Effects of Substance-Related Cues on Response Inhibition in Addicted Individuals

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Date: 2019-05-29T00:00:00+00:00

Abstract

The uncontrolled substance seeking and use in individuals with addiction is closely associated with response inhibition. Numerous studies have examined this relationship within contexts involving substance-related cues. Such cues can be processed through automatic attentional mechanisms and can also evoke non-automatic approach motivational states. Consequently, they may consume limited cognitive resources via both stimulus-driven and state-dependent pathways, thereby impairing response inhibition—a process that plays a crucial role in the development and maintenance of addictive behaviors. Future research should address several key areas: elucidating the underlying neural mechanisms, clarifying the moderating effects of substance use motivation or attitudes, conducting studies in ecologically valid real-world settings, and developing effective intervention methods.

Full Text

Preamble

The Effects of Substance-Related Cues on Response Inhibition in Addicts

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Abstract: The loss of control over substance seeking and use in addicts is closely related to response inhibition, and many studies have explored this relationship within the context of substance-related cues. Such cues can be automatically processed by attention and also induce non-automatic approach-motivated states. Consequently, they may consume limited cognitive resources through both stimulus-driven and state-dependent mechanisms, thereby influencing response inhibition and playing important roles in the development and maintenance of addictive behaviors. Future research should investigate the underlying neural mechanisms, clarify how motivations and attitudes toward substance use modulate these effects, conduct studies in real-world settings, and develop more effective interventions.

Keywords: substance addiction; substance-related cues; response inhibition; stimulus-driven effects; state-dependent effects

Substance addiction is defined as the loss of control over substance use, compulsive substance seeking and consumption, despite adverse consequences (Nestler, 2001). Repeated intake of substances (e.g., opioids, cocaine, alcohol, cigarettes) can lead to persistent changes in brain structure and function (Koob & Le Moal, 2005; Koob & Volkow, 2010; Nestler, 2001; Yang et al., 2015). On one hand, the mesolimbic system becomes sensitized to substance-related incentives (Robinson & Berridge, 1993), and through repeated pairing with substance use, associated cues acquire incentive salience features that automatically capture attention and trigger craving and automatic approach behaviors (Franken, 2003; Robinson & Berridge, 1993; Tiffany, 1990). On the other hand, executive functions regulated by the prefrontal cortex (PFC) system are impaired, preventing individuals from effectively controlling their behavior when faced with substances or related cues. This impairment is considered an important factor in maintaining substance use or causing relapse after abstinence (Field & Cox, 2008; Goldstein & Volkow, 2002; Perry & Carrol, 2008; Wiers et al., 2007; Wiers & Stacy, 2006).

Response inhibition, a crucial component of executive function, is defined as the ability to suppress inappropriate yet dominant behaviors (Barkley, 1997; Miyake et al., 2000). Previous research has found that substance addicts exhibit deficits in inhibitory function (Behan et al., 2014; Smith, Mattick, Jamadar, & Iredale, 2014). Such deficits may predate substance use and contribute to addiction development, as longitudinal studies show that weaker response inhibition predicts future substance abuse initiation and escalation in adolescents (Mahmood et al., 2013; Nigg et al., 2006). However, chronic substance use also damages brain regions involved in response inhibition, including the PFC, further reinforcing uncontrolled substance seeking and use (Goldstein & Volkow, 2002, 2011; Perry & Carrol, 2008; Wiers et al., 2007; Wiers & Stacy, 2006; Yuan et al., 2010; Yuan et al., 2009).

Most existing research and theories discuss the relationship between response inhibition and substance use based on its "trait" attribute—that is, response inhibition is relatively stable. However, response inhibition also has a "state" attribute that can fluctuate temporarily due to internal and external factors (de Wit, 2009; Jones, Christiansen, Nederkoorn, Houben, & Field, 2013). For example, disinhibition priming (Jones et al., 2011), consumption of small amounts of substances (e.g., 0.65 g/kg alcohol) (Weafer & Fillmore, 2008), and exposure to substance-related cues (Field & Jones, 2017; Su, Yang et al., 2017) can all reduce addicts' response inhibition and lead to subsequent increased substance use. Since substance-related cues are a critical factor in maintaining substance use and triggering relapse (Field & Cox, 2008; Robinson & Berridge, 1993), increasing attention has focused on their effects on response inhibition. Unlike previous theories that explained persistent substance seeking through attentional bias and craving induced by cues or through response inhibition dysfunction caused by substance use, this article systematically reviews recent research on how substance-related cues affect response inhibition and their role in addiction development and maintenance, providing insights for understanding the psychological mechanisms of addictive behavior and identifying future research directions.

2. Experimental Paradigms for Investigating the Effects of Substance-Related Cues on Response Inhibition

Commonly used experimental paradigms for measuring response inhibition include the Go/NoGo task, Stop-signal task, and dual-choice Oddball task. In the Go/NoGo task, participants must respond quickly and accurately to Go stimuli while withholding responses to NoGo stimuli. Since a dominant response is established to Go stimuli, inhibition is required when NoGo stimuli appear (Simmonds, Pekar, & Mostofsky, 2008; Smith et al., 2014). Although equiprobable Go/NoGo tasks are sometimes used, researchers argue that a dominant response is only established when Go stimuli occur with high probability (e.g., 75%) (Barry & Rushby, 2006). The Stop-signal task includes high-probability Go trials and low-probability Stop trials, requiring participants to make choice or categorization responses to target stimuli (Go condition) but stop their response when a stop signal (auditory or visual) appears (Stop condition). The stop signal typically occurs after a variable or fixed delay, and stop-signal reaction time (SSRT) is estimated as an index of response inhibition, with longer SSRT indicating poorer inhibition (Verbruggen & Logan, 2009). The dual-choice Oddball task includes high-probability standard stimuli and low-probability deviant stimuli, requiring different key responses to each. Responding to low-probability stimuli requires suppressing the dominant response tendency to high-probability stimuli, resulting in longer reaction times and higher error rates (Yuan, He, Zhang, Chen, & Li, 2008; Yuan, Xu, Yang, & Li, 2017).

These three paradigms are widely recognized but have distinct characteristics. First, Go/NoGo and Stop-signal tasks more directly operationalize response inhibition concepts, involving suppression of a dominant response and cancellation of an initiated response, respectively, whereas the dual-choice Oddball task involves suppressing a dominant response tendency (Yuan et al., 2008). Second, Go/NoGo and Stop-signal tasks typically use single behavioral indices (NoGo error rate and SSRT, respectively), while the dual-choice Oddball task provides comprehensive measures of both reaction time and error rate. Third, Go/NoGo tasks require careful consideration of speed-accuracy trade-offs, Stop-signal tasks must address potential waiting strategies, and the less demanding dual-choice Oddball task relies on probability ratios, requiring attention to the larger number of trials needed.

Current studies examining the effects of substance-related cues on response inhibition typically combine these cues with inhibition tasks. Video, odor, and auditory cues are simply presented before or simultaneously with the tasks without modifying the tasks themselves, so these approaches will not be detailed further. The combination of picture and word cues with inhibition tasks is more complex, with three main approaches based on the relevance and synchrony between cues and task targets.

First, **task-relevant synchronous presentation** uses substance-related or neutral cues directly as target stimuli requiring judgment or categorization, including cue-related Go/NoGo tasks (Adams, Ataya, Attwood, & Munafo, 2013; Noël et al., 2007), dual-choice Oddball tasks (Xin, Ting, Yi, Li, & Bao, 2015), and Stop-signal tasks (Kreusch, Billieux, & Quertemont, 2017). Second, **task-irrelevant synchronous presentation** uses substance-related cues as backgrounds unrelated to target stimuli, including cue-related Go/NoGo tasks (Luijten, Littel, & Franken, 2011; Petit, Kornreich, Noël, Verbanck, & Campanella, 2012), Stop-signal tasks (Nederkoorn, Baltus, Guerrieri, & Wiers, 2009), and dual-choice Oddball tasks (Su, Yang, et al., 2017). Third, **cue-priming approaches** present target stimuli after substance-related cues. For example, in cue-primed Go/NoGo tasks, substance-related and neutral pictures predict the subsequent occurrence of Go or NoGo stimuli with certain probabilities (Weafer & Fillmore, 2012).

Among these approaches, task-relevant synchronous presentation may enhance performance by making salient stimuli easier to detect (Pennington, Qureshi, Monk, & Heim, 2016), potentially offsetting some interference effects. In contrast, task-irrelevant synchronous and cue-priming approaches avoid this issue. Compared to synchronous presentation, cue-priming methods present target stimuli after cue offset, separating the effects of attentional processing of cues from the dependent measures and more clearly reflecting fluctuations and persistence of response inhibition. Moreover, different combination approaches may involve distinct mechanisms, which will be clarified in subsequent sections.

3.1 Mechanisms of Substance-Related Cue Effects on Response Inhibition

Although many studies have examined how substance-related cues affect response inhibition, theoretical frameworks explaining these mechanisms are lacking. Some attention resource perspectives posit that cognitive or attentional resources for response inhibition are limited, and that implementing inhibitory function essentially involves protecting these limited resources from allocation to task-irrelevant stimuli or responses through attentional suppression (Eysenck, Derakshan, Santos, & Calvo, 2007; Pessoa, 2009). The dual competition model proposes that emotionally meaningful stimuli can affect competition at both perceptual and executive levels, suggesting stimulus-driven and state-dependent influences. Specifically, the emotional salience features of stimuli and the emotional and motivational state changes they evoke allocate limited cognitive resources differently, thereby affecting executive functions including response inhibition (Pessoa, 2009).

Numerous neuroimaging studies have found that exposure to substance-related cues activates the orbitofrontal cortex (OFC), anterior/posterior cingulate cortex (ACC/PCC), dorsolateral prefrontal cortex (DLPFC), insula, and perceptual-attention systems (occipital lobe, posterior parietal lobe, medial temporal lobe, etc.) (Engelmann et al., 2012; Kang et al., 2012; Yalachkov, Kaiser, & Naumer, 2012). Research also shows that visual attentional processing correlates with ACC and DLPFC activation during cue exposure, while increased craving correlates with OFC, PCC, and insula activation (Kang et al., 2012). Since OFC, ACC, and DLPFC are also key brain regions for inhibitory function, these findings indirectly suggest that substance-related cues can affect addicts' response inhibition through different pathways. Given that substance-related cues have incentive salience features, they can capture addicts' attention through bottom-up stimulus-driven processes and also induce enhanced craving, which is considered an emotionally motivated state (Franken, 2003). Based on this, we apply the dual competition model to understand how substance-related cues affect addicts' response inhibition, hypothesizing two distinct influences: stimulus-driven and state-dependent.

3.1.1 Stimulus-Driven Effects

Stimulus-driven effects refer to how the incentive salience features of substance-related cues automatically drive attentional processing of these cues, thereby affecting response inhibition. This influence depends on cue presentation and is relatively transient. Extensive evidence comes from studies embedding substance-related and neutral cues (e.g., words and pictures) as within-block factors in response inhibition tasks.

At the behavioral level, using cue-related Go/NoGo tasks, some studies found that alcohol addicts showed faster Go reaction times and higher NoGo error rates for alcohol-related cues, with correlations to higher arousal ratings for alcohol-related pictures (Czapla et al., 2015; Kreusch, Vilenne, & Quertemont, 2013; Petit et al., 2012). Lannoy, Maurage, D' Hondt, Billieux, and Dormal (2018) found that binge drinkers (who consume large amounts of alcohol in short periods) showed reduced post-error slowing for alcohol-related NoGo stimuli compared to controls, suggesting that alcohol-related cues impair behavioral regulation following inhibitory errors. Using cue-related Stop-signal tasks, Zack et al. (2011) found that problem drinkers showed faster Go reaction times and significantly longer SSRT for task-irrelevant alcohol words than neutral words. Monk, Qureshi, Pennington, and Hamlin (2017) found that regular drinkers showed faster Go reaction times, lower error rates, and significantly longer SSRT for task-irrelevant alcohol and non-alcohol desire-related pictures compared to neutral pictures, with higher arousal ratings for desire pictures. The researchers suggested that desire for alcohol may generalize to other desired stimuli, reducing drinkers' response inhibition. Using cue-related dual-choice Oddball tasks, Su, Yang et al. (2017) found that heroin abstainers showed significantly longer reaction times to low-probability deviant stimuli presented against heroin-related versus neutral backgrounds. Other studies using cue-primed Go/NoGo tasks found faster Go reaction times and higher NoGo error rates following substance-related cues in drinkers (Fleming & Bartholow, 2014; Weafer & Fillmore, 2012, 2015) and cocaine-dependent individuals (Pike, Marks, Stoops, & Rush, 2015; Pike, Stoops, Fillmore, & Rush, 2013). These studies across different task types demonstrate that substance-related cues interfere with addicts' response inhibition, possibly because attentional processing of these cues consumes limited cognitive resources (Su, Yang et al., 2017).

However, these studies cannot determine whether interference results from bottom-up stimulus-driven or top-down goal-driven attentional processing. Some findings address this question. For example, Pike et al. (2015) found that brief cue presentation (100-200 ms) produced significantly more inhibition errors than longer presentation (300-500 ms). The researchers argued that brief presentations primarily involve automatic attentional orienting, while longer presentations allow cognitive control to disengage attention from relevant cues, indicating that interference effects are mainly driven by automatic attentional processing. Wilcockson and Pothos (2015) used a substance-related cue attention fixation task with eye-tracking in light drinkers, requiring participants to maintain visual attention on a central fixation point while ignoring peripheral distractors. The task measured how often gaze deviated from the fixation point as an index of attentional control and distractor inhibition. Results showed poorer inhibition of alcohol-related distractors compared to neutral distractors. The researchers suggested that even when addicts are not consciously aware of the information contained in substance-related distractors, they still have difficulty suppressing attentional orienting to these stimuli, reflecting automatic attentional processing. These behavioral findings provide evidence for stimulus-driven effects.

Other studies, however, show that substance-related cues do not always interfere with response inhibition. For instance, Pennington et al. (2016) used both alcohol-related sounds and pictures as cues, finding that alcohol users had lower error rates for alcohol pictures as NoGo targets but faster Go reaction times and higher NoGo error rates for task-irrelevant alcohol sound cues. This suggests that while substance-related cues can trigger automatic attentional processing, they reduce response inhibition when task-irrelevant but enhance it when task-relevant. However, some studies using different substance-related cues as task targets have yielded inconsistent results. Noël et al. (2007) found that detoxified alcohol addicts showed significantly longer reaction times for alcohol-related words as Go targets and higher error rates as NoGo targets compared to controls. Adams et al. (2013) used word and picture cues as targets in two Go/NoGo tasks, finding that alcohol-related words reduced response inhibition in social drinkers, while alcohol-related pictures enhanced it. The researchers suggested that pictures are more intuitive and clear than words, thus facilitating task performance. When words serve as task targets, addicts may engage in semantic processing of substance-related words after initial attentional orienting, interfering with response inhibition. This indicates that different types of substance-related cues may affect response inhibition through different mechanisms, requiring further investigation.

At the EEG level, the N2 component reflects early conflict monitoring and cognitive control, while the P3 component reflects later top-down inhibitory mechanisms to resolve conflict. Larger N2 and P3 amplitudes indicate more cognitive resources allocated to response inhibition, whereas longer latencies reflect slower cognitive processing (Bokura, Yamaguchi, & Kobayashi, 2001; Kopp, Mattler, Goertz, & Rist, 1996). Petit et al. (2012) found that heavy drinkers showed longer NoGo-P3 latencies for alcohol-related versus neutral cues. Fleming and Bartholow (2014) found larger N2 and P3 amplitudes for substance-related versus neutral cues in heavy drinkers. These findings indicate that substance-related cues consume more cognitive resources, interfering with response inhibition, and that this interference appears in the early N2 component (around 200-300 ms). Additionally, Detandt et al. (2017) found that moderate/light smokers showed more response errors than controls, but compared to neutral cues, smokers showed lower inhibition error rates and larger P3 amplitudes for substance-related cues. The researchers suggested this indicates that substance-related backgrounds enhance response inhibition in smokers. Although substance-related pictures were task-irrelevant in this study, they persisted as backgrounds from before target onset until response completion, helping maintain smokers' attention on the task.

At the neuroimaging level, using cue-related Go/NoGo tasks, Ames et al. (2014) found that compared to light drinkers, alcohol-related NoGo stimuli activated the right DLPFC, anterior/middle cingulate, and right anterior insula (associated with craving) to a greater extent in heavy drinkers. The researchers suggested that salient alcohol-related NoGo stimuli required heavy drinkers to mobilize more cognitive resources to inhibit responses. Czapla et al. (2017) found that detoxified alcohol patients and controls showed higher NoGo error rates for alcohol-related versus neutral cues, but detoxified patients showed greater occipital activation rather than activation in inhibition-related brain regions for alcohol-related NoGo stimuli. This suggests that due to the visual salience of alcohol-related cues, some visual attention shifted from the inhibition task to processing the cues themselves. Hester and Garavan (2009) used a working memory task and found that substance-related cues impaired performance in cocaine addicts under high working memory load, with behavioral results reflected in greater activation in the occipital lobe and right inferior frontal gyrus (IFG). The researchers suggested this reflects substance-related cues capturing addicts' visual attention, requiring greater cognitive control to prevent interference with the primary task. These neuroimaging results imply that stimulus-driven effects involve the occipital lobe (visual processing), inhibition-related regions such as DLPFC, IFG, and ACC, while insula activation may reflect state-dependent effects. This can be explained by the dual competition model (Pessoa, 2009), where stimulus-driven perceptual competition occurs primarily in primary visual cortex, after which emotional information is transmitted to the ACC and interacts with DLPFC, IFG, and anterior insula to produce executive-level competition.

3.1.2 State-Dependent Effects

State-dependent effects refer to how the incentive salience features of substance-related cues can induce non-automatic changes in appetitive states, leading to increased craving. On one hand, regulating craving consumes limited cognitive resources; on the other hand, increased craving can drive attention toward substances or related cues, reducing cognitive resources available for response inhibition. Craving induction and dissipation are relatively slow processes, and once induced, craving can persist independent of cue presentation. Some studies have used substance-related cues (e.g., videos, odors) to induce craving, manipulating craving induction (without modifying the response inhibition task) as a between-block or between-subjects factor.

At the behavioral level, using Go/NoGo tasks, Tolliver et al. (2012) had participants complete an auditory Go/NoGo task while viewing methamphetamine-related or neutral videos. They found that methamphetamine addicts showed slower Go reaction times and higher error rates for both Go and NoGo trials than controls in the neutral condition, and that cue exposure further increased addicts' error rates, which correlated significantly with enhanced craving. Monk, Sunley, Qureshi, and Heim (2016) found that heavy problem drinkers showed higher NoGo error rates after exposure to alcohol-related olfactory cues (5ml of Glenn vodka diluted 1:5) than control olfactory cues (5ml of citrus oil diluted 1:10). Using Stop-signal tasks, Muraven and Shmueli (2006) found that social drinkers who sniffed a glass of wine showed higher stop-signal error rates and reported higher craving than those who sniffed water, with craving significantly predicting Stop-signal performance. Gauggel et al. (2010) found that alcohol abstainers who sniffed a glass of wine showed longer SSRT and reported higher craving than those who sniffed water. Field and Jones (2017) found that heavy drinkers in a simulated bar environment who sniffed a glass of wine showed longer SSRT and reported higher craving than those in a neutral environment who sniffed water. Subsequent mediation analysis showed that heavy drinkers who showed reduced response inhibition and enhanced craving after alcohol cue exposure consumed more alcohol in a subsequent bogus taste test. These studies suggest that craving state induction reduces addicts' response inhibition, possibly due to cognitive resource consumption from craving suppression (Muraven & Shmueli, 2006; Tiffany & Conklin, 2000).

Other studies have manipulated craving induction as a between-block or between-subjects factor while requiring participants to complete substance-related cue response inhibition tasks, providing evidence for separating stimulus-driven and state-dependent effects. For example, Kreusch et al. (2017) found that detoxified alcohol patients who sniffed a glass of wine reported higher craving and showed significantly higher inhibition error rates for substance-related cues in a subsequent cue-related Stop-signal task, with a significant positive correlation between craving and inhibition errors in the alcohol sniffing group. DiGirolamo, Smelson, and Guevremont (2015) used a cue-related antisaccade task with eye-tracking in cocaine addicts, who first completed a passive viewing task with substance-related pictures to induce craving, followed by the antisaccade task. They found that the passive viewing task enhanced craving, and addicts showed more inhibition errors for substance-related than neutral cues, with the high-craving group showing more errors than the low-craving group. Further regression analysis revealed that craving induced by substance-related cues predicted higher inhibition error rates. These results support the existence of both stimulus-driven and state-dependent influences, showing that state-dependent effects are stronger and more persistent than stimulus-driven effects. They also demonstrate that attentional processing of substance-related cues can induce stronger craving, while craving induced before tasks can drive attention toward substance-related cues, amplifying effects on response inhibition.

At the neuroimaging level, Mainz et al. (2012) examined the effects of olfactory cues on response inhibition in alcohol addicts using fMRI. Eleven alcohol abstainers (one week abstinent) were exposed to alcohol vapor with imagined drinking scenes and neutral control conditions with imagined non-drinking scenes in random order, then completed a neutral Stop-signal task. Compared to the neutral condition, the substance-related cue condition induced enhanced craving and greater activation in the left hippocampus and left amygdala (associated with emotion and memory), but reduced activation in the PCC (associated with response inhibition and attentional processes), possibly reflecting craving induction reducing cognitive resources available for response inhibition. They also found greater right IFG activation and reduced globus pallidus activation in the cue-inhibition condition. The researchers suggested that the globus pallidus connects with the PFC during response inhibition, and that the pattern might indicate excessive inhibitory effort in addicts under cue-inhibition conditions (reflected in enhanced right IFG activation), leading to subsequent brain functional impairment (reflected in reduced globus pallidus activation). However, this study found no behavioral differences and had a small sample size, factors that future research should address while investigating different addict populations.

3.2 Relationship Between Cue Effects on Response Inhibition and Substance Use

Some studies have examined how the effects of substance-related cues on response inhibition relate to substance use frequency and quantity. For example, Weafer and Fillmore (2015) found that reduced response inhibition after alcohol cues in social drinkers predicted daily binge drinking and uncontrolled drinking patterns. Czapla et al. (2015) found that response inhibition for alcohol-related cues predicted binge drinking patterns in alcohol addicts, explaining 19% of the variance. Wilcockson and Pothos (2015) found in their eye-tracking study that heavy weekly drinkers showed poorer inhibition of alcohol cues than light drinkers. Watson, Newton-Mora, and Pirkle (2016) found that high-intoxication-frequency drinkers showed larger alcohol-related NoGo-N2 amplitudes than low-intoxication-frequency drinkers, indicating greater cue effects on response inhibition. Field and Jones (2017) found that heavy drinkers who showed reduced response inhibition and enhanced craving after alcohol cue exposure consumed more alcohol in a subsequent bogus taste test. These studies indicate that greater substance use frequency and quantity enhance cue effects on response inhibition, and that fluctuations in response inhibition induced by cues are an important factor in subsequent substance use and development of severe addiction.

Other studies have examined relationships with substance use severity. Noël et al. (2007) found that the effects of alcohol-related cues on response inhibition in detoxified alcohol patients were related to pre-detoxification drinking severity. Zack et al. (2011) found that reduced response inhibition for alcohol-related cues in problem drinkers correlated with higher alcohol dependence. Fleming and Bartholow (2014) found that substance-related cues reduced response inhibition in heavy drinkers but not light drinkers. Using similar procedures, Field and Jones (2017) found that cue exposure reduced response inhibition in heavy drinkers, and while light drinkers were generally unaffected, correlation analyses showed that individuals with stronger craving showed poorer response inhibition (Jones, Rose, Cole, & Field, 2013). These results suggest that substance-related cues have greater effects on response inhibition in severe addicts, but effects on light users may show substantial individual differences. Findings for light users are inconsistent across studies. While some research shows that substance-related cues reduce response inhibition in non-addicts (as described in Section 3.1), other studies found no such effects in light drinkers (Nederkoorn et al., 2009; Zhao, Qian, Fu, & Maes, 2017) or light smokers (Luijten et al., 2011; Mashhoon, Betts, Farmer, & Lukas, 2018; Zhao, Liu, Zan, Jin, & Maes, 2016). Additionally, Xin et al. (2015) used a cue-related dual-choice Oddball task and found that light smokers showed significantly longer reaction times to low-probability cigarette-related deviant stimuli compared to normal controls, but found no group differences for high-probability neutral standard stimuli. Without control conditions (cigarette-related pictures as standard stimuli and neutral pictures as deviant stimuli), these results may only indicate general inhibitory deficits in smokers. Beyond methodological differences, these inconsistent results may reflect individual differences in progression from light to more severe substance use patterns (e.g., addiction, substance use disorders).

3.3 Relationship Between Cue Effects on Response Inhibition and Withdrawal/Relapse

Some studies have examined the effects of substance-related cues on response inhibition in addicts after withdrawal. Su, Yang et al. (2017) used a cue-related dual-choice Oddball task and found that short-term abstainers (2-6 months) showed poorer response inhibition against heroin-related backgrounds than long-term abstainers (19-24 months). The researchers suggested that the salience of substance-related cues may decrease with longer abstinence duration, potentially explaining why addicts are more prone to relapse during early withdrawal. Su, Wang et al. (2017) used a cue-related dual-choice Oddball task with EEG in heroin abstainers (minimum 8 months, mean 18 months) and found reduced response inhibition in cue conditions, reflected at the EEG level by reduced N2 amplitudes associated with conflict monitoring. This indicates that the salient features of substance-related cues persist long after withdrawal, continuing to interfere with response inhibition. These results suggest that while cue effects on response inhibition may weaken with abstinence, they are difficult to extinguish completely, representing a risk factor for post-withdrawal relapse. Additionally, Gauggel et al. (2010) found that olfactory alcohol cues still increased craving and reduced response inhibition ability in addicts after at least four weeks of detoxification (mean 18 months). This result is not contradictory to previous findings; unlike the earlier studies using substance-related pictures or words, this study used olfactory cues that induced enhanced craving, and although the mean abstinence duration was relatively long, it included short-term abstainers. Future research should examine differences in response inhibition among substance addicts at different withdrawal stages from both stimulus-driven and state-dependent perspectives.

Other studies have examined the relationship between cue effects on response inhibition and relapse. Luijten, Kleinjan, and Franken (2016) investigated whether attentional processing of smoking cues and response inhibition in cue contexts predicted smoking cessation outcomes at weeks 4, 8, and 12 in 62 individuals planning to quit. They found that reduced post-error slowing and smaller NoGo-P3 amplitudes in a cue-related Go/NoGo task predicted post-quit relapse and increasing daily cigarette consumption over time. Petit et al. (2014) used a cue-related Go/NoGo task and found that detoxified alcohol addicts showed higher error rates for both alcohol-related and neutral NoGo cues than controls, along with larger NoGo-P3 amplitudes. They found that P3d (difference wave between NoGo and Go stimuli) was significantly larger in relapsers than non-relapsers at 3-month follow-up, with regression analysis showing that larger P3d predicted relapse status and time to relapse. Gilman et al. (2018) found that reduced anterior insula activation during cigarette-related NoGo stimuli in smokers predicted relapse after 12 weeks of cessation treatment. These studies demonstrate that fluctuations in response inhibition induced by substance-related cues are an important cause of relapse after abstinence.

4. Summary and Future Directions

This article systematically reviewed recent research on the effects of substance-related cues on response inhibition in addicts. Based on the perspective that cognitive or attentional resources for response inhibition are limited (Eysenck, Derakshan, Santos, & Calvo, 2007; Pessoa, 2009), we propose that substance-related cues affect addicts' response inhibition through two distinct mechanisms: stimulus-driven and state-dependent effects. Stimulus-driven effects occur primarily because the salient features of substance-related cues automatically divert addicts' attention. State-dependent effects arise because cues can induce increased craving, which not only consumes limited cognitive resources through craving regulation but also drives attention toward substances or related cues. Moreover, the effects of substance-related cues on response inhibition cannot be overlooked in the development and maintenance of addictive behavior. It is worth noting that some evidence comes primarily from alcohol user studies and may require validation in other substance addiction domains. Additionally, we believe future research should continue to deepen investigation in the following areas.

First, the neural mechanisms underlying cue effects on response inhibition. Based on only a few neuroimaging studies, we summarized that the neural basis involves the occipital lobe for visual processing, limbic structures (hippocampus and amygdala) for emotional arousal and memory, the insula for desire, and various PFC regions for inhibition. In reality, different types of cues have different meanings for addicts (as discussed in Section 3.1). Beyond visual processing regions, it remains unclear whether corresponding sensory processing regions are involved and interact with inhibition-related regions for cues in different sensory modalities (e.g., sound, odor). Most importantly, how these brain regions connect and interact is unknown. More research should consider different cue types and addiction categories to investigate the neural mechanisms of stimulus-driven and state-dependent effects at the network level.

Second, the role of substance use motivation or attitude in cue effects on response inhibition. Motivation or attitude toward substance use is key to continued use or maintained abstinence. For example, Luehring-Jones, Tahaney, and Palfai (2018) found in college students that self-control effects on daily drinking quantity and heavy drinking frequency were partially mediated by implicit approach-avoidance motivation toward alcohol (less approach motivation). That is, students with stronger self-control drank less frequently in part because they had less approach motivation toward alcohol. Brevers et al. (2018) found that although cannabis addicts seeking treatment due to abstinence motivation showed less effective proactive response inhibition, they showed better proactive response inhibition after cannabis-related cue priming, which the researchers suggested might reflect their abstinence motivation. However, Kreusch, Quertemont, Vilenne, and Hansenne (2014) found that drinkers with high alcohol avoidance attitudes showed more inhibition errors in a cue-related Go/NoGo task. At the EEG level, low alcohol avoidance individuals showed larger P3 amplitudes for cue-related NoGo versus Go stimuli, while high avoidance individuals showed no difference. The researchers suggested this indicates that high alcohol avoidance individuals have more difficulty inhibiting alcohol stimuli, possibly because their self-reported avoidance attitudes conceal true approach motivation toward alcohol. Currently, the role of substance use motivation or attitude in cue effects on response inhibition remains unclear.

Third, increasing real-world contextual research to improve ecological validity. Recently, ecological momentary assessment has been widely used in substance addiction research (Chen & Zhou, 2017). For example, one study used ecological momentary assessment to examine how fluctuations in response inhibition in real-world environments affect drinking behavior in heavy drinkers attempting restraint (Jones, Tiplady, Houben, Nederkoorn, & Field, 2018). Two weeks of testing revealed that daily planned drinking amount, craving, and the magnitude of response inhibition decline between two daily assessments significantly predicted later alcohol consumption that day, whereas average daily response inhibition did not. This indicates that transient reductions in response inhibition are a risk factor for drinking episodes. Therefore, ecological momentary assessment could be used to examine the effects of substance-related cue exposure on response inhibition and its relationship with substance use in real-world contexts.

Fourth, implications for reducing substance abuse interventions. The effects of substance-related cues on response inhibition occur because of their incentive salience features. Research shows that inhibitory training for approach bias toward positive-valence stimuli can reduce their value (Veling, Holland, & van Knippenberg, 2008). Some studies have found that response inhibition training using cue-related Go/NoGo tasks (Bowley et al., 2013; Houben, Havermans, Nederkoorn, & Jansen, 2012; Houben, Nederkoorn, Wiers, & Jansen, 2011) and cue-related Stop-signal tasks (Bartsch, Kothe, Allom, Mullan, & Houben, 2016; Jones & Field, 2013) can reduce alcohol intake in immediate taste tests (Bowley et al., 2013; Jones & Field, 2013), weekly alcohol consumption, and positive attitudes toward alcohol (Houben et al., 2011, 2012). In contrast, general response inhibition training without alcohol cues did not improve cognitive function or weekly alcohol use (Bartsch et al., 2016). However, these intervention studies focused on light alcohol users, and their effects on heavy alcohol addicts or other substance addicts remain unclear. Moreover, these studies only assessed training effects at three time points (pre-training, post-training, and one week later), so long-term effects are unknown. Based on our proposed distinction between stimulus-driven and state-dependent effects, these intervention approaches need reconsideration. Future research should develop more effective training tasks, increase training sessions, explore mechanisms of action, track long-term effects, and clarify the role of response inhibition training for substance-related cues in reducing substance abuse, extending its clinical application to different substance-addicted populations.

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Effects of substance-related cues on response inhibition in addicts

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Abstract: Loss of control in substance seeking and use of addicts is closely related to response inhibition. Many studies have explored this relationship in context of substance-related cues. Substance cues can be automatically captured by attention and also induce non-automatic approach-motivated state. As a consequence, these cues may consume limited cognitive resources through a stimulus-driven and a state-dependent manner in order to influence addicts' response inhibition. And these effects also play important roles in the development and maintenance of addictive behaviors. Further research should be carried out to reveal the neural mechanisms of both manners, clarify how motivations and attitudes towards substance use modulate these effects, conduct research in real situations, and discover more effective interventions.

Keywords: substance addiction; substance-related cues; response inhibition; stimulus-driven effects; state-dependent effects

Note: Figure translations are in progress. See original paper for figures.