Magnetic resonance imaging for smoking abstinence: symptoms, mechanisms, and interventions

Yanzhi Bi\(^1,2\) (✉), Li Hu\(^1,2\)

1 CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
2 Department of Psychology, University of Chinese Academy of Sciences, Beijing 100101, China

**ARTICLE INFO**

**Received:** 27 April, 2021  
**Revised:** 21 June, 2021  
**Accepted:** 23 June, 2021

© The authors 2021. This article is published with open access at journals.sagepub.com/home/BSA

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

**KEYWORDS**  
smoking abstinence, magnetic resonance imaging, relapse, psychophysiological intervention

**ABSTRACT**

Tobacco smoking is the leading preventable cause of morbidity and mortality worldwide. Although a number of smokers are aware of the adverse outcomes of smoking and express a strong desire to stop smoking, most smoking quit attempts end in relapse within the first few days of abstinence, primarily resulting from the aversive aspects of the nicotine withdrawal syndrome. Therefore, studying the neural mechanisms of smoking abstinence, identifying smokers with heightened relapse vulnerability prior to quit attempts, and developing effective smoking cessation treatments appear to be promising strategies for improving the success of quit attempts. In recent years, with the development of magnetic resonance imaging, the neural substrates of smoking abstinence have become extensively studied. In this review, we first introduce the psychophysiological changes induced by smoking abstinence, including affective, cognitive, and somatic signs. We then provide an overview of the magnetic resonance imaging-based evidence regarding abstinence-related functional changes accompanied by these psychophysiological changes. We conclude with a discussion of the neural markers that could predict relapse during quit attempts and a summary of the psychophysiological interventions that are currently often used to help with smoking cessation. This review extends our understanding of the role of the central nervous system in smoking abstinence.

1 Introduction

As the world’s largest tobacco manufacturing and consuming country, both the prevalence of tobacco use and the associated burden of morbidity and mortality are extremely high in China [1]. Cigarette smoking is linked to many negative health consequences, such as cancer, cardiovascular disease, and pulmonary disease [2]. Although a number of smokers are aware of the adverse outcomes of smoking and express a strong desire to stop smoking, most smoking quit attempts end in relapse within the first few days of abstinence, primarily resulting from the aversive aspects of the nicotine withdrawal syndrome, which remains poorly understood.
Smoking withdrawal can lead to many psychophysiological changes, making it difficult for people to quit. Studies have demonstrated that smoking withdrawal-induced psychophysiological changes are key predictors of relapse to smoking [3–5]. As such, understanding the neurobiological mechanisms underlying nicotine withdrawal in the nicotine deprivation state is crucial to the development of effective smoking cessation treatment interventions that aim to improve smoking cessation rates.

Nicotine addiction is a brain disorder. The emergence of neuroimaging techniques, including magnetic resonance imaging (MRI), positron emission tomography, electroencephalography, and magnetoencephalography, has enabled researchers to noninvasively investigate the role of the central nervous system in smoking abstinence [6–9]. Of all these neuroimaging techniques, functional neuroimaging techniques, especially functional MRI (fMRI) based on the contrast of blood oxygen level-dependent (BOLD) signals, allow for the objective examination of brain mechanisms associated with smoking abstinence [10–17]. Moreover, studies that aimed to develop relapse predictors or smoking cessation treatment interventions have also applied neuroimaging techniques to associate brain responses with the changes in smoking withdrawal symptoms [18–21], thus providing a deeper understanding of the mechanisms of relapse and treatment effectiveness.

In this review, we first introduce smoking-abstinence-induced psychophysiological changes, including affective, cognitive, and somatic signs. We then provide an overview of the MRI-based evidence regarding abstinence-related functional changes accompanied by these psychophysiological changes. Finally, we summarize the possible neural markers that could predict relapse as well as the neural substrates of psychophysiological interventions that are often used to help facilitate smoking cessation (Fig. 1).

## 2 Tobacco abstinence symptoms

Abstinence from chronic tobacco use produces a series of withdrawal symptoms, including affective, cognitive, and physical or somatic components [22]. Affective symptoms include craving and a depressed mood (e.g., depression, anxiety, irritability, restlessness, stress, and difficulty in concentrating). Cognitive components include decreased cognitive performance (e.g., inhibitory control and working memory). Somatic components include increased appetite or weight gain, sleep disturbance, and increased pain sensitivity. According to the duration of nicotine withdrawal, the symptoms of nicotine withdrawal can be divided into acute (7–10 episodes

![Fig. 1 Schematic diagram of the framework of this review. MRI, magnetic resonance imaging.](https://mc03.manuscriptcentral.com/brainsa)
of withdrawal) and chronic (7–10 days after withdrawal) withdrawal symptoms. In general, nicotine withdrawal symptoms begin to appear as early as 4 hours after the last cigarette, peak in ~3 days to 1 week, and last for 2 to 4 weeks [22]. Some withdrawal symptoms, such as craving for cigarettes, are still measurable 1 month after the cessation of tobacco use [23]. Although abstinence-induced somatic signs are unpleasant for smokers, studies have demonstrated that of all withdrawal symptoms, affective and cognitive components play critical roles in the maintenance of nicotine dependence [24, 25].

3 Potential neural mechanisms of withdrawal symptoms

Nicotine, the main addictive substance in cigarettes, can produce profound physiological modulations by binding to nicotinic acetylcholine receptors (nAChRs) [26]. Chronic exposure to nicotine results in the desensitization and upregulation of nAChRs and neuroadaptations throughout the brain [27]. Research has shown that the desensitization and upregulation of nAChRs following chronic nicotine exposure are influential in producing withdrawal symptoms upon cessation of smoking [28–30]. In addition to evaluating the contribution of nAChRs in producing withdrawal symptoms, assessing brain changes may yield a better understanding of the neural substrates of smoking abstinence.

3.1 Craving

Craving is a prominent feature of nicotine dependence and is an important factor that can precipitate relapse during smoking quit attempts [3, 31]. After smoking cessation, craving develops rapidly, which is known as abstinence-induced craving. Abstinence-induced craving is sensitive to the effects of nicotine delivery. In addition to this unprovoked craving, smoking cue-induced craving, which is thought to arise from a behavioral conditioning process, in which stimuli associated with smoking trigger drug-seeking behavior, develops. Numerous studies have examined the neural substrates of cravings elicited by smoking abstinence [17, 32–35] and smoking-related cues during the abstinence state [14, 36–39] (Table 1).

3.1.1 Abstinence-induced craving

Abstinence-induced cigarette craving can promote relapse in abstinent smokers, and smoking a cigarette can rapidly reverse the symptoms that develop. The neural substrates of abstinence-induced craving have been extensively investigated using fMRI techniques [11, 13, 17, 33, 35, 67] [Fig. 2(a)]. The within-subject experimental design has been commonly used to measure abstinence-induced brain functional changes in smokers. During the experiments, smokers were scanned at resting state on two occasions, in a counterbalanced order: (1) smoking satiety, and (2) smoking abstinence (after several hours of smoking deprivation).

Resting-state brain functional changes induced by smoking abstinence have been usually examined by measuring spontaneous brain activity, circuitry connectivity, and network connectivity using resting-state fMRI. Zhao et al. [11] used the functional connectivity density mapping method and found that 12-hour abstinence (vs. satiety) induces higher local functional connectivity density and global functional connectivity density in regions commonly implicated in nicotine addiction, which include the striatal subregions (i.e., bilateral caudate and putamen), frontal regions [i.e., anterior cingulate cortex (ACC) and orbital frontal cortex (OFC)], insula, and thalamus. A lesion study demonstrated that damage to the insula disrupts smoking behavior in stroke patients [40], as characterized by their ability to quit smoking easily, immediately, without
| Author group (year) | Modality/task | Study population and smoking behavior(s) | Abstinence manipulation | Analysis | Abstinence behavior(s) | Region(s) |
|---------------------|---------------|------------------------------------------|------------------------|----------|-----------------------|-----------|
| Naqvi et al. (2007) [40] | Brain damage | 19 smokers: • > 5 cigarettes/d for > 2 y | Brain damage | – | Craving | Insula |
| Ding et al. (2013) [41] | Resting-state | 21 smokers: • > 15 cigarettes/d for > 5 y | Two sessions: • abstinence for > 12 h; • smoking as usual | Independent component analysis; Granger causality analysis | – | SN, DMN, and ECN; Insula, parahippocampus, precuneus, ACC, SMA, and vmPFC/DLPFC |
| Lerman et al. (2014) [32] | Resting-state | 37 smokers: • at least 10 cigarettes/d for at least 6 mo • no history of smoking | Two sessions: • abstinence for > 24 h; • smoking as usual | Group independent component analysis; Resource allocation index | Abstinence-induced craving; Working memory | SN, DMN, and ECN |
| Wang et al. (2014) [42] | Resting-state | 22 smokers: • at least 8 cigarettes/d 20 nonsmokers: • no history of smoking | Two sessions: • abstinence for 12 h; • smoke 2 cigarettes before second session | Voxel-based morphometry; Global brain connectivity | – | Insula, SFG, and DMN |
| Bi et al. (2017) [35] | Resting-state | 33 smokers: • at least 10 cigarettes/d for at least the past 6 mo | Two sessions: • smoking as usual; • overnight abstinence for > 12 h | Resting-state functional connectivity | Abstinence-induced craving | Right AI, right medial OFC, vmPFC, and ACC |
| Li et al. (2017) [17] | Resting-state | 25 smokers: • at least 10 cigarettes/d for at least 1 y | Two sessions: • smoking as usual; • overnight abstinence for >12 h | Regional homogeneity | Abstinence-induced craving | Frontostriatal circuits, including bilateral caudate, ACC, and bilateral DLPFC; DMN, including PCC/precuneus and angular gyrus |
| Wang et al. (2018) [13] | Resting-state | 25 smokers: • at least 10 cigarettes/d for at least 1 y | Two sessions: • smoking as usual; • abstinence for >12 h | Resting-state functional connectivity | Abstinence-induced craving | Left thalamus, right DLPFC, and right ACC |
| Zhao et al. (2019) [11] | Resting-state | 31 smokers: • at least 10 cigarettes/d for at least 1 y | Two sessions: • smoking as usual; • overnight abstinence for > 12 h | Functional connectivity density mapping | Abstinence-induced craving | Striatal subregions (i.e., bilateral caudate and putamen), frontal regions (i.e., ACC and OFC), bilateral insula, and bilateral thalamus |
| Abulseoud et al. (2020) [43] | Resting-state | 30 healthy smokers: • 18 males and 12 females; • age range, 18-60 y | Two sessions after abstinence from smoking for 36 h: • nicotine or placebo patch after 12 h of abstinence; • second patch 1-2 h prior to the scan | Resting-state functional connectivity | Abstinence-induced craving and withdrawal symptoms | Dorsal ACC and several frontal cortical regions, including left SFG and right MFG |
| Author group (year) | Modality/task | Study population and smoking behavior(s) | Abstinence manipulation | Analysis | Abstinence behavior(s) | Region(s) |
|---------------------|---------------|------------------------------------------|------------------------|----------|-----------------------|-----------|
| McClernon et al. (2005) [39] | Cue exposure task: • smoking, control, and target cues | 13 smokers: • at least 15 cigarettes/d for at least 2 y; • CO of > 15 ppm | Two sessions: • smoking as usual; • overnight abstinence | Activation | Smoking cue reactivity; Abstinence-induced craving | Ventral ACC, SFG, left IFG, and bilateral middle frontal gyrus |
| McClernon et al. (2009) [37] | Cue exposure task: • smoking and control cues | 18 smokers: • at least 10 cigarettes/d for at least 2 y; • CO of > 10 ppm | Two sessions: • smoking as usual; • 24 h of abstinence | Activation | Smoking cue reactivity; Abstinence-induced craving | Parietal; frontal (right dmPFC, including SFG, ACC, and SMA); occipital; and central cortical regions as well as dorsal striatum (putamen) and thalamus |
| Engelmann et al. (2012) [38] | Cigarette cue reactivity: • smoking and neutral cues | – | – | Activation likelihood estimation meta-analysis | – | Extended visual system and dorsal prefrontal cortex |
| Sweitzer et al. (2014) [44] | Rewarded guessing task | 38 smokers: • ≥ 5 cigarettes/d during the past year; • CO of 8 ppm; • willingness to quit attempt | Two sessions: • smoking without restriction; • 24 h of abstinence | Activation | Abstinence-induced craving and withdrawal symptoms | Bilateral caudate and medial prefrontal cortex |
| Haemans et al. (2017) [45] | Cue exposure task: • pictures of cigarettes and pencils or chairs | 14 right-handed, current smokers: • a minimum of 10 cigarettes/d on average for at least 1 y | Two sessions: • 10 h of nicotine abstinence; • ad libitum smoking | Multivoxel pattern analysis | Smoking cue reactivity | Bilateral lateral occipital complex |

**Inhibitory control**

| Author group (year) | Modality/task | Study population and smoking behavior(s) | Abstinence manipulation | Analysis | Abstinence behavior(s) | Region(s) |
|---------------------|---------------|------------------------------------------|------------------------|----------|-----------------------|-----------|
| Kozlinski et al. (2010) [46] | X-Y go/no-go task | 18 smokers: • at least 10 cigarettes/d for at least 2 y; • CO of > 10 ppm | Two sessions: • smoking as usual; • 24 h of smoking abstinence | Activation | Inhibitory control | Right IFG |
| Azizan et al. (2010) [47] | Stroop color-word interference task | 20 smokers: • at least 15 cigarettes/d for 2 y; • CO of at least 10 ppm | Two sessions: • overnight abstinence for > 12 h; • smoke 2 cigarettes prior to the scan | Activation | Inhibitory control | Right ACC, right MFG, and DLPFC |
| Author group (year) | Modality/task | Study population and smoking behavior(s) | Abstinence manipulation | Analysis | Abstinence behavior(s) | Region(s) |
|---------------------|---------------|-----------------------------------------|------------------------|----------|------------------------|-----------|
| Zhao et al. (2020) [48] | Cue exposure task: • smoking and neutral pictures; Stop-signal task | 26 smokers: • at least 10 cigarettes/d for at least 2 y | Two sessions under 10–12 h of abstinence: • a neutral cue reactivity task; • a smoking cue reactivity task | Support vector regression analysis | Inhibitory control | Insula, amygdala, ACC, pre-SMA, and putamen |
| Xu et al. (2005) [49] | N-Back working memory task | 8 smokers: • 13–30 cigarettes/d for 2–42 y | Two sessions: • ad libitum smoking; • abstinence for 14–16 h | Activation | Working memory | Left DLPFC |
| Xu et al. (2006) [50] | N-Back working memory task | 6 smokers: • 13–20 cigarettes/d for 2–26 y | Two sessions: • overnight abstinence for >13 h; • ad libitum smoking | Activation | Working memory | Left DLPFC |
| Jacobsen et al. (2007) [51] | Auditory N-back task | 55 smokers and 38 non-smokers | Two sessions: • ad libitum smoking; • 24 h of abstinence | Activation | Working memory | Left VlPFC and left inferior parietal lobe |
| Loughead et al. (2010) [52] | Visual N-back working memory task | 22 smokers: • at least 10 cigarettes/d for at least 6 mo; • treatment seeking | Two sessions: • 3 days of abstinence while on varenicline; • 3 days of abstinence while on placebo | Activation | Working memory | Dorsal ACC/medial frontal cortex and DLPFC |
| Sweet et al. (2010) [53] | 2-Back working memory task | 12 smokers: • 13.42 ± 5.66 cigarettes/d | Two sessions after overnight abstinence: • a nicotine patch before one session; • a placebo patch prior to the other session | Activation | Working memory | Bilateral temporal poles and left medial frontal gyrus |
| Falzone et al. (2014) [54] | Visual N-back task | 63 smokers: • 10 cigarettes/d for 6 mo; • treatment seeking | Two sessions: • smoking as usual; • 24 h of abstinence | Activation | Working memory | Medial frontal/cingulate gyrus and bilateral DLPFC |
| Ashare et al. (2016) [55] | Montreal Imaging Stress Task | 39 smokers: • at least 10 cigarettes/d for at least 6 mo; • treatment seeking | Two conditions: • 24 h of abstinence; • smoking as usual | Activation | Stress | IFG, ACC, precuneus, and supramarginal gyrus |
| Author group (year) | Modality/task | Study population and smoking behavior(s) | Abstinence manipulation | Analysis | Abstinence behavior(s) | Region(s) |
|---------------------|---------------|------------------------------------------|------------------------|----------|-----------------------|-----------|
| Allenby et al. (2020) [56] | Montreal Imaging Stress Task | 75 smokers: • 5 cigarettes/d for 6 mo; • CO of at least 8 ppm; • treatment seeking | Two occasions: • smoking satiety; • 24 h of abstinence | Activation | Stress | Left IFG |
| Janes et al. (2009) [36] | Cue exposure task: • smoking, neutral, and target cues; • Emotional Stroop task: • smoking-related and neutral words | 13 smokers: • at least 10 cigarettes/d in the last 6 mo; • CO of > 10 ppm | Two sessions: • prior to a smoking cessation attempt; • during extended smoking abstinence aided by nicotine replacement therapy | Activation | Smoking cue reactivity | Caudate nucleus, prefrontal cortex, SI, temporal cortex, parietal cortex, ACC, and PCC |
| Janes et al. (2010) [57] | Cue exposure task: • smoking, neutral, and target cues; • Emotional Stroop task: • smoking-related and neutral words | 21 smokers: • 10 cigarettes/d in the last 6 mo; • CO of > 10 ppm | • pre-quit imaging; • quit smoking during the 8-wk smoking cessation treatment aided by nicotine replacement therapy | Activation | Attentional bias | Insula, dorsal ACC, and DLPFC |
| Sweitzer et al. (2016) [34] | Resting-state | 37 smokers: • at least 5 cigarettes/d during the past year; • CO of at least 8 ppm; • willing to quit attempt | Two sessions: • ad libitum smoking; • 24 h of abstinence | Resting-state functional connectivity | Ventral striatum, insula, superior temporal gyrus, ACC/MCC, mPFC, PCC, hippocampus, and SMA |
| Sweitzer et al. (2016) [58] | Rewarded guessing task | 36 smokers: • at least 5 cigarettes/d during the past year; • CO of 8 ppm; • willingness to quit attempt | Two sessions: • ad libitum smoking; • 24 h of abstinence | Activation | Smoking cue reactivity | Striatum |
| Froeliger et al. (2017) [59] | Inhibitory control task Smoking relapse analog task | All smokers: • ≥ 10 cigarettes/d; • CO of at least 10 ppm; • 81 interested in quitting smoking in study 1; • 26 not interested in quitting smoking in study 2 | Study 1 • satiety state before a quit attempt; • followed up for 10 wk after their quit date Study 2 Two sessions: • smoking a cigarette • 24 h of abstinence | Voxel-based morphometry; Task-based functional connectivity | Inhibitory control | Right IFG, thalamus, and corticothalamic circuit |
| Author group (year) | Modality/task | Study population and smoking behavior(s) | Abstinence manipulation | Analysis | Abstinence behavior(s) | Region(s) |
|---------------------|---------------|------------------------------------------|-------------------------|----------|------------------------|-----------|
| Zelle et al. (2017) [16] | Cue exposure task | 38 smokers: • 15–40 cigarettes/d for the past year; • motivated to quit | Quit attempt 12 h before fMRI scan | Functional connectivity | – | Left AI and DLPFC |
| Gilman et al. (2018) [15] | Smoking-related go/no-go task: • smoking or neutral images | 22 smokers: • at least 5 cigarettes/d; • urine cotinine level of at least 30 ng/mL; 19 nonsmokers | 12-wk smoking cessation trial | Activation | Inhibitory control | AI |
| Owens et al. (2018) [14] | Cue exposure task: • smoking and neutral images | 32 smokers: • at least 10 cigarettes/d; • treatment seeking | • smoke prior to fMRI scan; • a 9-wk smoking cessation treatment with nicotine replacement therapy | Activation | Smoking cue reactivity | Right ventral striatum, left amygdala, and ACC |
| Yuan et al. (2018) [60] | Diffusion tensor imaging | 53 smokers: • CO of at least 10 ppm; 58 nonsmokers: • CO of at least 3 ppm | • smoke one cigarette; • not allowed to smoke between 10:00 PM and 10:00 AM | Seed-based probabilistic tractography | – | Striatum-medial OFC, striatum-vIPFC, striatum-lIFG, striatum-PCC, and left striatum-DLPFC circuit |
| Allenby et al. (2020) [10] | Cue exposure task: • smoking and neutral cues | 75 smokers: • 5 cigarettes/d for 6 mo; • CO of at least 8 ppm; • treatment seeking | Two sessions: • smoking satiety; • 24 h of abstinence A 7-day short-term quit attempt | Activation | Smoking cue reactivity | ACC |

**Psychophysiological intervention**

| Author group (year) | Modality/task | Study population and smoking behavior(s) | Abstinence manipulation | Analysis | Abstinence behavior(s) | Region(s) |
|---------------------|---------------|------------------------------------------|-------------------------|----------|------------------------|-----------|
| Wilson et al. (2005) [61] | Cue exposure task: • smoking and neutral cues | 22 smokers: • 20–40 cigarettes/d for at least 24 mo | Smoking expectancy: • deprived of nicotine for 8 h | Activation | Expectancy | ACC and prefrontal cortex (i.e., vmPFC, vIPFC, and DLPFC) |
| McBride et al. (2006) [62] | Cue exposure task: • smoking and neutral videotape | 20 smokers: • at least 15 cigarettes/d | Two sessions: • abstinence for 12 h; • smoke as usual | Activation | Expectancy | DLPFC and thalamocingulate connectivity |
| Janse Van Rensburg et al. (2009) [63] | Cue exposure task: • smoking and neutral images | 10 smokers: • at least 10 cigarettes/d for at least 2 y; • no attempt to quit | 15 h of abstinence; • exercise: 10 min of moderate-intensity stationary cycling; • control session: passive sitting | Activation | Exercise | Caudate nucleus, OFC, parietal lobe, parahippocampus, and fusiform gyrus |
| Author group (year) | Modality/task | Study population and smoking behavior(s) | Abstinence manipulation | Analysis | Abstinence behavior(s) | Region(s) |
|---------------------|---------------|------------------------------------------|-------------------------|----------|-----------------------|-----------|
| Janse Van Rensburg et al. (2012) [64] | Cue exposure task: • smoking and neutral images | 20 smokers: • at least 10 cigarettes/d for at least 2 y; • no attempt to quit | 15 h of abstinence: • exercise: 10 min of moderate-intensity stationary cycling; • control session: passive sitting | Activation | Exercise | Cuneus as well as middle and inferior occipital lobes |
| Xu et al. (2012) [65] | Cue exposure task: • partner vs. acquaintance image • cigarette cue vs. pen image | 18 smokers: • at least 8 cigarettes/d for at least 6 mo | 8 h of abstinence | Activation; A model of self-expansion in the context of romantic love | Self-expansion activity | Cuneus and PCC |
| Xu et al. (2014) [66] | Two-player cooperative game: • self-expanding vs. not; • cigarette cue present vs. absent | 20 smokers: • at least 8 cigarettes/d; • no attempt to quit | 8 h of abstinence | Activation | Self-expansion activity | Caudate and TPJ |
| Westbrook et al. (2013) [18] | Cue exposure task: • smoking, neutral, and aversive images | 47 smokers: • at least 10 cigarettes/d; • treatment seeking | 12 h of abstinence | Psychophysiological interaction analysis | Mindful attention | Subgenual ACC |

SN, salience network; DMN, default mode network; ECN, executive control network; ACC, anterior cingulate cortex; SMA, supplementary motor area; vmPFC, ventromedial prefrontal cortex; DLPPC, dorsolateral prefrontal cortex; SFG, superior frontal gyrus; AI, anterior insula; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; CO, carbon monoxide; dmPFC, dorsomedial prefrontal cortex; SMA, supplementary motor area; vPFC, ventrolateral prefrontal cortex; S1, primary somatosensory cortex; MCC, middle cingulate cortex; mPFC, medial prefrontal cortex; fMRI, functional magnetic resonance imaging; TPJ, temporoparietal junction; min, minute; h, hour; d, day; wk, week; mo, month; y, year.
relapse, and without the persistence of the urge to smoke. This observation emphasizes the critical role of the insula in the maintenance of smoking addiction. Increased circuit connectivity of the insula with the parahippocampus, precuneus, ACC, supplementary motor area, and ventromedial prefrontal cortex (PFC)/dorsolateral PFC (DLPFC) was also detected in the abstinence state relative to the satiety state using seed-based resting-state functional connectivity analysis [35, 41]. In particular, the abstinence-induced resting-state functional connectivity changes between the right anterior insula and right lateral OFC were found to be significantly correlated with craving changes [35], which contributes new insights into the functional role of the insula in abstinence-induced craving.

Cigarette smoking exerts its initial reinforcing effects by activating reward circuits and releasing dopamine in the striatum [68, 69]. Long-term cigarette smoking triggers dopamine system dysfunctions and the neuroplasticity of the frontostriatal circuits associated with craving and cognitive control [17, 60, 70–72]. Converging lines of evidence demonstrated the functional changes in these circuits during withdrawal as well as their relationship with abstinence-induced craving [17, 34, 43]. For example, higher regional homogeneity in the frontostriatal circuits, including the bilateral caudate, ACC, and bilateral DLPFC,
was detected in the abstinence state (> 12 hours) relative to the satiety state. Moreover, the regional homogeneity changes in the ACC and bilateral caudate were found to be positively correlated with abstinence-induced craving changes in young adult smokers [17]. In addition, with the dorsal ACC (dACC) regarded as the seed, Abulseoud et al. [43] found an increase in resting-state functional connectivity between the dACC and several frontal cortical regions, including the left superior frontal gyrus and right middle frontal gyrus, after 36 hours of nicotine abstinence. Moreover, the change in circuit strength between the dACC and left superior frontal gyrus was found to be negatively correlated with the changes in withdrawal symptoms, including craving. The ventral and dorsal striatum are key neural substrates of reward processing and motivation, and they have been repeatedly linked to nicotine dependence [60, 71–73]. Researchers have examined the effects of abstinence on brain connectivity with ventral and dorsal striatum seed regions and observed robust abstinence-induced changes (24 hours of abstinence) in the connectivity of both ventral and dorsal striatum with a network of regions implicated in addictive disorders. These findings suggest the critical role of the frontostriatal circuits in abstinence-induced craving [34].

The human brain is a complex patchwork of interconnected regions. Recent literature has indicated that not only the activity within each functional network but also, and especially, the interaction between these networks is critical for elucidating abstinence-induced craving and cognitive impairments [74]. Three networks have received the most attention in smoking addiction, namely, an executive control network (ECN) implicated in attention to and processing of exogenous stimuli, a default mode network (DMN) involved in stimulus-independent thought processes (e.g., self-referential thinking), as well as a salience network (SN) facilitating orientation to external (ECN) and internal (DMN) information processing and allocating attention. Sutherland et al. [74] proposed that, in the nicotine-deprived state, the SN allocates enhanced attentional resources toward internal symptoms of withdrawal, thereby biasing activity toward the DMN and away from the ECN. In line with this hypothesis, researchers have observed higher brain activity/connectivity within the DMN [17, 42], weaker inhibition between the DMN and SN, as well as lower connectivity between the ECN and SN [41] in the abstinence state (> 12 hours of abstinence) relative to the satiety state. Furthermore, the weaker internetwork connectivity between the DMN and SN could predict abstinence-induced cravings to smoke and less suppression of DMN activity during the performance of a subsequent working memory task [32]. Therefore, alterations in the coupling of the SN and DMN as well as the inability to disengage from the DMN may be critical in cognitive/affective alterations that underlie nicotine dependence.

Using arterial spin labeled perfusion MRI technique, mixed results were reported across studies, possibly due to differences in their sample size, duration of smoking deprivation, methodologies, and individual differences, such as variants in the dopamine D2 receptor [75]. For example, Wang et al. [33] detected increased cerebral blood flow (CBF) in the ACC/medial OFC and left OFC in the abstinence state relative to the satiety state after 12 hours of smoking deprivation. Abstinence-induced cravings were predicted by CBF increases (abstinence minus satiety) in regions commonly implicated in visuospatial and reward processing, such as the right OFC, right DLPFC, occipital cortex, ACC, ventral striatum/nucleus accumbens, thalamus, amygdala, bilateral hippocampus, left caudate, and right insula. On the other hand, another study
using a shorter period of abstinence manipulation (after 4 hours of nicotine deprivation) found significantly reduced regional CBF in the hippocampus and ventral striatum. Similar to prior research, the abstinence-induced regional CBF changes in the medial and lateral OFC and anterior ventral insula were also found to be correlated with the magnitude of the change in craving [76], confirming the role of the OFC and insula in abstinence-induced craving. Furthermore, given the role of the ventral striatum, thalamus, and medial frontal cortex in nicotine addiction, a study that focused on regions of interest in these three regions did not find significant CBF changes after smoking abstinence. Despite this negative result, nicotine replacement could significantly increase CBF in the ventral striatum, and a significant correlation between the increase in withdrawal symptoms and a reduction in thalamic CBF was detected [67].

3.1.2 Smoking cue-induced craving

Frequent pairings of the visual, tactile, and olfactory sensations of smoking with the rewarding effects of nicotine result in a classical conditioning effect, such that exposure to smoking cues (e.g., the sight and smell of a burning cigarette, cigarette packs, and lighters and smoking-related pictures and videos) even for several seconds or minutes can elicit a strong urge to smoke and promote tobacco use in addictive smokers, especially when they are abstinence from smoking. Indeed, abstinent smokers experience greater difficulty in suppressing their desire to consume cigarettes when they are exposed to these salient smoking cues [38]. Smoking-related cues may be an important factor that promotes relapse among smokers who are trying to quit.

In typical cue reactivity paradigms, brain responses between conditions using smoking-related and neutral cues are compared. Studies using fMRI have indicated that smoking cues reliably evoke larger brain responses in the extended visual system, precuneus, posterior cingulate gyrus, anterior cingulate gyrus, dmPFC, insula, and dorsal striatum than neutral cues in smokers [38]. Under nicotine deprivation, smoking abstinence significantly potentiates neural responses to smoking-related cues versus neutral cues in brain regions subserving reward processing, visual sensory processing, attention, and action planning [36, 48], including the striatum, occipital cortex [45], insula, amygdala, ACC, and putamen [48] [Fig. 2(a)]. In detail, drug use, including smoking, is associated with dysregulated reward processing, attentional bias to smoking-related cues, as well as dysfunctional inhibitory control and action planning [37, 44, 45, 58, 77]. This dysregulated processing is further exacerbated during deprivation from smoking. For example, an increased BOLD response (e.g., striatum) in anticipation of smoking reward, decreased BOLD activation in anticipation of monetary reward [44, 58], and elevated lateral occipital complex activation in response to smoking-related cues [45] were detected after a period of nicotine deprivation. Furthermore, attenuation of monetary reward-related activation and increased smoking cue activation in the dmPFC, which is involved in action planning and decision making [37], during abstinence were found to be significantly correlated with abstinence-induced increases in craving and withdrawal [37, 44] and to potentially predict smoking lapse during a quit attempt [58]. These findings suggest that smoking abstinence can evoke hyperactive brain reactivity to smoking-related cues and that this heightened brain reactivity is a precipitating factor in smoking relapse. Thus, reducing reactivity to smoking cues appears to be a promising strategy for improving the success of quit attempts.
3.2 Cognitive impairments

Acute nicotine use can produce short-term cognitive enhancement [78, 79]. However, long-term cigarette smoking would induce cognitive impairment and cognitive decline, especially during nicotine withdrawal [80, 81]. Cognitive impairments, including inhibitory control and working memory impairments, are commonly reported in abstinent smokers [49, 50, 52, 53, 82] and contribute to greater relapse vulnerability [5]. Understanding the neurobiology of abstinence-induced cognitive impairments using fMRI paradigms is of great interest to improve tobacco dependence treatment outcomes [Fig. 2(b) and Table 1].

3.2.1 Inhibitory control

Long-term cigarette smoking was found to be associated with decrements in inhibitory control, especially during withdrawal [46]. The attenuated inhibitory control of smokers is a stumbling block for treating nicotine dependence. Response inhibition, an important form of behavioral impulse control, is the ability to inhibit behavioral responses to salient approach cues. The go/no-go task, Stroop color-word task, and stop-signal task are common measures of response inhibition and have highlighted inhibitory control deficits in smokers [46–48, 83]. Using a go/no-go task, Kozink et al. [46] examined neural correlates of response inhibition and error monitoring in abstinent smokers and found that smoking abstinence (after 24 hours of abstinence) robustly increased errors of commission in stop trials and event-related BOLD signals in the right inferior frontal gyrus. Previous fMRI research using a Stroop color-word paradigm has also demonstrated that smokers had significantly higher task-related activity in the right ACC after overnight abstinence from smoking (> 12 hours of abstinence) compared with the satiety state [47].

Two other studies using a stop-signal task detected similar greater neural activation in the inferior frontal gyrus during successful response inhibition in abstinent smokers [83] and a hyperactive right pre-supplementary motor area during reactive inhibition in smoking cue versus neutral cue conditions [48]. All these findings suggest that successful inhibitory control during withdrawal is associated with increased cognitive processing demands on a cortical center associated with attention to inhibitory signals [46].

3.2.2 Working memory

When smokers abstain from smoking, specific deficits in working memory emerge [50, 54, 80] and promote smoking relapse [84]. For example, abstinence (versus smoking) was associated with longer response latencies and reduced accuracy of working memory performance [50, 54]; these performance decrements were more severe with earlier age of onset of smoking and in male smokers than in female smokers [80]. Many investigators have employed fMRI paradigms, such as the visual N-back working memory task, to examine brain functions associated with working memory deficits during the abstinence state. Researchers have observed that these deficits are accompanied by reduced activation in executive control regions (e.g., DLPFC) [54] and less suppression of activation in task-independent regions (e.g., posterior cingulate cortex) [5, 32, 53]. Furthermore, these working memory-related brain activities could predict subsequent smoking relapse [5]. Inconsistent results on whether overnight abstinence (> 14 hours of abstinence) was associated with higher task-related neural activity in the left DLPFC at the 1-back level following abstinence as compared with smoking, which indicates that neural processing related to working memory in the left DLPFC is less efficient during acute abstinence than in the satiety state, have also been reported [49]. In one study,
a task with a high working memory load in the context of smoking abstinence required more cognitive processing demands, as reflected by greater activation of the working memory neurocircuit during the task [51]. nAChRs play a key role in cognition. Evidence has shown that cognitive deficits could be reversed by treatment with the α4β2 nicotinic receptor partial agonist varenicline by increasing working memory-related brain activity in the dACC/medial frontal cortex and bilateral DLPFC [52]. This observation provides a method to improve tobacco dependence treatment outcomes.

### 3.3 Affective symptoms

#### 3.3.1 Stress

Subjective stress is considered to be a well-documented predictor of early smoking relapse. Thus, understanding the neural correlates of stress during acute nicotine withdrawal is important to intervene in stress-induced relapse. The Montreal Imaging Stress Task is a psychosocial stress task that requires solving difficult mental arithmetic problems while receiving negative performance feedback. Researchers have found that taking the Montreal Imaging Stress Task while undergoing fMRI not only increased subjective measures of stress [55] but also induced significantly greater activation in the inferior frontal gyrus, ACC, precuneus, and supramarginal gyrus in deprived smokers (24 hours of abstinence compared with the satiety state) [56] and non-deprived smokers [55] (Table 1). Further correlation results revealed that an abstinence-induced change in the brain response to stress is positively associated with a change in self-reported stress [56]. Therefore, investigating stress-related activation during nicotine withdrawal may identify those who are most vulnerable to relapse and represent a target for novel pharmacological intervention.

#### 3.4 Somatic signs

##### 3.4.1 Increased pain sensitivity

Cigarette smoking serves as a nicotine delivery vehicle in humans. Experimental studies have suggested that nicotine has analgesic properties [85]. Acute nicotine intake can suppress pain among animals and humans [85]. However, chronic nicotine exposure may alter pain processing and contribute to the development of chronic pain [86]. The pain processing alterations are pronounced especially when individuals quit smoking or are abstinent from smoking. Both clinical and experimental studies have consistently found enhanced pain perception in chronic smokers when deprived of smoking [87, 88]. Furthermore, clinical evidence has shown that, in addition to and in line with their increased pain sensitivity, patients deprived of cigarettes require a higher quantity of postoperative analgesics compared with nonsmoking patients [87]. Therefore, revealing the mechanisms underlying the effect of nicotine withdrawal on pain perception not only is of scientific interest but also has clinical relevance in the practice of anesthesiology and pain medicine. Currently, the underlying psychophysiological bases of this hypersensitivity are not completely understood. Future research using fMRI to explore the neural pathways responsible for these effects is needed.

##### 3.4.2 Sleep disturbance

Subjective quality of sleep, which includes less total sleep time, longer sleep onset latency, increased difficulty in falling asleep as well as maintaining sleep, and waking up earlier than desired, is impaired in smokers compared with nonsmokers [89]. Several lines of evidence suggest that smoking abstinence during nicotine withdrawal not only can induce craving, negative affect, cognitive impairments, and increased pain sensitivity but also often worsens sleep [22].
Sleep disturbance may contribute to the risk for depressed mood and decreased smoking cessation outcomes [90]. However, the neural mechanism of abstinence-induced sleep disturbance remains poorly understood. Further research should focus on the neurobiological basis and consequences of sleep disturbance during tobacco cessation.

4 Prediction of relapse

Relapse to smoking after an initial abstinence period is a major challenge during smoking cessation. Identifying smokers with heightened relapse vulnerability during quit attempts could enable treatment personalization and improve smoking cessation treatment outcomes. Relapse-vulnerable smokers can be identified prior to a quit attempt. By measuring pre-quit behavior, brain activity, and connectivity, researchers have found that smokers who relapse have both greater smoking cue reactivity and lower inhibitory control compared with those who remain abstinent [15] [Fig. 2(c) and Table 1].

4.1 Smoking cue reactivity

A 9-week smoking cessation treatment study revealed that the neural response to smoking cues was greater in the insula, DLPFC, posterior cingulate, parahippocampus, putamen, thalamus, and cerebellum in participants who lapsed at any point during the subsequent smoking cessation treatment [57]. Another research compared smoking cue reactivity during acute abstinence with that in the satiety state and found that participants who showed greater smoking cue reactivity in the ACC during acute abstinence were more likely to relapse [10]. Greater abstinence-induced change in ACC activation also predicted fewer days of abstinence. These results suggest that lower smoking cue reactivity prior to smoking cessation or during acute abstinence may be associated with successfully maintaining abstinence during treatment.

4.2 Inhibitory control impairments

Several studies have highlighted the role of impaired inhibitory control in promoting relapse during smoking cessation. Gilman et al. [15] designed a go/no-go inhibitory control task in the presence of smoking-related cues and found that smokers who remained abstinent at the end of a 12-week smoking cessation program had greater neural activation in the anterior insula during no-go trials with smoking-related cues compared with those who relapsed. These findings indicate that decreased inhibitory control activation during exposure to smoking cues may be a marker of difficulty in quitting and relapse vulnerability in cigarette smokers [15]. Two other reports supported this result and observed that smokers who slipped had decreased functional connectivity between the insula and brain regions involved in cognitive control, including the dACC and DLPFC, possibly reflecting reduced top-down control of smoking-related cue-induced emotions [16, 57]. Moreover, an investigation in two cohorts of smokers found that greater activation in the inhibitory control circuitry (e.g., right inferior frontal gyrus) was associated with quicker relapse to smoking [59], indicating that the neural response to inhibition may be a potential marker that determines whether a patient is likely to attain long-term abstinence.

4.3 Other predictors

With the striatal circuits being critical substrates of reward processing and motivation in nicotine dependence, their dysfunction has been implicated in smoking behaviors and lapses during quit attempts [17, 60, 70–72]. Yuan et al. [60] observed that abstinence-induced increases in craving were associated with the tract strength of the left striatum-medial OFC and striatum-ventrolateral PFC in abstinent smokers. Notably, the tract
strength of the left striatum-DLPFC predicted lapse in smokers with an accuracy of 68.3% [60]. In addition, a functional study revealed that 24-hour abstinence induced decreased functional connectivity between the ventral striatum and a network of regions implicated in addictive disorders, including the insula, superior temporal gyrus, and anterior/mid-cingulate cortex, among smokers who later lapsed, whereas the opposite pattern was observed among non-lapsers. These findings suggest that modulation of striatal connectivity with the cingulo-insular network during early withdrawal may be associated with smoking cessation outcomes [34].

5 Psychophysiologcal interventions

Considering the high relapse rate among smokers who attempt quitting without assistance, identifying ways to reduce the adverse effects of smoking abstinence may be important in increasing the success of quit attempts. Currently, numerous therapies have been extensively applied to increase the smoking cessation rate, including pharmacotherapy (i.e., nicotine replacement therapy, bupropion therapy, and varenicline therapy) [9, 20, 21, 91]; neuromodulation (i.e., transcranial magnetic stimulation and transcranial direct current stimulation) [19, 92–94]; and psychophysiologcal interventions (i.e., expectancy, exercise, self-expanding activity, mindful attention, and emotion regulation strategy) [18, 61–64, 95]. Among these intervention therapies, psychophysiological interventions for reducing smoking cue reactivity and cravings play an important role in potentially disrupting the maintenance of cigarette smoking owing to their convenience, low cost, and ease of implementation. The neural substrates underlying these psychophysiological interventions have been examined using fMRI [18, 61–64, 95] [Fig. 2(d) and Table 1].

5.1 Expectancy

Cues associated with cigarette smoking can trigger craving, tobacco seeking, and relapse in deprived smokers. Behavioral studies have suggested that expectations regarding the opportunity to smoke a cigarette influence the pattern of neural responses to smoking cues, which ultimately modulates the level of craving to smoke [61, 62]. In people expecting to smoke immediately after an MRI scan, smoking cues activated brain areas implicated in arousal, attention, and cognitive control. However, when subjects knew that they would not be allowed to smoke for 4 hours, almost no brain activation in response to smoking cues was detected, despite equivalent reported levels of craving. In particular, subregions of the PFC (i.e., ventromedial, ventrolateral, and dorsolateral) were found to exhibit cue-elicited activation that was modulated by smoking expectancy [62]. Therefore, smoking expectancy could regulate craving to smoke by modulating smoking cue reactivity. For individuals seeking treatment to quit smoking, decreasing their expectation of an opportunity to smoke a cigarette might be an optional strategy to help them quit smoking.

5.2 Exercise

Exercise has been found to be an effective non-pharmacological method of reducing cigarette cravings and withdrawal symptoms among smokers attempting to quit smoking and among temporarily abstinent smokers [63, 64]. Evidence has demonstrated that the cravings, withdrawal symptoms, and adverse effects in abstinent smokers were significantly reduced during and following exercise [96]. Further post-exercise (i.e., using the Monark cycle ergometer) scanning showed hypoactivation in areas related to reward (caudate nucleus), motivation (OFC), and
visuospatial attention (parietal lobe, parahippo-campus, and fusiform gyrus) with a concomitant shift of activation toward areas identified in the default mode network during smoking cue exposure [63]. Rensburg et al. [63] suggested that brief bouts of moderately intense physical activity have the potential to downregulate smoking cue reactivity and thereby possibly reduce cue-elicited cravings.

5.3 Self-expanding activity

With regard to dysfunctional reward processing during abstinence, researchers have found that engaging in novel/exciting (“self-expanding”) activities (e.g., learning a new skill, taking an exciting course, and engaging in romantic love) can potentially substitute for the reward from nicotine by activating the mesolimbic dopamine pathway [65, 66]. This self-regulation strategy effectively attenuates cigarette cue reactivity among nicotine-deprived smokers and appears to be beneficial as an aid in smoking abstinence and cessation [66]. Using a model of self-expansion in the context of romantic love, Xu et al. [65] observed that among nicotine-deprived smokers who were experiencing moderate levels of craving, cigarette cue reactivity regions (e.g., cuneus and posterior cingulate cortex) showed significantly less activation during self-expansion conditions compared with control conditions. These results provide evidence that rewards from self-expansion can act as a substitute for the reward from nicotine to attenuate cigarette cue reactivity. Future research could focus on the parameters of self-expanding activities that produce this effect and test the utility of self-expansion in clinical interventions for smoking cessation.

5.4 Mindful attention

Mindfulness is often defined as attention to a moment-to-moment experience coupled with a nonjudgmental, accepting attitude toward that experience. An emerging body of research suggests that mindfulness-based treatment is beneficial for smoking cessation, possibly by alleviating emotional states, such as distress, and therefore reducing cue-induced cravings [18]. Westbrook et al. [18] confirmed this hypothesis in treatment-seeking smokers (12 hours of abstinence). They found that mindful attention could significantly reduce smokers’ cue-induced cravings as well as neural activation in a craving-related region of the subgenual ACC and its connectivity to other craving-related regions compared with nontreatment conditions, suggesting that mindfulness may decouple the craving neurocircuitry in smokers when viewing cues [18].

6 Prospects and conclusion

Although the smoking relapse biomarkers and strategies of psychophysiological interventions to help smoking cessation reported to date are promising, some issues remain to be determined. First, neuroimaging-based biomarkers for smokers with heightened relapse vulnerability prior to quit attempts have been developed, but their clinical applications have yet to be fully explored. Translating laboratory findings to the clinical setting should be carefully carved in the future. Second, regarding the convenience, low cost, and ease of implementation of psychophysiological interventions, combining these intervention strategies with traditional pharmacotherapy or neuromodulation therapies might improve smoking cessation outcomes. However, psychophysiological intervention-related studies are limited, and several intervention details or parameters should be investigated in future studies. For example, the extent to which the observed intervention effects may change or evolve over time is unclear. Whether exercise
treatments with varying intensity, time, and frequency differentially affect smoking quit attempts remains unknown. Whether less intense but widely experienced self-expansion activities (e.g., interactions with friends and family members) as well as self-expansion at the individual level (e.g., engaging in a new sport or hobby or in spiritual experiences) would be useful to help smokers quit remains to be discovered. Therefore, further research that systematically and conclusively evaluates these questions should be performed to help improve smoking cessation outcomes.

In summary, the rapid development of neuroimaging techniques has significantly extended our understanding of the role of the central nervous system in smoking abstinence. Notably, among the smoking withdrawal symptoms, increased craving to smoke (especially smoking cue-induced craving) and decreased cognitive performance mainly contribute to heightened relapse vulnerability during quit attempts. Identifying smokers with heightened relapse vulnerability prior to quit attempts and using psychophysiological treatments to reduce the neural response to smoking cues appear to be promising strategies for improving the success of quit attempts.

**Conflict of interests**

The authors declare that there is no conflict of interest.

**Funding**

This work was supported by the National Natural Science Foundation of China (Nos. 31800926, 32071061, 31822025) and the Scientific Foundation of Institute of Psychology, Chinese Academy of Sciences (No. Y8CX351005).

**References**

[1] Zhang J, Ou JX, Bai CX. Tobacco smoking in China: prevalence, disease burden, challenges and future strategies. *Respirology* 2011, 16(8): 1165–1172.

[2] Iribarren C, Tekawa IS, Sidney S, et al. Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. *N Engl J Med* 1999, 340(23): 1773–1780.

[3] Killen JD, Fortmann SP. Craving is associated with smoking relapse: findings from three prospective studies. *Exp Clin Psychopharmacol* 1997, 5(2): 137–142.

[4] van Zundert RM, Ferguson SG, Shiffman S, et al. Dynamic effects of craving and negative affect on adolescent smoking relapse. *Health Psychol* 2012, 31(2): 226–234.

[5] Loughead J, Wileyto EP, Ruparel K, et al. Working memory-related neural activity predicts future smoking relapse. *Neuropsychopharmacology* 2015, 40(6): 1311–1320.

[6] Brody AL, Gehlbach D, Garcia LY, et al. Effect of overnight smoking abstinence on a marker for microglial activation: a [11C]DAA1106 positron emission tomography study. *Psychopharmacology* 2018, 235(12): 3525–3534.

[7] Liu C, Dong F, Li YD, et al. 12 h abstinence-induced ERP changes in young smokers: electrophysiological evidence from a go/NoGo study. *Front Psychol* 2019, 10: 1814.

[8] Cui YT, Dong F, Li XJ, et al. Electrophysiological evidence of event-related potential changes induced by 12 h abstinence in young smokers based on the flanker study. *Front Psychiatry* 2020, 11: 424.

[9] Beaver JD, Long CJ, Cole DM, et al. The effects of nicotine replacement on cognitive brain activity during smoking withdrawal studied with simultaneous fMRI/EEG. *Neuropsychopharmacology* 2011, 36(9): 1792–1800.

[10] Allenby C, Falcone M, Wileyto EP, et al. Neural cue reactivity during acute abstinence predicts short-term smoking relapse. *Addict Biol* 2020, 25(2): e12733.

[11] Zhao SZ, Li YD, Li M, et al. 12-h abstinence-induced functional connectivity density changes and craving in young smokers: a resting-state study. *Brain Imaging Behav* 2019, 13(4): 953–962.
[12] Faulkner P, Ghahremani DG, Tyndale RF, et al. Neural basis of smoking-induced relief of craving and negative affect: Contribution of nicotine. Addict Biol 2019, 24(5): 1087–1095.

[13] Wang CY, Zhang Y, Yan CY, et al. The thalamo-cortical resting state functional connectivity and abstinence-induced craving in young smokers. Brain Imaging Behav 2018, 12(5): 1450–1456.

[14] Owens MM, MacKillop J, Gray JC, et al. Neural correlates of tobacco cue reactivity predict duration to lapse and continuous abstinence in smoking cessation treatment. Addict Biol 2018, 23(5): 1189–1199.

[15] Gilman JM, Radoman M, Schuster RM, et al. Anterior insula activation during inhibition to smoking cues is associated with ability to maintain tobacco abstinence. Addict Behav Rep 2018, 7: 40–46.

[16] Zelle SL, Gates KM, Fiez JA, et al. The first day is always the hardest: Functional connectivity during cue exposure and the ability to resist smoking in the initial hours of a quit attempt. Neuroimage 2017, 151: 24–32.

[17] Li YD, Yuan K, Bi YZ, et al. Neural correlates of 12-h abstinence-induced craving in young adult smokers: a resting-state study. Brain Imaging Behav 2017, 11(3): 677–684.

[18] Westbrook C, Creswell JD, Tabibnia G, et al. Mindful attention reduces neural and self-reported cue-induced craving in smokers. Soc Cogn Affect Neurosci 2013, 8(1): 73–84.

[19] Aronson Fischell S, Ross TJ, Deng ZD, et al. Transcranial direct current stimulation applied to the dorsolateral and ventromedial prefrontal cortices in smokers modifies cognitive circuits implicated in the nicotine withdrawal syndrome. Biol Psychiatry Cogn Neurosci Neuroimaging 2020, 5(4): 448–460.

[20] Sutherland MT, Carroll AJ, Salmeron BJ, et al. Down-regulation of amygdala and Insula functional circuits by varenicline and nicotine in abstinent cigarette smokers. Biol Psychiatry 2013, 74(7): 538–546.

[21] Cole DM, Beckmann CF, Long CJ, et al. Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. Neuroimage 2010, 52(2): 590–599.

[22] Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob Res 2007, 9(3): 315–327.

[23] Hughes JR. Craving among long-abstinent smokers: an Internet survey. Nicotine Tob Res 2010, 12(4): 459–462.

[24] Hall FS, Der-Avakian A, Gould TJ, et al. Negative affective states and cognitive impairments in nicotine dependence. Neurosci Biobehav Rev 2015, 58: 168–185.

[25] Besson M, Forget B. Cognitive dysfunction, affective states, and vulnerability to nicotine addiction: a multifactorial perspective. Front Psychiatry 2016, 7: 160.

[26] Sher E, Chen Y, Sharples TJ, et al. Physiological roles of neuronal nicotinic receptor subtypes: new insights on the nicotinic modulation of neurotransmitter release, synaptic transmission and plasticity. Curr Top Med Chem 2004, 4(3): 283–297.

[27] Buisson B, Bertrand D. Nicotine addiction: the possible role of functional upregulation. Trends Pharmacol Sci 2002, 23(3): 130–136.

[28] Brody AL, Mandelkern MA, London ED, et al. Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. Arch Gen Psychiatry 2006, 63(8): 907–915.

[29] Cosgrove KP, Esters I, McKee S, et al. Beta2* nicotinic acetylcholine receptors modulate pain sensitivity in acutely abstinent tobacco smokers. Nicotine Tob Res 2010, 12(5): 535–539.

[30] Cosgrove KP, Batis J, Bois F, et al. beta2-Nicotinic acetylcholine receptor availability during acute and prolonged abstinence from tobacco smoking. Arch Gen Psychiatry 2009, 66(6): 666–676.

[31] Allen SS, Bade T, Hatsukami D, et al. Craving, withdrawal, and smoking urges on days immediately prior to smoking relapse. Nicotine Tob Res 2008, 10(1): 35–45.

[32] Lerman C, Gu H, Loughead J, et al. Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. JAMA Psychiatry 2014, 71(5): 523–530.

[33] Wang Z, Faith M, Patterson F, et al. Neural substrates of abstinence-induced cigarette cravings in chronic smokers. J Neurosci 2007, 27(51): 14035–14040.

[34] Sweitzer MM, Geier CF, Addicott MA, et al. Smoking abstinence-induced changes in resting state functional connectivity with ventral striatum predict lapse during a quit attempt. Neuropsychopharmacology 2016, 41(10): 2521–2529.

[35] Bi Y, Zhang Y, Li Y, et al. 12h abstinence-induced...
right anterior Insula network pattern changes in young smokers. Drug Alcohol Depend 2017, 176: 162–168.

[36] Janes AC, Frederick BD, Richardts S, et al. Brain fMRI reactivity to smoking-related images before and during extended smoking abstinence. Exp Clin Psychopharmacol 2009, 17(6): 365–373.

[37] McClernon FJ, Kozink RV, Lutz AM, et al. 24-h abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. Psychopharmacology 2009, 204(1): 25–35.

[38] Engelmann JM, Versace F, Robinson JD, et al. Neural substrates of smoking cue reactivity: a meta-analysis of fMRI studies. Neuroimage 2012, 60(1): 252–262.

[39] McClernon FJ, Hiott FB, Huettel SA, et al. Abstinence-induced changes in self-report craving correlate with event-related FMRI responses to smoking cues. Neupyschopharmacology 2005, 30(10): 1940–1947.

[40] Naqvi NH, Rudrauf D, Damasio H, et al. Damage to the Insula disrupts addiction to cigarette smoking. Science 2007, 315(5811): 531–534.

[41] Ding XY, Lee SW. Changes of functional and effective connectivity in smoking replenishment on deprived heavy smokers: a resting-state FMRI study. PLoS One 2013, 8(3): e59331.

[42] Wang K, Yang J, Zhang S, et al. The neural mechanisms underlying the acute effect of cigarette smoking on chronic smokers. PLoS One 2014, 9(7): e102828.

[43] Abulseoud OA, Ross TJ, Nam HW, et al. Short-term nicotine deprivation alters dorsal anterior cingulate glutamate concentration and concomitant cingulate-cortical functional connectivity. Neupyschopharmacology 2020, 45(11): 1920–1930.

[44] Sweitzer MM, Geier CF, Joel DL, et al. Dissociated effects of anticipating smoking versus monetary reward in the caudate as a function of smoking abstinence. Biol Psychiatry 2014, 76(9): 681–688.

[45] Havermans A, van Schayck OCP, Vuurman EFPM, et al. Nicotine deprivation elevates neural representation of smoking-related cues in object-sensitive visual cortex: a proof of concept study. Psychopharmacology 2017, 234(16): 2375–2384.

[46] Kozink RV, Kollins SH, McClernon FJ. Smoking withdrawal modulates right inferior frontal cortex but not presupplementary motor area activation during inhibitory control. Neupyschopharmacology 2010, 35(13): 2600–2606.

[47] Azizian A, Nestor LJ, Payer D, et al. Smoking reduces conflict-related anterior cingulate activity in abstinent cigarette smokers performing a Stroop task. Neupyschopharmacology 2010, 35(3): 775–782.

[48] Zhao HC, Turel O, Brevets D, et al. Smoking cues impair monitoring but not stopping during response inhibition in abstinent male smokers. Behav Brain Res 2020, 386: 112605.

[49] Xu JS, Mendrek A, Cohen MS, et al. Brain activity in cigarette smokers performing a working memory task: effect of smoking abstinence. Biol Psychiatry 2005, 58(2): 143–150.

[50] Xu JS, Mendrek A, Cohen MS, et al. Effects of acute smoking on brain activity vary with abstinence in smokers performing the N-Back task: a preliminary study. Psychiatry Res 2006, 148(2/3): 103–109.

[51] Jacobsen LK, Mencel WE, Constable RT, et al. Impact of smoking abstinence on working memory neurocircuitry in adolescent daily tobacco smokers. Psychopharmacology 2007, 193(4): 557–566.

[52] Loughead J, Ray R, Wileyto EP, et al. Effects of the alpha4beta2 partial agonist varenicline on brain activity and working memory in abstinent smokers. Biol Psychiatry 2010, 67(8): 715–721.

[53] Sweet LH, Mulligan RC, Finnerty CE, et al. Effects of nicotine withdrawal on verbal working memory and associated brain response. Psychiatry Res 2010, 183(1): 69–74.

[54] Falcone M, Wileyto EP, Ruparel K, et al. Age-related differences in working memory deficits during nicotine withdrawal. Addict Biol 2014, 19(5): 907–917.

[55] Ashare RL, Lerman C, Cao W, et al. Nicotine withdrawal alters neural responses to psychosocial stress. Psychopharmacology 2016, 233(13): 2459–2467.

[56] Allenby C, Falcone M, Ashare RL, et al. Brain marker links stress and nicotine abstinence. Nicotine Tob Res 2020, 22(6): 885–891.

[57] Janes AC, Pizzagalli DA, Richardts S, et al. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. Biol Psychiatry 2010, 67(8): 722–729.

[58] Sweitzer MM, Geier CF, Denlinger R, et al. Blunted striatal response to monetary reward anticipation during smoking abstinence predicts lapse during
a contingency-managed quit attempt. *Psychopharmacology* 2016, 233(5): 751–760.

[59] Froeliger B, McConnell PA, Bell S, et al. Association between baseline corticothalamic-mediated inhibitory control and smoking relapse vulnerability. *JAMA Psychiatry* 2017, 74(4): 379–386.

[60] Yuan K, Zhao M, Yu DH, et al. Striato-cortical tracts predict 12-h abstinence-induced lapse in smokers. *Neuropsychopharmacology* 2018, 43(12): 2452–2458.

[61] Wilson SJ, Sayette MA, Delgado MR, et al. Instructed smoking expectancy modulates cue-elicited neural activity: a preliminary study. *Nicotine Tob Res* 2005, 7(4): 637–645.

[62] McBride D, Barrett SP, Kelly JT, et al. Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers: an fMRI study. *Neuropsychopharmacology* 2006, 31(12): 2728–2738.

[63] Janse van Rensburg K, Taylor A, Hodgson T, et al. Acute exercise modulates cigarette cravings and brain activation in response to smoking-related images: an fMRI study. *Psychopharmacology* 2009, 203(3): 589–598.

[64] Janse van Rensburg K, Taylor A, Benattayallah A, et al. The effects of exercise on cigarette cravings and brain activation in response to smoking-related images. *Psychopharmacology* 2012, 221(4): 659–666.

[65] Xu X, Wang J, Aron A, et al. Intense passionate love attenuates cigarette cue-reactivity in nicotine-deprived smokers: an FMRI study. *PLoS One* 2012, 7(7): e42235.

[66] Xu X, Aron A, Westmaas JL, et al. An fMRI study of nicotine-deprived smokers’ reactivity to smoking cues during novel/exciting activity. *PLoS One* 2014, 9(4): e94598.

[67] Tanabe J, Crowley T, Hutchison K, et al. Ventral striatal blood flow is altered by acute nicotine but not withdrawal from nicotine. *Neuropsychopharmacology* 2008, 33(3): 627–633.

[68] Brody AL, Olmstead RE, London ED, et al. Smoking-induced ventral striatum dopamine release. *Am J Psychiatry* 2004, 161(7): 1211–1218.

[69] Volkow ND, Wang GJ, Fowler JS, et al. Addiction: Beyond dopamine reward circuitry. *PNAS* 2011, 108(37): 15037–15042.

[70] Kober H, Mende-Siedlecki P, Kross EF, et al. Prefrontal-striatal pathway underlies cognitive regulation of craving. *PNAS* 2010, 107(33): 14811–14816.

[71] Cai CX, Yuan K, Yin JS, et al. Striatum morphometry is associated with cognitive control deficits and symptom severity in Internet gaming disorder. *Brain Imaging Behav* 2016, 10(1): 12–20.

[72] Li YD, Yuan K, Cai CX, et al. Reduced frontal cortical thickness and increased caudate volume within *Fronto-striatal circuits in young adult smokers. Drug Alcohol Depend* 2015, 151: 211–219.

[73] Yuan K, Yu DH, Cai CX, et al. Frontostriatal circuits, resting state functional connectivity and cognitive control in Internet gaming disorder. *Addict Biol* 2017, 22(3): 813–822.

[74] Sutherland MT, McHugh MJ, Pariyadath V, et al. Resting state functional connectivity in addiction: Lessons learned and a road ahead. *Neuroimage* 2012, 62(4): 2281–2295.

[75] Wang Z, Ray R, Faith M, et al. Nicotine abstinence-induced cerebral blood flow changes by genotype. *Neurosci Lett* 2008, 438(3): 275–280.

[76] Franklin TR, Jagannathan K, Hager N, et al. Brain substrates of early (4h) cigarette abstinence: Identification of treatment targets. *Drug Alcohol Depend* 2018, 182: 78–85.

[77] Liu S, Wang SC, Zhang M, et al. Brain responses to drug cues predict craving changes in abstinent heroin users: a preliminary study. *Neuroimage* 2021, 237: 118169.

[78] Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology* 2010, 210(4): 453–469.

[79] Kumari V, Gray JA, flytche DH, et al. Cognitive effects of nicotine in humans: an fMRI study. *Neuroimage* 2003, 19(3): 1002–1013.

[80] Jacobsen LK, Krystal JH, Mencel WE, et al. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biol Psychiatry* 2005, 57(1): 56–66.

[81] Campos MW, Serebrisky D, Castaldelli-Maia JM. Smoking and cognition. *Curr Drug Abuse Rev* 2017, 10(2): 76–79.

[82] Ashare RL, Wileyto EP, Ruparel K, et al. Effects of tolcapone on working memory and brain activity in abstinent smokers: a proof-of-concept study. *Drug Alcohol Depend* 2013, 133(3): 852–856.

[83] Chaaarani B, Specghla PA, Ivanciu A, et al. Multimodal
neuroimaging differences in nicotine abstinent smokers versus satiated smokers. *Nicotine Tob Res* 2019, **21**(6): 755–763.

[84] Patterson F, Jepson C, Loughead J, et al. Working memory deficits predict short-term smoking resumption following brief abstinence. *Drug Alcohol Depend* 2010, **106**(1): 61–64.

[85] Ditre JW, Heckman BW, Zale EL, et al. Acute analgesic effects of nicotine and tobacco in humans: a meta-analysis. *Pain* 2016, **157**(7): 1373–1381.

[86] LaRowe LR, Ditre JW. Pain, nicotine, and tobacco smoking: current state of the science. *Pain* 2020, **161**(8): 1688–1693.

[87] Shen L, Wei K, Chen QB, et al. Decreased pain tolerance before surgery and increased postoperative narcotic requirements in abstinent tobacco smokers. *Addict Behav* 2018, **78**: 9–14.

[88] LaRowe LR, Kosiba JD, Zale EL, et al. Effects of nicotine deprivation on current pain intensity among daily cigarette smokers. *Exp Clin Psychopharmacol* 2018, **26**(5): 448–455.

[89] McNamara JP, Wang JT, Holiday DB, et al. Sleep disturbances associated with cigarette smoking. *Psychol Health Med* 2014, **19**(4): 410–419.

[90] Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep* 2013, **36**(7): 1059–1068.

[91] Tiffany ST, Cox LS, Elash CA. Effects of transdermal nicotine patches on abstinence-induced and cue-elicited craving in cigarette smokers. *J Consult Clin Psychol* 2000, **68**(2): 233–240.

[92] Li XB, Hartwell KJ, Henderson S, et al. Two weeks of image-guided left dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation improves smoking cessation: a double-blind, sham-controlled, randomized clinical trial. *Brain Stimul* 2020, **13**(5): 1271–1279.

[93] Wang YY, Liu Z, Chen F, et al. Effects of acupuncture on craving after tobacco cessation: a resting-state fMRI study based on the fractional amplitude of low-frequency fluctuation. *Quant Imaging Med Surg* 2019, **9**(6): 1118–1125.

[94] Kang OS, Kim SY, Jahng GH, et al. Neural substrates of acupuncture in the modulation of cravings induced by smoking-related visual cues: an fMRI study. *Psychopharmacology* 2013, **228**(1): 119–127.

[95] Ghahremani DG, Faulkner P, M Cox C, et al. Behavioral and neural markers of cigarette-craving regulation in young-adult smokers during abstinence and after smoking. *Neuropsychopharmacology* 2018, **43**(7): 1616–1622.

[96] Taylor AH, Ussher MH, Faulkner G. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect and smoking behaviour: a systematic review. *Addiction* 2007, **102**(4): 534–543.

Yanzhi Bi received her Ph.D. degree in bioinformatics science and technology from Xidian University, China (2018) and is now working in the Institute of Psychology, Chinese Academy of Sciences, China. Her research interests focus on the neural mechanism of pain and addiction. E-mail: biyz@psych.ac.cn

Li Hu received his Ph.D. degree in biomedical engineering from the University of Hong Kong, Hong Kong, China (2010). He is now a professor in the Institute of Psychology, Chinese Academy of Sciences, Beijing, China. He has published many papers on high-quality journals, including *PNAS*, *Trends in Neurosciences*, *Journal of Neuroscience*. His current research interests focus on the psychophysiological mechanism of pain and the development of non-pharmacological analgesic strategies. E-mail: huli@psych.ac.cn