

Paradise Lost: The relationships between neurological and psychological changes in nicotine-dependent patients

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The neural reward circuit and cognitive distortion play an important role in addiction; however, the relationship between the two has not yet been addressed. In this article, we review recent findings on nicotine dependence and propose a novel hypothesis. Previous research using functional magnetic resonance imaging (fMRI) has shown that while activation of the reward circuit (ventral striatum) appears in response to tobacco-related rewards in nicotine dependence, responses to rewards other than tobacco (e.g. food and money) are reduced. Moreover, this change is observed at the very early stages of smoking, even when a person has smoked fewer than 10 cigarettes in his/her lifetime. Thus, we propose the following hypothesis, called the Paradise Lost theory: given addicts' lower ventral striatal responses to non-tobacco rewards, nicotine addiction disables smokers from sensing the pleasures of ordinary life (the Paradise Lost state). However, since smokers do not notice this, they produce an overestimation of tobacco (cognitive distortion), such that they do not have many pastimes other than smoking or feel that quitting smoking would reduce the happiness and pleasure and increase the difficulty of life. Cognitive distortion thus makes it difficult for smokers to take the initiative to quit smoking and even causes relapse after smoking cessation. This theory furthers our understanding of addiction and could improve our approach to the prevention and treatment of addiction.

Keywords: fMRI, nicotine dependence, the Paradise Lost theory, smoking, ventral striatum

INTRODUCTION

One of the most striking features of smoking cessation is the discrepancy between early success rates and long-term outcomes. In most studies and large-scale treatment programs for dependent smokers, more than 50% of participants initially manage to achieve abstinence for at least a few weeks (Judge, Bauld, Chesterman, & Ferguson, 2005); however, there is a high rate of relapse following such initial success, with approximately 75% of those abstinent at four weeks relapsing by one year (Ferguson, Bauld, Chesterman, & Judge, 2005). Therefore, the identification of effective treatments to maintain initial success has become an important concern for clinicians.

This high relapse rate is common with other addictions. The human reward circuit has been extensively examined via functional neuroimaging methods such as functional magnetic resonance imaging (fMRI). The use of functional neuroimaging has improved researchers' understanding of nicotine dependence in humans, because it allows them to observe the structure and functioning of smokers' brains both directly and indirectly. In this article, we review and discuss these new studies of human reward circuitry. We then propose some insights about the relationships between nicotine-induced neurological changes and the psychological changes that underlie relapse. As for neurological changes, functional alteration of the ventral striatum has been found in nicotine-dependent individuals (Bühler et al., 2010), and as for psychological aspects, the cognitive distortion in which nicotine-dependent individuals engage is assumed to play an important role in relapse (Otani et al., 2009). Therefore, this study focuses on exploring the relationship between activation levels in the ventral striatum and

cognitive distortion in individuals who are addicted to nicotine. The Reset Behavior Research Group Committee for the Protection of Human Subjects in Research approved this study.

IS ADDICTION ONLY SENSITIZATION OF THE REWARD SYSTEM?

Most initial fMRI studies of addiction focused on cue reactivity (i.e. neural responses during the processing of drug-related cues). In these studies, the brains of subjects with addictions typically demonstrated abnormally high responses to drug-related cues in the reward circuit, including the ventral striatum and orbitofrontal and ventromedial prefrontal cortex (David et al., 2005; Diekhof, Falkai, & Gruber, 2008).

These results are consistent with the incentive-sensitization theory of drug addiction (Robinson & Berridge, 2003). According to this theory, sensitization of the reward circuit increases the incentive salience of drug-related cues compared with non-drug-related ones, leading to higher probabilities of drug-seeking and drug-taking behaviors and decreased probabilities of non-drug-related ones. However, this theory does not fully explain how sensitization becomes directed towards one particular target, such as taking drugs (Robinson & Berridge, 2003). For example, some results have reported reduced reactivity to visual erotic stimuli (Garavan et al., 2000) and monetary gain (Goldstein et al., 2007) in individuals who were addicted to cocaine; similar results were found in individuals with alcoholism (Wrase et al., 2007). These studies show that the transition from occasional use to addiction includes not only increased reactivity to drug-related cues, but also decreased responsiveness to non-drug-related ones.

SMOKERS' HYPORESPONSE TO NON-DRUG-RELATED CUES

Bühler et al. (2010) compared occasional smokers with nicotine-dependent ones and identified the importance of changes in the balance between ventral striatal responses to drug-related versus non-drug-related ones in terms of incentive salience. They found similar levels of activation in the ventral striatum in response to cigarette-related stimuli among dependent and nondependent smokers; however, those groups' levels of ventral striatal activation differed in response to monetary-related stimuli. Occasional smokers demonstrated greater activation of the reward circuit in response to monetary-related stimuli compared with cigarette-related ones. In contrast, dependent smokers demonstrated similar activation levels in response to both monetary- and cigarette-related stimuli (Bühler et al., 2010). Therefore, the authors speculate that sensitization to the incentive motivational effects of drugs and drug-related stimuli may not be crucial in the development of addiction. Rather, they argue that

changes in the balance between the incentive salience of drug reward and that of non-drug reward are critical for addiction (Bühler et al., 2010).

LOWER VENTRAL STRIATAL ACTIVATION IN ADOLESCENT SMOKERS WHO HAVE SMOKED FEWER THAN 10 CIGARETTES IN THEIR LIFETIMES

In the study of Bühler et al. (2010), the control group was composed of occasional smokers who smoked less than one cigarette daily. Peters et al. (2011), however, compared smokers with nonsmokers. They noted that adolescents are particularly vulnerable to addiction (Paus, Keshavan, & Giedd, 2008). Smoking during the adolescent period often leads to long-lasting nicotine dependence (Giovino, Henningfield, Tomar, Escobedo, & Slade, 1995). In the study by Peters et al. (2011), fMRI was performed during reward anticipation in 43 adolescent smokers and 43 age-, gender-, and IQ-matched nonsmokers. The participants performed a monetary incentive delay task; each trial involved anticipation, response, and feedback phases and a fixation period. During the anticipation phase, cues signaling the amount of potential reward available in a given trial were shown for 4 sec. Following a random time interval, a response cue was displayed, and the subject was instructed to respond as quickly as possible to this cue. The points were converted to treats (small chocolate candies) following testing.

In both groups, the fMRI data showed significant activation in the ventral striatum when the reward anticipation cues were shown. However, smokers showed lower ventral striatal responses to reward anticipation than the comparison subjects did. Notably, lower responses to reward anticipation in the ventral striatum and the neighboring putamen were also observed in extremely mild smokers ($n=14$) who had smoked on fewer than 10 total occasions in their lifetimes. Furthermore, these responses were correlated with smoking frequency (ventral striatum: $r=-0.23$, $p=0.07$; putamen: $r=-0.42$, $p=0.004$). That is, frequent smokers tended to show a greater reduction in ventral striatal response than did mild smokers.

Peters et al. (2011) suggested that hyporesponsivity of the reward system may predispose adolescents to early nicotine use. They also suggested two possibilities to explain the observation that smoking frequency is significantly correlated with hypoactivation in the ventral striatum either (1) more frequent smoking further attenuates reward-related activation or (2) subjects with particularly hyporesponsive reward circuits are more likely to increase their nicotine use.

Therefore, the reward circuits of individuals who are addicted to nicotine are hyperresponsive to tobacco-predicting stimuli but show lower responses to non-tobacco-predicting ones. Furthermore, this hypoactivation was observed in extremely mild smokers who had just begun to smoke; it is presumed that further

response reduction will appear with increased smoking frequency.

A UNIQUE CHARACTERISTIC OF THE ADOLESCENT REWARD SYSTEM

Learning occurs when outcomes deviate from expectations (prediction error). Human neural learning depends on reward-related prediction errors (Schultz, Dayan, & Montague, 1997). Cohen et al. (2010) found that neural prediction error signals in the striatum peaked in adolescence and suggested that this finding directly explains the risky reward-seeking behavior often observed in adolescents. According to their discussion, this increased risky behavior in adolescence could reflect either decreased sensitivity to potential negative outcomes or increased sensitivity to potential positive outcomes. They assert that their data are consistent with the latter explanation; that is, elevated prediction error signals (which putatively reflect higher phasic dopamine signals) reflect greater hedonic impacts of positive outcomes (Berridge & Robinson, 1998). This results in increased motivation to obtain positive outcomes and take greater risks. Thus, an overactive dopaminergic prediction error response in adolescents could result in an increase in reward-seeking behaviors, particularly when coupled with an immature cognitive control system.

The discussion presented by Cohen et al. (2010) complements sensitization theory in that it explains the mechanism that results in nicotine dependency among adolescents. The fact that neural prediction error signals reach their peak in adolescence is consistent with sensitization theory, because drugs that boost phasic dopamine reward prediction error might generate powerful teaching signals and produce lasting behavioral changes through synaptic modifications.

Given these findings, what then is the relationship between the facts that prediction error signals peak in adolescence and that adolescent smokers show lower responses to non-tobacco-predicting stimuli? While Cohen et al. (2010) considered an overactive dopaminergic response as the cause of increased risky behavior in adolescence, Peters et al. (2011) found lower ventral striatal activation in adolescent smokers and suggested two possibilities to explain their findings. One explanation is that lower striatal responses cause an increase in smoking frequency, and the other is that lower striatal responses are a consequence of smoking. While there seems to be a cause-and-effect relationship between smoking and hyporesponse, we propose that the former explanation – that hyporesponsiveness to rewards may exist and lead to smoking behavior – is inconsistent with the view of Cohen et al. (2010). According to Cohen et al., the increase in reward-related neural activity in adolescents increases risky behavior. Further, in our daily clinical experience, most, but not all, young people tried their first cigarette out of curiosity

(reward-seeking behavior) rather than for self-therapeutic purposes (to heal hyporesponse of the reward system). Therefore, in order to establish consistency with the findings of Cohen et al. (2010), we should take up the latter explanation (i.e. that hyporesponsiveness to rewards is a consequence of smoking). We think that the hypothesis that lower striatal responses result from smoking is consistent with cognitive distortion, a characteristic condition in nicotine dependence that is often encountered in clinical settings. In the next section, we develop this hypothesis further.

MEANING OF THE LOWERED RESPONSE TO NON-TOBACCO-RELATED REWARD ANTICIPATION

The low ventral striatal reactivity discovered by Peters et al. (2011) is not necessarily contradictory with sensitization theory. Sensitization theory hypothesizes that sensitization of the reward system to drug-related cues leads to the transition to addiction and that such sensitization is accompanied by enduring structural changes. This theory, however, does not describe how the reward system responds to non-drug-related cues. Therefore, according to sensitization theory, even when striatal responses to non-drug stimuli decrease, if enduring sensitization of the reward system to drug-related stimuli has been induced, then drug dependence continues, and relapse can occur. Yet, how does sensitization to drug-related rewards appear and sustain itself while responses to non-drug-related rewards decrease?

There are three points to recall here. First, the stimulus magnitude of an addictive drug can easily be strengthened through increases in the frequency and quantity of consumption, unlike that of non-drug rewards. Second, neural prediction error signals and risky reward-seeking behavior reach their peaks in adolescence, and learning by prediction error could be strengthened through synaptic modifications. Finally, drug rewards have a self-reproductive element: the reward from the resolution of withdrawal symptoms caused by the drug itself.

Adolescence is the period when novelty-seeking behavior increases. We would like to illustrate the above hypotheses using the fictional case of Boy A. When he was an adolescent, Boy A had a strong tendency towards novelty-seeking behavior and tried to smoke a cigarette.

Note that at this point, Boy A did not engage in any cognitive distortion, such as overestimation of tobacco. Boy A tried his first cigarette simply out of curiosity and a novelty-seeking impulse, like most other young people. Therefore, it seems that cognitive distortion comes after neurological change.

After smoking his first cigarette, Boy A's reward system might respond excessively to the reward stimuli, as Cohen et al. (2010) predict. In addition, his hyperresponsive reward system was exposed not

only to tobacco but also to other rewards (horse races, pachinko, etc.) common to his generation.

However, after he began to smoke, his reward system also began to change. First, tobacco itself elicits reward-induced alteration because of two factors: (1) the pharmacological effects of nicotine as an addictive substance and (2) the act of smoking itself is a novelty-seeking behavior. Initially, the pharmacological and physiological effects of nicotine are unpleasant, not rewarding. In fact, at this stage, the ventral striatum is not activated by smoking-related cues (David et al., 2005). Therefore, the initial rewards obtained from tobacco smoking will be restricted to satisfaction in having found a novel activity, the ritual of smoking a cigarette or social rewards (e.g. a sense of belonging with friends). If rewards were limited to only these factors, neither addiction nor cognitive distortion would occur. We know this because similar rewards are obtained when children play with chocolates shaped like cigarettes.

However, the influences of smoking occur within Boy A's brain, even at the very early stages, unnoticed by the boy himself. That is, the reward system, which includes parts such as the ventral striatum, becomes less responsive to other rewards. The results of Peters et al. (2011) indicated that even when he has smoked fewer than 10 cigarettes, Boy A will not be as glad to see chocolate candy to the degree as he used to be.

According to findings of Bühler et al. (2010), Boy A's sensitivity to monetary rewards will also decrease.

If Boy A stops smoking after only a few cigarettes, none of those consequences would occur. However, if he continues to smoke, he would invariably experience what is known as the "pleasure of tobacco." Although research on brain waves (Knott, 1977) and mechanisms of pharmacological treatment (Foulds, 2006) suggest that the "pleasure of tobacco" experienced by smokers can be attributed to the resolution of nicotine withdrawal, the most important point is that Boy A will begin to experience the rewarding effects of smoking. After this, Boy A will change his behavior and start to buy cigarettes for himself regularly. He begins to understand the "pleasure of tobacco," and thus, the door to sensitization opens.

We surveyed the experiences of the "pleasure of tobacco" among young people. Our findings indicate that the peak of subjects' smoking frequencies once they had experienced the "pleasure of tobacco" for the first time was located at 1–5 cigarettes per day. About 80% (41 out of 52) of those surveyed said that they experienced the "pleasure of tobacco" after fewer than 40 lifetime occasions of smoking (Figure 1). Interestingly, the period when they reported experiencing the "pleasure of tobacco" overlaps with that of the striatal changes identified by Peters et al. (2011) and Bühler et al. (2010).

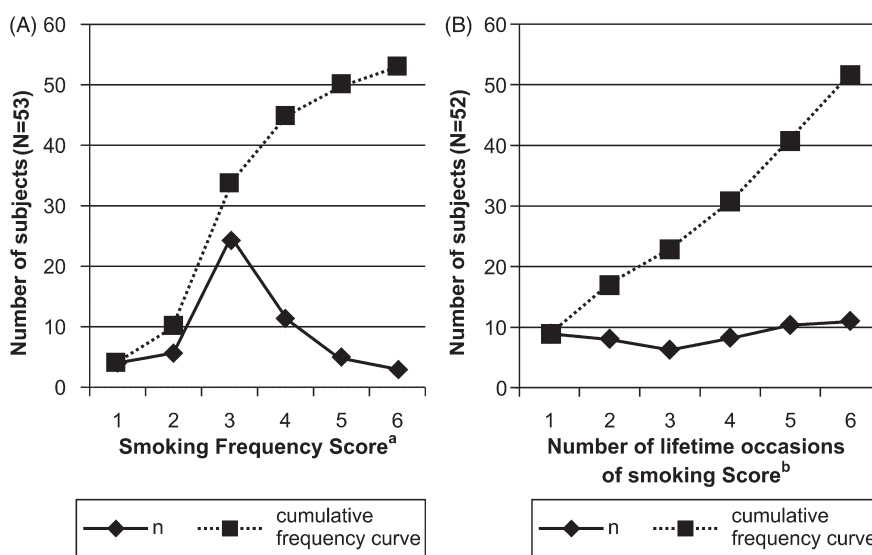


Figure 1. Smoking frequency and experience when young people first experienced the "pleasure of smoking." A total of 115 vocational students (age range: 19–29 years; mean age (SD): 22.4 (1.7) years; 102 male and 13 female participants) were surveyed. In all, 42 were current smokers, 10 former smokers, 18 nonsmokers who experimented with smoking, and 45 never-smokers. In all, 53 students (all of the current and former smokers and one nonsmoker who had experimented with smoking) answered they had experienced the "pleasure of smoking." The average smoking frequency and the lifetime number of cigarettes smoked when respondents first experienced the "pleasure of smoking" are shown above. One subject did not answer regarding his lifetime number of cigarette smoked.

^aLess than 1 cigarette weekly (score = 1), less than 1 cigarette daily (score = 2), 1–5 cigarettes daily (score = 3), 6–10 cigarettes daily (score = 4), 11–20 cigarettes daily (score = 5), and more than 20 cigarettes daily (score = 6). ^b1–2 (score = 1), 3–5 (score = 2), 6–9 (score = 3), 10–19 (score = 4), 20–39 (score = 5), and 40 or more (score = 6). These categorizations followed those of the European School Survey Project on Alcohol and Drugs (Hibell et al., 2003).

In our illustrative case of Boy A, he does not notice his neurological changes; yet, he repeatedly seeks the “pleasure of tobacco,” which causes his reward system to become less responsive to non-tobacco-related stimuli. As this pattern progresses, his tolerance to nicotine begins to appear. In order to increase his sensation of reward, he can easily strengthen the stimulus by increasing the number of cigarettes smoked. If Boy A is a risk taker by nature, he is likely to smoke more cigarettes. Of course, there might be differences among individuals in terms of their degrees of physiologic resistance to nicotine. For example, a boy who shows more physiologic resistance to nicotine might smoke more cigarettes. An adolescent surrounded by permissive attitudes toward cigarettes, such as those of family or friends who smoke, will smoke more than another person who is not in such a situation. Even though smoking was initiated largely as a result of their traits and social circumstances, the very act of smoking eventually results in strong neural alterations, including synaptic modification (i.e. sensitization to smoking-related cues).

On the one hand, the experience during the moment when smoking changes from unpleasant to rewarding acts as a prediction error signal, because it is unexpected and helps to develop sensitization. On the other hand, if Boy A was to become more aware of his nicotine withdrawal as he increased the number of cigarettes smoked, he would attempt to treat said nicotine withdrawal by smoking, which in turn would promote nicotine withdrawal further. Thus, his smoking continues endlessly, and his

operant conditioning to tobacco is strengthened further.

The results of all these patterns are dependent. At this stage, Bühler et al. (2010) found that dependent smokers showed almost equivalent activity to both monetary and tobacco-related rewards. Therefore, when Boy A continues to smoke, his ventral striatal activity elicited by non-tobacco-related rewards would decrease further and eventually falling as low as the activity level that occurs in response to tobacco-related ones. Therefore, we propose a hypothetical activity curve for the ventral striatum in the course of development of nicotine dependence (Figure 2). As smoking experience increases, the brain’s response to non-tobacco-related reward-predicting stimuli decreases. Alternatively, a neural response to tobacco-related reward-predicting stimuli might emerge.

RELATIONSHIP BETWEEN HYPOACTIVATION OF REWARD CIRCUITS AND COGNITIVE DISTORTION

The hypothesis that drugs induce lower ventral striatal responses to non-drug rewards provides some insight about the relationship between neurological and psychological changes. In fact, statements analogous to this hypothesis have been anecdotally reported by individuals with addiction to explain why they continue in their consumption of addictive substances rather than pursuing ordinary pleasures or pastimes. For example, some smokers say they do not have any

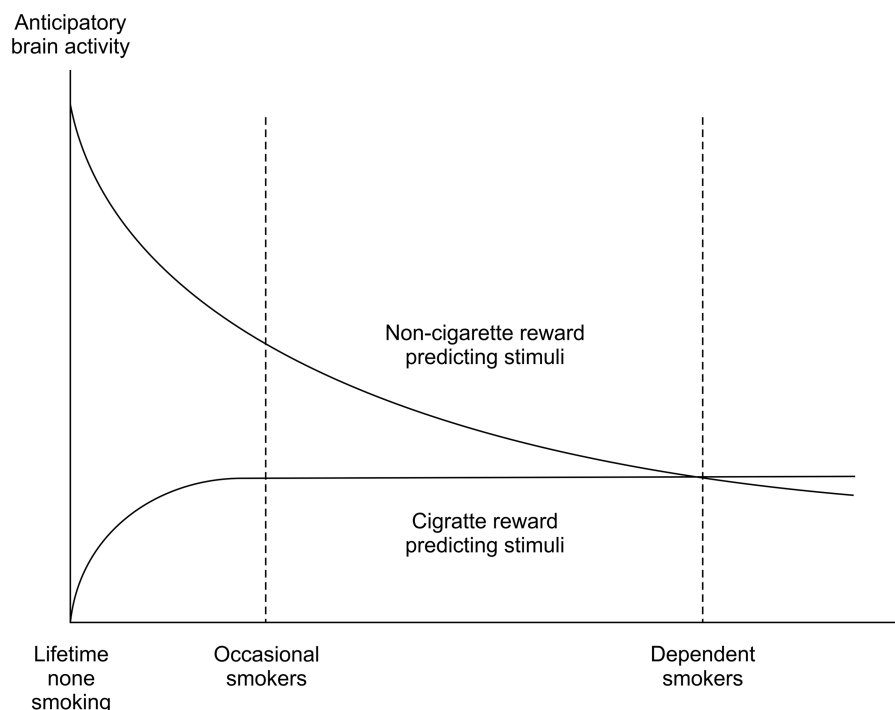


Figure 2. Hypothetical anticipatory brain activity curve in the course of development of addiction, according to the Paradise Lost theory.

hobbies other than smoking, and some individuals with alcoholism insist that they cannot enjoy nonalcoholic beverages and are uninterested in pursuing pleasurable activities that they had previously enjoyed.

This kind of alteration in thinking has been described as the cognitive distortion associated with addiction (Beck, Wright, Newman, & Liese, 1993; World Health Organization, 2004). According to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, dependence syndrome is defined as “a cluster of behavioral, cognitive, and physiological phenomena... that are typically [characterized by]... a higher priority given to drug use than to other activities and obligations.” Since repeated smoking, drinking, and gambling can lower the response to non-drug rewards, addiction can disable addicts from sensing the pleasures of ordinary life. When this happens, the resulting cognitive change can be strong and have lasting effects, because it is often accompanied by a physical feeling. For example, an individual who is addicted to gambling and used to buy his family souvenirs with his winnings (i.e. social reward was obtained from the family’s smiling faces) will no longer buy souvenirs at all (i.e. the reward is no longer obtained from his family after the transition to addiction). This kind of change is the most common and essential feature of the onset of addiction. That is, even if addicts try to enjoy themselves by other means, they can no longer experience the previous level of reward from ordinary, everyday happiness, because their reward systems have been weakened neurologically.

This pattern reminds us of Adam and Eve in the biblical tale of “Paradise Lost” in Genesis, Chapter 3. Adam and Eve, tempted by the snake, ate the “forbidden fruit” and were banished from the Garden of Eden. Using tobacco in an analogy to this situation, we can understand the nature of addiction in the following way: the individual lost his/her of “Paradise,” or the everyday happiness he/she previously enjoyed, after eating the apple. After being banished from paradise, the individual become obsessed with drugs, which provide instant happiness because their stimulus strength can easily be elevated by increasing the quantity or frequency of consumption. Of course, there is a possibility that the individual’s risk-taking trait also plays a role. Nevertheless, the constant strengthening of the stimulus further increases the risk of lowering the reward system’s response to everyday happiness. Ultimately, the individual finds himself/herself in a vicious cycle of obsession with drug use.

LACK OF AWARENESS OF “PARADISE LOST” IS CRUCIAL

Neurological alterations begin at the very early stages of nicotine dependence (after fewer than 10 cigarettes have been smoked) and progress gradually.

Therefore, smokers are not generally aware of these changes, and this lack of awareness is crucial.

As long as smokers remain unaware of the effects of nicotine on their ability to experience happiness from ordinary pleasures, it is understandable for them to smoke cigarettes for instant gratification, even if short-lived. It is also understandable for smokers to be anxious about quitting, because they might be afraid that quitting will decrease the happiness and pleasure and increase the difficulty of life. Moreover, this cognitive alteration or misunderstanding among smokers (i.e. over-evaluation of tobacco) might continue even after they quit smoking, because it is established without smokers’ awareness.

We developed an index to assess this cognitive alteration: the Kano Test of Social Nicotine Dependence (KTSND; Otani et al., 2009). The maximum possible score is 30, and higher scores are associated with increased justification and admiration of smoking. Nonsmokers have been shown to display the lowest KTSND scores, nonsmokers who had experimented with smoking display the next-lowest scores, current smokers have the highest scores, and ex-smokers still show relatively high scores. This finding might indicate that the cognitive alteration continues for a long time, even after smoking cessation. Moreover, this persistent cognitive distortion may predispose former users to relapse because of their lack of awareness of being in a Paradise Lost state while they had been smoking.

The Paradise Lost theory on the development of nicotine dependence may be summarized by the following pattern of neurological and psychological events. First, smoking reduces the ventral striatal response to non-tobacco-related reward stimuli, which decreases happiness in daily life to such an extent that quotidian rewards cannot henceforth match the reward intensity of tobacco-related ones. Next, cognitive and behavioral changes occur, giving priority to smoking over happiness in daily life. Then, smokers continue to smoke, which causes further alteration of the neurological system. Finally, after smoking cessation, this cognitive distortion tends to remain and might cause relapse. These stages are illustrated in Figure 3.

These stages and the Paradise Lost theory may be applicable to other addictive substances and behaviors, such as alcohol, cocaine, and gambling. We suggest that this proposed mechanism may be a shared feature of all addictions and could help us to connect biological changes with psychological meanings.

This review has some limitations. First, it specifically focuses on the reward network, especially the ventral striatum. Other brain areas, such as the limbic system/emotional centers, are also relevant to addiction (Franklin et al., 2007). Therefore, this review does not encompass the entirety of the mechanism by which nicotine dependence develops. As for the mechanism of nicotine dependence, we do not imply that smoking a few cigarettes results in long-lasting hyporeactivity of

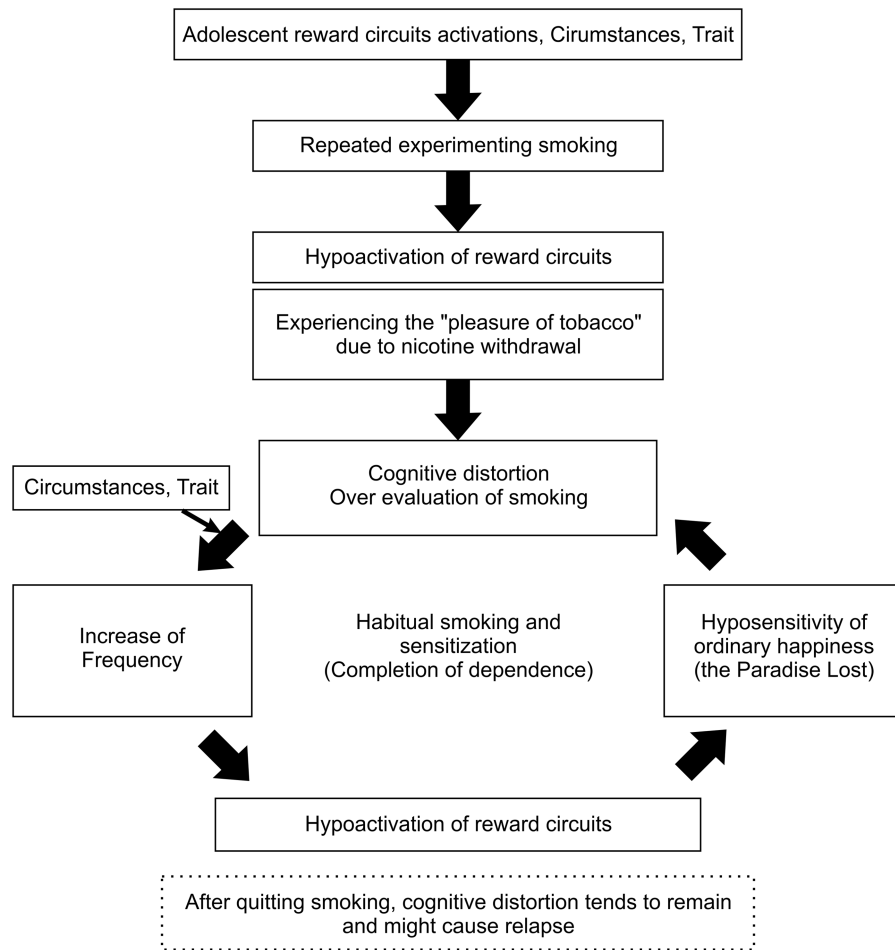


Figure 3. The process of formation of nicotine dependence, according to the Paradise Lost theory.

the reward circuits. Rather, we suggest that when hyporeactivity of the reward circuits is combined with cognitive distortion, people tend to continue smoking and become absorbed therein until they become dependent. In our study (Figure 1), 53 out of 115 students experienced the “pleasure of smoking.” Among them, only one remained a nonsmoker. The others were current or former smokers.

The factors that generate the difference in dependence between nondependent and dependent smokers have not been identified. Traits, circumstances, and experience should play important roles in making this determination. Van Rensburg, Taylor, Benattayallah, and Hodgson (2012) showed that abstinent smokers feel lower levels of cigarette cravings after exercise. They speculate that exercise functions as a tool to increase the strain on the brain’s information-processing capacity, causing hypoactivation in areas of the frontal cortex that are involved in reward processing and linked with cigarette cravings (Van Rensburg et al., 2012). Therefore, people whose lifestyles include much exercise and many activities that increase strain on the frontal cortex might be more capable of controlling their cravings and protecting themselves from addiction, as long as they can maintain their lifestyles if it is possible.

Dependent smokers who are ambivalent about smoking often report that exercise ameliorates their cigarette cravings. Then, what kind of particular thinking which needs higher cognitive function is suppressed in the frontal cortex when exercise is performed? More research is required in order to answer this question. However, smokers’ answers on this subject might emphasize the “positive” side of smoking, which would reflect cognitive distortion.

Tobacco smoking remains a major public health problem, and patients continue to struggle to maintain sustained cessation from it. By understanding the mechanisms by which nicotine dependence develops, we may better equip ourselves to offer effective treatments. Further research on the neurobiology of nicotine dependence is needed to confirm the Paradise Lost theory.

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