind et al., 2022). Associations between changes in cue-reactivity and abstinence at t_1 and t_2 (Hypothesis 2) were assessed using logistic regressions with abstinence predicted by cue-reactivity changes, group, and their interaction. Associations between cue-reactivity and behavioral variables (AAT effect scores, craving ratings; Hypothesis 3) were examined using LMMs with changes in behavioral variables predicted by cue-reactivity changes, group, and their interaction. Supplementary analyses assessed the association between cue-reactivity changes and smoking-related variables (cigarettes per day, tobacco dependence severity, CO value; see Appendix B.1). Across analyses, interaction effects (e.g., time × group) were evaluated using omnibus tests (analysis of variance [ANOVA]; *Anova* function). To control the false discovery rate (FDR) at 5%, we applied the Benjamini-Hochberg correction (Benjamini & Hochberg, 1995) for multiple comparisons across ROIs, separately for interaction and time effects. The reliability of each study measure was estimated (see Appendix A.5).

Results

Sample Characteristics and Adherence

Sociodemographic and clinical characteristics are depicted in Table 1-III. Participants showed a chronic smoking history (*M* = 22.81 years, *SD* = 11.19) and moderate-to-heavy tobacco dependence (cigarettes per day: *M* = 18.23, *SD* = 5.97; FTND score: *M* = 5.33, *SD* = 1.63, scores ≥ 3 indicate at least moderate dependence; AWMF [2021]). No significant baseline differences between groups emerged. Retention rates at t_1 (TAU+ApBM: 85.7%, TAU+Sham: 86.1%, TAU-only: 89.7%; see Figure 2-III [participant flow]) and training adherence were high (84.7% completing at least five training sessions; see Table 1-III).

Table 1-III

Baseline Characteristics and Training Adherence

Variables	Whole sample (N = 117)	TAU+ApBM (n = 42)	TAU+Sham (n = 36)	TAU-only (n = 39)	Tests for group differences (p-value)
Sociodemographic Information					
Age in years	41.47 (11.67)	42.83 (11.89)	41.58 (10.35)	39.90 (12.65)	.530
Sex [n, (% female)]	53 (45.3)	19 (45.2)	15 (41.7)	19 (48.7)	.829
German university entrance qualification "Abitur" [n, (%)]	68 (58.1)[2]	28 (66.7)[2]	17 (47.2)	23 (59.0)	.173
Clinical characteristics					
Cigarettes per day	17.96 (5.99)	18.26 (5.08)	18.00 (6.78)	17.59 (6.25)	.881
Smoking duration in years	22.81 (11.19)[1]	23.77 (11.41)	22.90 (10.23)[2]	21.71 (11.93)	.710
CDS-12 (scale range: 0–48)	35.41 (5.59)	36.31 (5.22)	34.64 (5.41)	35.15 (6.12)	.399
FTND (scale range: 0–10)	5.33 (1.63)	5.38 (1.45)	5.58 (1.75)	5.05 (1.70)	.362
CO value	33.47 (17.25)	34.57 (16.73)	31.89 (15.54)	33.74 (19.49)	.788
Psychiatric disorders[2] [n, (%)]	93 (79.5)	33 (78.6)	30 (83.3)	30 (76.9)	.777
Training adherence (N = 72)[3]					
Mean number of absolved training sessions	7.06 (2.57)	7.41 (2.34)	6.64 (2.79)	–	.205
Number of participants who completed ≥ 5 training sessions [n, (%)]	61 (84.7)	35 (89.7)	26 (78.8)	–	.338

Note. Values are presented as M (SD) unless otherwise indicated. Baseline group differences were analyzed using ANOVAs or t-tests (ApBM versus Sham training group for adherence variables) for continuous variables and chi-square or Fisher's exact tests for categorical variables. TAU = Treatment-as-usual; ApBM = Approach bias modification; CDS-12 = Cigarette dependence scale, 12-item version; FTND = Fagerström test for nicotine dependence; CO = Carbon monoxide.

[1] $n = 1$ missing value.

[2] Operationalized as exceeding the cut-off score on the Web Screening Questionnaire (WSQ) for at least one of the following disorders: depression, generalized anxiety disorder, panic disorder, agoraphobia, panic disorder with agoraphobia, specific phobia, social phobia, post-traumatic stress disorder, obsessive-compulsive disorder, and alcohol abuse/dependence.

[3] Six participants (TAU+ApBM: $n = 3$; TAU+Sham: $n = 3$) had missing values, as they did not receive training due to non-attendance at the smoke-free course (TAU).

Smoking Cue-Reactivity at Baseline

Whole-Brain Analysis

Whole-brain one-sample *t*-tests on the contrast [smoking > neutral] at t_0 identified three clusters surviving a voxel-wise threshold of $p < .001$ and an extent threshold of FWEc = 336 voxels ($p_{FWE} < .05$): right middle cingulate and paracingulate gyri (MCC; cluster size = 782; MNI coordinates: X = 6, Y = -26, Z = 30; $t_{max} = 5.69$, $p_{FWE\text{-}corr} < .001$), right precuneus (cluster size = 336; MNI coordinates: X = 16, Y = -70, Z = 48; $t_{max} = 4.83$, $p_{FWE\text{-}corr} = .023$), and right supramarginal gyrus (cluster size = 381; MNI coordinates: X = 62, Y = -20, Z = 32; $t_{max} = 4.39$, $p_{FWE\text{-}corr} = .014$). These regions were included in subsequent intervention analyses.

Region of Interest Analysis

At t_0, the contrast [smoking–neutral] was significantly greater than zero in the left ACC ($Z = 4.50$, $p < .001$, $p_{FDR} < .001$, $r = 0.42$[23]; see Table 2-III for descriptive statistics), indicating higher activity in smoking-related versus neutral blocks. Conversely, it was significantly lower than zero in the right thalamus ($t[112] = -3.42$, $p < .001$, $p_{FDR} = .002$, $d = 0.32$) and dorsal striatum ($Z = -2.94$, $p = .003$, $p_{FDR} = .005$, $r = 0.28$), reflecting reduced activity in smoking-related blocks. No significant differences emerged in the left angular gyrus ($t[112] = -0.65$, $p = .520$), amygdala ($t[112] = 0.184$, $p = .855$), nucleus accumbens ($Z = 1.24$, $p = .215$), and medial prefrontal cortex ($Z = -0.65$, $p = .515$), suggesting comparable activity in smoking-related and neutral blocks.

[23] Effect sizes are reported as Cohen's *d* (Cohen, 1988) for *t*-tests and Rosenthal's *r* (Rosenthal & Rubin, 2003) for Wilcoxon tests, with 0.20 to 0.50 indicating small to medium effects.

Table 2-III

Descriptive Statistics and Results of the ANOVAs (Omnibus Tests) for the Effects of Time and Time × Group on Neural and Behavioral Outcomes

Outcome variable	Time	Whole sample (N = 117)		TAU+ApBM (n = 42)		TAU+Sham (n = 36)		TAU-only (n = 39)		Effect of predictor
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Neuroimaging										
Selected from a meta-analysis on smoking cue-reactivity										
Left ACC	t_0	0.079	0.178	0.070	0.153	0.027	0.169	0.132	0.199	Time: $F(1, 105.34) = 8.75$, $\mathbf{p = .004}$, $\mathbf{p_{FDR} = .024}$ Time × group: $F(2, 109.46) = 0.50$, $p = .607$
	t_1	0.030	0.211	0.071	0.215	-0.012	0.197	0.025	0.216	
Left angular gyrus	t_0	-0.010	0.161	0.004	0.119	-0.044	0.172	0.006	0.186	Time: $F(1, 104.76) = 0.01$, $p = .919$ Time × group: $F(2, 108.89) = 0.48$, $p = .621$
	t_1	-0.005	0.215	0.040	0.190	-0.064	0.236	0.001	0.214	
Right thalamus	t_0	-0.047	0.145	-0.038	0.113	-0.078	0.178	-0.028	0.144	Time: $F(1, 105.34) = 0.19$, $p = .663$ Time × group: $F(2, 109.46) = 0.36$, $p = .700$
	t_1	-0.084	0.184	-0.042	0.180	-0.145	0.151	-0.072	0.205	
Dorsal striatum	t_0	-0.029	0.093	-0.026	0.082	-0.053	0.107	-0.010	0.087	Time: $F(1, 105.28) = 0.001$, $p = .970$ Time × group: $F(2, 109.40) = 0.66$, $p = .519$
	t_1	-0.029	0.134	0.013	0.133	-0.075	0.100	-0.031	0.150	
Regions with [smoking > neutral] at t_0 in the present sample										
Right MCC	t_0	0.091	0.143	0.090	0.120	0.064	0.150	0.113	0.158	Time: $F(1, 105.34) = 7.48$, $\mathbf{p = .007}$, $\mathbf{p_{FDR} = .024}$ Time × group: $F(2, 109.46) = 0.54$, $p = .582$
	t_1	0.056	0.213	0.104	0.197	-0.012	0.156	0.066	0.257	
Right supramarginal gyrus	t_0	0.080	0.179	0.075	0.162	0.064	0.228	0.098	0.149	Time: $F(1, 105.07) = 5.05$, $\mathbf{p = .027}$, $\mathbf{p_{FDR} = .067}$ Time × group: $F(2, 109.20) = 0.72$, $p = .491$
	t_1	0.008	0.222	0.025	0.219	-0.010	0.228	0.009	0.225	
Right precuneus	t_0	0.094	0.216	0.087	0.186	0.052	0.269	0.136	0.191	Time: $F(1, 104.80) = 8.20$, $\mathbf{p = .005}$, $\mathbf{p_{FDR} = .024}$ Time × group: $F(2, 108.93) = 0.37$, $p = .691$
	t_1	0.025	0.278	0.035	0.258	0.001	0.264	0.037	0.314	
Derived from alcohol ApBM studies										
Amygdala	t_0	0.003	0.160	-0.003	0.137	-0.008	0.181	0.018	0.167	Time: $F(1, 105.34) = 1.12$, $p = .291$ Time × group: $F(2, 109.46) = 0.26$, $p = .775$
	t_1	-0.065	0.202	-0.090	0.232	-0.079	0.160	-0.026	0.202	

Nucleus accumbens	t_0	0.026	0.199	0.005	0.189	0.010	0.243	0.063	0.163	Time: $F(1, 104.78) = 2.04$, $p = .157$ Time × group: $F(2, 107.79) = 1.47$, $p = .234$
	t_1	-0.025	0.230	0.015	0.226	-0.095	0.237	-0.004	0.219	
Medial prefrontal cortex	t_0	0.001	0.163	-0.005	0.163	-0.041	0.164	0.043	0.158	Time: $F(1, 106.13) = 1.23$, $p = .271$ Time × group: $F(2, 109.18) = 0.43$, $p = .650$
	t_1	-0.037	0.195	-0.028	0.186	-0.090	0.192	<0.000	0.202	
Behavioral										
AAT effect score	t_0	-19.009	67.119	-31.829	73.054	-7.694	55.437	-15.974	69.833	Time: $F(1, 108.33) = 5.67$, $\mathbf{p = .019}$ Time × group: $F(1, 108.83) = 1.89$, $p = .156$
	t_1	-28.854	55.608	-34.865	47.441	-5.045	54.163	-44.500	58.781	
Craving rating	t_0	54.007	26.006	54.976	22.487	57.844	22.709	49.423	31.738	Time: $F(1, 105.86) = 16.09$, $\mathbf{p<.001}$ Time × group: $F(1, 106.74) = 2.46$, $p = .091$
	t_1	29.924	24.437	32.643	21.654	26.447	23.621	30.129	27.992	

Note. TAU = Treatment-as-usual; ApBM = Approach bias modification; t_0 = Baseline; t_1 = Post-intervention; AAT = Approach-avoidance task; ACC = anterior cingulate cortex; MCC = middle cingulate cortex.

Hypothesis 1: Intervention Effects on Smoking Cue-Reactivity

Whole-Brain Analysis

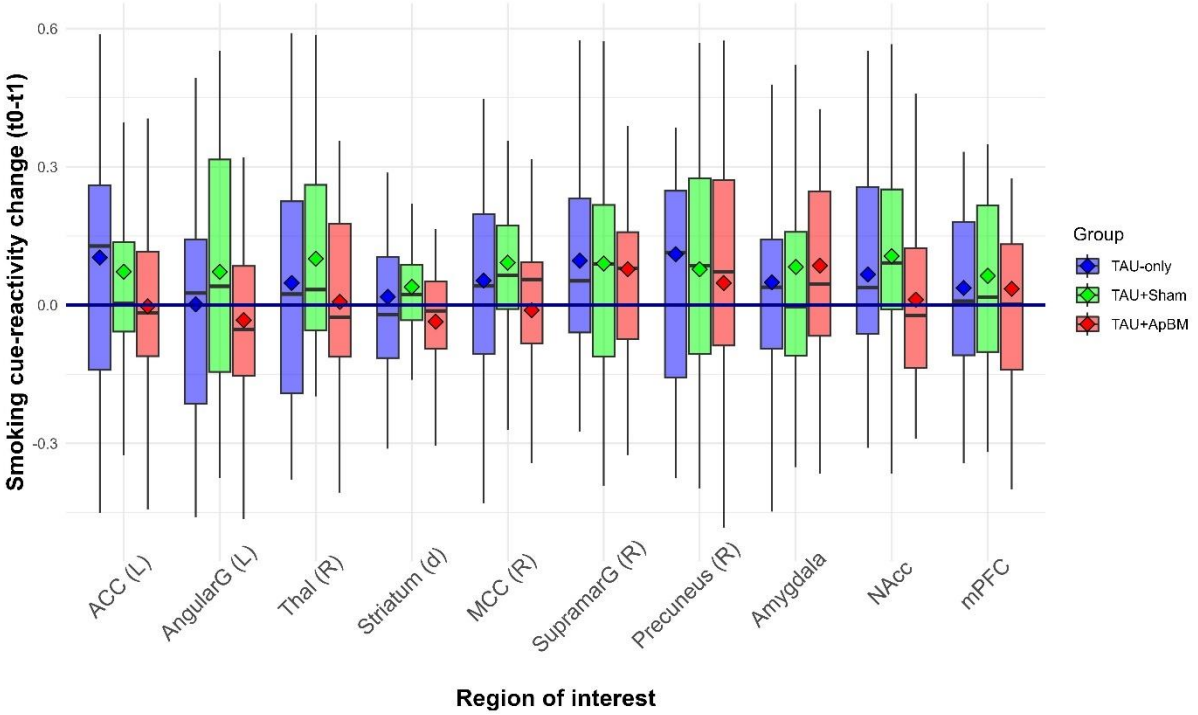
Whole-brain voxel-wise ANOVAs on the contrast (pre[smoking–neutral]–post[smoking–neutral]) across the 98 participants with complete t_0 and t_1 data revealed no significant BOLD activity changes surviving a height threshold of $F_{2,93} = 7.45$, $p < .001$.

Region of Interest Analysis

Smoking cue-reactivity significantly decreased from t_0 to t_1 in the left ACC, right MCC, right precuneus, and right supramarginal gyrus, reflecting reduced activity contrast between smoking-related and neutral blocks (see Table 2-III and Figure 4-III). No significant time effects were found in other regions, suggesting similar cue-reactivity at t_0 and t_1. Contrary to our hypothesis, no significant group × time interactions emerged in any ROI, indicating comparable changes in cue-reactivity across groups. Results remained unchanged when only participants with ≥ 5 training sessions were considered.

Figure 4-III

Boxplots of Smoking Cue-Reactivity Changes from t_0 to t_1 in each ROI per Group



Note. Black lines represent the median, while diamonds denote the mean. Higher positive values indicate a greater decrease in smoking cue-reactivity from t_0 to t_1, whereas higher negative values indicate a greater increase. R = right; L = left; ACC = anterior cingulate cortex; AngularG = Angular gyrus; Thal = Thalamus; d = dorsal; MCC = middle cingulate cortex; SupramarG = Supramarginal gyrus; NAcc = Nucleus accumbens; mPFC = Medial prefrontal cortex; TAU = Treatment-as-usual; ApBM = Approach bias modification.

Hypothesis 2: Association between Changes in Smoking Cue-Reactivity and Abstinence

No significant group differences in abstinence rates were found at t_1 (short-term abstinence; whole sample: 56 of 117 [47.9%], TAU+ApBM: 19 of 42 [45.2%], TAU+Sham: 19 of 36 [52.8%], TAU-only: 18 of 39 [46.2%]; $\chi^2[2] = 0.51$, $p = .775$) or at t_2 (long-term abstinence; whole sample: 26 of 117 [22.2%], TAU+ApBM: 11 of 42 [26.2%], TAU+Sham: 6 of 36 [16.7%], TAU-only: 9 of 39 [23.1%]; $\chi^2[2] = 1.04$, $p = .594$).

Regarding short-term abstinence, a significant effect emerged only for cue-reactivity in the amygdala (non-significant after FDR-correction), indicating that a greater reduction in amygdala reactivity toward smoking-related versus neutral stimuli was linked to a higher abstinence probability (β = 2.75, *95% CI* [0.21 to 5.84], p = .049, p_{FDR} = .278; see Table 3-III); however, this effect was not further moderated by group. Regarding long-term abstinence, no significant associations with cue-reactivity changes emerged. However, a significant interaction with group was found in the right precuneus (see Figure 5-III) and right supramarginal gyrus (both non-significant after FDR-correction). In the TAU+ApBM group, increased cue-reactivity in the right precuneus was significantly (non-significant after FDR-correction) associated with a higher probability of long-term abstinence (β = -3.82, *95% CI* [-7.58 to -0.91], p = .021, p_{FDR} = .061) and showed a non-significant trend for the right supramarginal gyrus (β = -3.56, *95% CI* [-7.80 to -0.18], p = .061). In both control groups, the opposite, but non-significant trend was observed, with decreased cue-reactivity linked to higher abstinence probability (right precuneus: TAU+Sham: β = 3.38, *95% CI* [-0.53 to 8.47], p = .128; TAU-only: β = 1.24, *95% CI* [-1.13 to 3.84], p = .304; right supramarginal gyrus: TAU+Sham: β = 2.54, *95% CI* [-1.07 to 6.85], p = .193; TAU-only: β = 1.61, *95% CI* [-1.86 to 5.21], p = .359). These findings suggest that ApBM training may moderate the link between cue-reactivity changes and long-term abstinence in these regions.

Table 3-III

Results of the ANOVAs (Omnibus Tests) for the Effects of Time and Time × Group on Abstinence Probability

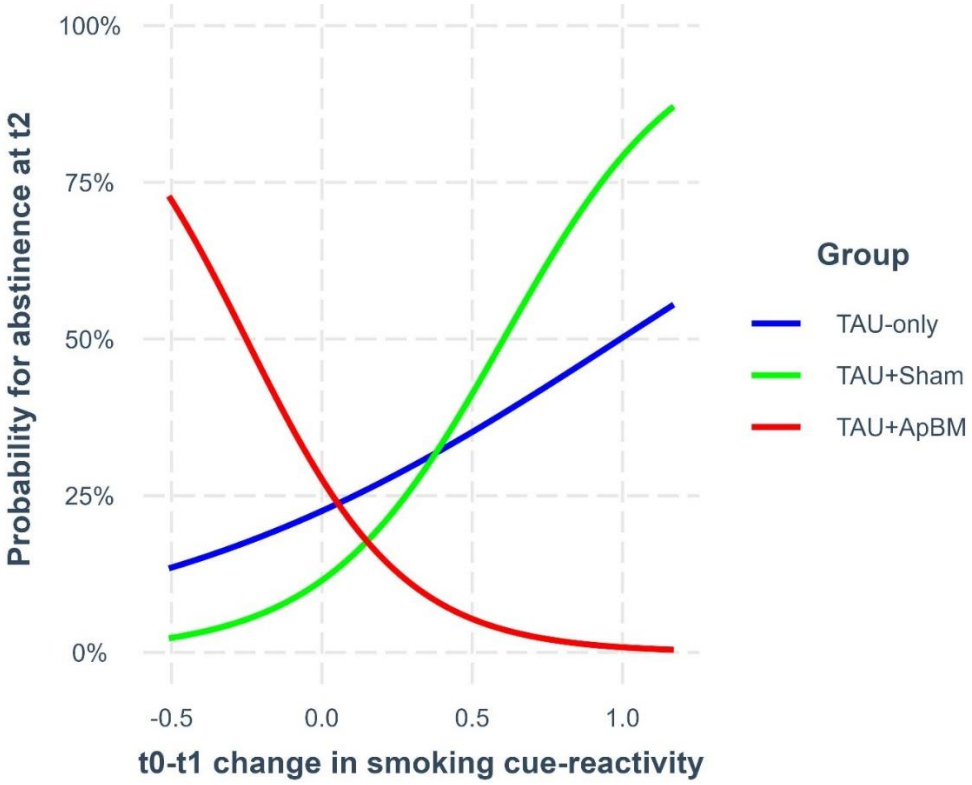
Region of interest	Effect	(df_1,df_2)	Abstinence at t_1		Abstinence at t_2	
			F	*p*	*F*	*p*
Selected from a meta-analysis on smoking cue-reactivity						
Left ACC	t_0-t_1 change	1,92	3.07	.083	2.71	.103
	t_0-t_1 change × group	2,92	0.97	.384	1.15	.322
Left angular gyrus	t_0-t_1 change	1,92	0.54	.465	1.47	.228
	t_0-t_1 change × group	2,92	0.30	.740	0.24	.788
Right thalamus	t_0-t_1 change	1,92	0.73	.395	1.60	.209
	t_0-t_1 change × group	2,92	0.42	.659	0.88	.417
Dorsal striatum	t_0-t_1 change	1,92	3.70	.058	1.07	.304
	t_0-t_1 change × group	2,92	0.60	.549	0.69	.502
Regions with [smoking > neutral] at t_0 in the present sample						
Right MCC	t_0-t_1 change	1,92	1.01	.318	1.29	.258
	t_0-t_1 change × group	2,92	0.26	.769	1.05	.354
Right supramarginal gyrus	t_0-t_1 change	1,92	0.81	.370	0.79	.377
	t_0-t_1 change × group	2,92	0.53	.592	3.27	**.042**[1]
Right precuneus	t_0-t_1 change	1,92	0.13	.718	1.04	.309
	t_0-t_1 change × group	2,92	0.58	.561	5.25	**.007**[1]
Derived from alcohol ApBM studies						
Amygdala	t_0-t_1 change	1,92	4.28	**.041**[1]	3.03	.085
	t_0-t_1 change × group	2,92	1.50	.230	1.41	.250
Nucleus accumbens	t_0-t_1 change	1,91	0.37	.547	<0.01	.991
	t_0-t_1 change × group	2,91	1.45	.239	0.35	.704
Medial prefrontal cortex	t_0-t_1 change	1,91	2.31	.132	3.83	.053
	t_0-t_1 change × group	2,91	3.04	.053	2.44	.092

Note. *df* = Degrees of freedom; t_1 = Post-intervention; t_2 = Follow-up; ACC = anterior cingulate cortex; MCC = middle cingulate cortex.

[1] non-significant after Benjamini-Hochberg correction.

Figure 5-III

Interaction of t_0-t_1 Smoking Cue-Reactivity Changes and Group on Long-Term Abstinence in the Right Precuneus



Note. Higher positive values in t_0-t_1 change indicate a greater decrease in smoking cue-reactivity, whereas higher negative values indicate a greater increase. TAU = Treatment-as-usual; ApBM = Approach bias modification; t_0 = Baseline; t_1 = Post-intervention; t_2 = 6-month follow-up.

To further explore this interaction regarding behavioral correlates, we conducted an exploratory analysis examining the interaction between group (0: TAU-only and TAU+Sham combined; 1: TAU+ApBM) and cue-reactivity changes in the right precuneus on AAT performance. Specifically, we focused on RT changes for pushing untrained smoking-related stimuli, as both the precuneus and the supramarginal gyrus are thought to play a significant role in visuomotor processes, including the integration of visual input with motor planning and

the preparation of automatized motor responses, such as guiding hand movements when reaching for objects (Jeannerod & Jacob, 2005; Yalachkov et al., 2010). A trend toward significance emerged (β = -87.74, *95% CI* [-177.04 to 1.57], p = .054), suggesting that in the TAU+ApBM group, increased cue-reactivity in the right precuneus was associated with a trend toward faster pushing of untrained smoking-related stimuli (Spearman's r = -.31, p = .072). In contrast, the control groups showed a near-zero correlation (r = .07, p = .563).

Hypothesis 3: Behavioral Outcomes and Association with Smoking Cue-Reactivity

At t_0, participants pushed smoking-related stimuli faster than they pulled them, resulting in a significant negative AAT effect score (avoidance bias; Z = -3.50, p < .001, r = 0.27; see Table 2-III for descriptive statistics). During the cue-reactivity task, craving ratings were significantly higher after smoking-related than neutral blocks (Z = 8.01, p < .001, r = 0.75). No significant group differences were observed in either behavioral variable at t_0, ps ≥ .299. Regarding intervention effects, both the AAT effect scores and craving ratings after smoking-related blocks significantly decreased from t_0 to t_1 across the sample, suggesting stronger avoidance biases and reduced craving in response to smoking-related stimuli post-intervention. However, these reductions did not significantly differ between groups (see Table 2-III).

In terms of associations between behavioral and neural outcomes, the only significant correlation (non-significant after FDR-correction) was that higher reductions in cue-reactivity in the left ACC were associated with greater reductions in craving ratings after smoking-related blocks (β = 33.80, *95% CI* [7.27 to 60.33], p = .013, p_{FDR} = .131; see Table 4-III). No significant group effects emerged, suggesting similar associations between behavioral and neural outcomes across groups. Supplementary analyses showed no significant associations between changes in cue-reactivity and smoking-related variables (cigarettes per day, tobacco dependence severity, CO value), nor did group moderate these associations (see Appendix B.1).

Table 4-III

Results of the ANOVAs (Omnibus Tests) for the Effects of Time and Time × Group on Behavioral Variables

Region of interest	Effect	AAT effect score			Craving ratings		
		(df_1,df_2)	*F*	*p*	(df_1,df_2)	*F*	*p*
Selected from a meta-analysis on smoking cue-reactivity							
Left ACC	t_0-t_1 change	1,91	0.42	.520	1,92	6.40	**.013**[1]
	t_0-t_1 change × group	2,91	1.76	.178	2,92	0.66	.520
Left angular gyrus	t_0-t_1 change	1,91	2.30	.133	1,92	1.31	.254
	t_0-t_1 change × group	2,91	2.29	.107	2,92	0.08	.924
Right thalamus	t_0-t_1 change	1,91	2.60	.110	1,92	0.92	.339
	t_0-t_1 change × group	2,91	1.47	.235	2,92	0.76	.470
Dorsal striatum	t_0-t_1 change	1,91	1.16	.284	1,92	0.003	.956
	t_0-t_1 change × group	2,91	1.11	.334	2,92	0.13	.875
Regions with [smoking>neutral] at t_0 in the present sample							
Right MCC	t_0-t_1 change	1,91	2.03	.158	1,92	2.83	.096
	t_0-t_1 change × group	2,91	2.20	.117	2,92	1.74	.181
Right supramarginal gyrus	t_0-t_1 change	1,91	1.68	.194	1,92	2.00	.160
	t_0-t_1 change × group	2,91	1.29	.281	2,92	1.92	.153
Right precuneus	t_0-t_1 change	1,91	0.20	.654	1,92	0.09	.760
	t_0-t_1 change × group	2,91	0.42	.659	2,92	1.76	.179
Derived from alcohol ApBM studies							
Amygdala	t_0-t_1 change	1,91	0.55	.460	1,92	0.20	.652
	t_0-t_1 change × group	2,91	0.38	.685	2,92	1.05	.354
Nucleus accumbens	t_0-t_1 change	1,90	1.86	.177	1,91	1.27	.262
	t_0-t_1 change × group	2,90	1.31	.276	2,91	0.66	.521
Medial prefrontal cortex	t_0-t_1 change	1,90	0.53	.467	1,91	2.05	.156
	t_0-t_1 change × group	2,90	0.54	.587	2,91	0.08	.923

Note. *df* = Degrees of freedom; t_0 = Baseline; t_1 = Post-intervention; AAT = Approach-avoidance task; ACC = anterior cingulate cortex; MCC = middle cingulate cortex.

[1] non-significant after Benjamini-Hochberg correction.

Reliability of Measures

The reliability of AAT effect and CDS-12 scores (tobacco dependence severity) was estimated as good to excellent (≥ .64), whereas smoking cue-reactivity measures showed poor reliability (ranging from -.36 to .28; see Appendix A.5; Hedge et al., 2018).

Discussion

This fMRI study investigated the effects of ApBM on neural smoking cue-reactivity in a sub-sample ($N = 117$) of participants from a randomized-controlled trial examining the efficacy of ApBM as an add-on to smoking cessation treatment (TAU) in adults with chronic, moderate-to-heavy tobacco dependence. TAU+ApBM did not significantly reduce smoking cue-reactivity compared to TAU+Sham and TAU-only, aligning with clinical outcomes that showed no added benefit of ApBM (Wittekind et al., under review). However, preliminary evidence suggests that ApBM may moderate the relationship between changes in cue-reactivity in sensorimotor regions (precuneus, supramarginal gyrus) and long-term abstinence, with increased cue-reactivity in these regions predicting higher abstinence probability. Overall, the findings contrast with reduced alcohol cue-reactivity in reward-related regions after ApBM in AUD (C. E. Wiers et al., 2015). In the following, potential explanations for these discrepancies are discussed.

First, chronic smoking may involve neural mechanisms that differ from those underlying AUD. ApBM is based on the assumption that SUDs are driven by strong approach biases toward drug cues (Kakoschke et al., 2017), mediated by heightened activity in subcortical mesolimbic structures (Robinson & Berridge, 2025). However, we observed *hypo*activation in mesolimbic structures (e.g., thalamus, striatum) in response to smoking-related versus neutral stimuli, challenging this assumption in the context of chronic smoking. Instead, *hyper*activation was found in the left ACC, right MCC, right precuneus, and right supramarginal gyrus—regions associated with response preparation (precuneus, supramarginal gyrus; Yalachkov et

al., 2010) and motor coordination and control (ACC[24], MCC; Rolls, 2019; Vogt, 2016). This suggests that, in individuals with chronic tobacco dependence, smoking-related stimuli may elicit automatized, habitual motor responses rather than incentive salience processes (Yalachkov et al., 2010). Thus, interventions targeting the inhibition of automatized, habitual actions may prove more effective and merit further investigation.

Second, the smoking-related stimuli used in the ApBM training may have lacked personal relevance, limiting their ability to elicit and modify reward-related brain activity. Given the habitual nature of heavy and chronic smoking (Ray et al., 2020), incorporating individualized smoking- and environmental cues may be crucial to eliciting appetitive responses (e.g. Conklin et al., 2019). Third, unlike C. E. Wiers et al. (2015) who conducted ApBM in a clinical setting with alcohol-abstinent inpatients, the training in our study was delivered at home. Notably, evidence suggests that interventions like ApBM are more effective in institutional settings (Jones & Sharpe, 2017). It may therefore be warranted to examine the neural effects of smoking ApBM with personalized and contextualized stimuli and delivered in an institutional setting.

While no significant group effects on smoking cue-reactivity changes emerged, reactivity decreased in the left ACC, right MCC, right precuneus, and right supramarginal gyrus across the whole sample. Accordingly, smoking cue-reactivity reductions within regions involved in response preparation (precuneus, supramarginal gyrus; Yalachkov et al., 2010) and motor coordination and control (ACC, MCC; Rolls, 2019; Vogt, 2016) may be relevant for smoking cessation; however, their specific role remains unclear due to limited associations with clinical or behavioral outcomes. Nevertheless, three observed associations warrant attention (all non-significant after FDR-correction). First, a greater reduction in ACC cue-reactivity was significantly associated with stronger craving reduction post-intervention, supporting prior

[24] Notably, the ACC is involved not only in motor-related functions but also in reward processing (Rolls, 2019). However, given the observed *hypo*activation in mesolimbic regions alongside *hyper*activation in visuomotor areas, it seems more plausible to interpret smoking cue-reactivity in the ACC as reflecting the integration of motor-related signals.

findings on the role of the ACC in subjective cue-induced craving (Janes et al., 2020). Second, a greater decrease in amygdala cue-reactivity was linked to a higher probability of short-term abstinence (post-intervention), suggesting that reduced incentive salience attribution may facilitate short-term smoking cessation (Warlow & Berridge, 2021). Third, preliminary evidence suggests that ApBM may moderate the relationship between long-term abstinence probability and cue-reactivity in the precuneus and supramarginal gyrus. Specifically, among participants who received TAU+ApBM, *increased* cue-reactivity significantly (precuneus) or at trend level (supramarginal gyrus: p=.061) predicted higher abstinence probability at the 6-month follow-up. In contrast, in the TAU+Sham and TAU-only groups, abstinence probability tended to increase as cue-reactivity *decreased*. Both the precuneus and the supramarginal gyrus are implicated in visuomotor processes, such as integrating visual input with motor planning and preparing automatized motor responses, such as movement guidance towards an object (Jeannerod & Jacob, 2005; Yalachkov et al., 2010). Accordingly, the moderating effect of ApBM may indicate that consistently executing avoidance (i.e., "push") movements toward smoking-related stimuli strengthened automatized tendencies to disengage from such cues. Over time, this may have facilitated avoidance responses when encountering smoking-related cues in daily life, thereby promoting long-term abstinence. Supporting this interpretation, cue-reactivity increases in the precuneus correlated weakly to moderately with faster push movements toward *untrained* (i.e., not included in ApBM training) smoking-related stimuli within the TAU+ApBM group (r = -.31, p = .072). However, this interpretation remains speculative, and the absence of overall ApBM superiority suggests that heightened smoking cue-reactivity in visuomotor areas may only benefit a small subgroup, requiring further research.

Limitation

Our results should be interpreted against important limitations. First, the time since participants' last cigarette before the scan session was not assessed for consideration in statistical analyses, as recommended for drug cue-reactivity studies (Ekhtiari et al., 2022). Thus, it remains unclear whether nicotine satiation status may have confounded the results. Second, the cue-reactivity paradigm included both trained smoking-related stimuli from the ApBM training and untrained smoking-related stimuli to ensure consistency between the AAT and cue-reactivity paradigm, facilitating the analysis of behavioral and neural reactivity to the same stimuli. However, since stimuli were randomly presented across smoking-related blocks, it was not possible to analyze training effects or generalization to untrained stimuli. Thus, it remains unclear whether observed neural changes reflect training-specific effects or generalized responses. Third, the split-half reliability of cue-reactivity outcome measures in each ROI was unsatisfactory (Hedge et al., 2018), potentially leading to spurious findings or obscure effects (see Appendix A.5; Loken & Gelman, 2017; Parsons et al., 2019). Thus, findings should be interpreted with caution, and replication is needed to draw firm conclusions. Overall, low reliability appears to be a common problem in drug cue-reactivity tasks, underscoring the need for systematic improvements in the reliability of outcome measures (Bach et al., 2022; Sangchooli et al., 2024).

Conclusion

This study is the first to examine the effects of ApBM on neural smoking cue-reactivity. Unlike findings in AUD, our results do not provide convincing evidence that ApBM reduces cue-reactivity in reward-related brain regions. Future research should explore alternative intervention targets (e.g., automatized, habitual motor responses toward smoking-related stimuli) and investigate the efficacy and neural mechanisms of training procedures aimed at these processes.

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STUDY IV

Efficacy and Working Mechanisms of a Go/No-Go Task-Based Inhibition Training in Smoking: A Randomized-Controlled Trial

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Efficacy and Working Mechanisms of a Go/No-Go Task-Based Inhibition Training in Smoking: A Randomized-Controlled Trial

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Abstract

Objective: Deficits in inhibitory control contribute to smoking behavior. Inhibitory control training (ICT), which involves repeatedly inhibiting responses to general or substance-related stimuli, shows promise in reducing problematic substance use. This preregistered randomized-controlled trial is the first to investigate the efficacy of general and smoking-specific Go/No-Go task-based ICT on smoking behavior compared to control groups receiving no ICT. Three potential working mechanisms were examined: inhibitory enhancement, automatic stimulus-stop associations, and stimulus devaluation. **Method**: Individuals who smoke (N = 122) were randomly assigned to complete 28 sessions of smoking-specific Go/No-Go, general Go/No-Go, Sham training, or to a Waitlist control condition. Clinical outcomes included daily cigarettes (primary outcome), carbon monoxide levels, tobacco dependence severity, and craving, assessed at post-intervention and 3-month follow-up. **Results**: Go/No-Go training resulted in a significantly greater reduction in tobacco dependence (β = -0.88, p = .004) and craving (β = -4.31, p = .012) post-intervention compared to both control groups. The greater reduction in craving remained significant when compared to the Sham training group only (β = -4.64, p = .026). No significant effects of group were observed on daily cigarette consumption (β = -1.97, p = .093) or carbon monoxide levels (β = 2.16, p = .818) post-intervention. At the 3-month follow-up, no significant effects of group emerged (all ps > .794). Smoking-specific Go/No-Go training did not outperform general Go/No-Go training (all ps > .075). No working mechanism for clinical outcome improvements was identified. **Conclusions**: Preliminary evidence suggests that (smoking-specific) Go/No-Go training reduces tobacco dependence severity and craving post-intervention in individuals who smoke compared to non-ICT-based control conditions. Its efficacy as an add-on in smoking cessation needs to be investigated.

Clinical trial registration number: DRKS00014652

Keywords: smoking, inhibitory control training, response inhibition, Go/No-Go

Introduction

The inability to control drug consumption is a core symptom of substance use disorders, including smoking (American Psychiatric Association, 2013). In terms of dual-process models, problematic substance use has been conceptualized as an imbalance between two interacting systems: the impulsive and the reflective system. The impulsive system is characterized by strong, automatically activated, associative processes, while the reflective system is resource-dependent and comprises more-controlled processes such as inhibitory control (Bechara, 2005; Deutsch & Strack, 2006). According to the Incentive Sensitization Theory (IST) of addiction (Robinson & Berridge, 1993), this imbalance results from (associative) learning processes and neuro-adaptive changes. More specifically, it is argued that repeated drug use is associated with a sensitization of the mesolimbic reward system. This *incentive salience* leads to biased processing of drug-related stimuli and a strong motivation for drugs ("wanting"; Robinson & Berridge, 1993). Importantly, in the case of problematic substance use, it has been postulated that the strong impulsive motivational processes cannot sufficiently be inhibited by the more controlled processes (Stacy & Wiers, 2010).

Corroborating these theoretical claims, it has been shown that problematic substance use is typically associated with different cognitive biases (e.g., attention biases [Field & Cox, 2008], approach biases [Kakoschke et al., 2019; Loijen et al., 2020]) and deficits in inhibitory control, such as response inhibition ability (e.g., Smith et al., 2014). Based on theoretical assumptions and neurobiological findings, different avenues have been pursued to exert positive effects on problematic substance use behavior (Verdejo-Garcia, 2016): on the one hand, procedures including substance-related stimuli, termed Cognitive Bias Modification (CBM, Koster et al., 2009), have been developed to directly alter the cognitive biases to induce more functional information processing. On the other hand, there are training regimes that aim to improve general cognitive abilities, for example, working memory or inhibitory control. In

the case of *inhibitory control training* (ICT), training regimes are mostly based on the Stop-Signal Task (SST, Logan & Cowan, 1984) and the Go/No-Go (GNG) Task (Drewe, 1975; Luria, 1973) paradigms, with the latter being utilized more frequently. During training, participants need to respond to Go stimuli while inhibiting responses to No-Go stimuli (Allom et al., 2016; Jones et al., 2016). Although the designation suggests that general inhibitory abilities are targeted, according to Wiers (2018), trainings including substance-related stimuli fall within the CBM framework. In general, CBM has shown positive effects on substance use disorders, including alcohol and smoking; however, the findings for smoking have been less promising (Boffo et al., 2019; Wittekind et al., 2025). Regarding the efficacy of ICT, two meta-analyses have shown that trainings including substance-related stimuli exert positive effects on eating behavior and alcohol consumption (Allom et al., 2016; Jones et al., 2016).

In smoking research, only a few studies have assessed the efficacy of GNG task-based ICT including smoking-related stimuli. Their results rather consistently suggest that smoking-specific GNG training is *not* more effective in reducing smoking behavior compared to control GNG training (e.g., Adams et al., 2017; Bos et al., 2019; Hughes et al., 2021). However, two key methodological limitations must be considered when interpreting earlier findings. First, except for Adams et al. (2017) who utilized a 75:25 Go/No-Go trial ratio (see Table F.1-IV, Appendix F for a study comparison), all previous studies employed a 50:50 trial ratio, resulting in an equiprobable distribution of Go and No-Go trials. Notably, equiprobable designs have been shown to place lower demands on inhibitory control (Wessel, 2018), potentially diminishing training effects. Supporting this, a recent study on the efficacy of GNG training in alcohol use disorder (AUD) demonstrated a positive add-on effect in the treatment of AUD, but only if a higher Go/No-Go trial ratio (i.e., 75:25) was used (Stein et al., 2023). Second, all previous studies compared a smoking-specific GNG training (i.e., smoking-related stimuli [almost] consistently paired with a No-Go response) with a GNG control training that either

comprised smoking-related stimuli in only 50% of the No-Go trials (Adams et al., 2017) or that included neutral stimuli in No-Go trials (Bos et al., 2019; Hughes et al., 2021). As a result, the control groups in these studies also received an inhibition training, albeit without the consistent inhibition of smoking-related stimuli, which may have primarily enhanced general inhibitory control abilities rather than specifically targeting inhibition of smoking-related stimuli. Following the theoretical assumption that substance abuse is characterized by both easily activated impulsive motivational processes toward substance-related stimuli *and* deficits in inhibitory control (Stacy & Wiers, 2010), it is conceivable that these control interventions also exerted positive effects on smoking behavior by improving general inhibitory control abilities. Finally, as both interventions were potentially effective, no significant differences in their efficacy might have been observed.

Given these two methodological limitations of previous studies, it would be misleading to conclude that smoking-specific GNG training is generally ineffective in smoking. To unravel the question whether high-demand GNG trainings (i.e., Go/No-Go trial ratio: 75:25)—with and without smoking-specific stimulus material—are effective and outperform control trainings, it is crucial to include a "real" Sham training condition which does not improve general inhibitory control abilities. The design of the present study closes this gap.

Working Mechanisms

Three working mechanisms have been proposed to potentially mediate the effects of ICT on behavior. First, the *stimulus devaluation* hypothesis (Veling et al., 2008) proposes that the positive valence of an appetitive stimulus diminishes when it is consistently paired with the inhibition of approach behavior. Second, the *automatic-inhibition* hypothesis assumes that pairing stimuli with a stop response leads to the formation of automatic stimulus-stop associations, whereby response inhibition becomes stimulus-driven and automatically activated (Verbruggen & Logan, 2008). Third, strengthening of *top-down inhibitory control* has

been proposed as a potential working mechanism; however, this has been considered as rather unlikely given that the GNG task demands primarily automatic, bottom-up inhibition (Houben & Aulbach, 2023; Verbruggen & Logan, 2008).

The stimulus devaluation account has been examined most frequently. Studies using explicit measures (e.g., valence ratings of stimuli) rather consistently revealed that if a response toward an appetitive stimulus has to be inhibited, this stimulus is evaluated as less positive (e.g., Scholten et al., 2019; Veling et al., 2017); however, studies investigating implicit measures (e.g., positive associations toward smoking-related stimuli assessed with the Implicit-Association Test [IAT; Greenwald et al., 1998]) yielded inconsistent findings regarding stimulus devaluation (e.g., Houben et al., 2012; Houben et al., 2011; Jones et al., 2016). Besides, there is also evidence supporting the assumptions of the automatic-inhibition hypothesis. For instance, research has shown that after ICT training, participants exhibited greater inhibitory control toward stimuli that were included in the training intervention (e.g., Bowditch et al., 2016; Verbruggen & Logan, 2008). Lastly, it has not been investigated systematically whether GNG training indeed strengthens top-down inhibitory control (e.g., by using a GNG task with stimuli different from those used in the GNG training).

The Present Study

The objective of this study was to assess the efficacy of ICT based on the GNG task as a stand-alone training in reducing tobacco consumption and craving among adults who smoke. Participants were randomized to one of four conditions: (1) smoking-specific GNG training, (2) general GNG training (i.e., smoking-unrelated stimuli only), (3) Sham training, and (4) Waitlist control (WLC). In terms of clinical outcomes, we hypothesized that (a) GNG training (smoking-specific and general) would lead to a significant reduction of smoking-related outcomes after 28 days of training and at the 3-month follow-up compared to the control groups. If GNG training shows superiority, we hypothesized (b) that the smoking-specific GNG

training would outperform the general GNG training. If no superiority was observed, we hypothesized (c) that the smoking-specific GNG training condition alone would be superior compared to both control conditions. Finally, we hypothesized (d) that the potential superiority of the (smoking-specific) GNG training condition remains robust when compared to the Sham condition only. In terms of potential working mechanisms, we expected that (e) improvements in clinical outcomes would be associated with enhanced performance in a general (i.e., strengthened *top-down inhibitory control*) and/or smoking-specific GNG task (i.e., formation of *automatic stimulus-stop associations*), as these represent the targeted processes of GNG training. However, the study also conducted exploratory analyses of several other task measures to assess strengthened *top-down inhibitory control*, formation of *automatic stimulus-stop associations*, and *stimulus devaluation* as potential working mechanisms.

Methods

Participants

An a-priori power analysis conducted with G*Power (Faul et al., 2007) determined that a sample size of 120 participants (i.e., 30 per group) was required to detect a medium effect size (Jones et al., 2016) for a within-between interaction, given $\alpha = .05$, $1\text{-}\beta = .90$, and an anticipated dropout rate of 20% (Kiss et al., 2016, unpublished results). A total of $N = 122$ individuals who smoke were included in the present study. Inclusion criteria were: (1) age 18 to 70 years, (2) carbon monoxide (CO) level in the exhaled air of ≥ 10 ppm, (3) a total score of ≥ 3[25] in the Fagerström Test for Cigarette Dependence (FTCD; Fagerström, 2012; originally named as Fagerström Test for Nicotine Dependence [FTND]; Heatherton et al., 1991), (4) no use of nicotine replacement therapy (including e-cigarettes), (5) not actively involved in pharmacological or psychological smoking cessation treatment, and (6) willingness to abstain from any therapy for smoking cessation during study participation. Exclusion criteria were: (1)

[25] A FTCD score of at least 3 indicates a minimum level of moderate dependence (AWMF, 2021).

current or previous diagnosis of severe psychiatric (e.g., schizophrenia, bipolar disorder) or neurological (e.g., epilepsy, Parkinson disease, multiple sclerosis) disorders, (2) moderate to severe substance use disorder other than tobacco within the last 12 months (i.e., ≥ 4 fulfilled criteria according to DSM-5 assessed with the Mini International Neuropsychiatric Interview [MINI; Sheehan, 2016]), (3) acute suicidality, (4) current pregnancy or nursing period, (5) uncorrectable visual impairments, and (6) insufficient German language skills. Participants were recruited through various means, including notices in university buildings, ads on the university mailing list, flyers displayed in pharmacies and physicians' waiting rooms, and social media platforms such as Facebook.

The authors assert that all procedures contributing to this work comply with the ethical standards set by the relevant national and institutional committees on human experimentation, as well as with the Helsinki Declaration of 1975, revised in 2008. The study received approval from the ethics committee at the Ludwig-Maximilians-University Munich (72_Wittekind_b; 06/03/2018). The privacy rights of participants have been observed, and all participants provided written informed consent.

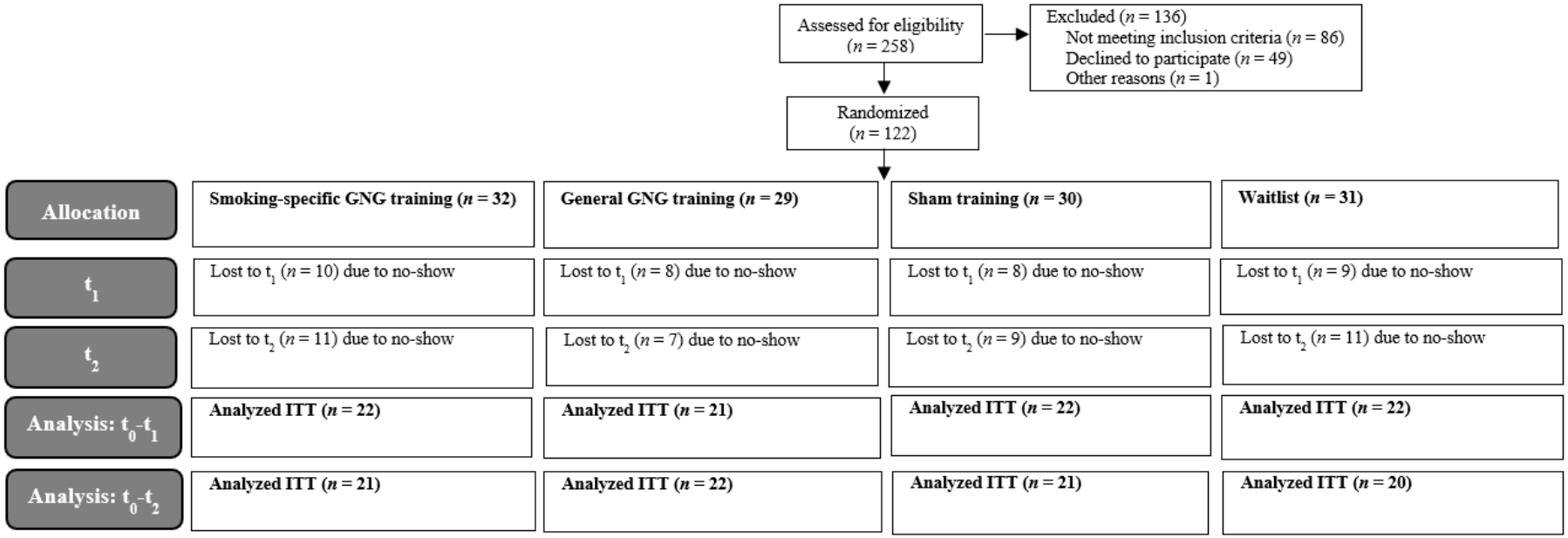
Design and Procedure

The present study consisted of a randomized-controlled, double-blind, parallel-group trial aiming to examine the efficacy of GNG task-based ICT in reducing tobacco consumption and craving (see Appendix A for more details on the study procedure; e.g., an overview of all measures assessed). At the end of the baseline assessment, participants were randomly assigned to one of four study arms (allocation ratio: 1:1:1:1): (1) smoking-specific GNG training, (2) general GNG training, (3) Sham training, and (4) WLC. The randomization plan was computer-generated (www.randomizer.org). Only authors who did not enroll or assess participants had access to the randomization sequence. After completing the baseline assessment (t_0), participants received a sealed envelope containing information on whether they would receive

training and, if so, instructions for performing the computer-based training daily within the next 28 days by using Inquisit (version 4, www.millisecond.com). Therefore, assessors were blinded in all assessments. Participants in the training groups were blinded about the specific types of training that were available, while blinding was not feasible for the WLC group. Participants were re-assessed upon training completion (t_1; 4 weeks after t_0) and at follow-up (t_2; 3 months after t_1). See Figure 1-IV for the flow of participants.

Figure 1-IV

Flow of Participants



Note. As linear mixed-effects models (LMMs; Gueorguieva & Krystal, 2004) were used for the statistical analyses, all available data points could be considered. This approach allowed each participant to be included in the statistical models, even if data from the t_1 and/or t_2 assessment(s) were missing. Some participants (n = 8) who did not show up at the t_1 assessment completed the t_2 assessment. GNG = Go/No-Go; ITT = Intention-to-treat.

Training Interventions

Each of the three training interventions included 20 practice trials and 320 training trials. The stimuli used were pictures from a *training set* of 20 smoking-related and 20 neutral pictures (see Appendix C for the picture selection and randomization of stimuli for tasks and trainings). In each training trial, participants were presented with a single picture, though the type of stimuli and the instructions varied between the three training interventions.

Two versions of GNG task-based ICT were employed. In the smoking-specific GNG training, participants were presented with 20 smoking-related and 20 neutral stimuli. They were instructed to press the space bar as quickly and accurately as possible using the index finger of their dominant hand when a neutral stimulus was presented, and to withhold their response when a smoking-related stimulus was presented (i.e., content-relevant feature task instruction). The 20 neutral stimuli were presented 12 times each (240 Go trials, 75% of all trials; prepotent response), while the 20 smoking-related stimuli were presented four times each (80 No-Go trials, 25% of all trials). The general GNG training differed in that it presented 40 pictures depicting only neutral content, each framed in color. Participants responded based on the color of the frame (i.e., content-irrelevant feature task instruction), with the instruction (Go trials: yellow frame vs. Go trials: blue frame) counterbalanced across participants. Again, a 75:25 Go/No-Go trial ratio was used (i.e., each picture was displayed six times for Go responses and two times for No-Go responses). In both GNG trainings, the inter-trial interval was 500 ms. If participants missed the response in a Go trial (i.e., omission error) or responded during a No-Go trial (i.e., commission error), the error message “error” was presented for 400 ms.

The Sham training was conceptualized as a categorization task and used the same 40 stimuli as in the smoking-specific GNG training. To achieve the same exposure effect to stimulus content, neutral pictures were presented 12 times (240 trials, 75 % of the trials), and smoking-related pictures were presented four times (80 trials, 25% of the trials). Participants

were instructed to categorize smoking-related and neutral pictures by pressing the "D" or "K" key (counterbalanced across participants). Pictures disappeared only after a correct response (inter-trial interval: 250 ms; red "X" for 400 ms after incorrect responses). Participants in the WLC received no training during the actual training interval, but access to the smoking-specific GNG training upon study completion.

Measures

Test sessions were carried out individually in a laboratory at the university. Questionnaires were administered in paper-pencil format, while reaction time tasks were computer-based and conducted using Inquisit.

Clinical Assessments and Ratings

Basic smoking- and drug-related information was collected during the baseline interview (e.g., smoking duration, daily cigarettes). As an objective measure of cigarette consumption, the level of CO in the participants' breath was measured (used as a criterion for eligibility and clinical outcome). Tobacco dependence was evaluated using the 6-item FTCD (Fagerström, 2012; Heatherton et al., 1991; used as a criterion for eligibility and clinical outcome). Six participants did not answer the FTCD items at t_2 because they had stopped smoking, reporting zero cigarettes per day. Therefore, their FTCD score was recorded as zero. For the FTCD, Cronbach's alpha was estimated at $\alpha = .481$, *95% CI* [.334 – .587]. Craving was assessed through the Questionnaire of Smoking Urges, brief version (QSU; Cox et al., 2001), a 10-item questionnaire on current smoking urges using a 7-item Likert-like scale (used as a clinical outcome; $\alpha = .805$, *95% CI* [.738 – .851]). To assess how committed participants were to abstain from smoking, the Thoughts About Abstinence Scale (TAAS; Hall et al., 1990) was administered. General intelligence was screened with a German vocabulary test (Wortschatztest [WST]; Schmidt & Metzler, 1992). The raw test scores were converted into IQ scores according to the manual. Participants' trait impulsivity was assessed by using the 15-

item Barratt Impulsiveness Scale (BIS-15; German version: Meule et al., 2011; Spinella, 2007; α = .739, *95% CI* [.650 – .796]).

Experimental Tasks to Assess Potential Working Mechanisms

Conceptually similar to the GNG task-based ICTs (i.e., inter-trial interval, error message, response instruction, 75:25 Go/No-Go trial ratio), two GNG tasks were employed to assess changes in performance outcomes as the targeted processes of the GNG trainings. The GNG task paradigm is designed to assess response inhibition, with a specific focus on the ability to engage in automatic bottom-up inhibition or action restraint (Schachar et al., 2007; Verbruggen & Logan, 2008). Additionally, the study exploratory investigated working mechanisms using the following task/questionnaire measures: the SST and the BIS-15 to assess strengthened *top-down inhibitory control*, and the Approach-Avoidance Task [AAT; Rinck & Becker, 2007] and IAT, both evaluating *stimulus devaluation*. The set-up of these tasks is described in Appendix B.

GNG Task. In the general GNG task, stimuli were white digits ranging from 1 to 8. Each digit was presented 40 times in a fully randomized order, resulting in 320 test trials. Participants had to respond to all digits, except for "3" and "6" (response window: 1,000 ms). Since the general GNG task used digits as stimuli, which were not presented in the GNG trainings, it served to assess the strengthening of *top-down inhibitory control* as a potential working mechanism of the GNG trainings. The smoking-specific GNG task differed in that it presented 20 smoking-related and 20 neutral pictures framed in blue and yellow (see Appendix C for the picture selection procedure). Similar to the general GNG training, participants were instructed to respond based on the color of the frame. Since the smoking-specific GNG task included smoking-related stimuli for which inhibitory responses were trained during the smoking-specific GNG training, it can assess not only the mechanism of *top-down inhibitory control* but also the development of *automatic stimulus-stop associations* toward smoking-related stimuli

following the smoking-specific GNG training. Before performing the experimental tasks, participants completed eighteen training trials. Split-half reliability[26] for the general GNG task measure was estimated at r = .858, *95% CI* [.802 – .914], as well as for the smoking-specific GNG task for smoking-related trials at r = .613, *95% CI* [.529 – .696], and for neutral trials at r = .773, *95% CI* [.678 – .867].

Statistical Analysis

Data Preprocessing and Aggregation

For both the general and smoking-specific GNG task, the commission error (CE) rate was calculated (general: across all No-Go trials; smoking-specific: for smoking-related and neutral stimuli separately). No participant needed to be excluded for exceeding a 35% error rate on Go trials, which was established as the cutoff. The mean error rates of the GNG tasks, as well as the preprocessing and aggregation of measures for alternative potential working mechanisms, are described in Appendix D.

Strategy of Data Analysis

Data were preprocessed and analyzed using R, version 4.3.0 (R Core Team, 2023). The primary preregistered clinical outcome was the t_0-t_1 reduction in daily cigarette consumption (cigarettes per day [CPD]). Secondary clinical outcomes were t_0-t_1 reductions in the CO value, tobacco dependence (FTCD), current craving (QSU), and t_0-t_2 reductions in CPD, CO, and FTCD (with QSU not assessed at t_2). The targeted processes of the GNG trainings were the t_0-t_1 reduction in the CE rates of the GNG tasks (working mechanism: strengthening *top-down inhibitory control*). Specific for the smoking-specific GNG training group, the targeted process was the t_0-t_1 reduction in the CE rate in smoking-related trials (working mechanism: development of *automatic stimulus-stop associations*). The procedure for the statistical

[26] To analyze split-half reliabilities of all task measures, we used the R package *splithalfr* (Pronk, 2023) with 5,000 random splits and applied the Spearman-Brown correction.

analysis of measures for alternative potential working mechanisms is provided in Appendix E.2.

The analyses followed the intention-to-treat (ITT) approach in accordance with CONSORT guidelines (Moher et al., 2010). All available data were considered via linear mixed-effects models (LMMs; Gueorguieva & Krystal, 2004) using the *lme4* package [version 1.1-34] (Bates et al., 2015). Following the preregistration, we initially collapsed both the general and smoking-specific GNG training groups (GNG training groups) and both the Sham and WLC groups (control groups) to enhance statistical power. Thus, we first compared (a) the GNG training vs. control groups. If the GNG training condition proved to be superior, a comparison between (b) the smoking-specific and the general GNG training group was planned. If no superiority was observed, a comparison between (c) the smoking-specific GNG training group and both control groups was planned. Finally, we proposed to investigate (d) whether the potential superiority of GNG training remains robust when compared to the Sham group only. Dummy codes for time (t_1 coded as 0, 1, 0; t_2 coded as 0, 0, 1), group allocation, and their interaction were used to predict the outcome variables. For models that included both time effects, t_1 and t_2, we assumed that time effects vary across participants (i.e., random effects). Variables with group differences at the $p < .10$ level were considered as potential covariates. If adding a variable resulted in a better relative model fit, it was included in the linear mixed model as a covariate. The result tables of linear mixed model analyses provide information on whether and which variable was included in a linear mixed model as a covariate.

For our directional hypotheses on group × time interactions in each model, one-sided *p*-values were used for statistical inference. The Bonferroni correction was applied to interaction effects to account for multiple clinical outcomes ($n = 4$, see Table 3-IV, *p*-threshold: .05/4 = .0125) and working mechanisms ($n = 3$, see Table 5-IV, *p*-threshold: .05/3 = .01$\overline{6}$.). Significant

interaction effects were examined through post-hoc comparisons using the *emmeans* package (Lenth, 2024), adjusted with Bonferroni correction (*p*-threshold: .05/4 = .0125).

In addition to the preregistered statistical analyses, we conducted the following additional and exploratory analyses (methods and results are reported in Appendix E): (1) non-preregistered Bayesian analyses (Appendix E.1) to complement the inference statistics on clinical outcomes by quantifying the relative evidence for both the null (e.g., no group effect on t_0-t_1 changes) and the alternative (e.g., presence of a group effect on t_0-t_1 changes) hypothesis (Beard et al., 2016), (2) an investigation of whether group was associated with t_0-t_1 changes in other task/questionnaire measures, such as the SST and BIS-15 for assessing *top-down inhibitory control*, and the AAT and IAT, both of which evaluate *stimulus devaluation* (Appendix E.2), and (3) per-protocol (PP) analyses (Appendix E.3). A summary of the main findings is given in the Results section of the main manuscript.

Transparency and Openness

The data and analysis code are openly available in OSF at https://osf.io/rxu78/. The design of the study and its analysis were preregistered prospectively before data were collected (see German Clinical Trials Register, DRKS00014652; 24/04/2018).

Results

Sample Characteristics

Participants smoked an average of 19.55 cigarettes per day (*SD* = 9.34; range: 7–60), for 22.28 years (*SD* = 13.20; range: 1–56), and showed moderate tobacco dependence (FTCD: *M* = 5.23, *SD* = 1.85, range: 3–10; CO: *M* = 22.64, *SD* = 10.65, range: 10–54). For descriptive statistics and group comparisons of baseline characteristics, see Table 1-IV.

Table 1-IV

Descriptive Statistics and Group Comparisons for Sample Characteristics and Task-Related Variables at Baseline

Variables	GNG training groups		Control groups		Smoking-specific GNG training group		General GNG training group		Sham training group		Waitlist control group		
	n	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	Statistics
Baseline characteristics													
Age (years)	61	41.48 (12.28)	61	41.39 (13.86)	32	41.81 (12.40)	29	41.10 (12.36)	30	41.33 (13.69)	31	41.45 (14.25)	*ps* ≥ .824
Male[a] (%)	61	44.26	61	40.98	32	43.75	29	44.83	30	36.67	31	45.16	*ps* ≥ .642
High school graduation (%)	61	65.57	61	62.30	32	62.50	29	68.97	30	60.00	31	64.52	*ps* ≥ .773
Cigarettes per day (n)	61	19.48 (10.75)	61	19.62 (7.76)	32	18.03 (8.79)	29	21.07 (12.53)	30	19.67 (9.40)	31	19.58 (5.93)	*ps* ≥ .274
Smoking duration (years)	61	22.36 (12.69)	61	22.20 (13.80)	32	23.14 (12.27)	29	21.50 (13.31)	30	22.47 (13.45)	31	21.95 (14.34)	*ps* ≥ .618
CO value	61	22.79 (11.00)	61	22.49 (10.38)	32	21.34 (9.68)	29	24.38 (12.26)	30	22.57 (9.72)	31	22.42 (11.14)	*ps* ≥ .285
FTCD[b]	61	5.20 (1.78)	61	5.26 (1.93)	32	5.09 (1.80)	29	5.31 (1.77)	30	5.07 (2.03)	31	5.45 (1.84)	*ps* ≥ .639
QSU-brief[c]	59	30.42 (11.29)	60	26.97 (8.36)	31	29.77 (10.46)	28	31.14 (12.30)	30	25.37 (8.03)	30	28.57 (8.51)	(a) p = .061 (b)(c) *ps* ≥ .168 (d) ***p* = .017**
TAAS abstinence goals[d]	57	4.39 (1.32)	59	4.24 (1.69)	30	4.30 (1.44)	27	4.48 (1.19)	29	4.17 (1.73)	30	4.30 (1.66)	*ps* ≥ .526
TAAS desire to quit[e]	60	5.36 (2.37)	61	5.71 (2.04)	31	4.85 (2.33)	29	5.90 (2.34)	30	5.85 (1.85)	31	5.58 (2.23)	(a)(d) *ps* ≥ .323 (b) p = .090 (c) p = .073
BIS-15[f]	60	32.48 (5.52)	61	32.44 (6.23)	32	32.66 (5.40)	28	32.29 (5.73)	30	32.70 (5.68)	31	32.19 (6.81)	*ps* ≥ .798
WST-IQ[g]	61	104.56 (10.55)	61	105.15 (11.52)	32	104.12 (12.33)	29	105.03 (8.36)	30	103.67 (9.66)	31	106.58 (13.07)	*ps* ≥ .692
Task-related variables													
General GNG task CE rate													
all stimuli	61	19.20 (10.87)	61	15.31 (10.37)	32	17.81 (11.52)	29	20.73 (10.09)	30	16.46 (6.91)	31	14.19 (12.90)	(a) ***p* = .045** (b)(c)(d) *ps* ≥ .148
Smoking-specific GNG task CE rate													
smoking-related stimuli	61	7.66 (6.63)	61	4.75 (5.30)	32	7.19 (6.53)	29	8.19 (6.81)	30	5.00 (4.45)	31	4.52 (6.07)	(a)(d) ***ps* ≤ .026** (b) p = .600 (c) p = .056
neutral stimuli	61	6.93 (9.14)	61	5.00 (5.99)	32	7.73 (9.25)	29	6.03 (9.10)	30	4.42 (4.85)	31	5.56 (6.94)	(a)(b)(c) *ps* ≥ .137 (d) p = .091

Note. GNG = Go/No-Go; GNG training groups = collapsed general and smoking-specific GNG training group; control groups = collapsed Sham and Waitlist control group; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU-brief = Questionnaire on Smoking Urges, brief version; TAAS = Thoughts About Abstinence Scale; BIS = Barratt Impulsiveness Scale, 15-item version; WST = Wortschatztest (German vocabulary test); CE = Commission Error.

Baseline differences of continuous and categorical variables were assessed using chi-square and independent *t*-tests. Statistics refer to group comparisons (a) = GNG training vs. control groups; (b) = smoking-specific GNG training vs. general GNG training group; (c) = smoking-specific GNG training group vs. control groups; (d) GNG training groups vs. Sham training group. All baseline characteristic variables were collected via paper-pencil format, with the possibility that some questions might not have been answered, resulting in missing data. Therefore, the final sample sizes for each variable are indicated in the current table.

[a] collected on the concept of biological sex; [b] range: 0–10; [c] range: 10–70; [d] 6 = total abstinence, never use again, 5 = total abstinence, but realize a slip is possible, 4 = occasional use when urges strongly felt, 3 = temporary abstinence, 2 = controlled use, 1 = no goal; [e] total range: 0–9; [f] total range: 15–60; [g] total range: 60–139.

Training Compliance and Evaluation, Blinding, and Attrition

Overall, training evaluation and compliance were moderate (see Table 2-IV). In terms of training compliance, around half (51%) of the participants in the training groups completed at least 14 out of 28 (~ 50%) designated training sessions (M = 14.55; SD = 12.21)[27]. Blinding can be considered successful in the smoking-specific GNG training group, with only 27% correctly identifying their assigned training (see Table 2-IV). However, it was not successful in the general GNG training group, where 86% correctly identified their training. Importantly, the success of blinding was not predictive[28] for clinical outcomes at t_1, all $ps \geq .308$. The attrition rate was higher than the anticipated 20% for the power analysis, with 71% of the sample completing the t_1 assessment, 69% the t_2 assessment, and 62% all assessments. Attrition rates did not significantly differ across groups, all $ps \geq .552$. A comparison between completers and non-completers revealed that completers were more highly educated (p = .042), had a higher verbal intelligence (p < .001), lower trait impulsivity (p = .044), and a slightly higher (but non-significant) desire to quit than non-completers (completers: M = 5.77, SD = 2.25; non-completers: M = 4.96; SD = 2.02; total range: 0–9).

[27] Of the participants who completed t_1, 89% completed at least one training, with no significant differences between groups, p = .381. When analyses were restricted to these participants, the results remained unchanged.

[28] The classification of whether blinding was successful or not was only assessable for a minority of participants (due to, for example, the fact that participants in the WLC group were not blinded, because participants in the Sham group could not indicate that they received a Sham training, or missing data). So, it was not feasible to include blinding (successful: yes/no) as a covariate to the linear mixed models.

Table 2-IV

Descriptive Statistics and Group Comparisons for Training Compliance, Evaluation, and Blinding

Variables	Smoking-specific GNG training group	General GNG training group	Sham training group	Statistics
Compliance				
Number of participants who completed ≥ 14 training sessions (*n*/total *N*)	12/32	17/29	17/30	$p = .184$
Mean absolved training sessions [*M* (*SD*)]	11.94 (12.02)	15.14 (11.11)	16.77 (13.27)	$p = .119$
Evaluation				
Perceived effects on desire to smoke (no change/decrease/increase)	12/7/0	12/6/1	15/5/1	$p = .917$
Overall evaluation[a] [*M* (*SD*)]	2.84 (1.12)[b]	3.42 (1.71)[b]	3.32 (1.25)[c]	$p = .289$
Willing to use training again (*n*/total *N*)	12/19	9/20	11/22	$p = .504$
Blinding				
Not successful (*n*/total *N*)	6/22	18/21	–	$p < .001$

Note. Data on training evaluation and blinding are only available for participants who completed t_1. These data were collected via paper-pencil format, with the possibility that some questions might not have been answered, resulting in missing data. Therefore, the final sample sizes for each variable are indicated in the current table. Group differences of continuous and categorical variables were assessed using ANOVAs and chi-square/fisher's exact tests. GNG = Go/No-Go.

[a] 1 = very good to 6 = very bad; [b] $n = 19$, [c] $n = 22$

Outcome Analyses

Clinical Outcomes

Group Comparison (a): GNG Training Groups vs. Control Groups. All groups showed a significant reduction in clinical outcomes at t_1 and t_2, except the FTCD score at t_1 (see Tables 3-IV [inference statistics] and 4-IV [descriptive statistics]). For the primary clinical outcome (CPD from t_0 to t_1), there is insufficient evidence to suggest that the GNG training

groups showed a greater reduction compared to the control groups (effect of group × t_1 in a model without t_2 as predictor: β = -1.97, *95% CI* [-4.85 – 0.93], p = .093). Also, no significant interaction between group and t_1 was found for the CO value (see Table 3-IV).

However, the GNG training groups showed a significantly greater reduction in the FTCD and QSU scores at t_1 than the control groups (see Tables 3-IV and 4-IV, and Figure 2-IV [interaction plots]). Post-hoc pairwise comparisons revealed that the GNG training groups showed a significant decrease in the FTCD scores from t_0 to t_1, $t(92.2) = -5.29$, $p < .001$ (one-tailed), whereas the reduction in the control groups was not significant, $t(91.8) = -1.60$, $p = .114$. Additionally, the GNG training groups had significantly lower FTCD scores at t_1 compared to the control groups, $t(178.1) = -2.24$, $p = .013$ (one-tailed, non-significant after Bonferroni correction). For the QSU scores, post-hoc pairwise comparisons indicated that both the GNG training groups and the control groups exhibited significant reductions from t_0 to t_1 (GNG training groups: $t[94.4] = -5.34$, $p < .001$ [one-tailed]; control groups: $t[93.2] = -2.08$, $p = .040$, non-significant after Bonferroni correction). The GNG training groups did not show significantly lower QSU scores at t_1 compared to the control groups, $t(190.6) = -0.69$, $p = .246$ (one-tailed).

At t_2, there were no significant interactions with group for any of the clinical outcomes (see Table 3-IV). Overall, based on the findings from group comparison (a), it remained inconclusive whether the GNG training condition was superior. Therefore, both subsequent between-group analyses (i.e., [b] and [c]) were conducted.

Table 3-IV

Group Comparisons (a) to (d): Results of the Linear Mixed Effects Models for all Clinical Outcomes

Fixed effects	CPD[+]			CO			FTCD[1]			QSU[2,3]		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*
Group comparison (a): GNG training groups vs. control groups												
Intercept	19.62	17.33 – 21.92	**<.001**	22.49	19.75 – 25.23	**<.001**	5.54	5.01 – 6.07	**<.001**	23.77	20.44 – 27.09	**<.001**
Group	-0.15	-3.40 – 3.10	.929	0.30	-3.58 – 4.17	.881	0.11	-0.56 – 0.78	.754	1.68	-1.86 – 5.23	.350
Time (t_1)	-2.95	-5.04 – -0.86	**.007**	-4.22	-7.51 – -0.93	**.013**	-0.30	-0.75 – 0.15	.195	-2.86	-5.47 – -0.24	**.034**
Time (t_2)	-6.13	-8.67 – -3.58	**<.001**	-4.37	-8.57 – -0.18	**.043**	-1.47	-2.00 – -0.94	**<.001**	–	–	–
Group × t_1	-1.77	-4.74 – 1.19	.121	2.16	-2.51 – 6.83	.818	-0.88	-1.52 – -0.24	**.004**[*]	-4.31	-8.02 – -0.60	**.012**[*]
Group × t_2	1.49	-2.07 – 5.04	.794	2.68	-3.15 – 8.51	.816	0.46	-0.29 – 1.20	.885	–	–	–
Group comparison (b): smoking-specific GNG training vs. general GNG training group												
Intercept	21.07	17.28 – 24.85	**<.001**	24.38	20.25 – 28.51	**<.001**	5.31	4.65 – 5.97	**<.001**	31.09	27.14 – 35.03	**<.001**
Group	-3.04	-8.26 – 2.19	.252	-3.04	-8.73 – 2.66	.296	-0.22	-1.12 – 0.69	.637	-1.34	-6.79 – 4.11	627
Time (t_1)	-4.35	-7.70 – -1.01	**.011**	-3.91	-9.04 – 1.23	.139	-0.85	-1.62 – -0.08	**.031**	-7.26	-11.49 – -3.04	**.002**
Time (t_2)	-6.51	-9.56 – -3.45	**<.001**	-1.18	-6.08 – 3.72	.636	-1.14	-1.78 – -0.49	**.001**	–	–	–
Group × t_1	-0.58	-5.26 – 4.09	.403	3.24	-3.94 – 10.43	.812	-0.64	-1.71 – 0.43	.123	0.02	-5.87 – 5.92	.503
Group × t_2	3.72	-0.63 – 8.06	.950	-1.26	-8.63 – 6.10	.368	0.28	-0.65 – 1.20	.720	–	–	–
Group comparison (c): smoking-specific GNG training group vs. control groups												
Intercept	19.62	17.60 – 21.65	**<.001**	22.49	19.91 – 25.08	**<.001**	5.26	4.79 – 5.74	**<.001**	27.35	24.95 – 29.76	**<.001**
Group	-1.59	-5.04 – 1.86	.366	-1.15	-5.56 – 3.26	.609	-0.17	-0.98 – 0.64	.684	2.39	-1.72 – 6.50	.253
Time (t_1)	-2.93	-5.03 – -0.84	**.007**	-4.18	-7.76 – -0.59	**.024**	-0.30	-0.76 – 0.16	.208	-2.80	-5.31 – -0.28	**.032**
Time (t_2)	-6.05	-8.59 – -3.52	**<.001**	-4.08	-8.08 – -0.08	**.048**	-1.46	-1.99 – -0.94	**<.001**	–	–	–
Group × t_1	-2.17	-5.79 – 1.45	.121	3.23	-2.95 – 9.41	.847	-1.20	-2.00 – -0.40	**.002**[*]	-4.43	-8.77 – -0.09	**.024**
Group × t_2	3.33	-1.02 – 7.67	.932	1.24	-5.77 – 8.25	.636	0.59	-0.31 – 1.49	.898	–	–	–
Group comparison (d): GNG training groups vs. Sham group												
Intercept	19.67	16.13 – 23.21	**<.001**	22.57	18.70 – 26.43	**<.001**	5.07	4.40 – 5.74	**<.001**	23.20	19.49 – 26.90	**<.001**
Group	-0.19	-4.52 – 4.13	.931	0.22	-4.50 – 4.94	.927	0.13	-0.69 – 0.95	.755	3.86	-0.37 – 8.10	.074
Time (t_1)	-3.28	-6.24 – -0.32	**.033**	-5.86	-10.38 – -1.34	**.012**	-0.63	-1.34 – 0.07	.083	-2.61	-6.35 – 1.14	.174

Time (t_2)	-7.12	-10.65 – -3.58	**<.001**	-6.49	-11.77 – -1.20	**.019**	-1.57	-2.33 – -0.80	**<.001**	–	–	–
Group × t_1	-1.43	-5.06 – 2.20	.220	3.69	-1.86 – 9.24	.904	-0.55	-1.42 – 0.32	.109	-4.64	-9.26 – -0.02	**.026**
Group × t_2	2.41	-1.90 – 6.72	.863	4.81	-1.63 – 11.26	.927	0.56	-0.37 – 1.50	.879	–	–	–

Note. For the group × t_1 and group × t_2 effects, one-sided *p*-values are reported, otherwise two-sided; CI = Confidence Interval; CPD = Cigarettes Per Day; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU = Questionnaire on Smoking Urges, brief version.

* significant after Bonferroni correction.

[+] the group × t_1 interaction effect for CPD (primary outcome) remained non-significant in models without t_2 as a predictor for group comparisons (a), (b), (c), and (d), all *ps* ≥ .093.

Baseline variables with group differences at the $p < .10$ level (see Table 1-IV) were considered as potential covariates. If adding a variable resulted in a better relative model fit, it was included in the linear mixed model as a covariate: [1] The smoking-specific GNG task CE rate (smoking-related stimuli) at t_0 was added as a covariate to the model in group comparison (a), with results remaining unchanged. [2] The smoking-specific GNG task CE rate (smoking-related stimuli) and general GNG task CE rate at t_0 were added as covariates to the model in group comparison (a), with results remaining unchanged. [3] The smoking-specific Go/No-Go task CE rate (smoking-related stimuli) at t_0 was added as a covariate to the model for group comparison (d), with results remaining unchanged.

Table 4-IV

(a) GNG Training vs. Control Groups: Means (SDs) of Clinical Outcomes at t_0, t_1, and t_2

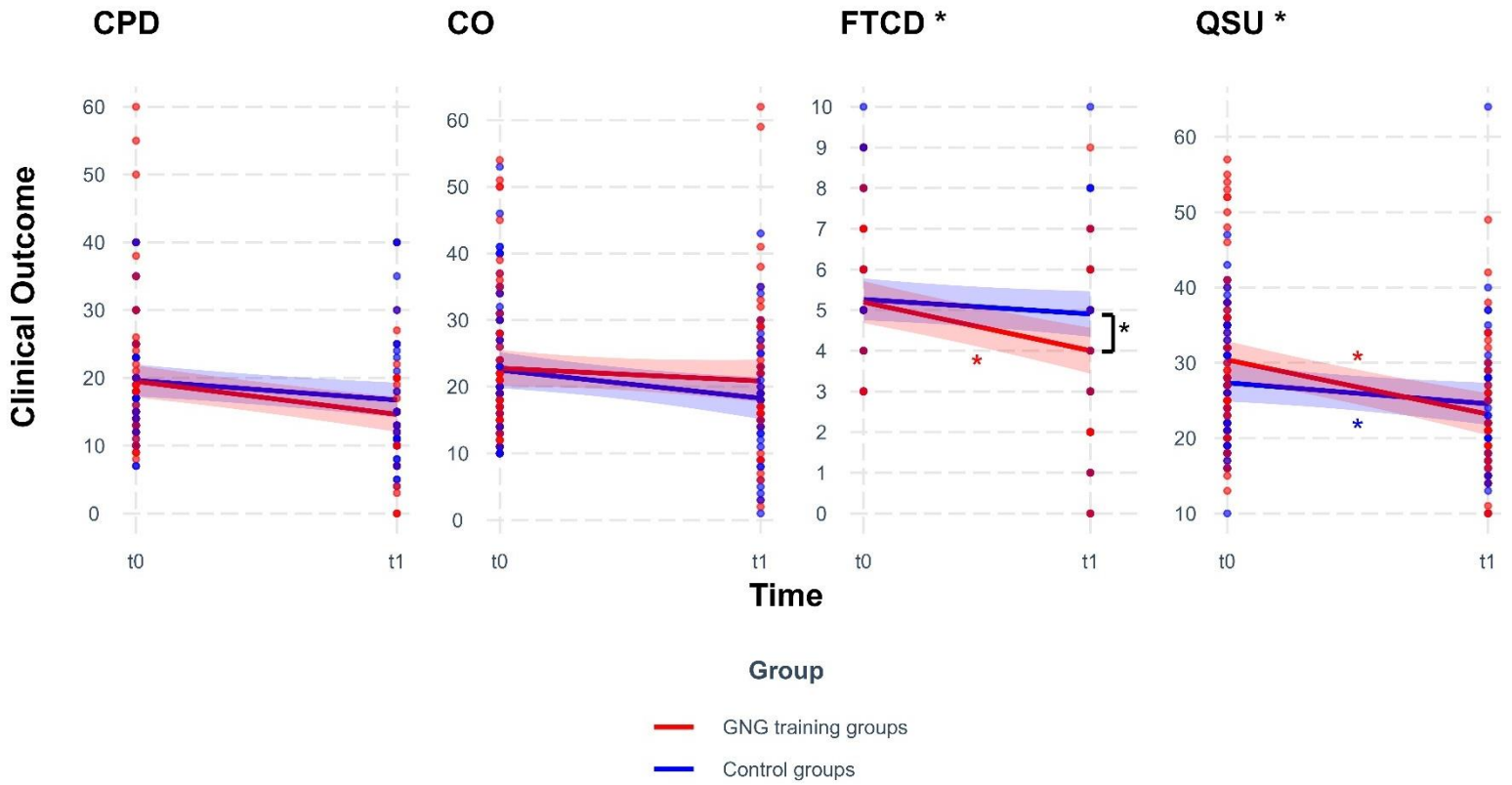
Outcome	GNG training groups			Control groups		
	t_0 (n = 61)	t_1 (n = 43)	t_2 (n = 43)	t_0 (n = 61)	t_1 (n = 44)	t_2 (n = 41)
CPD	19.48 (10.75)	14.33 (8.21)	15.81 (11.30)	19.62 (7.76)	16.09 (9.41)	13.17 (8.59)
CO	22.79 (11.00)	21.19 (12.57)	21.38 (14.73)[b]	22.49 (10.38)	18.36 (9.02)	18.91 (11.58)[e]
FTCD	5.20 (1.78)	3.98 (2.27)	4.35 (2.30)	5.26 (1.93)	4.68 (2.25)	3.66 (2.32)
QSU	30.42 (11.29)[a]	22.30 (8.68)	–	26.97 (8.36)[c]	24.47 (9.28)[d]	–

Note. CPD = Cigarettes Per Day; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU = Questionnaire on Smoking Urges, brief version; GNG training groups = collapsed general and smoking-specific Go/No-Go training group; Control groups = collapsed Sham and Waitlist control group.

[a] n = 59; [b] n = 37; [c] n = 60; [d] n = 43; [e] n = 34

Figure 2-IV

(a) GNG Training vs. Control Groups: Interaction Plots for Group × t_1 Effects



Note. Significant effects are marked with an asterisk. CPD = Cigarettes Per Day; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU = Questionnaire on Smoking Urges, brief version; GNG training groups = collapsed general and smoking-specific Go/No-Go training group; Control groups = collapsed Sham and Waitlist control group.

Group Comparison (b): Smoking-Specific GNG Training vs. General GNG Training Group. No superiority of the smoking-specific GNG training condition in reducing clinical outcomes at t_1 or t_2 was detectable when compared to the general GNG training condition (see Table 3-IV).

Group Comparison (c): Smoking-Specific GNG Training Group vs. Control Groups. When comparing the control groups with the smoking-specific GNG training group alone, the results were consistent with those observed when compared to both GNG training groups (group comparison [a]), except in one instance: the stronger decrease in the QSU scores at t_1 in the smoking-specific GNG training group did not fall below the Bonferroni correction threshold (see Table 3-IV).

Post-hoc pairwise comparisons revealed that the smoking-specific GNG training group showed a significant decrease in the FTCD scores from t_0 to t_1, $t(69.8) = -4.72$, $p < .001$ (one-tailed), whereas the reduction in the control groups was not significant, $t(69.2) = -1.56$, $p = .123$. Additionally, the smoking-specific GNG training group had significantly lower FTCD scores at t_1 compared to the control groups, $t(136.4) = -2.68$, $p = .004$ (one-tailed). For the QSU scores, post-hoc pairwise comparisons indicated that both the smoking-specific GNG training group and the control groups exhibited significant reductions from t_0 to t_1 (smoking-specific GNG training group: $t[71.3] = -4.03$, $p < .001$ [one-tailed]; control groups: $t[70.0] = -2.19$, $p = .032$, non-significant after Bonferroni correction). The smoking-specific GNG training group did not show significantly lower QSU scores at t_1 compared to the control groups, $t(144.5) = -0.87$, $p = .193$ (one-tailed).

Group Comparison (d): GNG Training Groups vs. Sham Group. The group comparison analysis (d) aimed to examine whether the superiority of the GNG training groups remained robust when compared to the Sham group alone. The group × t_1 interaction effect on the QSU scores remained significant, indicating that the GNG training groups exhibited a

significantly greater reduction in the QSU scores at t_1 compared to the Sham group (non-significant after Bonferroni correction; see Table 3-IV). Post-hoc pairwise comparisons revealed that the GNG training groups showed a significant decrease in the QSU scores from t_0 to t_1, $t(72.0) = -5.23$, $p < .001$ (one-tailed), whereas the reduction in the Sham group was not significant, $t(69.3) = -1.31$, $p = .194$. At t_1, the GNG training groups did not show significantly lower QSU scores compared to the Sham group, $t(142.8) = 0.11$, $p = .543$ (one-tailed). Lastly, the reduction in the FTCD scores observed in the GNG training groups at t_1 remained non-significant when compared to the Sham training group alone.

Working Mechanisms

Contrary to our expectations, no significant interactions were found between group ([a] GNG training vs. control groups) and t_0-t_1 changes in CE rates for either GNG task (see Table 5-IV). Due to the non-significant results in group comparison (a) and to avoid power issues caused by a reduced sample size, we refrained from conducting further group comparison analyses. Within the smoking-specific GNG training group, there was no significant t_0-t_1 change in the CE rate during smoking-related trials in the smoking-specific GNG task (β = -7.11, *95% CI* [-19.99 – 5.36], $p = .136$).

Table 5-IV

(a) GNG Training vs. Control Groups: Results of the Linear Mixed Effects Models for Working Mechanisms Measures

Fixed effects	General GNG task			Smoking-specific GNG task (smoking-specific stimuli)			Smoking-specific GNG task (neutral stimuli)		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*
Intercept	11.12	8.26 – 13.99	**<.001**	1.43	-0.92 – 3.77	.232	0.27	-2.41 – 2.96	.840
Group	1.33	-2.36 – 5.03	.477	2.06	-0.46 – 4.58	.108	0.72	-2.10 – 3.55	.613
t_1	0.29	-2.64 – 3.22	.847	0.57	-1.67 – 2.80	.618	0.12	-2.03 – 2.27	.913
Group × t_1	-0.40	-4.57 – 3.77	.425	-0.56	-3.73 – 2.61	.364	1.05	-2.01 – 4.10	.750

Note. Working mechanism measures ($n = 3$): CE rates in the general and smoking-specific (smoking-related and neutral stimuli separately) Go/No-Go tasks. For the group × t_1 effects,

one-sided *p*-values are reported, otherwise two-sided. CI = Confidence Interval; GNG = Go/No-Go.

Additional and Exploratory Analyses

The methods and results of (1) the Bayesian analyses, (2) an investigation of whether group was associated with t_0-t_1 changes in other task/questionnaire measures, such as the SST and BIS-15 for assessing *top-down inhibitory control*, and the AAT and IAT, both of which evaluate *stimulus devaluation*, and (3) PP-analyses, are reported in Appendix E. The main findings were that (1) the Bayes factor derived from the Bayesian models demonstrated that models fit the data best when the interaction term group × t_1 was included as a predictor, compared to models with either t_1 or group and t_1 only. Moreover, the greater reduction in the FTCD score at t_1 in the (a) GNG training vs. control groups and the (c) smoking-specific GNG training group vs. control groups analyses were of clinical significance. Concerning all other group effects on clinical outcomes at t_1, the clinical significance of these findings remains undecided. Further, that (2) no significant interactions were found between group ([a] GNG training vs. control groups) and t_0-t_1 changes in SST and BIS-15 measures (assessing *top-down inhibitory control*). Also, no significant t_0-t_1 changes were detected in AAT and IAT measures following smoking-specific GNG training (both assessing *stimulus devaluation*), and (3) the PP-analyses support the finding from the ITT-sample, showing that the GNG training groups had a significantly greater reduction in FTCD scores at t_1 compared to the control groups, while no significant effect was found for the QSU score.

Discussion

The present study is the first to investigate the efficacy of smoking-specific and general GNG task-based ICT as a stand-alone intervention in reducing tobacco consumption and craving in a sample of adults who smoke, compared to control conditions receiving no ICT

(i.e., categorization task [Sham training] and WLC). Overall, we provide preliminary evidence that both general and smoking-specific GNG training may exert positive effects in the short-term, but not in the long-term (i.e., 3 months after intervention). Partly consistent with our first hypothesis, GNG trainings resulted in a stronger reduction of tobacco dependence (FTCD) and craving (QSU) compared to control groups at post-intervention. However, no significant group effects on pre-post changes were found for daily cigarette consumption and the CO value. Contrary to our second and third hypotheses, smoking-specific GNG training did not outperform the general GNG training. Importantly, we could demonstrate that the significantly stronger reduction of craving at post-intervention in the GNG training groups remained robust when compared to the Sham training group alone, though not significant after Bonferroni correction. However, significant group effects on changes in clinical outcomes were no longer evident in any group comparisons at the 3-month follow-up. Also, no potential working mechanism for the effects on clinical outcomes could be identified.

One noteworthy finding of the present study is that in the (smoking-specific) GNG training group(s), the FTCD score was significantly reduced at post-intervention compared to the control groups, whereas no significant effects were observed for the number of smoked cigarettes per day (CPD). Above, Bayesian statistics confirmed the practical significance of the reduction in the FTCD score. One might, therefore, inquire as to the specific characteristics of the FTCD score that extend beyond the simple quantification of smoked cigarettes per day. One potential explanation for the discrepancy is that CPD more closely assesses the physiological aspect of dependence, whereas the FTCD additionally addresses behavioral aspects such as the desire to smoke and its difficulty to withstand (Heatherton et al., 1991). Indeed, a meta-analysis concluded that the desire to smoke is related to, but does not fully explain, tobacco consumption behavior (Gass et al., 2014). In line with the promising (yet preliminary) findings for the FTCD score at post-intervention, only the QSU score showed a

significantly greater reduction in the GNG training groups compared to the Sham group alone (though not significant after Bonferroni correction). Both findings suggest that (smoking-specific) GNG training may be particularly effective in reducing the subjective desire to smoke and increasing the ability to regulate or control cravings. However, more research is needed to test this assumption. For this purpose, it would be interesting to assess the effects of GNG training on induced craving using neural or psychophysiological cue-reactivity paradigms (Betts et al., 2021).

In terms of the comparison of the efficacy of general and smoking-specific GNG training, our results align with previous studies showing that smoking-specific GNG training does not outperform general GNG training (Bos et al., 2019; Hughes et al., 2021). However, it is important to note that detecting significant effects between two active interventions likely requires larger group sample sizes. Therefore, any conclusions drawn from this finding should be interpreted with caution.

Contrary to our hypotheses, the observed superiority effects of (smoking-specific) GNG training on clinical outcomes immediately post-intervention were no longer detectable at the 3-month follow-up, indicating a lack of long-term efficacy. This is not only an issue in the field of ICT, but rather a general problem in smoking CBM research (Machulska et al., 2021; Wittekind et al., 2019). Therefore, in addition to optimizing current ICT interventions, it is particularly important to focus on achieving sustainable positive changes in smoking behavior. One idea is to design ICT trainings that incorporate more personally relevant smoking-related stimuli (McClernon et al., 2016; Wiers et al., 2020). Additionally, easier access could be provided through smartphone applications (e.g., Machulska et al., 2024). This would allow individuals to train during high-risk situations for smoking, such as when experiencing strong cravings (Wiers et al., 2020). Both suggestions could increase training attractiveness, leading

to a higher rate of usage. This is an important goal, as training adherence for both GNG trainings was only moderate.

Based on the encouraging, yet preliminary findings of the present study, future research should focus on the following areas: First, investigating the efficacy of GNG trainings that incorporates healthier, more adaptive behaviors, such as engaging in positive activities during Go trials (Wiers et al., 2020). Second, examining the efficacy of combining general and smoking-specific GNG training. This approach can be derived from dual-process models, which suggest that general GNG training should strengthen reflective processes, while smoking-specific GNG training should aim to reduce impulsive responses toward smoking-related stimuli. Third, assessing the efficacy of GNG training in a sample of abstinence-motivated smoking individuals (as the current sample exhibited only a moderate motivation for abstinence, see Table 1-IV), in combination with a verified quit attempt (see Elfeddali et al., 2016), or even as an add-on to smoking cessation treatment (see Wittekind et al., 2022). This is due to the finding that CBM (and maybe cognitive training in general) is more effective when participants show at least some degree of intrinsic motivation to change their problematic behavior. Indeed, empirical findings in the field of AUD suggest that CBM is effective when integrated into clinical treatment and/or when participants have an abstinence goal, but not when participants aim merely to reduce their drinking behavior (Wiers et al., 2023).

Current research suggests three potential working mechanisms of ICT: (1) the strengthening of *top-down inhibitory control*, (2) *automatic stimulus-stop associations*, and (3) *stimulus devaluation*. Although the present study observed improvements in some clinical outcomes, no associations with any of the presumed mechanisms were observed. This aligns with previous studies (Adams et al., 2017; Hughes et al., 2021; Machulska et al., 2022). However, their non-significant findings may not be surprising, given the lack of significant group effects on changes in clinical outcomes. Another explanation might be the low number

of training sessions (n = 1; Adams et al., 2017) or the usage of a 50:50 Go/No-Go trial ratio (Hughes et al., 2021; Machulska et al., 2022; see Table F.1-IV). Regarding the latter, evidence suggests that the devaluation effect disappears in low-demanding GNG trainings with frequent No-Go trials (Chen et al., 2016).

Although our study employed a high-demand GNG training (i.e., 75:25 Go/No-Go trial ratio) and provided some evidence for its efficacy on clinical outcomes compared to control conditions, the specific mechanism underlying the observed positive effects remains unclear. The lack of evidence may be attributed to the following reasons: first, our study exclusively used implicit measures to assess the devaluation of smoking-related stimuli (i.e., AAT, valence IAT). However, meta-analytical results suggest that explicit measures are more successful in assessing devaluations after ICT (Jones et al., 2016). Second, the non-significant results may be attributed to low statistical power or the low reliability of some experimental task measures (Hedge et al., 2018). Third, the AAT and smoking-specific GNG task were implemented with content-irrelevant feature task instruction (i.e., responding based on the color of the frame rather than the content). However, evidence suggests that approach biases toward substance-related stimuli, and consequently, potential changes following intervention, can only be assessed when individuals are required to process the content of the stimuli through content-relevant feature task instruction (e.g., Field et al., 2011). All of these considerations should be taken into account in future research to identify the working mechanism(s) of ICT.

Limitations

Our results should be interpreted in light of several limitations. First, adherence to the training was only moderate across all training groups, but the lowest in the smoking-specific GNG training group. Thus, the observed group × time effects may have been reduced, and non-significant findings for working mechanisms or some clinical outcomes must be interpreted with caution. Second, the unexpectedly high dropout rate in our study reduced statistical power,

increasing the likelihood of both Type I and II errors (Button et al., 2013). Nevertheless, our findings suggest that replicating the study design with a larger sample would be a valuable contribution to the field. Third, as previously mentioned, the current sample demonstrated only a moderate goal for abstinence. Empirical research in the field of AUD suggests that CBM is more effective among individuals who are motivated to quit (Wiers et al., 2023). Consequently, the limited efficacy of (smoking-specific) GNG training observed in the current study may be attributed to a lack of motivation for smoking behavior change. Fourth, the estimated reliability of the SST, AAT, and FTCD in our sample was unsatisfactory (a finding that is not uncommon for the FTCD, see Sharma et al., 2021). Likely, biases for those measures were not reliably assessed, and therefore, non-significant results should be interpreted with caution. Fifth, the task instructions between the two GNG trainings differed (i.e., responding based on the color frame [general GNG training] vs. based on the stimulus content [smoking-specific GNG training]). This may have confounded the comparison between the trainings. However, we aimed to keep the two trainings as similar as possible in terms of stimulus material. As a result, no differentiation based on stimulus material was possible, which necessitated variations in the instruction. Lastly, participants who completed the post-assessment demonstrated higher verbal intelligence, lower trait impulsivity, and a slightly higher (but non-significant) desire to quit than non-completers. Therefore, our results may not apply to a representative sample of smoking individuals. Generally, this study is the first to investigate the differences between completers and non-completers in a GNG training intervention study in smoking individuals. As risk factors for dropout and non-compliance are highly relevant for clinical practice, we strongly recommend that future studies conduct completer vs. non-completer analyses. From a clinical point of view, smokers with higher levels of impulsivity and lower cognitive ability may benefit more from adapted ICT versions, including tools to promote motivation (e.g., reward incentives).

Conclusion

This study is the first to investigate short and long-term effects of both smoking-specific and general GNG task-based ICTs compared to non-ICT-based Sham and WLC groups on clinical outcomes and working mechanism measures in a sample of adults who smoke. The results indicate that both smoking-specific and general GNG training may have positive short-term effects on tobacco dependence scores and craving. However, there were no group differences at the 3-month follow-up, and no working mechanism could be identified. Future studies should optimize GNG task-based ICTs to increase their attractiveness, focusing on their implementation for long-term use, and investigating their efficacy as an add-on to smoking cessation treatment. Additionally, it is important to repeat analyses of working mechanisms using more reliable implicit task measures, as well as incorporating subjective self-report measures.

Author Contributions

Authors	Contributions
Franziska Motka	Data curation; Formal analysis; Investigation; Project administration; Software; Validation; Visualization; Writing—original draft; Writing – review and editing
Charlotte E. Wittekind	Conceptualization; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing—original draft; Writing – review and editing
Leonie Ascone	Data curation; Writing-review and editing
Simone Kühn	Conceptualization; Funding acquisition; Methodology; Software; Writing – review and editing

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CHAPTER III:

GENERAL DISCUSSION

Theoretical models emphasize the significant role of impulsive and reflective processes in SUDs. These processes are assumed to manifest in heightened appetitive responses toward drug-related stimuli and deficits in inhibitory control. Computerized training procedures have been developed to directly target these dysfunctional processes. For example, ApBM aims to re-train appetitive responses, while ICT aims to strengthen inhibitory control. However, previous research on the assessment and modification of impulsive and reflective processes in tobacco dependence is inconsistent and reveals substantial gaps. This dissertation seeks to fill some of these gaps and contribute to a better understanding of the observed inconsistencies by conducting two cross-sectional studies on appetitive responses and inhibitory deficits in individuals who smoke (Studies I and II), as well as two RCTs evaluating the efficacy and potential working mechanisms of ApBM and ICT interventions (Studies III and IV).

The general discussion is structured as follows: First, findings from the cross-sectional studies (Chapter 3.1) are reviewed. Next, results from the intervention studies (Chapter 3.2) are integrated. This is followed by a discussion of the clinical implications (Chapter 3.3), a reflection on general strengths and limitations (Chapter 3.4), and finally, a concluding summary and outlook (Chapter 3.5).

3.1 Cross-Sectional Studies on Impulsive and Reflective Processes

Previous basic research on impulsive and reflective processes in smoking has been marked by key limitations, including small samples, isolated single-method assessments, the neglect of individual differences, and uncertainty about the reliability of assessment measures. Studies I and II addressed these shortcomings by testing central assumptions derived from dual-process models and the IST within large samples of individuals with chronic, moderate-to-heavy tobacco dependence (Study I: $N = 362$, Study II: $N = 122$).

3.1.1 Summary of Findings

Study I aimed at investigating appetitive responses toward smoking-related stimuli and interference inhibition ability (assessed via Stroop task), their interrelations, and their associations with smoking-related variables. A multi-method approach combined self-report, cognitive-behavioral, psychophysiological, and neural assessments. Overall, the findings did not provide conclusive evidence for the assumption that individuals with chronic tobacco dependence exhibit appetitive responses across multiple levels of assessment[29]. Evidence for appetitive responding was limited to a significantly attenuated psychophysiological acoustic startle response toward smoking-related stimuli. Contrary to expectations, neural measures revealed significantly *decreased* reactivity toward smoking-related versus neutral stimuli in subcortical mesolimbic structures related to reward processing (e.g., thalamus, striatum). Instead, significantly *increased* cue-reactivity was observed in motor-related regions, including the anterior and middle cingulate cortex (ACC[30]/MCC; Rolls, 2019; Vogt, 2016), the precuneus, and the supramarginal gyrus (visuomotor regions; Yalachkov et al., 2010).

Findings regarding the associations between appetitive responses and smoking-related variables were mixed. Contrary to theoretical assumptions, greater dependence severity was associated with significantly *reduced* neural cue-reactivity in both motor- and reward-related regions. However, some evidence across cognitive-behavioral, psychophysiological, and neural measures supported the hypothesis that higher craving is linked to stronger appetitive responses. The results did not provide clear evidence for a common underlying mechanism driving appetitive responses, as measures from different assessment methods were largely

[29] Of note, the measure of zygomaticus activity demonstrated unacceptable reliability; therefore, non-significant findings involving this measure should be interpreted with caution.

[30] The ACC is involved not only in motor-related functions but also in reward processing (Rolls, 2019). However, in light of the reduced smoking cue-reactivity in reward-related regions, alongside increased cue-reactivity in visuomotor areas, it seems more plausible to interpret smoking cue-reactivity in the ACC as reflecting the integration of motor-related signals (Rolls et al., 2019).

unrelated. Finally, interference inhibition was not significantly associated with either dependence severity or craving.

Study II aimed at investigating general and smoking-specific deficits in action restraint. To this end, the performance on a general and a smoking-specific GNGT was compared between individuals who smoke and healthy controls, while accounting for individual differences related to age, sex, and intelligence. In line with dual-process models, individuals who smoke demonstrated significantly greater deficits in action restraint (higher commission error rates) compared to healthy controls. Importantly, deficits in the smoking-specific GNGT only became apparent after controlling for individual differences related to age, sex, and intelligence. This suggests that action restraint deficits in individuals who smoke are not uniform but vary by individual characteristics. Regarding commission error rates and RTs in Go trials toward smoking-related stimuli (interpreted as exacerbated responsivity reflecting appetitive responding), the results varied across measures: while individuals who smoke did not exhibit significantly greater action restraint deficits toward smoking-related versus neutral stimuli relative to controls, they showed significantly faster RTs in smoking-related Go trials.

Findings regarding the relationship between appetitive responses and smoking-related variables were mixed. While a significant positive association was found between craving levels and action restraint deficits toward smoking-related stimuli, no significant association emerged with the severity of tobacco dependence. Likewise, greater deficits in general action restraint were not significantly associated with higher levels of dependence severity. However, preliminary evidence suggests that associations may be age-dependent: among older individuals who smoke (≥ 54 years), greater action restraint deficits were associated with greater dependence severity and stronger craving.

Interim Summary of Findings from Studies I and II

In line with dual-process models, Studies I and II found some evidence that individuals with chronic tobacco dependence show dysfunctional reflective processes *and* impulsive processes toward smoking-related stimuli. However, the findings on impulsive processes were mixed and, overall, did not provide strong support for the core assumptions of the IST—that is, that smoking-related stimuli elicit appetitive responses in individuals with chronic tobacco dependence (Robinson & Berridge, 2025). Some results suggest that appetitive responses may become more pronounced during periods of elevated craving, but not with greater dependence severity. Neural evidence indicates that smoking-related stimuli elicit activity in motor-related rather than reward-related brain regions. Regarding reflective processes, results showed that individuals who smoke exhibit deficits in inhibitory control, specifically in the domain of action restraint. These deficits appeared to be more pronounced among individuals with greater dependence severity and stronger craving, but only among older individuals (≥ 54 years).

3.1.2 Discussion of the Findings on Impulsive Processes

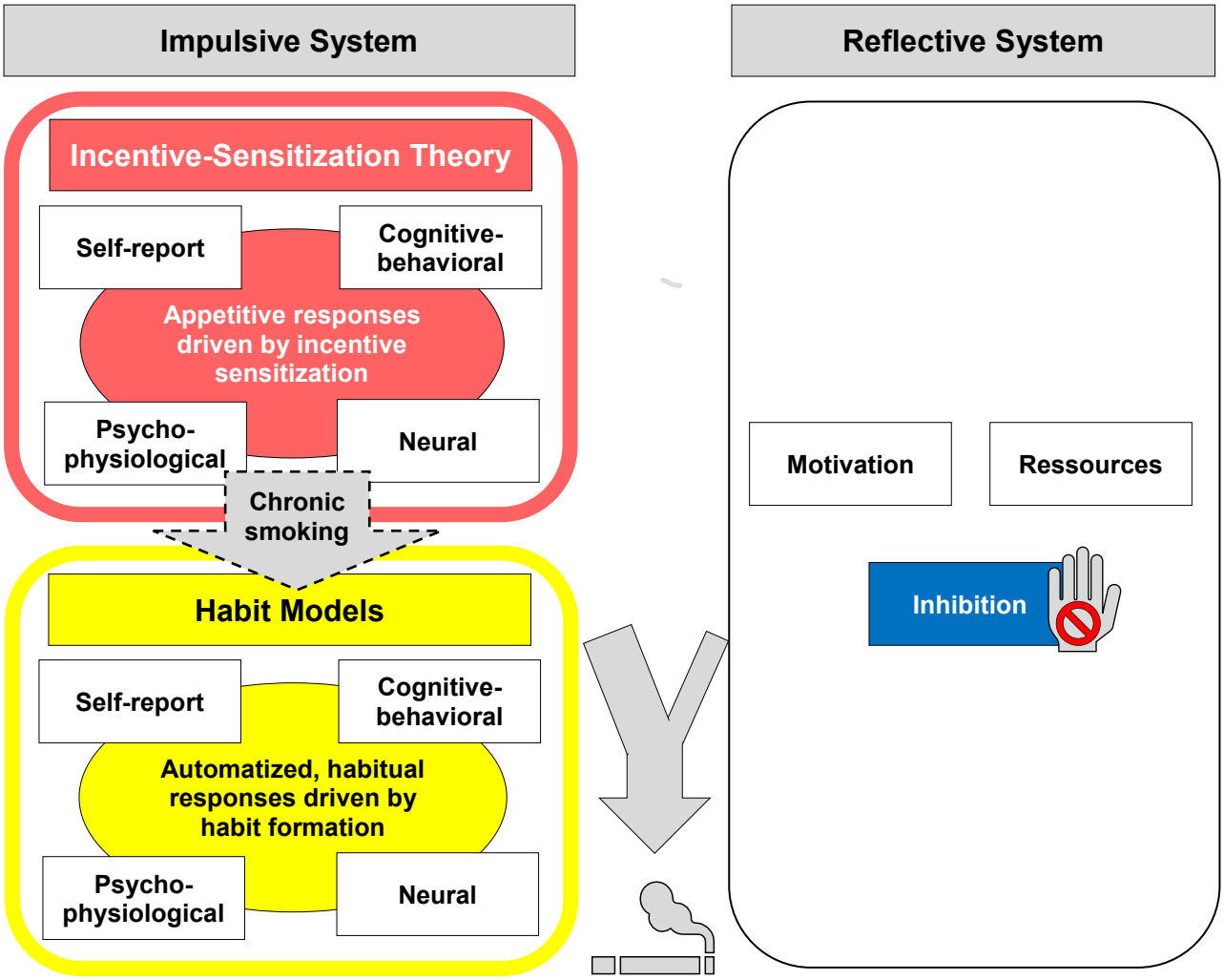
The IST is a prominent and widely cited theoretical model in research on SUDs. It posits that individuals who smoke exhibit appetitive responses toward smoking-related stimuli, driven by the sensitization of the mesocorticolimbic reward circuit toward the incentive-motivational value of these cues (Robinson & Berridge, 2025). Given the mixed and largely non-supportive findings regarding the assumptions of the IST, it is important to explore potential explanations for these inconsistencies as well as to reflect on future research directions that may help resolve them. To this end, the following sections first introduce alternative theoretical accounts of the development and maintenance of tobacco dependence; second, discuss individual and contextual factors that may have contributed to the lack of evidence for appetitive responses toward smoking-related stimuli; and third, conclude with a discussion of the observed evidence for appetitive responding during heightened craving.

Alternative Theoretical Accounts: Habit Models

Appetitive responses toward drug-related stimuli are central not only to the IST, but also to other theoretical accounts, such as habit models (e.g., Di Chiara, 2000; Everitt & Robbins, 2005; Tiffany, 1990). While the IST proposes incentive sensitization as the key mechanism underlying SUDs, habit models suggest that chronic drug use and more severe forms of SUDs are mainly driven by *habit formation*—that is, the gradual formation of automatic stimulus–*response* associations ("*habit* learning") as initial drug use becomes a chronic behavior. Importantly, the IST and habit models propose different trajectories for the development of SUDs. The IST emphasizes learning processes and neuroadaptations related to stimulus-*reward* associations ("*incentive* learning") throughout the entire course of constant drug use. In contrast, habit models suggest that these associations are primarily relevant during the early stages. As initial drug use becomes a chronic behavior, responses toward drug-related stimuli increasingly shift from *incentive*- to *habit*-driven patterns of responding (Di Chiara, 2000; Di Chiara & Bassareo, 2007; Everitt & Robbins, 2005; Tiffany, 1990). Simply put, chronically smoking individuals may no longer engage with smoking-related stimuli because of their incentive-motivational properties, but rather because such stimuli have become triggers for automatized, habitual smoking behavior. Figure 3 presents the theoretical framework of dual-process models and the IST, now integrating key principles of habit models.

Figure 3

Impulsive and Reflective Processes in Tobacco Dependence: Dual-Process Models, the IST, and Habit Models



Note. The illustration is based on publications of dual-process models (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007), the Incentive-Sensitization Theory (IST; Robinson & Berridge, 1993, 2025), and habit models (Di Chiara, 2000; Everitt & Robbins, 2005; Tiffany, 1990). The IST proposes incentive sensitization as the key mechanism underlying impulsive responses toward smoking-related stimuli, while habit models suggest that incentive sensitization is mainly relevant in early stages of drug use. In chronic tobacco dependence, responses are thought to be driven by habit formation. Importantly, incentive- and habit-driven responses should manifest differently across cognitive-behavioral, psychophysiological, neural, and self-report measures. The IST assumes incentive-driven appetitive responses, such as approach tendencies and the conscious experience of craving (Robinson & Berridge, 2025). Habit models postulate habit-driven responses, such as automatized motor responses (Everitt & Robbins, 2005; Yalachkov et al., 2010) or the reporting that smoking behavior feels like a routine (see Ray et al., 2020).

The assumptions of habit models may offer a useful framework for interpreting the findings of Studies I and II. According to these models, individuals with chronic, moderate-to-heavy tobacco dependence are *not* expected to show incentive-driven, appetitive responses toward smoking-related stimuli. Instead, they should exhibit habit-driven, automatized motor responses (Everitt & Robbins, 2005; Yalachkov et al., 2010). This assumption aligns with the observed neural activity pattern in response to smoking-related versus neutral stimuli in Study I. Specifically, contrary to the predictions of the IST, individuals with chronic tobacco dependence exhibited significantly *reduced* reactivity in reward-related brain regions when exposed to smoking-related versus neutral stimuli. Instead, significantly *heightened* cue-reactivity was found in motor-related areas, such as the ACC, MCC, precuneus, and supramarginal gyrus. The precuneus and supramarginal gyrus are implicated in response preparation (e.g., guiding hand movements when reaching for objects; Jeannerod & Jacob, 2005; Yalachkov et al., 2010), while the ACC and MCC are involved in motor coordination and control (Rolls, 2019; Vogt, 2016). Collectively, this neural response pattern may reflect the preparation of automatized, habitual motor responses triggered by smoking-related stimuli (Yalachkov et al., 2010), rather than the processing of these stimuli in terms of their reward value (Huang et al., 2018; Peters & Büchel, 2010).

Habit models may also account for the finding that higher dependence severity was associated with *reduced* cue-reactivity in reward-related brain regions. This result aligns with the notion that incentive-driven responses should diminish as dependence increases (Di Chiara & Bassareo, 2007). Of note, higher dependence severity was also linked to reduced activity in motor-related regions. One possible explanation is that, at high dependence levels, smoking behavior becomes less reliant on external cues (Vollstädt-Klein et al., 2011)—an idea that warrants further investigation.

Taken together, the findings from Studies I and II appear more consistent with the assumptions of habit models than with those of the IST. However, it remains to be clarified how the attenuated psychophysiological acoustic startle response (Study I) and the faster responsivity toward smoking-related stimuli (Study II) can be reconciled. For this, it may be important to distinguish between measures capturing "real" approach behavior (e.g., pull-movements or zygomaticus activity [“smiling” muscle] in response to smoking-related stimuli) and those assessing non-approach-related motor responses (e.g., key-presses or startle reflexes). The former is likely more indicative of incentive salience processes, whereas the latter may reflect habit formation (e.g., when interpreting prepotent responding in smoking-specific No-Go trials as a manifestation of habitual behavior). Consequently, the observed effects may reflect habitual rather than incentive-driven responding. Nonetheless, this interpretation remains speculative, as it is based solely on a mechanistic perspective and requires further research into the neural mechanisms of smoking-specific GNGT performance and greater external validation of facial EMG measures (e.g., in relation to craving intensity).

Lastly, a meaningful interpretation of the present findings through the lens of habit models requires considering their broader relevance within the literature on SUDs. Although habit models have received comparatively less empirical attention than the IST, they may be particularly relevant to smoking, given its strongly habitual nature (Stacy & Wiers, 2010). Specifically, smoking behavior often becomes ritualized and tied to specific times and contexts, such as the first cigarette after waking up or the one during a coffee break (Laurier et al., 2000). Nicotine has also been shown to directly affect the neural systems involved in habit formation (Davis & Gould, 2008; Gould & Leach, 2014). Further, some empirical evidence supports habit model assumptions: a few studies found stronger appetitive responses in individuals with lower than higher tobacco dependence severity (cognitive-behavioral measures: Hogarth et al., 2003; Mogg et al., 2005; psychophysiological measures: Rehme et al., 2009; neural measures:

Vollstädt-Klein et al., 2011). In conjunction with the current findings, these results highlight the need for more research on the development and maintenance of smoking behavior from a habit-based perspective. To this end, future research should include diverse samples in terms of smoking patterns to capture developmental differences in appetitive responding and focus on tasks that assess automatized, habitual behavior (see Doñamayor et al., 2022).

Individual and Contextual Factors

In addition to alternative theoretical explanations, individual and contextual factors may also account for the lack of evidence for appetitive responses. The following section will discuss two key factors in more detail.

First, the lack of clear evidence for appetitive responses in the present studies may partly be explained by the motivational context of the samples. Both Study I and II included participants who were enrolled in intervention studies aimed at smoking reduction or cessation. It is therefore likely that many participants were motivated to reduce or quit smoking, which may have attenuated their appetitive responses toward smoking-related stimuli. In line with dual-process models, reflective processes, such as the motivation for abstinence, may still attenuate appetitive responses to some extent, even when the reflective system is weakened (R. W. Wiers et al., 2007). This is supported by evidence showing reduced psychophysiological and neural appetitive responses in individuals motivated to quit smoking (psychophysiological measures: Gantiva, Ballén, et al., 2015; Muñoz et al., 2011, for an overview, see Boecker & Pauli, 2019; neural measures: Wilson et al., 2013; Wilson et al., 2012, for an overview, see Jasinska et al., 2014).

Nevertheless, the influence of abstinence motivation on the strength of appetitive responses toward smoking-related stimuli remains insufficiently understood. To date, no study has directly examined its association with cognitive-behavioral measures. Moreover, experimental designs are needed to disentangle causal effects from mere correlations. Initial

evidence in this regard comes from Gantiva, Guerra, and Vila (2015), who demonstrated that a brief motivational interviewing intervention significantly attenuated acoustic startle responses toward smoking-related stimuli relative to control conditions.

Second, the absence of appetitive responses may also be explained by the use of contextless and non-personalized smoking-related stimuli presented in artificial laboratory environments. Both the IST (Robinson & Berridge, 2025) and habit models (Di Chiara, 2000) emphasize the significant role of contextual factors in which drug-related stimuli are encountered in shaping individuals' responses. For example, appetitive responses may be reduced or even absent when stimuli are presented in settings that are not associated with actual drug use, such as when lying in an fMRI scanner (Berridge & Robinson, 2016). It is therefore essential to move beyond controlled laboratory assessments and examine responses in more ecologically valid, real-world contexts.

One step in this direction is the use of personalized, contextually relevant stimuli (e.g., personalized pictures such as a coffee accompanied by a cigarette), which have been shown to elicit stronger craving and shorter smoking latencies than simple ones (Conklin et al., 2019). Contextual cues may be particularly relevant for individuals with chronic tobacco dependence, as long-term conditioning could have strengthened their link with smoking behavior (Drummond, 2001). Another promising avenue involves assessing responses toward smoking-related stimuli in naturalistic settings via ecological momentary assessment (EMA). To this end, appetitive responses could be assessed through smartphone-based cognitive-behavioral tasks (see Zech et al., 2020) or ambulatory physiological measures like electrocardiography (see Bertz et al., 2018).

Interim Summary of Potential Explanations for the Absence of Appetitive Responses

Taken together, the lack of convincing evidence for incentive-driven appetitive responses toward smoking-related stimuli may be explained by alternative theoretical accounts, such as

habit models, as well as by sample characteristics (e.g., abstinence motivation) and experimental design features (e.g., non-personalized stimuli in artificial laboratory environments). Building on these considerations, future research should more directly test the assumptions of habit models, focus on measures capturing automatized, habitual responses toward smoking-related stimuli, and utilize more ecologically valid assessment methods (e.g., EMA).

Appetitive Responses during Heightened Craving

Although the assumptions of the IST were largely not supported by the results, they may still apply to certain individuals and/or under certain conditions. In particular, findings from Studies I and II indicate that individuals reporting elevated craving exhibited stronger appetitive responses toward smoking-related stimuli. This suggests that appetitive responses may play a significant role in chronic tobacco dependence, but primarily in state- and/or trait-like contexts characterized by a strong desire to smoke. To better account for the individual and dynamic nature of appetitive responses (i.e., distinguishing between their state- and trait-like components), future research should consider individual differences and, once again, utilize EMA. This may help clarify *under which circumstances* and *for whom* appetitive responses are most relevant in smoking behavior.

3.1.3 Discussion of the Findings on Reflective Processes

Deficits in inhibitory control are considered central to the development and maintenance of SUDs (e.g., Bechara, 2005; Deutsch & Strack, 2006; Feil et al., 2010; Goldstein & Volkow, 2002; Robinson & Berridge, 2003). Study II supports this notion concerning action restraint, as individuals who smoke showed greater deficits than healthy controls. Moreover, these deficits have been found to vary by individual differences in age, sex, and intelligence. Thus, deficits in action restraint do not appear to be uniform across all individuals who smoke and should therefore be considered more thoroughly in future research.

Interestingly, despite the observed group differences, neither action restraint (Study II) nor interference inhibition (Study I) was significantly associated with smoking-related variables, such as tobacco dependence severity and craving. These null findings contradict dual-process models, which posit that stronger dependence severity and craving are based on weakened reflective processes, manifested by greater inhibitory deficits (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007). However, Study II suggests that this association may emerge among older individuals. Accordingly, the proposed link between inhibitory deficits and dependence severity or craving may only become apparent in older individuals and/or those with longer smoking histories. Importantly, whether age or smoking duration is moderating their association remains unclear, due to the cross-sectional design of Study II.

Building on these findings, several important implications for future research can be drawn. *First*, future research should move beyond cross-sectional designs to elucidate the temporal relationship between inhibitory deficits and smoking behavior. Specifically, it remains unclear to what extent diminished inhibitory control arises as a consequence of prolonged tobacco use or serves as a predisposing factor for smoking initiation. Longitudinal studies are essential to disentangle the causal pathways underlying this association. *Second*, further research is needed to clarify which specific components of inhibitory control are impaired. This requires assessment batteries that include a variety of tasks to collect multiple components of inhibitory control within the same smoking sample, allowing for direct comparisons across domains. *Third*, the results of Study II call for more systematic investigation into individual differences in inhibitory deficits. Given that such deficits may be more pronounced—or only detectable—in specific subgroups, a deeper understanding of individual differences could help reconcile inconsistencies in prior research (Stop-Signal Task and GNGT: see Smith et al., 2014; Stroop task: e.g., Flaudias et al., 2016; Wagner et al., 2013).

To this end, studies require large samples encompassing a broad range of demographic and psychosocial characteristics (e.g., age, sex, ethnicity, socioeconomic status) to facilitate robust moderator and subgroup analyses. Online assessments could provide a practical and efficient means of achieving the required sample size.

3.2 Randomized-Controlled Trials of Training Interventions

In the context of tobacco dependence, research on ApBM and ICT reveals significant gaps and methodological limitations. These include an absence of research into the potential neural mechanisms underlying smoking ApBM, a lack of well-designed ICT trials to more conclusively determine its efficacy (i.e., by employing a high-demand ICT and including a non-ICT-based Sham condition), and insufficient consideration of measurement reliability when interpreting findings. Studies III and IV addressed these shortcomings through RCTs examining the efficacy and working mechanisms of ApBM and ICT.

3.2.1 Summary of Findings

Study III aimed at investigating whether ApBM, as an add-on to regular smoking cessation treatment (TAU+ApBM), compared to TAU+Sham and TAU-only, would reduce neural smoking cue-reactivity in reward-related brain regions as a potential working mechanism of ApBM. Results did not support this assumption, as changes in cue-reactivity following the intervention did not significantly differ between groups. These neurobiological findings are consistent with the null effects observed for clinical outcomes in the primary efficacy trial (Wittekind et al., under review) and the subsample of Study III.

Furthermore, it was expected that reductions in cue-reactivity following TAU+ApBM would be associated with: (1) higher short- and long-term abstinence probability (i.e., post-intervention and at the 6-month follow-up), (2) reduced post-intervention craving, and (3) decreased approach biases toward smoking-related stimuli; again, none of these assumptions were supported by the results. Nonetheless, exploratory analyses revealed a potentially

meaningful pattern: ApBM appeared to modulate the relationship between long-term abstinence and cue-reactivity changes in visuomotor regions (i.e., precuneus and supramarginal gyrus; Yalachkov et al., 2010). Specifically, *increased* post-intervention cue-reactivity in these regions predicted a higher probability of long-term abstinence in the ApBM group, whereas the opposite association emerged in both control conditions. However, given the unsatisfactory reliability estimates of fMRI measures, these findings should be interpreted with caution and require replication before firm conclusions can be drawn.

Study IV aimed at investigating whether high-demand general and smoking-specific GNG training, compared to non-ICT-based control conditions, would lead to significantly greater reductions in smoking-related variables, including cigarettes per day (primary outcome), tobacco dependence severity, and craving. Contrary to expectations, there was no clear evidence that (smoking-specific) GNG training was more efficacious in reducing the number of cigarettes smoked per day, both at post-intervention and 3-month follow-up. However, preliminary evidence suggests that general and smoking-specific GNG training significantly reduced tobacco dependence severity and craving post-intervention relative to control conditions, though these effects were not sustained at follow-up. Importantly, the study showed that the significantly stronger reduction of craving at post-intervention remained robust when compared to the "real" non-ICT-based Sham condition (categorization training) alone.

Despite the observed effects on clinical outcomes, no working mechanisms could be identified: GNG training was unrelated to changes in measures of general inhibitory control, the formation of automatic stimulus-stop associations, or stimulus devaluation. Notably, the reliability of some measures (the score assessing tobacco dependence severity and some working mechanism measures) was estimated as unsatisfactory, such that replications are needed before firm conclusions can be drawn.

Interim Summary of Findings from Studies III and IV

Current evidence does not support the efficacy of ApBM—neither in reducing smoking cue-reactivity as its potential treatment target process, nor in promoting smoking cessation (Wittekind et al., under review). In contrast, preliminary evidence supports the short-term efficacy of GNG training for reducing tobacco dependence and craving, though its mechanisms remain to be clarified.

3.2.2 Discussion on the Efficacy of Training Interventions

A direct comparison of Studies III and IV in terms of clinical efficacy might lead to the conclusion that GNG training could be effective in treating chronic tobacco dependence, whereas ApBM is not (complemented by the findings of the primary efficacy trial; Wittekind et al., under review). However, due to fundamental methodological differences between the two trials (e.g., focusing on smoking cessation [Study III] versus reduction [Study IV]), direct comparisons are not feasible. To draw firm conclusions, the two training procedures must be compared under equal conditions (see Machulska et al., 2022, for an ApBM versus smoking-specific ICT comparison, but limited by a low-demand ICT procedure). Nonetheless, the conclusion that ICT may be more efficacious than ApBM in chronic tobacco dependence gains plausibility in light of the current findings from basic research; that is, that responses toward smoking-related stimuli may be more automatized and habitual than incentive-driven. While ApBM targets the latter, ICT may be more suited to disrupt automatized, habitual action patterns. However, this assumption is based solely on a mechanistic perspective (pushing smoking-related stimuli versus inhibiting a response), highlighting the need for further investigation into the neural processes involved in performing smoking-specific ApBM versus GNG training.

Based on the findings regarding clinical efficacy, different future directions for ApBM and ICT appear warranted. In the case of ICT, the promising results from Study IV call for

future research on the efficacy of general and smoking-specific GNG training in a larger, well-powered RCT in individuals motivated to quit smoking (see limitations of Study IV, pages 173-174); for example, when added to regular cessation treatment. This is important for two reasons: first, cessation yields far greater health benefits than mere smoking reduction and is therefore considered the more desirable clinical outcome (Chang et al., 2020); second, CBM research in the alcohol domain indicates higher efficacy when the training is embedded in treatment as usual and/or when individuals aim for abstinence rather than reduction (R. W. Wiers et al., 2023).

In contrast, given the current null effects of ApBM and the generally mixed evidence of its clinical efficacy in the context of smoking (Wittekind et al., 2025), conducting further RCTs on modified ApBM procedures may be premature at this stage (e.g., personalized ApBM procedures as recently suggested by Machulska et al., 2024). A return to basic experimental research appears reasonable to clarify *under which circumstances* and *for whom* approach biases contribute to smoking behavior (Ehring et al., 2022). This could help refine ApBM interventions (e.g., by delivering them during periods of heightened state craving) and identify subgroups who are most likely to benefit from such training (e.g., individuals with consistently elevated trait craving).

3.2.3 Discussion on the Working Mechanisms of Training Interventions

Both RCTs were designed to investigate not only the clinical efficacy of ApBM and GNG training. They also examined the mechanisms underlying potential effects on clinical outcomes, recognizing the importance of mechanism-focused research (Ehring et al., 2022).

Approach Bias Modification (ApBM)

In Study III, no conclusive evidence was found that smoking ApBM reduced cue-reactivity in reward-related brain regions, as it was previously demonstrated for alcohol ApBM (C. E. Wiers et al., 2015). Moreover, whole-brain analyses revealed no significant post-

intervention differences between the three study groups at the whole-brain level. These findings challenge the assumption that smoking ApBM, compared to control conditions, can modify activity in reward-related regions or, more generally, affect neural processes involved in smoking cue-reactivity. Broadly speaking, they underscore that findings from AUD cannot be directly generalized to tobacco dependence. However, the results are limited by concerns about the low reliability of fMRI measures in Study III, highlighting the need for replication to ensure their robustness.

Although no evidence for changes in cue-reactivity or beneficial clinical effects of ApBM compared to control conditions was found, preliminary evidence suggests a potential moderating effect: within the ApBM group, *increased* post-intervention cue-reactivity in the precuneus and supramarginal gyrus was associated with higher long-term abstinence probability, whereas the opposite pattern emerged in the control groups. Both the precuneus and the supramarginal gyrus are involved in visuomotor functions, such as the integration of visual input with motor planning and the preparation of automatized motor responses (e.g., guiding movements toward objects; Jeannerod & Jacob, 2005; Yalachkov et al., 2010). Thus, the moderating effect of ApBM may reflect that repeatedly performing avoidance movements (i.e., "pushing" smoking-related stimuli) during ApBM strengthened automatized disengagement tendencies. These strengthened tendencies could, over time, support more effective avoidance of smoking-related stimuli in everyday life, thereby supporting sustained abstinence. Nonetheless, this interpretation is speculative, and the lack of clinical efficacy of ApBM suggests that increased visuomotor cue-reactivity may be beneficial only for a small subgroup of individuals. Further investigation is needed to clarify this moderating effect.

Go/No-Go (GNG) Training

In Study IV, GNG training yielded positive effects on tobacco dependence severity and craving, suggesting its engagement with mechanisms relevant to these smoking-related

variables. However, no working mechanisms could be identified. Three explanations seem plausible. *First*, the clinical effects may represent false positives caused by low statistical power, as the study groups were rather small (Button et al., 2013; see limitations of Study IV, pages 173-174). Still, it is noteworthy that Bayesian analyses provided some support for their robustness. *Second*, the pivotal mechanisms may not have been assessed. Study IV lacked explicit measures of stimulus devaluation (e.g., valence ratings), which may be more sensitive for detecting stimulus devaluation effects (Iannazzo et al., 2025; Jones et al., 2016). Above, additional research is needed to elucidate potential psychophysiological mechanisms of GNG training in smoking, such as neural correlates measured via fMRI. *Third*, methodological limitations in the analyses of working mechanisms may have obscured true effects, such as poor reliability or low statistical power (Parsons et al., 2019). To overcome these issues, a well-powered replication of Study IV is needed, using more reliable measures, explicit assessments of stimulus devaluation, and further exploration of psychophysiological effects of ICT.

3.3 Clinical Implications

The findings of Studies I to IV offer valuable insights into impulsive and reflective processes involved in chronic tobacco dependence; both of which are considered pivotal to the development and maintenance of SUDs. Several important clinical implications can be drawn. Regarding impulsive processes, the results indicate that responses toward smoking-related stimuli in individuals with chronic tobacco dependence may be more automatized and habitual rather than incentive-driven. This challenges the rationale behind ApBM, which aims to target incentive-driven behavioral approach tendencies (Kakoschke et al., 2017). In line with this, the findings of Study III cast doubt on the efficacy of ApBM as an add-on to regular smoking cessation treatment and align with broader evidence questioning its efficacy in tobacco dependence (Wittekind et al., 2025).

Although the findings of Studies I and II do not support the notion that individuals who smoke consistently exhibit incentive-driven responses toward smoking-related stimuli, they do suggest that such responses may become more relevant when individuals experience heightened craving. It may therefore be worthwhile to further examine the efficacy of ApBM in individuals with high trait craving or when applied during states of acute craving (e.g., Machulska et al., 2024). Further, given the apparent predominance of automatized, habit-driven responses, interventions aimed at improving inhibitory control to disrupt automatized, habitual action patterns may represent a promising avenue and warrant further investigation. In this vein, Study IV provides encouraging evidence for the efficacy of GNGT-based ICT. Finally, (smoking-specific) ICT could be particularly beneficial for older individuals who exhibit stronger dependence severity and report higher levels of craving.

Taken together, the present findings offer valuable implications for targeted interventions on impulsive and reflective processes in chronic tobacco dependence; yet, they should be interpreted with caution. Given the cross-sectional design of Studies I and II, they are based on correlational rather than causal evidence. Following an ideal translational path from basic to applied research (Ehring et al., 2022), clinical implications should be grounded in causal findings. Accordingly, experimental studies are needed to substantiate the present results and inform future intervention development.

3.4 General Strengths and Limitations

This dissertation provides important insights into impulsive and reflective processes contributing to chronic tobacco dependence and their modification through targeted interventions. Its key strengths are as follows:

First, this dissertation integrates the investigation and modification of impulsive processes (appetitive responses toward smoking-related stimuli) *and* reflective processes (general inhibitory control). Assessing both is essential not only for disentangling appetitive

responses from deficits in inhibitory control, and for comparing the effects of interventions targeting either process. It is also crucial for empirically testing key assumptions derived from dual-process models and the IST as part of an integrated theoretical framework. By doing so, this dissertation revealed, for example, that individuals with chronic, moderate-to-heavy tobacco dependence exhibit deficits in action restraint, whereas appetitive responses may primarily emerge under certain conditions, such as heightened craving. Moreover, it provides a preliminary indication that interventions targeting inhibitory control (i.e., ICT) may be effective, whereas those aiming to reduce approach biases (i.e., ApBM) appear less effective.

Second, across studies, impulsive and reflective processes were assessed using multiple methods, including self-report measures, various cognitive-behavioral tasks, as well as psychophysiological and neural assessments. This multi-method approach allowed the integration of various units of analysis, providing a more comprehensive and valid evaluation of impulsive and reflective processes in chronic tobacco dependence (Morris et al., 2015). For example, neural findings helped to contextualize the lack of evidence for approach biases by suggesting a corresponding lack of reward-related processing of smoking-related stimuli.

Third, the reliability of measures was rigorously estimated and transparently reported across all studies; an approach that remains rarely undertaken despite its critical importance for the validity of conclusions drawn from empirical findings (Hedge et al., 2018; Parsons et al., 2019). Notably, considering measurement reliability in Study I allowed for a deviation from conventional analytic practices. Rather than relying on difference scores between conditions (which exhibited mainly poor reliability), analyses were performed using response measures from the separate experimental task conditions (e.g., responses in smoking-related and neutral trials separately), which demonstrated mostly good-to-excellent reliability.

Fourth, this dissertation bridges basic and applied research by addressing multiple steps in the translational process toward the development of novel and more effective treatments for

tobacco dependence (Ehring et al., 2022). Specifically, Studies I and II contributed to the identification of potential treatment target processes, while Studies III and IV evaluated interventions aimed at targeting these processes. Moreover, this dissertation fostered a bidirectional translation between basic and applied research (Ehring et al., 2022; Kindt, 2018). For example, automatized, habitual responses toward smoking-related stimuli were discussed as a potentially promising treatment target process in chronic tobacco dependence. Conversely, it was argued that it may be worth prioritizing further basic research to better understand *under which circumstances* and *for whom* appetitive responses play a crucial role in smoking, before conducting further RCTs using modified ApBM protocols.

Despite these strengths, several limitations must be considered in the interpretation of the current results:

First, both Studies I and II employed a cross-sectional design, meaning that the results are correlational and do not allow for causal inferences regarding the association between impulsive and reflective processes and chronic tobacco dependence. Moreover, correlational findings can be misleading, as they may either over- or underestimate the true strength of associations (Sheeran et al., 2017). As outlined previously, experimental research is considered necessary to better understand the causal relationship between impulsive and reflective processes and chronic tobacco dependence before drawing clinical implications. Nevertheless, the findings provide an important first step toward the development of novel and optimized treatments for tobacco dependence by identifying potential treatment target processes (Ehring et al., 2022).

Second, while the basic research studies demonstrated mostly good-to-excellent reliability estimates of study measures, the reliability of measures assessing potential treatment target processes was often unsatisfactory, especially in Study III. As previously discussed, some findings and their interpretations should therefore be viewed with caution. To allow for more

definitive conclusions, reassessments and reanalyzes aimed at improving the reliability of treatment target measures are warranted.

Third, the interpretation of the current findings may be limited by concerns regarding *external (ecological) validity*. Across studies, impulsive and reflective processes were assessed using experimental tasks, raising the question of how well responses in these tasks generalize to individuals' responses in everyday life. Consequently, an absence of appetitive responses may reflect limited external validity rather than a true lack of such responses. As noted earlier, more ecologically valid assessments are needed to investigate impulsive and reflective processes in real-world contexts, such as through the use of EMA.

Lastly, the interpretation of the current findings may also be limited by concerns regarding *construct validity*. As in most previous research on appetitive responses toward drug-related stimuli, the present dissertation conceptualized measures as reflecting incentive-driven processes of drug-"wanting". However, it remains debated to what extent these measures genuinely capture processes of "wanting" rather than "liking", with the latter referring to the hedonic response to a stimulus (e.g., Meissner et al., 2019; Pool et al., 2016; Tibboel et al., 2015; Waters et al., 2009). This distinction is important, as the IST posits that chronic drug use is driven by processes of "wanting", irrespective of whether processes of "liking" remain stable or even decline (Robinson & Berridge, 2025). In this sense, concluding that individuals with chronic tobacco dependence do not exhibit incentive-driven appetitive responses would be misleading, as null findings would rather reflect a matter of poor construct validity. Similarly, as previously described, it remains questionable whether responses toward smoking-related stimuli in the GNGT truly reflect incentive-driven processes or rather habitual action patterns. Future research should prioritize measures with clearer evidence of validity for assessing processes of "wanting" (e.g., the novel Wanting Implicit Association Test [W-IAT]; Koranyi et

al., 2017) and further advance knowledge of the neural processes underlying task performance (Tibboel et al., 2015).

3.5 General Conclusion

This dissertation pursued two main objectives: (1) to examine key assumptions of dual-process models and the IST by investigating impulsive and reflective processes in individuals with chronic tobacco dependence (Studies I and II), and (2) to evaluate the efficacy and working mechanisms of ApBM and GNGT-based ICT aimed at modifying these processes in two RCTs (Studies III and IV).

Regarding the first objective, Studies I and II provided evidence that chronic tobacco dependence is characterized by both deficits in inhibitory control (specifically, action restraint) *and* strong impulsive processes toward smoking-related stimuli. However, findings on impulsive processes were mixed and, overall, offered limited support for the core assumptions of the IST; namely, that smoking-related stimuli elicit appetitive responses driven by their incentive-motivational value (e.g., approach tendencies). Instead, impulsive processes appeared to reflect automatized, habitual motor responses. Nevertheless, evidence suggests that incentive-driven appetitive responses may emerge when individuals experience heightened craving. Future research should more thoroughly investigate automatized, habitual action patterns as proposed by habit models and use assessment methods that capture the dynamic nature of responses toward smoking-related stimuli (e.g., EMA).

Regarding the second objective, Study III suggests that the beneficial effects of ApBM observed in AUD may not readily generalize to chronic tobacco dependence, neither in terms of cessation outcomes nor neural cue-reactivity. In contrast, GNG training appears promising, with Study IV demonstrating short-term reductions in dependence severity and craving compared to control conditions. However, its long-term efficacy and underlying mechanisms remain unclear. Accordingly, future research should pursue different directions for these

interventions: for ApBM, more basic research is needed to better understand *under which circumstances* and *for whom* appetitive responses are related to smoking behavior; for GNG training, a large-scale RCT in smoking cessation is warranted.

In conclusion, these findings contribute to a growing body of research dedicated to developing novel and effective computerized training interventions to help individuals overcome SUDs such as tobacco dependence—an essential step in addressing one of the leading preventable causes of disease and death worldwide.

CHAPTER IV:

DEUTSCHE ZUSAMMENFASSUNG

Tabakrauchen fordert jährlich über acht Millionen Todesopfer und gilt laut der Weltgesundheitsorganisation (WHO) als eine der größten globalen Bedrohungen für die öffentliche Gesundheit. Prognosen zufolge wird die weltweite 12-Monats-Prävalenz von Tabakrauchen im Jahr 2025 bei Personen ab 15 Jahren bei etwas über 15 % liegen (WHO, 2021, 2023). Angesichts der erheblichen negativen gesundheitlichen und gesellschaftlichen Folgen stellt Tabakrauchen, wie problematischer Substanzkonsum im Allgemeinen, ein paradoxes Verhalten dar (Stacy & Wiers, 2010): *Warum rauchen Menschen weiterhin, obwohl sie über die gesundheitlichen Risiken informiert sind oder den Wunsch haben aufzuhören?* Darüber hinaus bleibt die Rückfallquote trotz evidenzbasierter Behandlungsansätze hoch (Mottillo et al., 2009; Rigotti et al., 2022). Daraus ergibt sich eine zweite zentrale Frage: *Wie lassen sich bestehende Behandlungsansätze verbessern?* Die vorliegende Dissertation widmet sich diesen Fragestellungen mit dem Ziel, das Verständnis für dysfunktionale Prozesse die der chronischen Tabakabhängigkeit zugrunde liegen zu vertiefen und zur Verbesserung bestehender Behandlungsansätze beizutragen.

Theoretische Grundlage dieser Arbeit bilden Zwei-Prozess-Modelle des Substanzkonsums (Bechara, 2005; Deutsch & Strack, 2006; R. W. Wiers et al., 2007). Diese Modelle gehen davon aus, dass problematischer Konsum durch ein Ungleichgewicht zwischen starken impulsiven Prozessen (z. B. appetitive Reaktionen, wie unwillentliche Annäherungstendenzen gegenüber rauchrelevanten Reizen) und schwachen reflexiven Prozessen (z. B. Defizite in der Inhibitionskontrolle) gesteuert wird. Neurobiologische Theorien machen ergänzende Annahmen darüber, wie sich appetitive Reaktionen gegenüber substanzbezogenen Reizen entwickeln und aufrechterhalten werden: die Anreiz-Sensitivierungs-Theorie (engl. *Incentive-Sensitization Theory*; Robinson & Berridge, 1993, 2025) postuliert, dass appetitive Reaktionen durch eine Sensitivierung des mesokortikolimbischen Belohnungssystems (einschließlich, z. B. Striatum) hervorgerufen

werden. Dadurch wird substanzbezogenen Reizen eine gesteigerte anreiz-motivationale Bedeutung zugeschrieben (engl. *incentive salience*). Substanzbezogene Reize werden als „gewollt“ erlebt, was sich sowohl im bewussten Erleben von Verlangen (engl. *craving*), als auch in unbewussten und unwillkürlichen appetitiven Reaktionen gegenüber substanzbezogenen Reizen zeigen kann—etwa in automatischer Aufmerksamkeitszuwendung, unwillentlichen Annäherungstendenzen, neuronaler Reaktivität im Striatum, sowie in Gesichtsmuskelaktivität, die deren anreiz-motivationalen Wert widerspiegelt (Robinson & Berridge, 1993, 2025).

Einige empirische Befunde im Kontext des Tabakrauchens stützen diese theoretischen Annahmen: Studien konnten zeigen, dass rauchende Personen kognitive und behaviorale Annäherungstendenzen gegenüber rauchrelevanten Reizen aufweisen (De Houwer et al., 2006; Machulska et al., 2015; C. E. Wiers et al., 2013). Psychophysiologische Untersuchungen mittels Elektromyographie (EMG) belegten eine Gesichtsmuskelaktivität gegenüber rauchrelevanten Reizen, die der Reaktion auf positive Reize ähnelt (Drobes & Tiffany, 1997; Geier et al., 2000). Funktionelle Bildgebungsstudien wiederum konnten eine erhöhte Aktivierung in belohnungsbezogenen Hirnarealen (z.B. Striatum; David et al., 2005) bei der Konfrontation mit rauchrelevanten versus neutralen Reizen zeigen. Darüber hinaus konnten Defizite in der Inhibitionskontrolle im Vergleich zu nicht-rauchenden Personen nachgewiesen werden (Smith et al., 2014).

Aufbauend auf diesen empirischen Befunden wurden computergestützte Trainingsverfahren entwickelt, die darauf abzielen, dysfunktionale impulsive und reflexive Prozesse gezielt zu modifizieren (R. W. Wiers et al., 2013). Beim Annäherungsvermeidungstraining (engl. *Approach Bias Modification*) wird beispielsweise entgegen der Annäherungstendenz konstantes Vermeidungsverhalten gegenüber substanzbezogenen Reizen durch ein wiederholtes „Wegdrücken“ trainiert (Kakoschke et al.,

2017). Beim Inhibitionstraining (engl. *inhibitory control training*) hingegen soll entweder die generelle oder spezifische Inhibitionsfähigkeit gegenüber substanzbezogenen Reizen durch wiederholte Reaktionshemmung gefördert werden (Iannazzo et al., 2025). Tatsächlich konnte die Wirksamkeit dieser Verfahren im Kontext von problematischem Alkoholkonsum und ungesundem Essverhalten bereits in zahlreichen Studien belegt werden (Iannazzo et al., 2025; R. W. Wiers et al., 2023).

Im Kontext der Tabakabhängigkeit ist die empirische Evidenz zur Erfassung und Modifikation impulsiver und reflexiver Prozesse bislang begrenzt, weist erhebliche Forschungslücken auf und zeigt in vielen Bereichen inkonsistente Befunde. Letzteres lässt sich möglicherweise auf methodische Schwächen früherer Studien zurückführen, wie etwa kleine Stichprobengrößen, sowie eine geringe Reliabilität von Messungen zur Erhebung impulsiver und reflexiver Prozesse. Die vorliegende Dissertation zielte darauf ab, diese Limitationen zu adressieren und zentrale Forschungslücken zu schließen. Hierzu wurden zwei übergeordnete Ziele verfolgt.

Erstes Ziel war die Untersuchung zentraler Annahmen von Zwei-Prozess-Modellen und der Anreiz-Sensitivierungs-Theorie im Kontext chronischer Tabakabhängigkeit in zwei Querschnittsstudien. **Studie I** erfasste Reaktionen auf rauchrelevante Reize in einer großen Stichprobe von Personen mit chronischer Tabakabhängigkeit (N = 362) mittels eines multi-methodalen Ansatzes. Dieser kombinierte kognitiv-behaviorale Maße (Reaktionszeitaufgaben), psychophysiologische Maße (Gesichtsmuskelaktivität mittels EMG) und neuronale Maße (funktionelle Magnetresonanztomographie [fMRT]). **Studie II** verglich Personen mit chronischer Tabakabhängigkeit (N = 122) mit gesunden Kontrollpersonen (N = 69) hinsichtlich allgemeiner und rauchspezifischer Defizite in der Inhibitionskontrolle unter Verwendung von Go/No-Go Reaktionszeitaufgaben.

Die Ergebnisse beider Studien deuten darauf hin, dass chronische Tabakabhängigkeit durch Defizite in reflexiven Prozessen (d.h. Inhibitionskontrolle) *und* durch impulsive Prozesse gekennzeichnet ist. Wichtig ist jedoch, dass die Ergebnisse zu impulsiven Prozessen eher auf automatisierte, gewohnheitsbedingte Reaktionen gegenüber rauchrelevanten Reizen hinweisen und weniger auf anreizmotivierte Prozesse, wie von der Anreiz-Sensitivierungs-Theorie postuliert (Robinson & Berridge, 1993, 2025). Beispielsweise konnten weder Annäherungstendenzen durch schnelleres Heranziehen, noch eine höhere Hirnaktivität in belohnungsbezogenen Arealen gegenüber rauchrelevanten Reizen beobachtet werden. Stattdessen zeigte sich eine erhöhte Aktivität in motorischen Arealen, was auf die Vorbereitung automatisierter, gewohnheitsbedingter motorischer Reaktionen hindeutet (Yalachkov et al., 2010). Entsprechend der Anreiz-Sensitivierungs-Theorie (Robinson & Berridge, 1993, 2025) gab es jedoch Belege dafür, dass appetitive Reaktionen stärker ausgeprägt sind, wenn Personen ein stärkeres Verlangen nach Zigaretten verspüren.

Auf Basis dieser Befunde sollte sich zukünftige Forschung im Kontext von Tabakabhängigkeit stärker auf automatisierte, gewohnheitsbedingte motorische Reaktionen gegenüber rauchrelevanten Reizen fokussieren, sowie auf Erhebungsmethoden, die die dynamischen Verläufe von Reaktionen gegenüber rauchrelevanten Reizen besser abbilden können (z.B. Smartphone-basierte Echtzeiterhebungen). Vielversprechend könnte auch die Erforschung von Trainingsverfahren sein, die darauf ausgelegt sind, automatisierte, gewohnheitsbedingte Reaktionen zu inhibieren (z.B. Inhibitionstraining).

Zweites Ziel war die Wirksamkeit und die potenziellen Wirkmechanismen von Trainingsinterventionen, die auf dysfunktionale impulsive und reflexive Prozesse abzielen, in zwei randomisiert-kontrollierten Studien zu erforschen. **Studie III** untersuchte die neuronalen Effekte von Annäherungsvermeidungstraining als Ergänzung zu regulärer Rauchentwöhnungstherapie. Getestet wurde, ob Annäherungsvermeidungstraining im

Vergleich zu Kontrollbedingungen zu einer Reduktion neuronaler Aktivität in belohnungsbezogenen Hirnarealen bei der Konfrontation mit rauchrelevanten versus neutralen Reizen führt (rauchrelevante neuronale Reizreaktivität). Entgegen früherer Befunde aus der Alkoholforschung führte Annäherungsvermeidungstraining zu keiner signifikanten Veränderung der rauchspezifischen neuronalen Reizreaktivität im Vergleich zu den Kontrollbedingungen. Dieses Ergebnis steht im Einklang mit den beobachteten Abstinenzraten nach der Intervention: Weder in der Substichprobe von Studie III, noch in der entsprechenden klinischen Hauptstudie (Wittekind et al., under review), ließ sich eine Überlegenheit der Annäherungsvermeidungsbedingung feststellen. Es ist jedoch anzumerken, dass die erhobenen Maße neuronaler Reizreaktivität eine unzureichende Reliabilität aufwiesen, sodass Replikationen mit reliableren Verfahren erforderlich sind, bevor belastbare Schlussfolgerungen gezogen werden können.

Studie IV untersuchte die Wirksamkeit von allgemeinem und rauchspezifischem Inhibitionstraining basierend auf der Go/No-Go Aufgabe zur Rauchreduktion sowie dessen potentielle Wirkmechanismen. Die Studie konnte zeigen, dass allgemeines und rauchspezifisches Go/No-Go Training im Vergleich zu den Kontrollbedingungen kurzfristig zu einer signifikanten Reduktion des Schweregrads der Tabakabhängigkeit und des Rauchverlangens führte. Wichtig ist, dass sich die signifikante Reduktion des Verlangens auch gegenüber der aktiven Kontrollgruppe mit einem „Scheintraining“ (konkret: einer Kategorisierungsaufgabe) zeigte. Allerdings konnten keine Wirkmechanismen identifiziert werden, die diese positiven Effekte erklärten. Darüber hinaus waren die Effekte nach drei Monaten nicht mehr nachweisbar.

Insgesamt sprechen die Ergebnisse gegen die Effektivität von Annäherungsvermeidungstraining als Ergänzung zur Rauchentwöhnung. Dies verdeutlicht den Bedarf an weiterer Grundlagenforschung, um besser zu verstehen, *unter welchen Bedingungen*

und *für wen* Annäherungstendenzen, oder alternative Mechanismen, das Tabakrauchverhalten bedingen. Wichtig bleiben jedoch auch Replikationen oder Reanalysen unter Verwendung reliabler neuronaler Maße. Im Gegensatz dazu erscheint Go/No-Go Training als vielversprechender Ansatz zur Reduktion von Tabakabhängigkeit und Rauchverlangen. Zukünftige Studien sollten sowohl dessen Wirksamkeit, als auch zugrunde liegende Wirkmechanismen weiter untersuchen (z.B. mögliche psychophysiologische Effekte).

Zusammenfassend liefert die vorliegende Dissertation neue Erkenntnisse zu impulsiven und reflexiven Prozessen bei chronischer Tabakabhängigkeit, sowie zu deren gezielten Modifikation. Die Befunde stellen zentrale Annahmen der Anreiz-Sensitivierungs-Theorie infrage, nach der chronisches Rauchverhalten vorranging durch anreizmotivierte, appetitive Reaktionen auf rauchrelevante Reize gesteuert wird (Robinson & Berridge, 2025). Stattdessen legen die Befunde nahe, dass automatisierte, habitualisierte Handlungsmuster eine zentrale Rollen spielen—ein Mechanismus, der in sogenannten Habit-Modellen der Substanzabhängigkeit hervorgehoben wird (engl. *habit models*; Di Chiara, 2000; Everitt & Robbins, 2005; Tiffany, 1990). Insgesamt bietet die vorliegende Dissertation wertvolle Implikationen für zukünftige Forschung und Praxis, die langfristig zur Verbesserung der Behandlung von Tabakabhängigkeit beitragen können—eine der weltweit drängendsten Herausforderungen der öffentlichen Gesundheit.

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APPENDIX

APPENDIX OF STUDY I

Appendix A: Methods

Given the extensive methodological details of our multi-method approach, additional information not critical to the main manuscript is provided here.

Appendix A.1 Participants

Participants were recruited through various means, including social media advertisements, online marketing, flyers distributed at medical practices and local universities, as well as through newsletters. In addition to the inclusion criteria outlined in the main manuscript, further criteria included: (5) willingness to abstain from nicotine replacement therapy, e-cigarettes, and any other smoking cessation intervention during study participation, and (6) motivation to participate in the intervention study. Additional exclusion criteria were as follows: (3) current/previous diagnosis of major neurological disorders (e.g., multiple sclerosis, Parkinson's disease), (4) use of nicotine replacement therapy or pharmacological smoking cessation treatments within three months prior to study participation, (5) acute suicidality, (6) current pregnancy or nursing period, and (7) insufficient German language skills. Additional exclusion criteria for the fMRI investigation included: (1) standard MRI contraindications (e.g., pacemaker), (2) current use of psychotropic medication, (3) uncorrectable visual impairments, and (4) a history of head trauma.

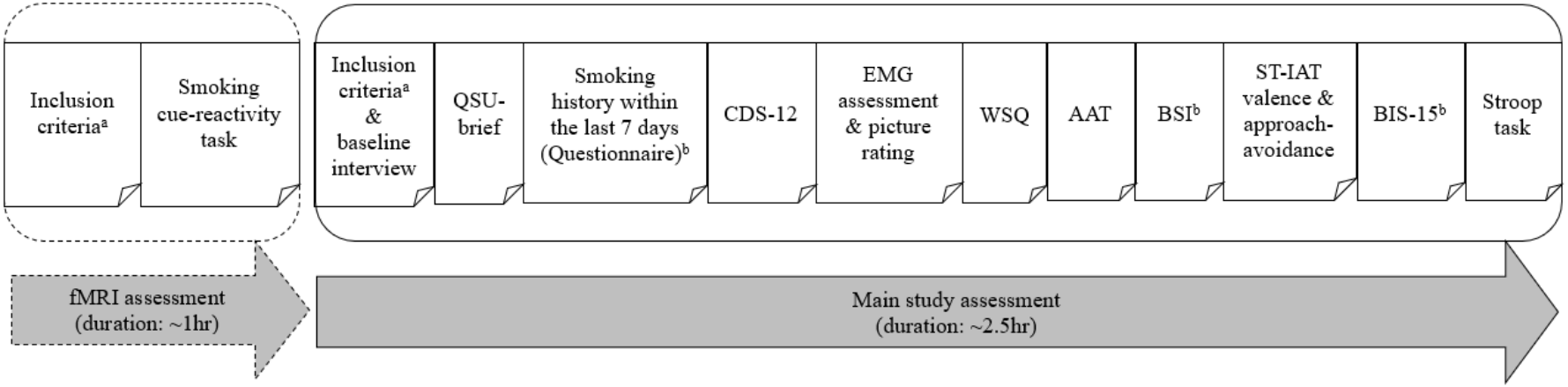
The COVID-19 restrictions led to the cancellation of one smoke-free course, which was the treatment-as-usual intervention in the main clinical trial. As a result, n = 8 participants underwent the pre-assessment but were not randomized for intervention in the clinical trial. Therefore, the present study included a total of N = 362 participants, with N = 354 included in the main clinical trial (see German Clinical Trials Register: DRKS00019221; 11/11/2019).

Appendix A.2 Procedures

All participants underwent an initial telephone screening, which included an explanation of the study procedure, verification of inclusion and exclusion criteria, and scheduling of the baseline assessment. The fulfillment of inclusion criteria was verified at the beginning of the baseline assessment through the FTND and CO values. Participants opting for the fMRI investigation attended a separate appointment, which was scheduled first. In this case, inclusion criteria were verified prior to the start of the fMRI session (see Figure A.2.1-I).

Figure A.2.1-I

Study procedure: Overview



Note. The fMRI investigation was optional (indicated by dashed lines) in addition to study participation and took place between March 2022 and March 2023. fMRI = functional Magnet Resonance Imaging; QSU-brief = Brief Questionnaire of Smoking Urges; CDS-12 = Cigarette Dependence Scale-12; EMG = Electromyography; WSQ = Web Screening Questionnaire; AAT = Approach-Avoidance Task; BSI = Brief Symptom Inventory; ST-IAT = Single-Target Implicit-Association Test; BIS-15 = Barratt Impulsiveness Scale-15.

[a] Carbon monoxide value in exhaled air (CO value) ≥ 10 and Fagerström Test for Nicotine Dependence (FTND) ≥ 3.

[b] Not relevant for the current study.

Appendix A.3 Experimental tasks and paradigms

Appendix A.3.1 Cognitive-behavioral tasks

All cognitive-behavioral tasks were administered on a computer using Inquisit ® Version 4 (www.millisecond.com).

Approach-Avoidance Task (AAT). A joystick-based AAT [1] was employed to measure behavioral approach tendencies. The task comprised a total of 40 smoking-related and 40 positive stimuli. Smoking-related stimuli, featuring pictures of (burning) cigarettes and cigarette packages, were sourced from previous studies [2,3], as well as from online platforms and picture agencies. The stimuli were presented in a pseudo-randomized order (no more than three pictures of the same category were presented consecutively) in two separate blocks (trials per block: $n = 80$). A content-relevant feature task instruction was used, directing participants to push or pull the joystick depending on the content of the picture (i.e., push smoking-related pictures and pull positive pictures or vice versa). The order of instruction (push smoking-related pictures first [incongruent task instruction] or pull smoking-related pictures first [congruent task instruction]) was counterbalanced across participants. The instruction switched after the first block. Response direction was linked to a "zoom"-function, such that pushing the joystick decreased the picture size, while pulling the joystick increased it. At the beginning of each test trial, a picture was presented centrally on the screen. Depending on the picture content, participants had to push or pull the joystick. Pictures only disappeared after the joystick had been fully extended in the correct direction; if moved in the wrong direction, the picture remained on the screen until the correct movement was executed. To initiate the next trial, participants were required to press the "fire" button while the joystick was in the central position. Before each block, participants completed six practice trials, resulting in a total of 172 trials.

Single-Target Implicit-Association Test (ST-IAT). Two ST-IATs [4] were employed to assess implicit associations between smoking (target category) and approach/avoidance as well as positive/negative valence (attribute categories). The attribute categories included six German words related to approach and avoidance, as well as six positively and negatively valenced words. The target category contained six German words related to smoking. All stimulus words are provided in the supplemental material of Wittekind et al. [5]. Both IATs consisted of five blocks. The stimulus word for each trial was presented centrally on a black screen in white ink. The labels of the attribute categories (German words for "approach" or "positive" versus "avoid" or "negative", written in green ink) and the target category (the German word for "smoking", written in white ink) were displayed in the upper corners of the screen. During the first block (attribute practice block: $n = 12$), attribute words were presented and participants were required to classify them using one of two response keys (i.e., "E" or "I"). In the second (practice combined block: $n = 24$) and third block (test combined block: $n = 48$), target and attribute words were presented and had to be classified using the same response keys (i.e., "E" for smoking-related and approach/positive words, "I" for avoidance/negative words; compatible condition). In the fourth (practice reversed combined block: $n = 24$) and fifth block (test reversed combined block: $n = 48$), the target category (i.e., "smoking") switched positions (i.e., "E" for approach/positive words, "I" for smoking-related and avoidance/negative words; incompatible condition). The order of conditions (congruent blocks first versus incongruent blocks first) was counterbalanced across participants, and the presentation of stimuli was randomized within each block. If the participant mistakenly pressed the wrong key, a red X appeared for 200 ms, and the correct key had to be pressed to proceed to the next trial.

Stroop Task. The color Stroop task [6] was employed to assess participants' inhibitory control performance. Four color words as well as rectangles were presented, printed in red,

green, blue, or black. The task consisted of three conditions (a: congruent trials [word = print color]; b: incongruent trials [word ≠ print color]; c: control trials [colored rectangles]) with a total of 72 trials (4 colors × 3 conditions × 6 repetitions). The trials were arranged in a fully randomized order with an inter-trial interval of 200 ms. During each trial, stimuli were presented at the center of the screen with key assignments displayed in the upper part of the screen (d = red; f = green; j = blue; k = black). Participants were instructed to indicate the print color of either the word or rectangle as quickly and accurately as possible by pressing one of four designated keys on the computer keyboard. After incorrect responses, a red X appeared for 400 ms and the next trial began.

Appendix A.3.2 Psychophysiological assessment

The psychophysiological assessment was implemented through the computer software Presentation (Neurobehavioral Systems). Electromyography (EMG) was used to measure the activity of three facial muscles during a passive picture-viewing task [7]: (1) *Musculus orbicularis oculi* (to assess the acoustic startle reflex), (2) *Musculus corrugator supercilii*, and (3) *Musculus zygomaticus major*. The stimuli were colored pictures from four distinct categories (neutral/positive/negative/smoking-related, n = 12 pictures per category). The smoking-related pictures were selected from previous studies [7,8] and an unpublished picture set by Mucha and Pauli. The pictures depicted events related to the initial stages of smoking, as previous research has indicated that these stimuli elicit stronger physiological responses associated with reward [8,9]. Neutral, positive, and negative stimuli were taken from the International Affective Picture System (IAPS, [10]). Positive and negative stimuli were matched to smoking-related stimuli according to the arousal and absolute valence ratings derived from the IAPS database.

The task was divided into three blocks with four pictures of each category per block (i.e., 16 pictures per block). In each trial, a picture was centrally presented on a black screen for an

average of 7.5 s (range: 7.0 to 8.0 s), followed by a black screen for 16.5 to 25.5 s (*M* = 21.0 s, inter-trial interval). During each block, an acoustic startle response was elicited through headphones, 2.5, 4.0, or 5.5 s after picture onset during three trials of each picture category (tone duration: 50 ms; volume: 105 dB; see Wittekind et al. [5] for further technical details). The order of picture category (neutral/positive/negative/smoking-related), the presentation of the startle stimulus (present/not-present), and its presentation time (2.5 s/4.0 s/5.5 s) were pseudo-randomly arranged (14 different orders), with the order of picture presentation randomized within each category.

Psychophysiological responses were recorded by using a 16-channel amplifier (Twente Medical Systems International [TMSi], EJ Oldenzaal, The Netherlands) and the recording software package Polybench 1.30 (TMSi) with a sampling frequency of 1024 Hz. Facial muscle activity was quantified using three pairs of Ag/AgCl electrodes (diameter: 2 mm), which were filled with EMG gel and placed onto the cleansed skin on the left side of the face.

After the passive picture viewing task was completed, participants rated all pictures presented in the same order on three dimensions using visual analogue scales. Participants were instructed to view each picture as long as desired and were asked to rate each picture regarding valence (*pleasant* [1] to *unpleasant* [9]), arousal (*relaxed* [1] to *aroused* [9]), and craving (*not at all* [1] to *very strongly* [9]).

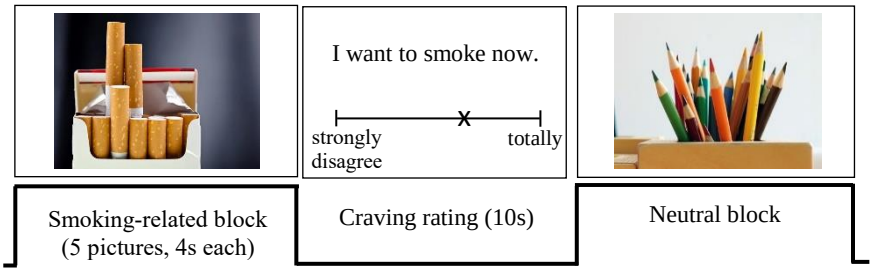
Appendix A.3.3 Functional MRI assessment

The smoking cue-reactivity paradigm [11] used in the current study was adapted from the alcohol cue-reactivity paradigm employed by Vollstädt-Klein et al. [12]. The same 40 smoking-related stimuli used in the AAT were presented. The control stimuli consisted of 40 neutral pictures (e.g., toothbrushes, boxes with pencils), which were matched according to shape and color.

The task comprised 16 blocks (eight blocks with five smoking-related pictures each, and eight blocks with five neutral pictures each). While the block order was pseudorandomized (no more than two blocks of the same category were presented consecutively), stimuli were presented randomly across blocks. Each stimulus was presented for four seconds. Participants were instructed to passively view the pictures. After each block, participants rated their current desire to smoke ("I want to smoke now.") using a visual analogue scale ranging from *strongly disagree* (0) to *totally agree* (100) within a 10 s time limit. For this purpose, participants used buttons to move a cursor to its appropriate position on the scale. The task lasted approximately 10 min. See Figure A.3.3.1-I for an illustration of the task design.

Figure A.3.3.1-I

fMRI smoking cue-reactivity task design



Note. fMRI smoking cue-reactivity task design with examples of smoking-related and neutral stimuli.

Neuroimaging data acquisition took place at the Neuroimaging Core Unit Munich (NICUM) of the LMU using a 3T Siemens Magnetom Prisma and a 32-channel head coil (Siemens AG, Erlangen, Germany). Functional sequences consisted of 320 volumes obtained using a T2*-weighted echo-planar imaging (EPI) sequence (48 slices per volume in ascending interleaved order with multiband factor 4, voxel size = 3 mm^3 isotropic, TR = 2000 ms, TE = 30 ms, flip angle = 45°, FoV = 210 mm). The first five functional volumes were discarded

before preprocessing to account for T1 saturation effects. The high-resolution anatomical images consisted of 160 T1-weighted slices acquired using a magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (voxel size = 1 mm³ isotropic, TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, FoV = 256 mm).

Appendix A.4 Data preprocessing and measure extraction

The cognitive-behavioral and psychophysiological data were preprocessed according to the pre-defined procedure outlined in Wittekind et al. [5]. Due to the exclusion criteria for participants with excessive missing trials in each task, data for certain measures are unavailable for some participants. The final sample size for each measure is reported in Table 1-I.

Appendix A.4.1 Cognitive-behavioral tasks

Approach-Avoidance Task (AAT). For the analysis, only correctly executed trials were considered, meaning trials without any joystick movements in the wrong direction. Initial RTs (i.e., time between picture onset and first joystick response) less than 200 ms and greater than 2.5 *SD* above the group mean were excluded. Consistent with previous AAT studies [13], participants with more than 35% missing trials were excluded from further analysis. The AAT effect score was calculated by subtracting the median final RT (i.e., time between picture onset and full extension of the joystick) between push and pull movements during trials of smoking-related stimuli (i.e., $push_{smoking} - pull_{smoking}$).

Single-Target Implicit-Association Test (ST-IAT). Following the procedure outlined by Karpinski and Steinman [14], any response times less than 350 ms were excluded from the analysis. Error responses were replaced with the individual block mean plus a penalty of 400 ms. Participants with more than 20% errors in a test block were excluded from further analysis. The ST-IAT effect scores were calculated by subtracting the mean of compatible test trials ([smoking + positive/approach]) from the mean of incompatible test trials ([smoking +

negative/avoidance]) and dividing the result by the pooled *SD* of all correct responses across the compatible and incompatible test blocks.

Stroop Task. Response trials with RTs below 200 ms or exceeding 2.5 *SD* above the group mean were excluded, as were incorrect trials. In line with the AAT preprocessing procedure, participants with more than 35% missing trials were excluded from further analysis. The Stroop interference score was calculated by subtracting the mean RT of control trials from the mean RT of incongruent trials.

Appendix A.4.2 Psychophysiological assessment

We used ANSLAB version 2.6 [15] to preprocess the EMG data. Some aspects of the preprocessing deviated from the procedure outlined in the preregistered study protocol [5]. We transparently describe when and why we adapted specific preprocessing steps. The data were filtered using a 50 Hz notch filter and a 28 Hz highpass filter, resulting in preprocessed data ranging from 28 to approximately 500 Hz. The data were then rectified. Contrary to the preregistration, an additional 500 Hz lowpass filter was not applied, as the prior preprocessing steps effectively reduced noise and extracted relevant EMG signals, making further filtering unnecessary. For the corrugator and zygomaticus muscle signal, EMG data were smoothed using ANSLAB's default moving average window of 50 ms. The 150 ms window stated in the preregistration was incorrect, as such a large window would have resulted in excessive smoothing and potential loss of significant signal information. For the startle response signal, a 15.9 Hz lowpass filter was applied, replacing the preregistered 50 ms moving average filter. This adjustment ensured that the preprocessing procedure for the startle response signal aligned with the recommendations of Blumenthal et al. [16].

Trials with evident movement artifacts or signal loss were marked as missing. In line with the preprocessing procedure for cognitive-behavioral measures, participants with more than 35% missing trials were excluded from the analyses. Table 1-I presents the final sample

size for each psychophysiological measure. Facial muscle activity of the corrugator (EMGcor) and zygomaticus (EMGzyg) muscles was assessed by calculating the average activity during a 7 s interval for trials with smoking-related and neutral stimuli, adjusted by subtracting the 1 s baseline activity prior to stimulus onset. EMGcor and EMGzyg effect scores were then calculated by subtracting the mean facial muscle activity during neutral trials from that during smoking-related trials.

The startle response was scored by two independent raters, blinded to the picture category, with excellent inter-rater reliability (Cohen's kappa = .84). Disagreements were resolved through discussion to ensure consistency. For training purposes, a random selection of ten participants was rated collectively. Following the procedure recommended by Blumenthal et al. [16], invalid-rated trials (e.g., where the peak of activity did not occur within the predefined time window [20–200 ms] after probe onset) were excluded, and non-response trials (amplitude < 5 μV) were set to zero but included in the mean calculation (termed as magnitude). Participants with more than 35% missing trials (invalid-rated or non-response) were excluded. In contrast to previous studies (e.g., [7]), we did not screen participants for the presence of an appropriate startle response prior to participation, leading to the exclusion of a significant number of participants due to a high rate of non-response in the startle trials. EMGstartle effect scores were calculated by subtracting the mean magnitude of neutral trials from that of smoking-related trials.

Appendix A.4.3 Functional MRI assessment

Neuroimaging data analysis was performed with SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and MATLAB R2023a (The Mathworks, Natick, MA, USA). The SPM12 preprocessing pipeline was utilized with standard settings, including spatial realignment, co-registration, normalization to a standard 2 mm MNI template, and spatial smoothing with a Gaussian kernel (8 mm FWHM). Given the task block design,

slice-timing correction was not performed. During preprocessing, four participants were excluded due to excessive head movement (> 3 mm in the x, y, or z direction or > 3° rotation in any direction), resulting in a final fMRI sample size of $n = 113$.

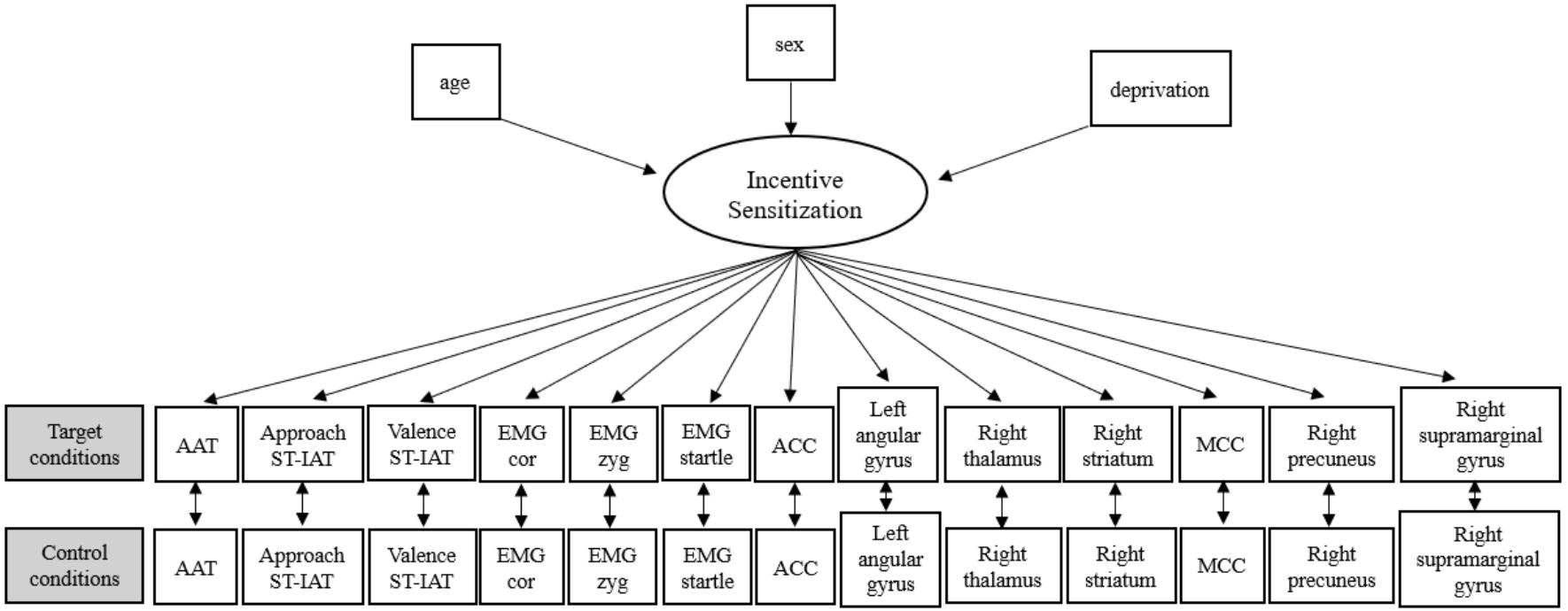
Statistical analysis of the preprocessed fMRI data at the first (individual) level was conducted using a general linear model (GLM). The model included one regressor for each of the three block conditions (smoking-related stimuli blocks, neutral stimuli blocks, and rating blocks). Regressors were modeled as boxcar functions and convolved with the canonical hemodynamic response function. A high-pass filter with a cut-off frequency of 1/128 Hz was used. Additionally, a constant term and motion correction parameters were included as regressors of no interest.

For the ROI analysis, we selected (sub)cortical grey matter regions associated with smoking cue-reactivity [smoking > neutral] in individuals who smoke, based on Lin et al.'s [17] meta-analysis. Masks were generated using the Automated Anatomical Labeling atlas (AAL3; [18]), encompassing the following five areas: (1) left anterior cingulate and paracingulate gyri (ACC; AAL3 labels: ACC_sub, ACC_pre, ACC_sup), (2) left angular gyrus (AAL3 labels: Angular), (3) right thalamus (AAL3 labels: Thal_AV, Thal_LP, Thal_VA, Thal_VL, Thal_VPL, Thal_IL, Thal_RE, Thal_MDm, Thal_MDl, Thal_LGN, Thal_MGN, Thal_PuA, Thal_PuM, Thal_PuL, Thal_PuI), and (4) right striatum (AAL3 labels: Caudate, N_Acc, Putamen, Olfactory). For the whole-brain analysis, regional labels for significant clusters were also derived from the AAL3 atlas. Mean β-estimates for the smoking and neutral conditions in the seven identified regions relevant for smoking cue-reactivity were extracted for statistical analyses.

Appendix B: Statistical analysis

Figure B.1-I

Model structure of the confirmatory factor analysis across all measures



Note. AAT = Approach-Avoidance Task; ST-IAT = Single-Target Implicit-Association Test; EMGcor = Electromyography over the corrugator supercilii muscle; EMGzyg = Electromyography over the zygomaticus major muscle; EMGstartle = Electromyography over the orbicularis oculi muscle; ACC = left anterior cingulate and paracingulate gyri; MCC = right middle cingulate and paracingulate gyri.

Appendix C: Results of partial correlations

Partial correlation analyses revealed no significant associations between measures from different assessment methods, except that greater zygomaticus activity was significantly associated with higher right supramarginal gyrus activity during exposure to smoking-related stimuli (non-significant after FDR-correction; see Table C.1-I). Several significant intercorrelations were observed between measures within the cognitive-behavioral and neural assessment methods. Among cognitive-behavioral measures, faster RTs in compatible trials of the approach ST-IAT (smoking–approach) were significantly correlated with faster RTs in compatible trials of the valence ST-IAT (smoking–positive), and with faster pull movements during smoking-related trials in the AAT (all effects non-significant when using AAT and ST-IAT difference scores as outcome measures). Most neural measures were significantly correlated, except for MCC and right precuneus activity with ACC and left angular gyrus activity. No significant intercorrelations emerged among EMG measures.

Table C.1-I

Partial correlations between measures

Measures	**Cognitive-behavioral**				**Psychophysiological**			**Neural**						
	AAT	Approach ST-IAT	Valence ST-IAT	Stroop	EMG cor	EMG zyg	EMG startle	ACC	Left angular gyrus	Right thalamus	Right striatum	MCC	Right precuneus	Right supramarginal gyrus
Cognitive-behavioral														
AAT	1													
Approach ST-IAT	**.107 (.048)**[b]	1												
Valence ST-IAT	.078 (.150)	**.324 (<.001)**[a,c]	1											
Stroop	.064 (.235)	.001 (.984)	-.042 (.444)	1										
Psychophysiological														
EMGcor	-.024 (.686)	.020 (.741)	.166 (.051)	.011 (.847)	1									
EMGzyg	.070 (.233)	.007 (.912)	-.010 (.869)	-.003 (.965)	-.075 (.206)	1								
EMGstartle	.044 (.572)	-.081 (.293)	-.030 (.699)	.035 (.654)	-.126 (.103)	.124 (.106)	1							
Neural														
ACC	-.014 (.885)	.052 (.594)	.064 (.512)	.122 (.213)	-.031 (.760)	.131 (.187)	.174 (.187)	1						
Left angular gyrus	.164 (.092)	.054 (.578)	.007 (.939)	.124 (.206)	.015 (.879)	.101 (.312)	.141 (.286)	**.600 (<.001)**[a]	1					
Right thalamus	.019 (.843)	-.041 (.673)	.065 (.500)	-.003 (.975)	.084 (.406)	.124 (.213)	.108 (.416)	**.568 (<.001)**[a]	**.466 (<.001)**[a]	1				
Right striatum	.163 (.093)	-.046 (.637)	-.015 (.877)	-.027 (.781)	.004 (.972)	.112 (.260)	.175 (.184)	**.511 (<.001)**[a]	**.469 (<.001)**[a]	**.702 (<.001)**[a]	1			
MCC	.121 (.215)	-.172 (.076)	.095 (.325)	-.032 (.742)	.183 (.067)	.031 (.759)	-.223 (.090)	.140 (.147)	.166 (.085)	**.515 (<.001)**[a]	**.436 (<.001)**[a]	1		
Right precuneus	.026 (.787)	-.125 (.197)	.048 (.620)	.040 (.683)	.039 (.699)	.025 (.803)	-.113 (.392)	.034 (.724)	.031 (.746)	**.483 (<.001)**[a]	**.323 (<.001)**[a]	**.494 (<.001)**[a]	1	
Right supramarginal gyrus	.113 (.247)	-.018 (.850)	.034 (.725)	.054 (.580)	.070 (.486)	**.205 (.038)**	.231 (.078)	**.638 (<.001)**[a]	**.643 (<.001)**[a]	**.649 (<.001)**[a]	**.554 (<.001)**[a]	**.447 (<.001)**[a]	**.234 (.014)**	1

Note. Non-parametric partial correlation coefficients (Spearman's rho), controlled for age, sex, and deprivation (if applicable), are reported with corresponding *p*-values in parentheses. AAT = Approach-Avoidance Task; ST-IAT = Single-Target Implicit-Association Test; EMGcor = Electromyography over the corrugator supercilii muscle; EMGzyg = Electromyography over the zygomaticus major muscle; EMGstartle = Electromyography over the orbicularis oculi muscle; ACC = left anterior cingulate and paracingulate gyri; MCC = right middle cingulate and paracingulate gyri.

[a] *p*-value remains significant after Benjamini-Hochberg correction.

[b] Using the AAT and approach ST-IAT difference scores, no significant correlation emerged (r = -.009, p = .864).

[c] Using the approach and valence ST-IAT difference scores, no significant correlation emerged (r = .054, p = .312).

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APPENDIX OF STUDY II

Appendix A: Additional methodological information

Appendix A.1: Participants and design

Between May 2018 and October 2023[31], a total of 122 non-deprived individuals who smoke took part in a pre-registered intervention study on the efficacy of impulse control training as a stand-alone intervention in reducing tobacco consumption and craving (see German Clinical Trials Register, DRKS00014652; 23/04/2018), completed the baseline assessment and were included in the present cross-sectional study. Inclusion criteria were: (1) a total score of ≥ 3 in the Fagerström Test for Nicotine Dependence (FTND; [1]), (2) a carbon monoxide (CO) level in the exhaled air of ≥ 10 ppm, (3) age 18–70 years, (4) no use of nicotine replacement products (including e-cigarettes), (5) currently non-attendance of pharmacological or psychotherapeutic smoking cessation treatment, and (6) willingness to abstain from any therapy for smoking cessation during study participation. Exclusion criteria were: (1) moderate to severe substance use disorder other than tobacco within the last 12 months (i.e., 4 ≥ fulfilled criteria according to DSM-5 assessed with the Mini International Neuropsychiatric Interview [MINI; [2]]), (2) current or previous diagnosis of severe psychiatric (e.g., schizophrenia, bipolar disorder) or neurological (e.g., epilepsy, Parkinson disease, multiple sclerosis) disorders, (3) acute suicidality, (4) current pregnancy or nursing period, (5) uncorrectable vision, and (6) insufficient German language skills.

Between February 2024 and May 2024, a total of 69 age-matched healthy individuals with no history of smoking or any other substance use disorder were recruited as a control group. Inclusion criteria were: (1) age 18–70 years, and (2) ≤ 10 cigarettes smoked in lifetime.

[31] The recruitment of participants commenced in May 2018. Due to the corona pandemic and the closing of university buildings, recruitment was suspended in November 2020, with n = 79 participants having been enrolled up to that point. Recruitment resumed in January 2023, and the final sample size of N = 122 was reached in October 2023.

Exclusion criteria were: (1) current psychiatric disorders (assessed with the short structured clinical interview for diagnosing mental disorders according to DSM-5 and ICD-10 [Mini-DIPS-OA; [3,4]]), (2) previous diagnosis of severe psychiatric (e.g., schizophrenia, bipolar disorder, substance use disorder) or neurological (e.g., epilepsy, Parkinson disease, multiple sclerosis) disorders, (3) current intake of psychotropic medication, and (4) insufficient German language skills.

For the non-smoking group, the health-related rigorous criteria were selected based on the assumption that deficits in response inhibition represent a transdiagnostic risk factor in psychopathology [5]. Similar to previous studies in the field (e.g., [6–8]), our exclusion criteria for the non-smoking sample did not account for passive smoking. However, research has shown that individuals who have never smoked but have been passively exposed to smoking also exhibit deficits in executive functioning [9]. Accordingly, GNGT performance in the non-smoking group may have been affected by passive smoke exposure (see the limitations section in the main manuscript for a critical discussion).

We used convenience sampling (see the limitations section for a critical discussion), with participants from both groups recruited through various means, including notices in university buildings, ads on the university mailing list, flyers displayed in pharmacies and physicians' waiting rooms, and social media platforms such as Facebook.

Appendix A.1.1: Flow of participants

For the smoking group, $n = 258$ individuals were assessed for eligibility. A total of $n = 136$ were excluded due to the following reasons: 36 with FTND < 3 or no regular smoking; 31 did not show up for assessment; 28 used e-cigarettes, NRT, etc.; 21 had personal or logistic reasons (e.g., lack of time); 14 with probable substance dependence except tobacco; 3 with insufficient German language skills; 2 with severe neurological disorder; 1 with CO < 10; 1 with severe psychiatric disorder; 1 was aged < 18 or > 70 years; 1 with no reason documented.

For the control group, $n = 108$ individuals were assessed for eligibility. A total of $n = 39$ were excluded due to the following reasons: 17 with > 10 cigarettes smoked in lifetime; 9 had personal or logistic reasons (e.g., lack of time); 8 with current psychiatric disorders and/or intake of psychotropic medication; 2 with insufficient German language skills; 2 did not show up for assessment; 1 was aged < 18 or > 70 years.

Appendix A.2: Power analysis

The sample size of $N = 122$ for the smoking group was determined in advance of the pre-registered clinical trial (see German Clinical Trials Register, DRKS00014652; 23/04/2018). The total sample size for the cross-sectional analysis was estimated to be $N = 128$ participants (i.e., 64 participants per group) to detect a medium effect of $d = 0.5$ by using G*Power [10], given $\alpha = .05$ and $\beta = .80$ for two-sample t-tests (see the pre-registration of the current study: AsPredicted.org, #172127). For both groups, the recruitment stopped after the necessary sample size had been reached.

Although a previous meta-analysis revealed a small effect size for performance differences in the Go/No-Go task (GNGT) between smoking and control groups [11], a medium effect size was assumed for the current study. This is because, according to the IST, the use of smoking-related stimuli should result in increased deficits in response inhibition in individuals who smoke. Above, the a-priori estimated reliability of the GNGT measures for the smoking group exceeded a standard of good reliability (see Appendix A.4.1 and [12]; [13]). However, reliability is not fully inherent to a task [14], so this cannot be automatically conveyed to previous GNGT research. Therefore, poor reliability scores may have constrained the observed effect sizes in previous studies.

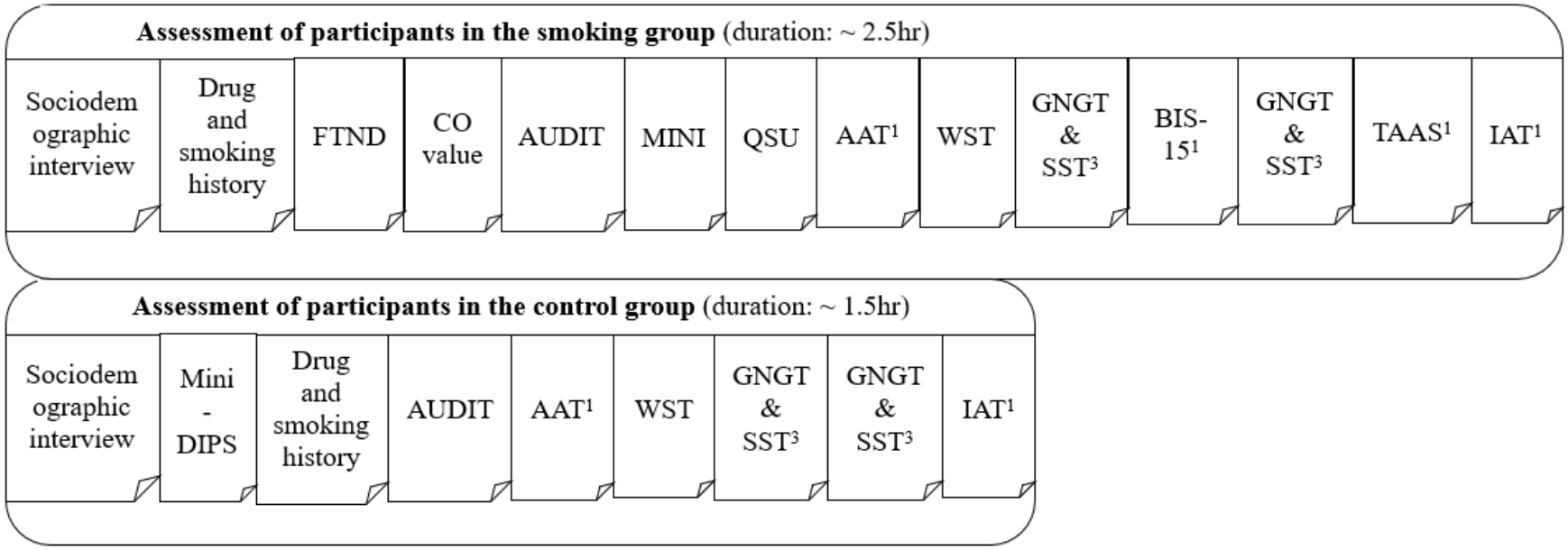
Appendix A.3: Procedure and measures

All participants underwent an initial telephone screening (including an explanation of the study procedure, the clearance of in-/exclusion criteria, and the appointment arrangement). The assessment was conducted individually in a laboratory at the university. The fulfilment of the inclusion/exclusion criteria was verified at the beginning of the assessment. Following a sociodemographic interview, a series of questionnaires and experimental tasks were conducted. See Figure A.3.1-II for an illustration of the assessment procedure. Some assessments specific to smoking (e.g., FTND) were not applicable to individuals in the control group. Consequently, the assessment duration was approximately 30 minutes shorter than in the smoking group. The participants received 8 Euros per hour for their participation in the assessment.

All questionnaires were administered in paper-pencil format, while the reaction time tasks were conducted using the computer-based software Inquisit (version 4, www.millisecond.com). The intervention study was designed to assess various potential working mechanisms of inhibitory control training. Accordingly, participants completed a series of tasks and questionnaires that were not relevant to the current investigation (see Figure A.3.1-II). In addition to the two GNGTs, the Stop-Signal task (SST; [15]) was administered in both a general and a smoking-specific version to assess response inhibition ability. However, in the course of publishing the results of the intervention study, split-half reliabilities were estimated, revealing that the outcome measure of the general SST in the smoking group was unsatisfactory (i.e., r = .472, *95% CI* [.316; .628]; [12]). Meanwhile, the RTs of the smoking-specific SST could not be evaluated due to a programming error in the staircase procedure [12]. Consequently, the present investigation utilized solely data from both GNGTs to assess response inhibition.

Figure A.3.1-II

Assessment procedure for smoking and control groups



Note. FTND = Fagerström Test for Nicotine Dependence; CO = Carbon Monoxide; AUDIT = Alcohol Use Disorder Identification Test; MINI = Mini International Neuropsychiatric Interview for substance use disorders; QSU = Questionnaire of Smoking Urges, brief version; AAT = Approach-Avoidance task; WST = Wortschatztest; GNGT = Go/No-Go task; SST = Stop-Signal task; BIS-15 = Barratt Impulsiveness Scale, 15-item version; TAAS = Thoughts About Abstinence Scale; IAT = Implicit-Association Test; Mini-DIPS = Short structured clinical interview for diagnosing mental disorders according to DSM-5 and ICD-10.

[1] not relevant for the current investigation.

[2] both tasks (GNGT and SST) were given in both a general and smoking-specific version across two blocks. One block had both tasks in the general version, and the other block had both tasks in the smoking-specific version. The order (block with general versions first vs. block with smoking-specific versions first) was randomized across participants. The two tasks in each block were performed in a fixed order: first the GNGT, and second the SST

Appendix A.3.1: Go/No-Go tasks and outcome measures

Response inhibition was assessed by using both a general and smoking-specific GNGT. In the general GNGT, stimuli comprised white digits ranging from 1 to 8. Each digit was presented 40 times in a fully randomized sequence, resulting in 320 test trials. These were preceded by eighteen training trials. In each trial, a single digit was displayed centrally on a black screen. Participants were instructed to respond as quickly as possible to all digits except for the digits "3" and "6" by pressing the space bar with the index finger of their dominant hand (response window and stimulus presentation time: 1,000 ms). Given that each digit was presented with equal frequency, 75% of the trials required a response (Go trials; prepotent response), whereas in 25% of the trials, the response had to be withheld (No-Go trials). The inter-trial interval was 500 ms. If participants failed to respond correctly, the error message "error" was displayed for 400 ms.

The smoking-specific GNGT (adapted from Luijten et al. [6]) used the same set-up parameters (e.g., timings, trials). However, the stimuli consisted of 20 smoking-related and 20 neutral pictures. The pictures were selected from previous studies (e.g., [6,16,17]) and freely available online sources (see Figure A.3.1.1-II for an impression of the stimuli).

Figure A.3.1.1-II

Examples of smoking-related and neutral stimuli

Note. Each smoking-related picture was paired with a neutral picture matched by content (e.g., a person versus a person smoking, coffee versus coffee and cigarettes). The colour frame (blue or yellow) signalled whether participants should respond or withhold a response.

Each of the 20 smoking-related pictures fell into one of 10 smoking-related categories, with two pictures per category (e.g., a person smoking, a person lighting a cigarette, coffee and cigarettes, alcoholic drink and cigarettes, etc.). Likewise, each of the 20 neutral pictures fell into one of 10 neutral categories, matched to the smoking-related categories (e.g., a person, a person brushing teeth, coffee, a glass of water, etc.). As a result, smoking-related pictures depicted content similar to that of neutral pictures (e.g., a person versus a person smoking, coffee versus coffee and cigarettes). This procedure ensured that the smoking-related and

neutral pictures were comparable in complexity, although no formal statistical comparison was conducted.

In each trial, a single smoking-related or neutral stimulus framed in either blue or yellow was displayed centrally on a black screen. Participants were instructed to respond (i.e., Go or No-Go) based on the colour of the frame. The assignment of frame colour to response type (Go trials: yellow frame vs. Go trials: blue frame) was counterbalanced across participants. Each picture was presented eight times: six times (75%) as a Go and two times (25%) as a No-Go stimulus. The order of picture content (smoking-related versus neutral) and trial type (Go versus No-Go) was completely randomized. Unlike Luijten et al. [6], the present study utilized a longer stimulus presentation duration of 1,000 ms (compared to 200 ms). This should entail a more realistic and sustained exposure to smoking-related cues. Additionally, participants were not required to abstain from smoking before the experiment, unlike the one-hour abstinence requirement in Luijten et al. [6]. This approach should permit a broader range of craving levels within the smoking group.

Appendix A.4: Statistical analysis

Appendix A.4.1: Data pre-processing, aggregation, and reliability

As pre-registered, participants with an OE rate above 35%[32] would have been excluded from further analyses on GNGT measures. As no participant reached this error rate, it can be concluded that task instruction adherence was excellent.

All questionnaires (see Table 1-II) were collected via paper-pencil format, with the possibility that some questions might not have been answered. This resulted in missing data for the QSU-brief (n = 3) and AUDIT (n = 2). In the latter case, 16 participants received the 8-item version of the questionnaire instead of the 10-item version, which resulted in a higher rate

[32] Thereby, we followed the pre-processing procedure as used for other reaction time tasks within the field of addiction research, see Wittekind et al. [18].

of missing data. It was assumed that the missing items in the questionnaires were missing at random, as participants completed them individually without expecting negative or positive consequences for their answers. For transparency, the final sample sizes for both variables (QSU-brief: n = 119; AUDIT: n = 104) are indicated in Tables 1-II, 4-II, and 5-II.

Missing data was handled as follows. Since the AUDIT score was used solely to describe the sample characteristics, missing values on this measure were not imputed. In the models using the QSU-brief score as a predictor in research question 3, the sample size was reduced (n = 119, instead of n = 122). The rate of missing data was 3 out of 122 (~ 2.46%). Some researchers suggest that a missing data rate below 5% is negligible (e.g., [19]). However, we also examined the robustness of our findings after imputing missing values. For two participants, only one of the 10 items on the QSU-brief was missing. These values were replaced by the participant's mean score on the remaining QSU-brief items. In the third case, the QSU-brief score was missing because the examiner accidentally omitted the questionnaire. This missing score was replaced by the sample mean QSU-brief score. After this imputation procedure, the results for all models using the QSU-brief score as a predictor in research question 3 remained unchanged.

To estimate the Spearman-Brown corrected split-half reliabilities of the GNGT measures, the R package *splithalfr* [20] was used with 5,000 random splits (see Table A.4.1.1-II). For questionnaire data, Cronbach's alpha was calculated (smoking group: QSU-brief: α = .805, *95% CI* [.738; .851]; FTND: α = .481, *95% CI* [.334; 587]).

Table A.4.1.1-II

Split-half reliability scores of task measures

Measures	Smoking group		Control group	
	r	*95% CI*	*r*	*95% CI*
General GNGT				
CE rate	.858	.802 – .914	.817	.702 – .933
Go-RT	.986	.983 – .990	.982	.976 – .987
Smoking-specific GNGT				
CE rate (all trials)	.838	.773 – .902	.791	.655 – .928
CE rate (smoking-related trials)	.613	.529 – .696	.609	.417 – .800
CE rate (neutral trials)	.773	.678 – .867	.646	.422 – .871
Go-RT (all trials)	.993	.991 – .995	.987	.982 – .993
Go-RT (smoking-related trials)	.986	.982 – .990	.975	.966 – .985
Go-RT (neutral trials)	.986	.982 – .989	.975	.963 – .986

Note. *r* = Split-half reliability, Spearman-Brown corrected; *CI* = Confidence Interval; GNGT = Go/No-Go task; CE = Commission Error; Go-RT = mean Reaction Time in Go trials.

Appendix A.4.2: Strategy of data analysis

In research question 1, we used *t*-tests and ANOVAs without considering covariates for comparative purposes, as these statistical methods have been predominantly employed in previous GNGT studies (e.g., [6,8,21–23]). For the statistical analyses addressing research questions 2 and 3, we chose linear regression models because they provide advantages over ANOVAs and *t*-tests by accommodating the modelling of nested structures (i.e., performance on smoking-related and neutral trials within each individual) and offering greater flexibility in incorporating covariates [24].

The assumptions for each statistical model were tested. For all models, we identified influential data points (i.e., outliers and/or leverage points, assessed using boxplots, studentized residuals, leverage plots, and Cook's distance). Additionally, we found that some model data violated the assumptions of normality (of residuals) and/or homogeneity of variances. Given that influential data points were primary concerns in our statistical analyses, we decided to employ data trimming for research question 1 and robust regression techniques for research

questions 2 and 3. These methods mitigate the impact of influential data points while also addressing issues related to non-normality and non-homogeneity of variances. This approach aligns with the general recommendations of Field and Wilcox [25] on handling the common challenges posed by violated assumptions in experimental data, which can easily distort the results obtained through standard statistical methods.

For research question 1 regarding the general GNGT, robust two-sample *t*-tests on trimmed means (*yuenbt* function, *WRS2* package, version 1.1-4; [26]; with the default trim proportion of 0.2 and 5,000 bootstraps) were conducted to examine the differences in performance measures between the smoking and control groups. Tests on trimmed means offer a good solution for skewed distributions, providing a balance between utilizing the mean (no trimming) and the median (maximum amount of trimming; [27]). The effect size is provided by ξ, a robust explanatory measure with values of = .10, .30, and .50 corresponding to a small, medium, and large effect [26]. For research question 1 regarding the smoking-specific GNGT, robust two-way mixed measures ANOVAs on trimmed means (*bwtrim* function, *WRS2* package, with the default trim proportion of 0.2) were performed, with the between-subject factor group (smoking/non-smoking) and the within-subject factor stimulus type (smoking-related/neutral). As the *bwtrim* function does not provide effect sizes, ξ was estimated with the *yuen* (independent samples) and *yuend* (dependent samples) functions. The classical frequentist analyses on group effects were complemented by post-hoc Bayesian two-sample *t*-tests (*ttestBF* function, *BayesFactor* package; [28]). Bayes factors (BF_{10}) > 3 were interpreted as substantial evidence in favour of a difference between groups [29].

For research question 2 regarding the general GNGT, robust multiple linear regressions (*rlm* function, *MASS* package, version 7.3-58.4; [30]) were conducted to examine whether group (smoking/non-smoking) was associated with GNGT performance, while controlling for age, sex, and IQ. Data of the smoking-specific GNGT had a 2-level structure, with smoking-

related and neutral trials nested within each subject. Therefore, robust linear mixed-effects models were utilized (*rlmer* function, *robustlmm* package, version 3.3-1; [31]) to examine whether group (smoking/non-smoking), stimulus type (smoking-related/neutral), and their interaction were associated with the performance in the smoking-specific GNGT, while controlling for age, sex, and IQ.

For research question 3, the performance of the smoking group in the general GNGT was examined by conducting three robust multiple linear regression models (*rlm* function) with either CPD, the FTND, or QSU-brief score (smoking-related variables) as main predictor. Each model included age, sex, and IQ as control variables as well as their interactions with the respective main predictor. For the performance in the smoking-specific GNGT, again, robust linear mixed-effects models were utilized, including stimulus type (smoking-related/neutral) and its interaction with CPD, FTND, or QSU-brief as additional predictors.

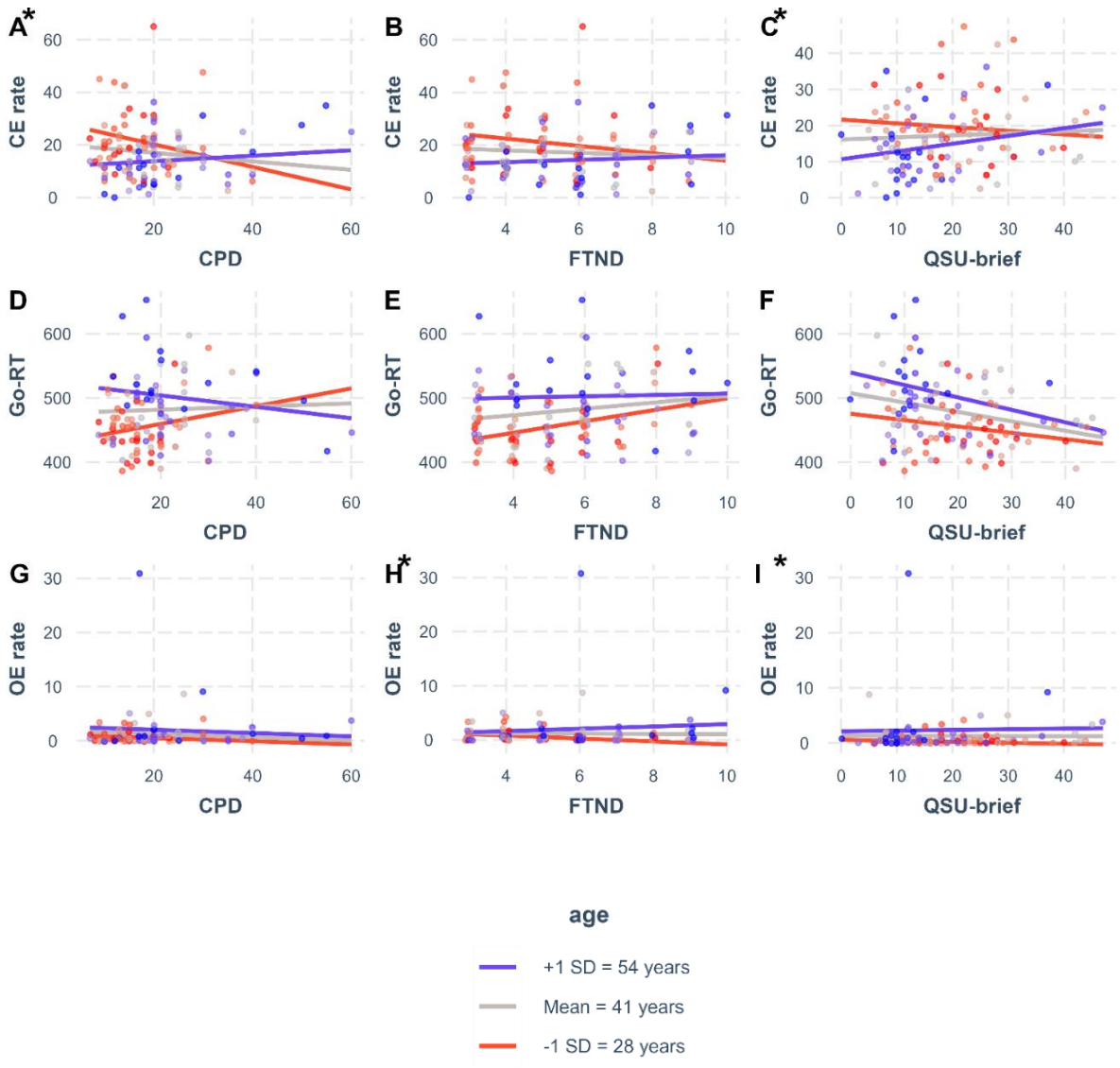
The Benjamini-Hochberg correction [32] was employed to adjust for several effects of interest on each GNGT outcome measure within each research question. The method controls the false discovery rate at 5% and demonstrates good performance with substantial power and reasonable protection against the Type I error [33,34]. For example, in each of research questions 1 and 2, three effects were corrected for the CE rate: the effect of group in the general GNGT as well as the effects of group and group × stimulus type in the smoking-specific GNGT. In research question 3, nine effects were corrected for the CE rate: the effects of the three smoking-related variables on the CE rate in the general GNGT, as well as the effects of the three smoking-related variables and smoking-related variables × stimulus type on the CE rate in the smoking-specific GNGT. The exploratory investigated interaction effects (smoking-related variables × age, × sex, and × IQ) were FDR-corrected separately (i.e., 18 effects for each GNGT outcome measure). All regression model predictors, except for sex, were grand-mean centred.

Appendix B: Figures of interaction effects

To the best of our knowledge, there is no package providing interaction plots for the robust regression model functions used for our analyses (see Appendix A.4.2). Therefore, the plots were compiled using the *interactions* package [35] on conventional (non-robust) regression models (*lm* and *lmer* functions, *lme4* package, version 1.1-34; [36]). The direction of the effects observed in the conventional and robust models remained consistent.

Figure B.1-II

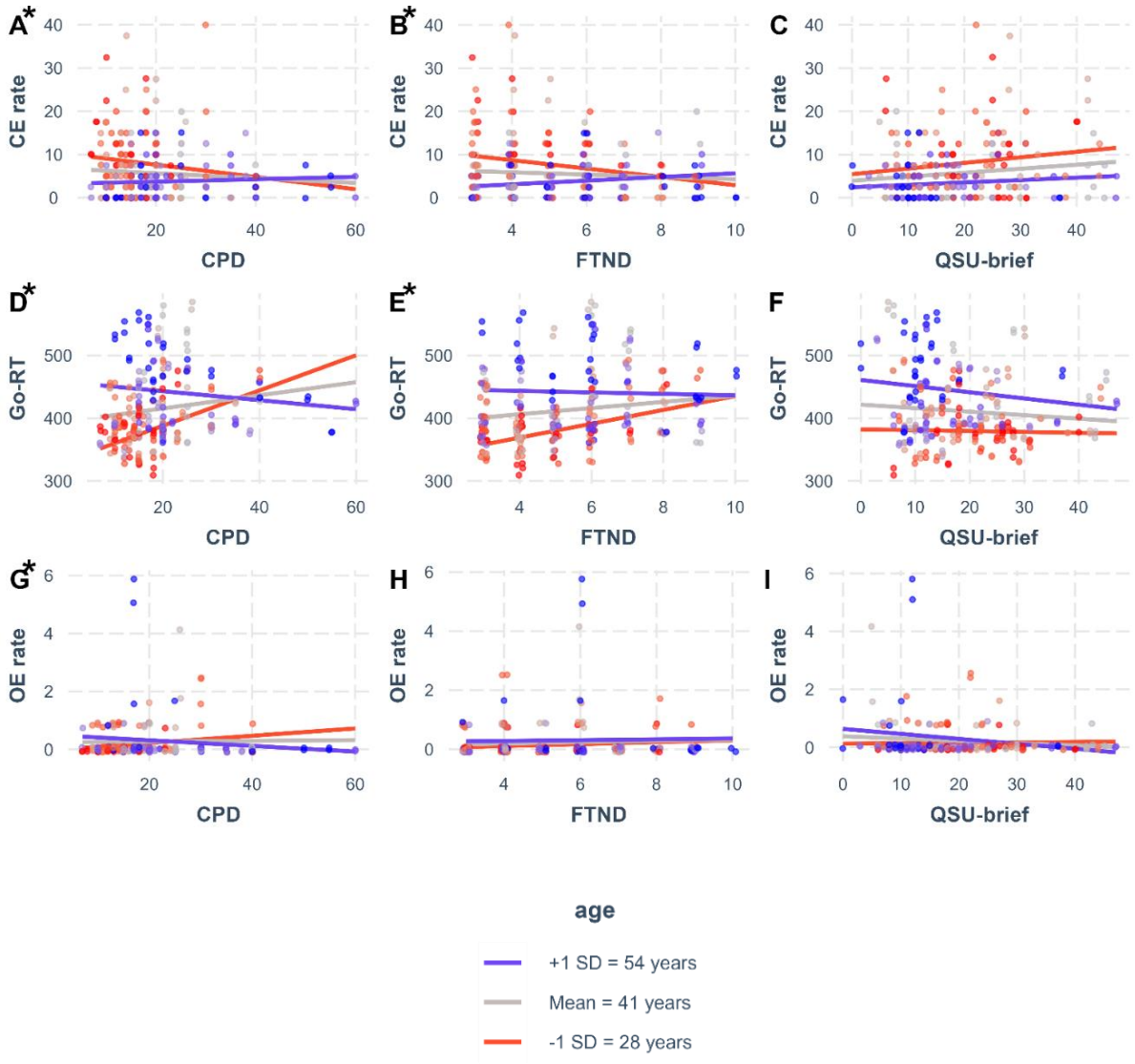
Smoking-related variable × age interaction plots on CE rates, Go-RTs, and OE rates in the general GNGT



Note. Significant smoking-related variable × age interactions are indicated by *. For better interpretability, variables were retained in their original scale (without grand-mean cantering). CPD = Cigarettes Per Day; FTND = Fagerström Test for Nicotine Dependence; QSU-brief = Questionnaire on Smoking Urges, brief version; CE = Commission Error; OE = Omission Error; Go-RT = mean Reaction Time in Go trials.

Figure B.2-II

Smoking-related variable × age interaction plots on CE rates, Go-RTs, and OE rates in the smoking-specific GNGT



Note. Significant smoking-related variable × age interactions are indicated by *. For better interpretability, variables were retained in their original scale (without grand-mean centring). CPD = Cigarettes Per Day; FTND = Fagerström Test for Nicotine Dependence; QSU-brief = Questionnaire on Smoking Urges, brief version; CE = Commission Error; OE = Omission Error; Go-RT = mean Reaction Time in Go trials.

Appendix C: Results with OE rates as outcome measure

Both GNGTs were implemented with a relatively large response window of 1,000 ms, which resulted in overall low OE rates (see Table 2-II). Accordingly, the OE rate may not be a sensitive measure for differentiating between individuals' performance. However, readers may be interested in the results of OE rates as outcome measure, and thus, we have provided them here. A summary of the results is given in the Results section of the main manuscript.

Research question 1: Group difference analyses on OE rates: Smoking vs. control group

Given the minimal overall variability in OE rates, trimming was not employed in their statistical analyses. Neither in the general GNGT (T_y = -1.04, p = .293, *95% CI* [-0.37; 0.11], ξ = .14[33], BF_{10} = 0.334[34]), nor in the smoking-specific GNGT (Q[1, 119.81] = 0.27, p = .604, ξ = .07, BF_{10} = 0.18), did frequentist and Bayes statistics provide evidence for a difference between groups on OE rates. In the smoking-specific GNGT, the main effects of stimulus type lacked statistical significance, Q(1, 120.80) = 0.43, p = .511, ξ = .03. Also, there was no statistical support for a significant interaction between group and stimulus type, Q(1, 120.80) < 0.01, p = .968.

Research question 2: Regression analyses with group and covariates as predictors

Regression models did not yield substantial evidence to suggest a difference in OE rates between the smoking and control groups in either GNGT (see Table C.1-II). Unlike the models using CE rates and Go-RTs as the outcome measure, no significant association between age and OE rates was observed. Also, no significant association with sex and IQ emerged.

[33] Robust explanatory effect size for *t*-tests on means: small: ξ = .10, medium: ξ = .30 [26].

[34] $3 < BF_{10} < 10$: indicates substantial evidence in favour of a difference between groups; $1 < BF_{10} < 3$: indicates weak evidence in favour of a difference between groups; $1/3 < BF_{10} < 1$: indicates weak evidence in favour of no difference between groups; $1/10 < BF_{10} < 1/3$: indicates substantial evidence in favour of no difference between groups [29].

Table C.1-II

Results of regression models on OE rates in both GNGTs

Predictors	OE rate		
	β	*95% CI*	*p*
	General GNGT		
Intercept	0.418	0.222 – 0.614	**<.001**
Group (1: smoking)	0.092	-0.098 – 0.282	.341
Age	0.006	-0.001 – 0.014	.084
Sex (1: female)	-0.032	-0.217 – 0.153	.733
IQ	-0.004	-0.013 – 0.005	.376
	Smoking-specific GNGT[1]		
Intercept	0.336	0.150 – 0.522	**<.001**
Group (1: smoking)	-0.111	-0.312 – 0.091	.281
Age	0.001	-0.005 – 0.006	.758
Sex (1: female)	-0.027	-0.168 – 0.113	.703
IQ	-0.003	-0.010 – 0.004	.379
Stimulus type (1: smoking)	-0.127	-0.352 – 0.097	.266
Stimulus type × Group	0.125	-0.156 – 0.407	.383

Note. All regression model predictors, except for sex, were grand-mean centred. *CI* = Confidence Interval; GNGT = Go/No-Go task.

[1] coefficients multiplied by 10^{13} for readability.

Research question 3: Regression analyses with smoking-related variables and covariates in smoking individuals

Effects of smoking-related variables and stimulus type on CE rates and Go-RTs

Smoking-related variables (i.e., CPD, FTND, and QSU-brief) did not show conclusive evidence of a relationship with performance in the GNGTs. Also, no significant interactions were observed between smoking-related variables and stimulus type on GNGT performance.

Effects of covariates on CE rates and Go-RTs

Contrary to the regression models that investigated CE rates and Go-RTs as outcome measures, age was not consistently associated with higher OE rates (see Table C.2-II; only in the general GNGT, exclusively in the model that included the QSU-brief score as main predictor). Also, a higher IQ was not consistently related to lower OE rates in the smoking-specific GNGT (only in the model with the QSU-brief score as main predictor). However, in

line with models that investigated CE rates and Go-RTs, IQ was not significantly associated with Go-RTs in the general GNGT or CE rates.

Interaction effects between smoking-related variables and covariates on CE rates and Go-RTs

None of the interaction effects were significant after FDR-correction; therefore, results should be regarded as preliminary and confirmed in subsequent studies before firm conclusions can be drawn. Some significant interactions between age and smoking-related variables on the performance in the GNGTs were observed (general GNGT: FTND × age, QSU-brief × age; smoking-specific GNGT: CPD × age; for interaction plots see Appendix B, Figures B.1-II and B.2-II). These effects indicate that older individuals (i.e., M_{age}+1 SD_{age} = 54 years) with higher severity of tobacco dependence and craving tended to exhibit higher OE rates in the general GNGT. Conversely, younger individuals (i.e., M_{age}-1 SD_{age} = 28 years) with higher severity of tobacco dependence and craving tended to exhibit lower OE rates. Simply put, older individuals who had greater tobacco dependence or reported stronger craving tended to make more OEs by incorrectly non-responding in Go trials. In contrast, younger individuals who had greater tobacco dependence or reported stronger craving tended to make fewer OEs by correctly responding in Go trials. In the smoking-specific GNGT, older individuals with a higher number of CPD tended to show lower OE rates, while in younger individuals, a higher number of CPD was tendentially associated with higher OE rates. Simply put, older individuals who smoked more tended to make fewer OEs by correctly non-responding in Go trials. In contrast, younger individuals who smoked more tended to make more OEs by incorrectly responding in Go trials. Again, there was no clear evidence of significant interactions between smoking-related variables and sex or IQ.

Table C.2-II

Results of regression models on OE rates in both GNGTs

Predictors	CPD			FTND			QSU-brief		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*
OE rate									
General GNGT									
Intercept	0.505	0.324 – 0.686	**<.001**	0.513	0.326 – 0.700	**<.001**	0.512	0.327 – 0.698	**<.001**
Age	0.007	-0.003 – 0.017	.149	0.008	-0.002 – 0.018	.100	0.017	0.006 – 0.027	**.002**
Sex (1: female)	-0.053	-0.288 – 0.182	.657	-0.056	-0.301 – 0.189	.651	0.051	-0.198 – 0.299	.687
IQ	-0.007	-0.018 – 0.004	.214	-0.009	-0.020 – 0.003	.139	-0.001	-0.013 – 0.010	.827
Variable	0.007	-0.012 – 0.027	.467	-0.019	-0.123 – 0.085	.715	0.020	-0.00004 – 0.040	.050
Variable × Age	0.0004	-0.001 – 0.001	.462	0.006	0.001 – 0.011	**.029**	0.001	0.0004 – 0.003	**.008**
Variable × Sex	-0.0003	-0.025 – 0.025	.980	0.064	-0.070 – 0.197	.345	-0.006	-0.031 – 0.019	.638
Variable × IQ	0.001	-0.0002 – 0.002	.105	0.002	-0.004 – 0.009	.462	-0.0002	-0.001 – 0.001	.775
Smoking-specific GNGT[1]									
Intercept	0.240	0.095 – 0.385	**.001**	0.264	0.087 – 0.442	**.003**	0.049	0.017 – 0.081	**.003**
Age	-0.004	-0.011 – 0.003	.247	-0.002	-0.010 – 0.006	.655	-0.0002	-0.002 – 0.001	.753
Sex (1: female)	0.023	-0.136 – 0.183	.773	0.017	-0.179 – 0.214	.862	0.0003	-0.036 – 0.036	.987
IQ	-0.008	-0.015 – -0.0003	**.040**	-0.009	-0.018 – 0.0006	.068	-0.002	-0.004 – -0.0004	**.018**
Variable	0.011	-0.005 – 0.027	.164	0.083	-0.015 – 0.181	.097	-0.001	-0.005 – 0.002	.460
Variable × Age	-0.001	-0.001 – -0.00003	**.042**	-0.003	-0.007 – 0.001	.175	-0.00002	-0.0002 – 0.0001	.760
Variable × Sex	0.004	-0.013 – 0.021	.651	-0.066	-0.172 – 0.041	.229	0.001	-0.002 – 0.005	.505
Variable × IQ	-0.0004	-0.001 – 0.0004	.322	-0.007	-0.012 – -0.002	**.007**	0.0002	-0.000006 – 0.0003	.058
Stimulus type (1: smoking)	-0.018	-0.173 – 0.137	.824	-0.010	-0.201 – 0.182	.922	-0.001	-0.035 – 0.033	.954
Variable × Stimulus type	-0.009	-0.026 – 0.008	.287	-0.083	-0.187 – 0.021	.116	-0.002	-0.005 – 0.002	.308

Note. The predictor *Variable* refers to either CPD, FTND, or QSU. All regression model predictors, except for sex, were grand-mean centred. None of the effects of smoking-related variables (× stimulus type) on the CE rate or Go-RT were significant after Benjamini-Hochberg correction. CPD = Cigarettes Per Day; FTND = Fagerström Test for Nicotine Dependence; QSU-brief = Questionnaire on Smoking Urges, brief version; *CI* = Confidence Interval; GNGT = Go/No-Go task. [1] coefficients multiplied by 10^{13} for readability

Appendix D: Results with years of smoking as predictor

Within research question 3, we aimed to control for the effect of age, but were also interested in the effect of smoking duration (in years) on the GNGT performance. However, it was not possible to include both variables in the regression models due to their multicollinearity (observed correlation between age and years of smoking: r = .909). Therefore, regression models were performed separately with age and years of smoking as predictors. A summary of the results is given in the Results section of the main manuscript. The discussion of the results is provided in Appendix E.2.

Research question 3: Regression analyses with smoking-related variables and covariates (including years of smoking) in smoking individuals

Effects of smoking-related variables and stimulus type on CE rates and Go-RTs

As in regression models with age as predictor, smoking-related variables (i.e., CPD, FTND, and QSU-brief) did not show conclusive evidence of a relationship with performance in the GNGTs (see Tables D.1-II and D.2-II), with one exception: higher QSU-brief scores were tendentially associated with faster Go-RTs in the general GNGT (non-significant after FDR-correction). Once more, in the smoking-specific GNGT, a significant interaction was observed between the QSU-brief score and stimulus type. This effect indicates that higher reported craving was associated higher CE rates during smoking-related trials compared to neutral trials.

Effects of covariates on CE rates and Go-RTs

In both GNGTs, a longer history of smoking was associated with significantly lower CE rates and slower Go-RTs. There was no clear evidence indicating an association between sex and CE rates or Go-RTs. In the smoking-specific GNGT, a higher IQ was associated with significantly faster Go-RTs (although this effect was non-significant in the model with QSU-brief as main predictor), whereas IQ was not significantly related to Go-RTs in the general GNGT or CE rates.

Interaction effects between smoking-related variables and covariates on CE rates and Go-RTs

Since the interaction effects between smoking-related variables and age, sex, and IQ were not pre-registered, they should be regarded as exploratory. Furthermore, none of the interaction effects were significant after FDR-correction; therefore, results should be regarded as preliminary and confirmed in subsequent studies before firm conclusions can be drawn.

Again, regression models revealed some significant interaction effects between years of smoking and smoking-related variables (i.e., CPD, FTND, and QSU-brief) on the performance in the GNGTs. In contrast to the models with age as predictor, the interactions between years of smoking and the FTND and QSU-brief score on CE rates in the general GNGT did not provide conclusive evidence of a relationship. Meanwhile, a significant interaction between years of smoking and CPD on Go-RTs in the general GNGT was observed. These effects indicate that in individuals with a longer history of smoking (i.e., $M_{\text{years of smoking}}+1\ SD_{\text{years of smoking}}$ = 35 years of smoking), a greater number of CPD and a higher severity of tobacco dependence were tendentially associated with higher CE rates and faster RTs in Go trials. Conversely, in individuals with a shorter history of smoking (i.e., $M_{\text{years of smoking}}-1\ SD_{\text{years of smoking}}$ = 9 years of smoking), a greater number of CPD and a higher severity of tobacco dependence were tendentially associated with lower CE rates, but also slower Go-RTs. Simply put, individuals with a longer history of smoking, who smoked more or reported stronger craving, tended to respond faster in Go trials and tended to make more CEs by incorrectly responding in No-Go trials. In contrast, individuals with a shorter history of smoking, who smoked more or reported stronger craving, tended to respond more slowly in Go trials and tended to make fewer CEs by correctly withholding responses in No-Go trials. Again**,** there was no clear evidence of significant interactions between smoking-related variables and sex or IQ.

Table D.1-II

Results of the regression models on CE rates and Go-RTs in the general GNGT with years of smoking as predictor

Predictor	CPD			FTND			QSU		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*
					CE rate				
Intercept	15.786	13.231 – 18.340	**<.001**	15.980	13.232 – 18.728	**<.001**	16.048	13.329 – 18.766	**<.001**
Years of smoking	-0.198	-0.335 – -0.062	**.005***	-0.197	-0.344 – -0.050	**.009***	-0.158	-0.309 – -0.008	**.040**
Sex (1: female)	-0.055	-3.378 – 3.267	.974	-0.175	-3.726 – 3.376	.922	0.114	-3.536 – 3.765	.951
IQ	-0.094	-0.248 – 0.059	.225	-0.096	-0.263 – 0.070	.253	-0.032	-0.205 – 0.141	.715
Variable	-0.135	-0.420 – 0.150	.825	-0.149	-1.685 – 1.387	.576	-0.002	-0.300 – 0.295	.506
Variable × Years of smoking	0.020	0.006 – 0.034	**.005**	0.058	-0.015 – 0.131	.118	0.011	-0.005 – 0.027	.176
Variable × Sex	0.313	-0.044 – 0.670	.085	0.431	-1.512 – 2.374	.661	0.041	-0.333 – 0.415	.830
Variable × IQ	-0.001	-0.020 – 0.017	.876	-0.003	-0.096 – 0.090	.948	-0.010	-0.028 – 0.009	.292
					Go-RT				
Intercept	478.994	465.755 – 492.234	**<.001**	477.618	463.750 – 491.487	**<.001**	475.965	462.431 – 489.498	**<.001**
Years of smoking	1.616	0.910 – 2.322	**<.001***	1.530	0.787 – 2.273	**<.001***	1.574	0.824 – 2.323	**<.001***
Sex (1: female)	-11.909	-29.125 – 5.308	.173	-10.993	-28.914 – 6.929	.227	-10.992	-29.162 – 7.178	.233
IQ	-0.402	-1.196 – 0.392	.318	-0.516	-1.354 – 0.323	.226	-0.703	-1.563 – 0.157	.108
Variable	0.097	-1.381 – 1.575	.897	3.638	-4.114 – 11.390	.354	-1.491	-2.972 – -0.010	**.048**
Variable × Years of smoking	-0.078	-0.150 – -0.006	**.034**	-0.244	-0.611 – 0.123	.190	-0.047	-0.128 – 0.033	.246
Variable × Sex	-0.171	-2.021 – 1.680	.855	-1.409	-11.215 – 8.396	.776	1.479	-0.382 – 3.340	.118
Variable × IQ	0.087	-0.008 – 0.182	.072	-0.203	-0.672 – 0.267	.395	0.062	-0.031 – 0.154	.189

Note. The predictor *Variable* refers to either CPD, FTND, or QSU. For the effects of smoking-related variables on CE rates, one-sided *p*-values are reported, otherwise two-sided. All regression model predictors, except for sex, were grand-mean centred. CPD = Cigarettes Per Day; FTND = Fagerström Test for Nicotine Dependence; QSU = Questionnaire on Smoking Urges, brief version; *CI* = Confidence Interval; CE = Commission Error; Go-RT = mean Reaction Time in Go trials. * significant after Benjamini-Hochberg correction.

Table D.2-II

Results of the regression models on CE rates and Go-RTs in the smoking-specific GNGT with years of smoking as predictor

Predictor	CPD			FTND			QSU		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*
CE rate									
Intercept	4.442	3.055 – 5.828	**<.001**	4.313	2.916 – 5.711	**<.001**	4.635	3.222 – 6.048	**<.001**
Years of smoking	-0.086	-0.155 – -0.016	**.016***	-0.101	-0.172 – -0.030	**.005***	-0.098	-0.172 – -0.024	**.009***
Sex (1: female)	0.510	-1.185 – 2.205	.555	0.647	-1.056 – 2.350	.457	0.131	-1.664 – 1.925	.887
IQ	-0.036	-0.114 – 0.042	.370	-0.034	-0.113 – 0.046	.409	-0.032	-0.117 – 0.053	.455
Variable	-0.072	-0.226 – 0.083	.819	-0.097	-0.876 – 0.682	.596	0.006	-0.147 – 0.159	.530
Variable × Years of smoking	0.008	0.001 – 0.015	**.029**	0.043	0.008 – 0.078	**.015**	-0.004	-0.012 – 0.004	.290
Variable × Sex	0.026	-0.156 – 0.208	.780	-0.519	-1.450 – 0.413	.275	-0.059	-0.243 – 0.124	.526
Variable × IQ	-0.008	-0.017 – 0.002	.105	-0.024	-0.069 – 0.020	.283	-0.004	-0.013 – 0.005	.432
Stimulus type (1: smoking)	0.527	-0.418 – 1.471	.275	0.507	-0.424 – 1.439	.286	0.441	-0.476 – 1.359	.346
Variable × Stimulus type	0.002	-0.099 – 0.104	.484	0.033	-0.473 – 0.539	.449	0.106	0.015 – 0.198	**.012***
Go-RT									
Intercept	413.925	398.398 – 429.452	**<.001**	412.191	396.829 – 427.552	**<.001**	410.648	394.748 – 426.548	**<.001**
Years of smoking	1.836	1.009 – 2.662	**<.001***	1.885	1.063 – 2.706	**<.001***	1.858	0.979 – 2.737	**<.001***
Sex (1: female)	6.211	-13.943 – 26.366	.546	6.441	-13.373 – 26.254	.524	2.293	-19.017 – 23.604	.833
IQ	-1.003	-1.933 – -0.073	**.034**	-0.931	-1.858 – -0.004	**.049**	-0.918	-1.927 – 0.091	.075
Variable	1.147	-0.586 – 2.880	.194	4.734	-3.851 – 13.320	.280	-0.703	-2.443 – 1.036	.428
Variable × Years of smoking	-0.118	-0.203 – -0.034	**.006**	-0.454	-0.859 – -0.048	**.028**	-0.039	-0.133 – 0.056	.423
Variable × Sex	-0.460	-2.627 – 1.706	.677	-0.665	-11.506 – 10.175	.904	0.874	-1.309 – 3.057	.433
Variable × IQ	0.034	-0.077 – 0.145	.545	-0.280	-0.800 – 0.239	.290	0.032	-0.077 – 0.140	.565
Stimulus type (1: smoking)	-0.953	-2.819 – 0.913	.317	-0.961	-2.828 – 0.905	.313	-1.095	-2.968 – 0.778	.252
Variable × Stimulus type	0.031	-0.170 – 0.232	.763	0.230	-0.784 – 1.244	.657	0.063	-0.124 – 0.251	.509

Note. The predictor *Variable* refers to either CPD, FTND, or QSU. For the effects of smoking-related variables (× stimulus type) on CE rates, one-sided *p*-values are reported, otherwise two-sided. All regression model predictors, except for sex, were grand-mean centred. CPD = Cigarettes Per Day; FTND = Fagerström Test for Nicotine Dependence; QSU = Questionnaire on Smoking Urges, brief version; *CI* = Confidence Interval; CE = Commission Error; Go-RT = mean Reaction Time in Go trials. * significant after Benjamini-Hochberg correction.

Appendix E: Supplementary discussion

Appendix E.1: OE rates

In terms of research questions 1 and 2, the smoking and control groups did not significantly differ in their OE rates. Regarding research question 3, the results for the moderating effect of age on the relationship between smoking-related variables and OE rates were inconclusive. In the smoking-specific GNGT, older individuals who smoked more CPD tended to exhibit somewhat lower OE rates, which is consistent with their tendentially faster RTs in Go trials. Meanwhile, younger, heavier smoking individuals tended to exhibit higher OE rates, which is consistent with their tendentially longer Go-RTs (speed-accuracy trade-off). However, in the general GNGT, the results are reversed and do not align with the observed performance pattern on CE rates and Go-RTs. More specifically, older individuals with higher severity of tobacco dependence and craving tended to show higher OE rates, whereas younger individuals tended to show lower OE rates. Although speculative, the contradictory findings may be explained by the differing difficulty levels (overall higher CE rates were observed in the general GNGT) or contexts (smoking-related/neutral versus digits) of the two GNGTs. Future research should investigate group differences and the moderating effects of age by employing GNGTs with shorter response windows to achieve OE rates that are more sensitive to differentiating between participants.

Appendix E.2: Years of smoking as predictor

The results of the regression models for research question 3 with smoking duration as predictor variable were found to be highly comparable to those of the models with age as predictor. As with age, a longer history of smoking was associated with lower CE rates. This is at odds with dual-process models of addiction, which posit that ongoing smoking promotes deficits in response inhibition. However, the design of the present study did not permit to distinguish the independent effects of the two predictors. Future research should examine

individuals of the same age but varying smoking duration to test the assumption that a longer history of smoking leads to stronger deficits in response inhibition.

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APPENDIX OF STUDY III

Appendix A: Methods and Materials

Appendix A.1: Participants and Power Analysis

In addition to the criteria outlined in the main manuscript, further exclusion criteria included: (7) use of nicotine replacement therapy or pharmacological smoking cessation treatments within three months prior to study participation, (8) acute suicidality, (9) current pregnancy or nursing period, and (10) insufficient German language skills. Participants were recruited by various means, including social media ads, online marketing, flyers distributed in medical practices and universities, and newsletters. Participants were compensated either financially or with course credit for their participation in the assessments (main study: 8€/hour; fMRI investigation: 25€ at baseline, 35€ at post-intervention).

The present fMRI study was designed to investigate the neural effects of ApBM in a sub-sample of participants from the main clinical trial (German Clinical Trials Register: DRKS00019221, 11/11/2019). It was scheduled to begin in March 2022, with 12 smoke-free courses planned prior to the completion of the main trial, each course involving up to 14 participants (i.e., a maximum of n = 168 remaining recruits). Based on this schedule, it was considered realistic to recruit 75 participants (i.e., ideally 25 participants per group) for the fMRI study within the timeframe of the remaining courses, considering factors such as scanner availability and personnel resources. Accordingly, a sensitivity analysis was conducted with G*Power (Faul et al., 2007) using parameters N = 75, α = .05, and 1-β = .80, indicating a minimum detectable effect size of d = 0.36. This effect size is lower than the one reported by C. E. Wiers et al. (2015), who found a between-group difference of d = 1.08 (t[30] = 2.97) for ApBM versus Sham training in alcohol cue-reactivity changes in the left amygdala. To minimize the risk of unequal study groups due to block-wise randomization (all participants in the same smoke-free course assigned to the same study arm), participants were recruited from all remaining courses without applying stopping guidelines.

Appendix A.2: Smoking Cessation Intervention (TAU)

The first section of the smoke-free course aims to enhance motivation by addressing ambivalence and increasing self-awareness of smoking behavior through psychoeducation and self-monitoring. The second section focuses on strengthening motivation by reducing anxiety, strengthening confidence in quitting abilities, and initiating the quit attempt. The third section prepares participants for the first 24 hours post-cessation by providing psychoeducation on craving, high-risk situations, and relapse prevention, along with coping strategies (e.g., emergency kit). The final section supports the development of a "non-smoker identity" and reinforces confidence (Wenig et al., 2013). Participants are offered a follow-up telephone counseling session one week after the course (e.g., to discuss negative side effects such as depressed mood). Smoke-free courses were conducted at the Department of Psychology, LMU Munich, and the outpatient treatment center for tobacco dependence at the LMU University Hospital Munich.

Appendix A.3: Approach-Avoidance Task (AAT)

Appendix A.3.1 Task Paradigm

The AAT included 80 stimuli (40 smoking-related, 40 positive) sourced from previous studies (Khazaal et al., 2012; Oliver & Drobes, 2012) and online platforms. Following prior alcohol studies (Eberl et al., 2013; Rinck et al., 2018; R. W. Wiers et al., 2011), simple, context-free pictures were used, depicting (burning) cigarettes, cigarette packages, and ashtrays with cigarettes (also used in the ApBM training). Stimuli were presented in a pseudo-randomized order, ensuring no more than three consecutive pictures from the same category.

The task comprised two blocks of 80 trials, with each stimulus appearing once per block. Participants followed a content-relevant feature task instruction, pushing or pulling the joystick based on the picture content (e.g., pushing smoking-related pictures and pulling positive ones, or vice versa). Instruction order (incongruent: push smoking-related stimuli first;

congruent: pull smoking-related stimuli first) was counterbalanced across participants and switched after the first block. Response direction was linked to a "zoom" function, where pushing reduced and pulling enlarged the picture. Each trial began with a black screen. Participants pressed the "fire" button while keeping the joystick centered to initiate stimulus presentation, then responded by pushing or pulling the joystick. Pictures remained on-screen until the correct movement was executed. Before each block, participants completed six practice trials. The AAT was programmed in Visual Basic.

Appendix A.3.2 Preprocessing

AAT preprocessing followed the preregistered procedure (see Wittekind et al., 2022). Only correctly executed trials (i.e., without any initial joystick movements in the incorrect direction) were considered. Reaction times below 200 ms or exceeding 2.5 *SD* above the group mean were excluded. Following previous AAT studies (e.g., R. W. Wiers et al., 2011), participants with more than 35% missing trials were excluded from further analysis (t_0: $n = 1$; t_1: $n = 1$).

Appendix A.4: Neural Smoking Cue-Reactivity Task

Appendix A.4.1: FMRI Data Acquisition

Data were collected using a 3T Siemens Magnetom Prisma with a 32-channel head coil (Siemens AG, Erlangen, Germany). Functional sequences included 320 volumes obtained via a T2*-weighted EPI sequence (48 slices per volume, ascending interleaved order, multiband factor = 4, voxel size = 3 mm^3 isotropic, repetition time = 2000 ms, echo time = 30 ms, flip angle = 45°, field of view = 210 mm). The first five functional volumes were discarded to mitigate T1 saturation artifacts. High-resolution anatomical images comprised 160 T1-weighted slices acquired with a magnetization-prepared rapid acquisition gradient-echo sequence (voxel size = 1 mm^3 isotropic, repetition time = 2300 ms, echo time = 2.98 ms, flip angle = 9°, field of view = 256 mm).

Appendix A.4.2: FMRI Data Preprocessing and Individual-Level Analysis

Neuroimaging data were preprocessed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm) in MATLAB R2023a (The Mathworks, Natick, MA, USA). The SPM12 pipeline included spatial realignment, co-registration, normalization to a standard 2 mm Montreal Neurological Institute [MNI] template, and spatial smoothing (Gaussian kernel, 8 mm full width at half maximum [FWHM]). Given the task block design, slice-timing correction was not applied. FMRI data of participants with excessive head movement at t_0 or t_1 (> 3 mm in any direction or > 3° rotation) were excluded from analysis (n = 5; see Figure 2-III for participant flow). Individual-level statistical analysis was conducted using a general linear model (GLM) with the three task conditions (smoking-related/neutral/rating blocks) as regressors, modeled as boxcar functions convolved with the hemodynamic response function. Motion parameters and a constant term were included as nuisance regressors, and a high-pass filter (1/128 Hz) was applied.

Appendix A.4.3: ROI Selection and Mask Generation

ROIs were selected to capture key regions involved in smoking cue-reactivity as well as regions previously implicated in alcohol-related approach biases and the effects of alcohol ApBM. A meta-analysis by Lin et al. (2020) identified heightened smoking cue-reactivity in the left ACC, left angular gyrus, right thalamus, and right striatum. Alcohol studies found reduced alcohol cue-reactivity in the amygdala following ApBM (C. E. Wiers et al., 2015) and observed associations between approach biases and activity in the nucleus accumbens and medial prefrontal cortex (C. E. Wiers et al., 2014). As the nucleus accumbens is considered part of the striatum (Rolls et al., 2020), we divided the striatum into the dorsal striatum (caudate and putamen) and the nucleus accumbens.

The medial prefrontal cortex mask was taken from the Harvard-Oxford probabilistic atlas (mask: MedFC; Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al.,

2006), while all other masks were generated using the Automated Anatomical Labeling atlas (AAL3; Rolls et al., 2020).

Appendix A.5: Reliability of Measures

The reliability of questionnaire measures was estimated using Cronbach's α. As the FTND showed unacceptable reliability in this study, the CDS-12 was used to assess dependence severity in all analyses (see Table A.5.1-III). Split-half reliabilities for both the AAT effect score and neural cue-reactivity measures ([smoking–neutral] contrast) were estimated using the R package *splithalfr* (Pronk, 2023) with 5,000 random splits and corrected using the Spearman-Brown formula.

Table A.5.1-III

Reliability of Measures

Measure	Time	Reliability
Questionnaire Measures		**Cronbach's α [95% CI]**
FTND	t_0	.43 [.26 to .55]
CDS-12	t_0	.76 [.68 to .82]
	t_1	.94 [.92 to .95]
Behavioral Measures		**Split-half reliability [95% CI]**
AAT effect score	t_0	.72 [.62 to .83]
	t_1	.64 [.53 to .75]
Neural Measures		**Split-half reliability [95%CI]**
Left ACC	t_0	.12 [-.21 to .46]
	t_1	.28 [.07 to .52]
Left angular gyrus	t_0	-.03 [-.37 to .27]
	t_1	.16 [-.05 to .39]
Right thalamus	t_0	-.23 [-.60 to .07]
	t_1	.05 [-.23 to .33]
Dorsal striatum	t_0	-.36 [-.74 to .08]
	t_1	.10 [-.24 to .42]
Right MCC	t_0	-.33 [-.67 to -.02]
	t_1	.06 [-.29 to .42]
Right supramarginal gyrus	t_0	.10 [-.25 to .42]
	t_1	.07 [-.31 to .41]
Right precuneus	t_0	-.14 [-.56 to .21]
	t_1	.17 [-.11 to .48]
Amygdala	t_0	-.20 [-.57 to .18]
	t_1	-.02 [-.39 to .31]
Nucleus accumbens	t_0	-.00007 [-.57 to .51]
	t_1	-.04 [.34 to .34]
Medial prefrontal cortex	t_0	-.01 [-.41 to .36]
	t_1	.08 [-.20 to .34]

Note. FTND = Fagerström Test for Nicotine Dependence; CDS-12 = Cigarette Dependence Scale, 12-item version; AAT = Approach-avoidance task; ACC = anterior cingulate cortex; MCC = middle cingulate cortex; t_0 = Baseline; t_1 = Post-intervention; CI = Confidence interval.

Appendix B: Results

Appendix B.1 Association between Cue-Reactivity Changes and Smoking-Related Variables

Associations between changes in smoking cue-reactivity and smoking-related variables were assessed using LMMs, with cue-reactivity changes, group, and their interaction as predictors.

Table B.1.1-III

Results of the ANOVAs (Omnibus Tests) for the Effects of Time and Time × Group on Smoking-Related Variables

Region of interest	Effect	Cigarettes per day			Tobacco dependence			CO value		
		(df_1,df_2)	F	p	(df_1,df_2)	F	p	(df_1,df_2)	F	p
Selected from a meta-analysis on smoking cue-reactivity										
Left ACC	t_0-t_1 change	1,91	0.27	.605	1,91	1.74	.190	1,92	0.28	.601
	t_0-t_1 change × group	2,91	1.93	.152	2,91	1.30	.278	2,92	0.50	.611
Left angular gyrus	t_0-t_1 change	1,91	0.02	.887	1,91	1.22	.273	1,92	0.86	.357
	t_0-t_1 change × group	2,91	1.84	.164	2,91	2.54	.085	2,92	0.88	.420
Right thalamus	t_0-t_1 change	1,91	1.51	.222	1,91	0.51	.478	1,92	0.06	.808
	t_0-t_1 change × group	2,91	0.43	.649	2,91	0.86	.426	2,92	0.33	.718
Dorsal striatum	t_0-t_1 change	1,91	0.79	.378	1,91	0.82	.368	1,92	0.19	.662
	t_0-t_1 change × group	2,91	0.24	.785	2,91	0.96	.388	2,92	1.02	.366
Regions with [smoking > neutral] at t_0 in the present sample										
MCC	t_0-t_1 change	1,91	0.39	.535	1,91	0.93	.338	1,92	0.27	.605
	t_0-t_1 change × group	2,91	0.78	.461	2,91	2.21	.116	2,92	0.22	.799
Supramarginal gyrus	t_0-t_1 change	1,91	1.73	.192	1,91	0.02	.901	1,92	0.62	.431
	t_0-t_1 change × group	2,91	0.56	.575	2,91	0.95	.390	2,92	0.16	.852
Precuneus	t_0-t_1 change	1,91	3.09	.082	1,91	0.09	.764	1,92	3.03	.085
	t_0-t_1 change × group	2,91	0.70	.497	2,91	0.37	.695	2,92	1.36	.263
Derived from alcohol ApBM studies										
Amygdala	t_0-t_1 change	1,91	0.01	.903	1,91	2.94	.090	1,92	0.73	.396
	t_0-t_1 change × group	2,91	0.02	.983	2,91	2.15	.122	2,92	0.74	.478
Nucleus accumbens	t_0-t_1 change	1,90	0.67	.414	1,90	<0.01	.999	1,91	1.55	.217
	t_0-t_1 change × group	2,90	0.55	.580	2,90	0.05	.954	2,91	0.59	.558
Medial prefrontal cortex	t_0-t_1 change	1,90	0.39	.532	1,90	2.46	.120	1,91	1.12	.293
	t_0-t_1 change × group	2,90	2.70	.073	2,90	0.62	.541	2,91	1.17	.315

Note. df = Degrees of freedom; t_0 = Baseline; t_1 = Post-intervention; CO = Carbon monoxide; ACC = anterior cingulate cortex; MCC = middle cingulate cortex.

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APPENDIX OF STUDY IV

Appendix A: Overview of the Study Procedure

The recruitment of participants commenced in May 2018. Due to the corona pandemic and the closing of university buildings, recruitment was suspended in November 2020, with *n* = 79 participants having been enrolled up to that point. Recruitment resumed in January 2023, and the final sample size of *N* = 122 was reached in October 2023. The participants received 8 Euros per hour for their participation in the assessments.

Table A.1-IV

Overview of Measures and Assessment Time Points

Time point	t_0	t_1*	t_2**
Assessments			
Sociodemographic interview	x		
Drug and smoking history	x	x	x
FTCD	x	x	x
CO measurement	x	x	x
AUDIT (Babor et al., 2001)	x		
MINI (substance use)	x		
QSU-brief	x	x	
AAT	x	x	
WST	x		
(general/smoking-specific)[1] GNG task, SST	x	x	
BIS-15	x	x	
(general/smoking-specific)[1] GNG task, SST	x	x	
TAAS	x		
IAT	x	x	
Training evaluation		x	

Note. The tasks are listed in the temporal sequence of the assessment. FTCD = Fagerström Test for Cigarette Dependence; CO = Carbon monoxide value; AUDIT = Alcohol Use Disorder Identification Test (Babor et al., 2001); MINI = Mini International Neuropsychiatric Interview;

QSU-brief = Questionnaire of Smoking Urges, brief version; AAT = Approach-Avoidance Task; WST = Wortschatztest (German vocabulary test); GNG task = Go/No-Go task; SST = Stop-Signal Task; BIS = Barratt Impulsiveness Scale, 15-item version; TAAS = Thoughts About Abstinence Scale; IAT = Implicit-Association Test.

* 4 weeks after t_0

** 3 months after t_1

[1] Both tasks (GNG and SST) were given in both a general and smoking-specific version across two blocks. One block had both tasks in the general version, and the other block had both tasks in the smoking-specific version. The order (block with general versions first vs. block with smoking-specific versions first) was randomized across participants. The two tasks in each block were performed in a fixed order: first the GNG task, second the SST.

Appendix B: Additional Measures

Appendix B.1: Clinical Assessments and Ratings

We cannot provide information on variables such as racial identity, ethnicity, or immigration history, as these are not commonly assessed in Germany due to their sensitive nature. All baseline characteristic variables were collected via paper-pencil format, with the possibility that some questions might not have been answered, resulting in missing data. It was assumed that the missing items in the questionnaires were missing at random, as participants completed them individually without expecting negative or positive consequences for their answers. The final sample size for each baseline variable is presented in Table 1-IV.

Appendix B.2: Experimental Tasks to Assess Alternative Potential Working Mechanisms

The targeted processes of the GNG trainings were the reduction in CE rates of the GNG task from t_0 to t_1. However, as discussed earlier in the introduction, other alternative working mechanisms are plausible. Therefore, this study employed several additional experimental

tasks before and after the GNG training interventions to evaluate other potential working mechanisms. To test the hypothesis of enhanced *top-down inhibitory control,* the study not only used the GNG task but also included the SST and BIS-15. In the specific case of the smoking-specific GNG training, the theory also posits the working mechanism of *stimulus devaluation*, which is assessed using the AAT and IAT.

Appendix B.2.1: Stop-Signal Task (SST)

Besides the GNG task, response inhibition was also assessed with the SST (Logan, 1994). In contrast to the GNG task, the SST specifically focuses on the ability to engage in top-down inhibition or action cancellation (Schachar et al., 2007; Verbruggen & Logan, 2008).

The task consisted of 20 training trials, followed by four blocks with 64 test trials each. Each trial began with a brief presentation of a black screen (500 ms), followed by a white circle (fixation sign) in the center of the screen (250 ms), and finally a white arrow in the center of the circle. Participants were instructed to indicate the direction of the arrow by pressing a computer key ("D" for left, "K" for right; max. response time window: 2000 ms), however, in 25% of the trials they had to withhold their response (i.e., stop-signal trial), as indicated by the presentation of an auditory signal after the arrow appeared. The duration between the appearance of the arrow and the presentation of the stop signal (Stop-Signal Delay; SSD) was adapted using a staircase procedure that depended on the participant's performance. The starting point of the SSD was set at a value of 250 ms. Each time the participant successfully inhibited a response, the SSD was increased by 50 ms for the subsequent trial (max. SSD: 1150 ms). In cases where the participant failed to inhibit a response, the SSD for the next trial was decreased by 50 ms (min. SSD: 50 ms). This staircase procedure enabled the task to adjust to the participant's performance accurately and aimed for a 50% success rate in inhibition. No feedback was given in case of incorrect or missing responses. The distribution of trials included arrows pointing to the left and right in a 50/50 ratio for each block as well as across both no-

signal and stop-signal trials. Split-half reliability for the SST measure was estimated at $r = .472$, *95% CI* [.316 – .628]. As preregistered, the study was conducted with an additional assessment of a smoking-specific SST; however, due to a programming error in the staircase procedure, the reaction time data could not be evaluated.

Appendix B.2.2: Approach-Avoidance Task (AAT)

Behavioral approach tendencies toward smoking-related stimuli were evaluated using the joystick AAT (Rinck & Becker, 2007). The rationale behind this task is that positive stimuli are approached faster than negative stimuli and vice versa (Loijen et al., 2020). Therefore, the task was utilized to assess the potential *devaluation* of smoking-related stimuli after the smoking-specific GNG training.

Twenty color-framed smoking-related and 20 neutral pictures were presented in a pseudorandomized order (no more than three consecutive stimuli of the same category and with the same color-frame) in one single test block. The color of the frame (yellow, blue) indicated whether the joystick should be pushed or pulled (i.e., content-irrelevant feature task instruction). The instruction (e.g., push pictures with a yellow frame or pull pictures with a yellow frame) was counterbalanced across participants. Each picture was presented four times, two times each with a yellow and blue frame, resulting in 160 test trials. Twenty training trials preceded the experimental trials. In each trial, one color-framed smoking-related or neutral picture was presented in the center of the computer screen. Participants were instructed to respond as fast and accurately as possible to the color of the frame by either pushing the joystick away (i.e., avoid) or pulling the joystick toward themselves (i.e., approach). Zooming was used to create a sense of approach and avoidance, whereby pulled pictures enlarged and pushed pictures shrunk. The picture disappeared once the joystick was fully extended in the correct direction. If moved in the wrong direction, the error message “error” was presented for 400 ms. The picture only disappeared if the correct movement was executed. Once the joystick was

returned to its center position, the subsequent picture was displayed on the screen after a 250 ms inter-trial interval. Split-half reliability for the AAT measure (using final RTs; see Appendix D) was estimated at r = -.327, *95% CI* [-.658 – .003] (initial RT: r = -.266, *95% CI* [-.577 – .045]).

Appendix B.2.3: Implicit-Association Test (IAT)

Implicit associations between smoking and positive/negative valence were assessed by using the IAT (Greenwald et al., 1998; Houwer et al., 2006). As with the AAT, the task was utilized to assess the potential *devaluation* of smoking-related stimuli after the smoking-specific GNG training.

The target categories were the German words for "smoking" [Rauchen] and "non-smoking" [Nicht-Rauchen] in white font, comprising 10 smoking-related and 10 neutral pictures. The attribute categories were the German words for "positive" [Positiv] and "negative" [Negativ] in green font, comprising five words in white font with positive valence (good [gut], relaxation [Entspannung], healthy [gesund], pleasant [angenehm], social [gesellig]) and five words in white font with negative valence (bad [schlecht], tension [Anspannung], harmful [schädlich], annoying [störend], antisocial [unsozial]). The IAT consisted of seven blocks. Throughout each block, the terms of the categories remained consistently displayed in the upper corners of a black screen while pictures/words were presented at the center. During the first block (target practice, n = 20), 10 smoking-related and 10 neutral pictures were presented in random order. Participants were instructed to assign the pictures using key press ("D" if the picture belonged to the category "smoking"; "K" if the picture belonged to the category "non-smoking"). During the second block (attribute practice, n = 20), participants were presented with the positive or negative words and had to assign them to the attribute categories "positive" ("D") or "negative" ("K"). The following two blocks were compatible test blocks (n = 40 each) in which target pictures and attribute words were presented

randomly and had to be categorized while the pairing of categories per key was compatible ("D" for "smoking" and "positive", "K" for "non-smoking" and "negative"). In the fifth block (target reversed practice, n = 20), the target categories switched positions (i.e., "D" for "non-smoking", "K" for "smoking"). Within the following two incompatible test blocks (n = 40 each), target pictures and attribute words had to be categorized while the pairing of categories per key was incompatible ("D" for "non-smoking" and "positive", "K" for "smoking" and "negative"). The order of the blocks (compatible first or incompatible first) was counterbalanced across participants. In case of an incorrect response, a red "X" appeared for 400 ms. Participants had to correct their response to proceed to the next trial (inter-trial interval: 250 in ms). Split-half reliability for the IAT measure was estimated at r = .941, *95% CI* [.924 – .958].

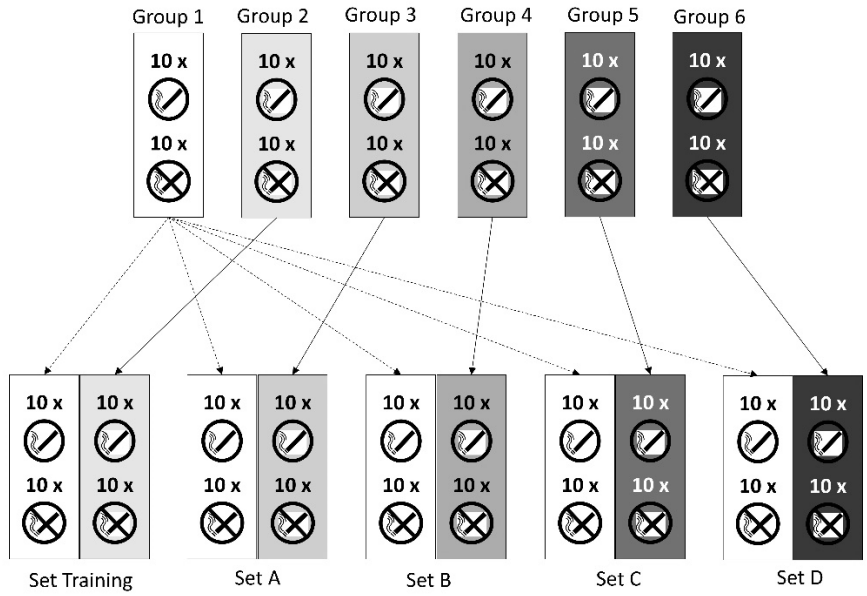
Appendix C: Picture Selection and Randomization

For the experimental tasks and trainings used in the current study, 60 smoking-related and 60 control pictures with neutral scenes were selected from 10 content categories (i.e., six pictures per category; e.g., a hand holding a cigarette, a person lighting a cigarette, smoking people, cigarette and coffee, cigarette and alcoholic drink, etc.). Equivalently, neutral stimuli were selected from 10 matching neutral categories (e.g., a hand holding a pen, a person brushing teeth, people eating/using their mobile phones, a cup, a glass of water, etc.). The pictures were collected from previous studies (e.g., Luijten, Littel, & Franken, 2011; Luijten, Veltman, et al., 2011; Wiers et al., 2013) and freely available online sources. All smoking-related pictures depicted events related to the initiation of smoke intake (Mucha et al., 2008; Stippekohl et al., 2010). After the collection process, smoking and neutral pictures were sorted into six groups of 10 smoking-related and 10 neutral pictures each (one picture out of each smoking category and its corresponding neutral control category; see Figure C.1-IV for an illustration of the picture allocation process). Five of the six picture groups were allocated to

five different picture sets. The sixth set was allocated to each of the five sets. Consequently, each of the five sets consisted of 20 novel pictures (10 smoking-related, 10 neutral) and 20 shared pictures (10 smoking-related, 10 neutral). Finally, one of the five picture sets was designated as the *training set* used for the training interventions[35]. The remaining four picture sets (*set A, B, C,* and *D*) were used in the four experimental tasks using smoking-related stimuli (AAT; IAT[36]; smoking-related GNG task, smoking-specific SST). The allocation of participants to picture sets was pseudorandomized, with each participant being assigned to each set once across the four experimental tasks. The allocation was identical at the t_1 assessment.

Figure C.1-IV

Overview of the Picture Randomization Process



[35] For the general GNG training, a total of 40 neutral pictures was used. Therefore, 20 additional pictures were selected besides the 20 neutral pictures of the training set.

[36] For the IAT, the number of stimuli was further reduced to 20 (10 smoking-related, 10 neutral) in each set (selection of five out of the 10 smoking-related and 10 neutral stimuli both of the novel and shared pictures).

Appendix D: Data Preprocessing and Aggregation of Experimental Tasks of Alternative Potential Working Mechanisms

Following the preprocessing recommendations outlined by Kahveci et al. (2024) for the AAT with content-irrelevant feature task instruction, error trials and RTs deviating more than 3 *SD* from the group mean were removed. Subsequently, double mean difference scores (i.e., [avoid/push smoking - approach/pull smoking] - [avoid/push neutral - approach/pull neutral]) were calculated by using both initial and final RTs. As final RTs are more commonly utilized in research (Kahveci et al., 2024), we report analyses using final RTs. However, the results did not differ when using initial RTs. The IAT data were preprocessed and analyzed using the D2 algorithm (Greenwald et al., 2003). Participants with more than 35% missing trials or more than 50% missing trials in one of the categories of the AAT (push/pull smoking, push/pull neutral) or one of the four relevant test blocks of the IAT were excluded from further analysis (see Table D.1-IV for exclusion rates per task). Higher AAT and IAT effect scores indicate a stronger approach bias for smoking-related stimuli.

For the SST, the measure of interest was the Stop-Signal Reaction Time (SSRT). We followed the preprocessing recommendations of Verbruggen et al. (2019), which include assigning a participant's maximum RT in Go trials to Go trials with no response and incorporating premature responses on unsuccessful stop-signal trials to calculate the probability of responding on stop-signal trials. Subsequently, SSRT scores were determined using the recommended integration method (Logan & Cowan, 1984). Participants were excluded from SSRT score calculation if they did not meet Verbruggen et al.'s (2019) recommended requirements (i.e., substantial deviation [$> \pm 0.25$] from a 0.50 probability of responding on stop trials or violation of the race model assumptions). A longer SSRT indicates greater behavioral impulsivity and lower response inhibition ability.

Table D.1-IV contains the number of excluded participants, error rates, rates of excluded RTs, and rates of missing trials per task.

Table D.1-IV

Number of Excluded Participants, Error Rates, Rates of Excluded RTs, and Rates of Missing Trials per Task

Task	Smoking-specific GNG training group		General GNG training group		Sham training group		WLC group	
	t_0	t_1	t_0	t_1	t_0	t_1	t_0	t_1
General GNG task								
exclusion	-	-	-	-	-	-	-	-
error rate (Go trials)	2.0%	1.0%	0.9%	0.3%	0.7%	0.3%	0.7%	0.6%
error rate (No-Go trials)	17.8%	16.8%	20.7%	20.4%	16.5%	15.4%	14.2%	15.5%
Smoking-specific GNG task								
exclusion	-	-	-	-	-	-	-	-
error rate (Go trials)	0.4%	0.4%	0.1%	<0.0%	0.2%	0.2%	0.1%	0.1%
error rate (No-Go trials)	7.5%	6.2%	7.1%	9.0%	4.7%	6.1%	5.0%	4.0%
SST								
exclusion	$n = 4$	$n = 2$	-	$n = 1$	-	$n = 1$	$n = 3$	$n = 1$
error rate (ns-trials)	5.2%	2.6%	1.7%	1.0%	6.1%	3.7%	5.1%	1.5%
error rate (ss-trials)	47.6%	48.2%	49.4%	48.9%	45.4%	47.5%	47.3%	47.6%
AAT (final)								
exclusion	$n = 1$	$n = 1$	$n = 1$	-	$n = 1$	$n = 1$	-	-
error rate	5.2%	4.8%	4.5%	4.7%	5.2%	4.1%	2.5%	2.8%
excluded RTs	0.5%	4.1%	0.8%	0.2%	0.8%	2.6%	1.2%	0.8%
missing trials	5.7%	8.9%	5.3%	4.9%	6.0%	6.7%	3.7%	3.5%
IAT								
exclusion	$n = 1$	$n = 1$	$n = 1$	$n = 1$	-	-	$n = 1$	-
error rate[1]	6.6%	8.4%	7.2%	6.0%	7.2%	7.0%	6.1%	4.9%
excluded RTs/missing trials	0.2%	0.1%	0.1%	<0.0%	0.1%	0.1%	0.1%	<0.0%

Note. Error rates were calculated after the exclusion of participants based on the defined exclusion criteria. Rates of excluded RTs were calculated after the exclusion of error trials. AAT = Approach-Avoidance Task; GNG task = Go/No-Go task; SST = Stop-Signal Task; ns-trials = no-signal trials; ss-trials = stop-signal trials; IAT = Implicit-Association Test.

[1]According to the preprocessing procedure of the D2 algorithm (Greenwald et al., 2003), the RTs of error trials are replaced with a built-in error penalty.

Appendix E: Additional and Exploratory Analyses

Appendix E.1: Bayesian Analyses

Methods

Apart from preregistration, we used linear mixed-effects models as the preferred method for analyzing repeated-measure data, rather than using ANOVAs (Gueorguieva & Krystal, 2004). Given that a post-hoc power analysis for already observed outcomes is not appropriate (Zhang et al., 2019), we opted to address potential issues arising from low statistical power by offering complementary Bayesian statistics. In this regard, two Bayesian statistics were conducted to complement classical hypothesis testing: (1) the calculation of Bayes factors and (2) Bayesian tests for practical equivalence. The classical hypothesis testing approach indicated a potential positive effect of GNG training conditions at t_1, but not at t_2. Consequently, Bayesian analyses were conducted to provide a complementary analysis of the main analyses on the group × t_1 effects.

Bayes factors were calculated by using the *brms* package (Bürkner, 2017, 2018). More specifically, three models were calculated for each clinical outcome: (1) a model with t_1 as the only predictor, (2) a model with both t_1 and group as predictors, and (3) a model with t_1, group, and their interaction as predictors. Subsequently, Bayes factors were calculated by pairwise comparing the three models. Accordingly, the Bayes factor suggests whether a model performs better after adding a certain predictor/interaction. A Bayes factor > 1 indicates that the more complex model (i.e., the model with more predictors) performs better than the less complex model (i.e., the model with fewer predictors). Following common benchmarks (van Doorn et al., 2021), a Bayes factor between 1 and 3 indicates a weak, between 3 and 10 a moderate to substantial, and a factor exceeding 10 a strong evidence that the more complex model performs better than the less complex one.

In Bayesian statistics, we can also test for practical equivalence, determining whether an effect is practically significant or not. This involves setting a region of practical equivalence (ROPE), which is considered to be "practically no effect" (Kruschke, 2014, 2018). Bayesian tests for practical equivalence were calculated using the *bayestestR* package (Makowski et al., 2019). The distribution of the 95% Highest Density Intervals (HDI) of posterior samples indicates the relationship of a parameter's distribution to the ROPE. Specifically, the HDI can lie entirely outside, entirely inside, or partially inside the ROPE. If the HDI is entirely outside the ROPE, the null hypothesis for this parameter is rejected. Conversely, if the ROPE completely encompasses the HDI, meaning that all the most credible values of the parameter fall within the region of practical equivalence, the null hypothesis for this parameter is accepted. In cases where the HDI partially overlaps with the ROPE, the decision to accept or reject the null hypothesis remains undecided. The ROPE limits were determined based on Kruschke's (2018) recommendation, which defines the ROPE as $0 \pm SD$ of the dependent variable * 0.1 for linear models.

Results

The Bayes factors for each model can be found in Table E.1.1-IV. The results suggest that models including the interaction term group × t_1 provide the best fit to the data for all clinical outcomes, compared to models with either t_1 or group and t_1 only. The results of the tests for practical equivalence can be found in Table E.1.2-IV. Tests for the FTCD score for the group comparisons (a) GNG training vs. control groups and (c) smoking-specific GNG training group vs. control groups showed the practical significance of the interaction effect between group and t_1. For all other tests, there was no clear evidence of its practical significance. However, for the QSU score in the group comparisons (a), (c), and (d), only a small percentage (3.8% or less) of the 95% HDI was found to lie within the ROPE.

Table E.1.1-IV

Bayes Factors with Standard Errors of Model Comparisons for all Clinical Outcomes

Model comparison	CPD	*SE*	CO	*SE*	FTCD	*SE*	QSU	*SE*
Group comparison (a): GNG training vs. control groups								
P2 vs. P1	4.3	0.04	5.3	0.04	1.3	0.01	6.1	0.04
P3 vs. P1	37.4	0.31	48.8	0.40	30.3	0.25	388.6	2.71
P3 vs. P2	8.9	0.08	9.1	0.07	23.8	0.17	64.5	0.47
Group comparison (b): smoking-specific GNG training vs. general GNG training group								
P2 vs. P1	17.1	0.06	11.8	0.04	1.9	0.01	7.7	0.03
P3 vs. P1	121.1	0.42	120.2	0.40	5.9	0.02	61.0	0.25
P3 vs. P2	7.1	0.02	10.4	0.04	3.2	0.01	7.9	0.03
Group comparison (c): smoking-specific GNG training group vs. control groups								
P2 vs. P1	13.6	0.07	4.1	0.02	2.8	0.02	5.0	0.02
P3 vs. P1	130.7	0.66	61.1	0.36	148.4	0.66	197.1	1.05
P3 vs. P2	9.6	0.05	15.0	0.09	54.0	0.29	38.8	0.20
Group comparison (d): GNG training groups vs. Sham group								
P2 vs. P1	5.5	0.03	7.4	0.03	1.0	0.01	17.0	0.09
P3 vs. P1	32.8	0.18	150.3	0.63	2.0	0.01	774.8	3.99
P3 vs. P2	6.1	0.03	20.3	0.10	1.9	0.01	45.7	0.24

Note. Bayes factors were calculated with $n = 100$ iterations. P1 = model with predictor t_1; P2 = model with predictors t_1 and group; P3 = model with predictor t_1, group, and $t_1 \times$ group; CPD = Cigarettes Per Day; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU = Questionnaire on Smoking Urges, brief version.

Table E.1.2-IV

Bayesian Tests for Practical Equivalence

Outcome	ROPE	Term	Decision on H_0	Inside ROPE	95%-HDI
Group comparison (a): GNG training vs. control groups					
CPD	[-0.94; 0.94]	Group × t_1	Undecided	21.7%	[-4.88; 0.91]
CO	[-1.08; 1.08]	Group × t_1	Undecided	23.6%	[-2.45; 7.25]
FTCD	[-0.21; 0.21]	Group × t_1	**Rejected**	0.0%	[-1.47; -0.21]
QSU	[-0.99; 0.99]	Group × t_1	Undecided	1.3%	[-8.38; -0.69]
Group comparison (b): smoking-specific GNG training vs. general GNG training group					
CPD	[-1.01; 1.01]	Group × t_1	Undecided	31.8%	[-6.03; 4.09]
CO	[-1.16; 1.16]	Group × t_1	Undecided	22.1%	[-5.87; 9.62]
FTCD	[-0.21; 0.21]	Group × t_1	Undecided	13.2%	[-1.79; 0.38]
QSU	[-0.99; 0.99]	Group × t_1	Undecided	28.9%	[-6.13; 6.42]
Group comparison (c): smoking-specific GNG training group vs. control groups					
CPD	[-0.87; 0.87]	Group × t_1	Undecided	17.5%	[-5.91; 1.17]
CO	[-1.04; 1.04]	Group × t_1	Undecided	17.6%	[-2.89; 9.32]
FTCD	[-0.21; 0.21]	Group × t_1	**Rejected**	0.0%	[-1.96; -0.38]
QSU	[-0.94; 0.94]	Group × t_1	Undecided	3.8%	[-8.90; 0.01]
Group comparison (d): GNG training groups vs. Sham group					
CPD	[-1.00; 1.00]	Group × t_1	Undecided	33.4%	[-5.08; 2.15]
CO	[-1.11; 1.11]	Group × t_1	Undecided	11.7%	[-1.48; 10.09]
FTCD	[-0.21; 0.21]	Group × t_1	Undecided	22.5%	[-1.33; 0.38]
QSU	[-1.01; 1.01]	Group × t_1	Undecided	3.2%	[-9.55; 0.09]

Note. ROPE = Region Of Practical Equivalence; HDI = Highest Density Interval; CPD = Cigarettes Per Day; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU = Questionnaire on Smoking Urges, brief version.

Appendix E.2: Alternative Potential Working Mechanisms

Methods

In exploring alternative potential workings mechanisms, we investigated whether GNG training led to an increase in response inhibition assessed via the SST (operationalized as the Stop-Signal Reaction Time [SSRT]; see Appendix D for a description of the measure; working mechanism: strengthened *top-down inhibitory control* [implicit measure]) and/or a reduction in self-reported impulsivity (BIS-15; working mechanism: strengthened *top-down inhibitory control* [explicit measure]). In terms of the smoking-specific GNG training group, we examined whether the training led to a reduction in behavioral approach (AAT) and positive association (IAT) biases (see Appendix D for a description of the measures; working mechanism: *stimulus*

devaluation). The procedures for the statistical analyses were identical to those conducted for the GNG task CE rates. Study groups did not differ in their SST, BIS-15, AAT, and IAT scores at t_0, all *ps* ≥ .117.

Results

Contrary to our expectations, no significant interactions between group ([a] GNG training vs. control groups) and the t_0-t_1 change in any alternative potential working mechanism measures were observed (SST: β = -1.82, *95% CI* [-48.74–45.09], p = .470; BIS-15: β = 0.96, *95% CI* [-0.48–2.41], p = .904; one-sided p-values). Due to the non-significant results in group comparison (a) and to avoid power issues caused by a reduced sample size, we refrained from conducting further group comparison analyses. In the case of the smoking-specific GNG training group, none of the alternative working mechanism measures significantly decrease from t_0 to t_1 (IAT: β = -0.13, *95% CI* [-0.39–0.15], p = .179; AAT: β = -1.65, *95% CI* [-4.38–1.10], p = .120; one-sided p-values).

Appendix E.3: Per-protocol (PP) analyses

Methods

In addition to ITT analyses, PP analyses were also conducted. The PP sample included participants who completed the t_1 and/or t_2 assessment within the specified time frame (t_1: starting 4 weeks after t_0 for 2 weeks; t_2: starting 3 months after t_1 for 4 weeks), completed at least 14 (i.e., 50%, selected as an arbitrary threshold) of the 28 designated training sessions and did not report the use of any other smoking cessation methods during study participation.

Due to the moderate training compliance and a dropout rate exceeding the expected 20%, the final PP-sample sizes per group were relatively small (PP-sample sizes per group for t_0-t_1 analyses: GNG training groups: n = 20 [smoking-specific GNG training group: n = 7; general GNG training group: n = 13], control groups: n = 31 [Sham training group: n = 12; WLC: n = 19]; t_0-t_2 analyses: GNG training groups: n = 14 [smoking-specific GNG training group: n = 4;

general GNG training group: n = 10], control groups: n = 25 [Sham training group: n = 10; WLC: n = 15]). Given that the small group sample sizes result in reduced statistical power, we elected to present the PP analyses in the supplementary material.

Sample Characteristics

The descriptive statistics and comparisons of baseline characteristics between groups of the PP-sample are displayed in Table E.3.1-IV.

Table E.3.1-IV

Descriptive Statistics and Group Comparisons for Baseline Characteristics and Task-Related Variables, PP-sample

Variables	GNG training groups		Control groups		
	n	*M* (*SD*)	*n*	*M* (*SD*)	Statistics
Baseline characteristics					
Age (years)	20	45.40 (11.90)	33	43.48 (14.35)	.619
Male[a] (%)	20	50.00	33	63.64	.491
High school graduation (%)	20	65.00	33	69.70	.959
Cigarettes per day	20	22.35 (10.91)	33	18.52 (7.58)	.137
Smoking duration (years)	20	27.40 (11.80)	33	23.38 (14.30)	.296
CO value	20	27.75 (13.28)	33	22.30 (11.06)	.114
FTCD[b]	20	5.20 (1.85)	33	4.88 (1.39)	.475
QSU-brief[c]	19	30.68 (11.40)	32	27.62 (8.33)	.275
TAAS abstinence goals[d]	19	4.74 (1.33)	31	4.26 (1.65)	.291
TAAS desire to quit[e]	20	6.12 (2.35)	33	5.64 (2.26)	.456
BIS-15[f]	19	31.84 (4.07)	33	31.27 (5.77)	.707
WST-IQ[g]	20	108.45 (9.39)	33	107.24 (13.11)	.721
Task-related variables					
General GNG task CE rate	20	19.81 (10.33)	33	14.02 (11.93)	.078
Smoking-specific GNG task CE rate					
smoking-related stimuli	20	8.12 (5.61)	33	4.47 (5.03)	**.018**
neutral stimuli	20	6.00 (8.94)	33	4.55 (4.78)	.508

Note. GNG = Go/No-Go; GNG training groups = collapsed general and smoking-specific GNG training group; Control groups = collapsed Sham and Waitlist control group; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU-brief = Questionnaire on Smoking Urges, brief version; TAAS = Thoughts About Abstinence Scale;

BIS = Barratt Impulsiveness Scale, 15-item version; WST = Wortschatztest (German vocabulary test); CE = Commission Error.

Baseline differences of continuous and categorical variables were assessed using chi-square and independent *t*-tests. All variables on baseline characteristics were collected via paper-pencil format, with the possibility that some questions might not have been answered, resulting in missing data. Therefore, the final sample sizes for each variable are indicated in the current table.

[a] collected on the concept of biological sex; [b] total range: 0–10; [c] total range: 10–70; [d] 6 = total abstinence, never use again, 5 = total abstinence but realize a slip is possible, 4 = occasional use when urges strongly felt, 3 = temporary abstinence, 2 = controlled use, 1 = no goal; [e] total range: 0–9; [f] total range: 15–60; [g] total range: 60–139.

Clinical Outcomes

For the primary clinical outcome (CPD from t_0 to t_1), there is insufficient evidence to suggest that the GNG training groups demonstrated a stronger reduction compared to the control groups (effect of group × t_1 in a model without t_2 as predictor: β = -1.69, *95% CI* [-5.37–1.98], p = .186). However, the GNG training groups showed a significantly greater reduction in the FTCD score at t_1 compared to the control groups (see Tables E.3.2-IV and E.3.3-IV). Post-hoc pairwise comparisons revealed that the GNG training groups showed a significant decrease in the FTCD scores from t_0 to t_1, $t(49.0) = -2.96$, p = .002 (one-tailed), whereas the reduction in the control groups was not significant, $t(49.8) = -0.50$, p = .618. The GNG training groups did not exhibit significantly lower FTCD scores at t_1 compared to the control groups, $t(67.7) = -0.88$, p = .190 (one-tailed).

Unlike the analysis with the ITT-sample, the PP-sample analysis did not reveal a significantly stronger reduction in the QSU score for the GNG training groups compared to the

control groups. Again, at t_2, no significant interactions with group were observed for any of the clinical outcomes. Due to the small PP-sample sizes in the study groups, we refrained from conducting further group comparisons other than (a) GNG training vs. control groups.

Table E.3.2-IV

(a) GNG Training vs. Control Groups: Results of the Linear Mixed Effects Models for all Clinical Outcomes in the PP-sample

Fixed effects	CPD			CO			FTCD			QSU[1]		
	β	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*	*β*	*95% CI*	*p*
Intercept	18.52	15.54 – 21.49	**<.001**	22.30	18.41 – 26.19	**<.001**	4.88	4.31 – 5.45	**<.001**	29.87	24.84 – 34.91	**<.001**
Group	3.83	-1.01 – 8.68	.122	5.45	-0.88 – 11.78	.093	0.32	-0.60 – 1.24	.494	3.03	-3.12 – 9.18	.331
Time (t_1)	-2.33	-4.76 – 0.10	.064	-4.92	-8.90 – -0.93	**.018**	-0.12	-0.60 – 0.36	.626	-2.36	-5.44 – 0.73	.137
Time (t_2)	-4.91	-7.84 – -1.99	**.002**	-4.54	-10.28 – 1.20	.125	-1.11	-1.74 – -0.49	**.001**	–	–	–
Group × t_1	-1.77	-5.67 – 2.13	.187	2.17	-4.23 – 8.57	.748	-0.78	-1.55 – -0.01	**.025**[*]	-3.03	-7.96 – 1.90	.114
Group × t_2	-0.40	-5.25 – 4.45	.435	4.27	-5.36 – 13.89	.807	0.39	-0.64 – 1.43	.771	–	–	–

Note. For the group × t_1 and group × t_2 effects, one-sided *p*-values are reported, otherwise two-sided. CI = Confidence Interval; CPD = Cigarettes Per Day; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU = Questionnaire on Smoking Urges, brief version; PP = Per-Protocol.

[*] non-significant after Bonferroni correction.

Baseline variables with group differences at the $p < .10$ level (see Table E.3.1-IV) were considered as potential covariates. If adding a variable resulted in a better relative model fit, it was included in the linear mixed model as a covariate: [1] The smoking-specific GNG task CE rate (smoking-related stimuli) at t_0 was added as a covariate to the model, with results remaining unchanged.

Table E.3.3-IV

(a) GNG Training vs. Control Groups: Means (SDs) of Clinical Outcomes at t_0, t_1, and t_2, PP-sample

Outcome	GNG training groups			Control groups		
	t_0 (n = 20)	t_1 (n = 20)	t_2 (n = 14)	t_0 (n = 33)	t_1 (n = 31)	t_2 (n = 25)
CPD	22.35 (10.91)	18.25 (8.30)	16.50 (8.00)	18.52 (7.58)	16.39 (9.33)	14.00 (8.54)
CO	27.75 (13.28)	25.00 (12.36)	28.08 (20.86)[b]	22.30 (11.06)	17.52 (9.06)	18.75 (11.11)[e]
FTCD	5.20 (1.85)	4.30 (2.03)	4.29 (1.94)	4.88 (1.39)	4.77 (2.06)	3.80 (2.24)
QSU	30.68 (11.40)[a]	25.10 (9.32)	–	27.62 (8.33)[c]	26.40 (10.17)[d]	–

Note. CPD = Cigarettes Per Day; CO = Carbon monoxide value; FTCD = Fagerström Test for Cigarette Dependence; QSU = Questionnaire on Smoking Urges, brief version; PP = Per-Protocol; GNG training groups = collapsed general and smoking-specific Go/No-Go training group; Control groups = collapsed Sham and Waitlist control group.

[a] n = 19; [b] n = 13; [c] n = 32; [d] n = 30; [e] n = 24

Appendix F: Overview of Peer-Reviewed Studies on GNG Task-based ICT in Smoking

Table F.1-IV

Overview of Peer-Reviewed Studies on GNG Task-based ICT in Smoking

Study	Sample	Level of dependence	Inclusion criteria: abstinence motivation	Depri vation	No. of training sessions	*M* (*SD*) of absolved training sessions	No. trails per session	Contingency (Go:No-Go trials)	GNG training	Control condition(s)
Present study	rep.	≥3 FTCD; FTCD: *M*=5.23; CPD: *M*=19.55	no	no	28	Smoking-specific GNG: 11.94 (12.02); general GNG: 15.14 (11.11) Sham: 16.77 (13.27)	320	75:25	**Smoking-specific GNG**: No-Go: 100% smoking-related stimuli; Go: 100% neutral stimuli **General GNG**: digits only	**Sham**: categorization task (75:25 neutral/smoking-related stimuli); **WLC**: no intervention during study participation
Adams et al. (2017)	young age (*M*=24; *SD*=8)	≥10 CPD; FTCD: *M*=4; CPD: *M*=13	no	12h	1	n/a	256	75:25	No-Go: 100% smoking-related stimuli; Go: 100% neutral stimuli	No-Go: 50% smoking-related and 50% neutral stimuli; Go: 100% neutral stimuli
Bos et al. (2019)	rep.	≥10 CPD; CPD: *M*=18.79; meeting criteria for moderate (*n*=41) or severe (*n*=66) tobacco use disorder (DSM-5)	yes	no	14	GNG: 10.50 (2.91); Control: 10.89 (3.20)	216	50:50	No-Go: 50% smoking-related and 50% neutral stimuli; Go: 50% relaxing and 50% neutral stimuli	No-Go: 50% household and 50% neutral stimuli; Go: 50% household and 50% neutral stimuli
Hughes et al. (2021)	rep.	same sample as Bos et al. (2019)	yes	no	14	same as Bos et al. (2019)	216	50:50	same as Bos et al. (2019)	same as Bos et al. (2019)
Machul ska et al. (2022)	rep.	≥6 CPD; FTCD: *M*=4.45–5.04; CPD: *M*=16.04–19.84	yes	no	5	A-AAT: 4.39 (0.88), Sham A-AAT: 4.25 (1.35), GNG-AAT: 4.29 (1.24), Sham GNG-AAT: 4.56 (0.85)	200	50:50	**GNG-AAT**: No-Go: 100% smoking-related stimuli; Go: 100% neutral stimuli	**Sham GNG-AAT**: No-Go: 50% smoking-related and 50% neutral stimuli; Go: 50% smoking-related and 50% neutral stimuli

Note. CPD = Cigarettes Per Day; FTCD = Fagerström Test for Cigarette Dependence; GNG = Go/No-Go; AAT = Approach-Avoidance Task.

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