Opinion

Circuitry of self-control and its role in reducing addiction

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We discuss the idea that addictions can be treated by changing the mechanisms involved in self-control with or without regard to intention. The core clinical symptoms of addiction include an enhanced incentive for drug taking (craving), impaired self-control (impulsivity and compulsivity), negative mood, and increased stress reactivity. Symptoms related to impaired self-control involve reduced activity in control networks including anterior cingulate (ACC), adjacent prefrontal cortex (mPFC), and striatum. Behavioral training such as mindfulness meditation can increase the function of control networks and may be a promising approach for the treatment of addiction, even among those without intention to quit.

Intention and self-control in behavioral change

Traditionally, intentions are viewed as being crucial for behavioral change [1]. However, many influences on behavior are not conscious. Dual process models provide a role for both automatic (implicit) and controlled (explicit) processes that make complementary and possibly interactive contributions to changing addictive behavior [2]. ‘Automatic’ usually refers to either attention or memory bias toward the substance cues related to the addiction, whereas ‘controlled’ involves motivation and refers to a conscious intention that can be reported by the person [2]. Both automatic and controlled processes are involved in attempts to modify addiction. In the case of alcohol addiction, pharmacological therapies have been used to induce change automatically in animals and humans [3]. Behavioral methods have also been used to induce changes in addictive behavior without a specific intention. For example, one study used evaluative conditioning to associate drinking with unpleasant experience, and found a reduction in craving and consumption [4]. In another study, smoking behavior was reduced by an association induced during sleep in subjects who wished to quit smoking [5]. A recent review of decision making indicates that behavioral changes can occur with or without conscious intention [6].

In this opinion article, we examine how behavioral training methods may be used to induce automatic changes in smoking addiction by targeting neurobiological circuits involved in self-control that have been shown to be disrupted in addictions [7,8]. Brain self-control networks mainly include the ACC, mPFC, and striatum. Support for this network comes from many fMRI studies of activation of these areas during tasks involving the resolution of conflict [9] and control of thoughts and feelings [10]. A recent developmental study highlighted reduced white matter in these same networks in vulnerability to smoking addiction [11].

The relation of control networks to the instantiation of goals is supported by the finding that lesions of the frontal lobes are associated with a tendency to neglect goals during task performance [12]. Goals often involve a complex hierarchy of subgoals, which must be implemented in a

Glossary

Cortisol: a steroid hormone, more specifically a glucocorticoid, is produced by the adrenal cortex. It is released in response to stress and to a low level of blood glucose. Its functions are to increase blood sugar and suppress the immune system.
Dopamine receptor type 2 (D2R): one subtype of dopamine receptors. Dopamine receptors are implicated in many neurological processes, including motivation, pleasure, cognition, memory, learning, and fine motor control, as well as the modulation of neuroendocrine signaling.
Fractional anisotropy (FA): a parameter in diffusion tensor imaging that images brain structures by measuring the diffusion properties of water molecules. Higher FA indicates more-efficient connectivity and provides information about the microstructural integrity of the white matter.
Frontal theta: the theta rhythm is 4–8 Hz oscillatory pattern in EEG signals recorded either from inside the brain or from scalp electrodes. Frontal theta appears to reflect a computation related to cognitive control.
Integrative body–mind training (IBMT): a form of mindfulness meditation that originates from ancient Eastern tradition. IBMT stresses less effort to control thoughts and the achievement of a state of restful alertness, allowing a high degree of awareness and balance of the body, mind, and environment. Several randomized trials indicate that IBMT improves attention and self-regulation and induces neuroplasticity through interaction between the central nervous system and autonomic nervous system.
Mindfulness meditation: a form of mental training that originally stems from Buddhist meditation traditions and is often described as non-judgmental attention to experience in the present moment.
Oligodendrocytes: a type of neuroglia that function to help create a myelin sheath insulating axons in the central nervous system.
Network training: repeated practice of a specific cognitive task (e.g., Stroop task, N-back working memory task) that thus exercises its specific brain network (e.g., a network related to resolving conflict or working memory).
Parasympathetic function: a division of the autonomic nervous system that is responsible for regulating the unconscious actions of the body.
Relaxation training (RT): a behavioral therapy focuses on relaxing different muscle groups in turn. With eyes closed, and in a sequential pattern, one is instructed to concentrate on the sensation of relaxation, such as the feelings of warmth or heaviness.
State training: practice to develop a brain state that may influence the operations of many networks. This state involves networks, but is not designed to train networks using a cognitive task.

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sequence. An fMRI study in which participants carried out a task involving multilevel goals [13] found that the ACC and anterior insula are core areas involved in switching between subgoals. As more complex switches are carried out, lateral frontal and parietal areas are recruited. Research on the regulation of action control has revealed a substantial gap between intentions and action [14,15]. A meta-analysis showed that a medium-to-large change in intention only leads to a small-to-medium change in behavior [15].

In the next section we discuss neurobiological findings from imaging studies of addiction. We then examine what is currently known about the development of the brain circuits (or functional networks) that are necessary for self-control and the transition of self-control from infancy and childhood to adulthood. Next we introduce mindfulness meditation methods that have been shown to modify brain regions within the self-control network, and demonstrate the promise of these methods in reducing drug-taking behaviors such as smoking. Finally we discuss future directions that may allow us to better understand the influence of intention in efforts to overcome addiction.

Addiction networks and deficits of self-control

Studies of humans are revealing neuroadaptations in frontocortical regions of the brain that underlie compulsive drug-seeking behaviors in addiction [16]. Imaging studies have provided compelling evidence for the involvement of the brain control network areas, such as ACC and adjacent mPFC, in the addiction process [17,18].

Dopamine

Humans addicted to drugs display a significant reduction in dopamine receptor type 2 (D2R) function in the striatum (including the nucleus accumbens, NAc) that is associated with reduced activity in ACC and adjacent prefrontal regions. The reductions in striatal D2R, which modulate the indirect striato-cortical pathway, have been implicated in impulsive and compulsive behaviors [7,19]. In addition, the capacity of cocaine addicts to control craving and reduce activation of the NAc upon exposure to drug cues is dependent on the proper activity of the prefrontal cortex [20]. Targeting the frontal impairments in addiction has been proposed as a therapeutic strategy to improve self-control [21,22]. Figure 1 illustrates the connection of the self-control circuits and those crucial for reward.

The circuits illustrated in Figure 1 are associated with compulsive behaviors and impulsivity, and impaired dopamine modulation of these regions is likely to contribute to the drug intake seen in addiction [18]. Low dopamine tone could also represent a pre-existing vulnerability for drug use, albeit one that is likely to be exacerbated with the further decreases in striatal D2R that are associated with repeated drug exposure.

Craving

A major problem in overcoming addiction is craving. Craving can lead to relapse during attempts to quit smoking. Craving is associated with activation in ACC, mPFC, orbitofrontal cortex (OFC), striatal areas [23], and insula [24]. Trying to resist the urge to smoke is almost always

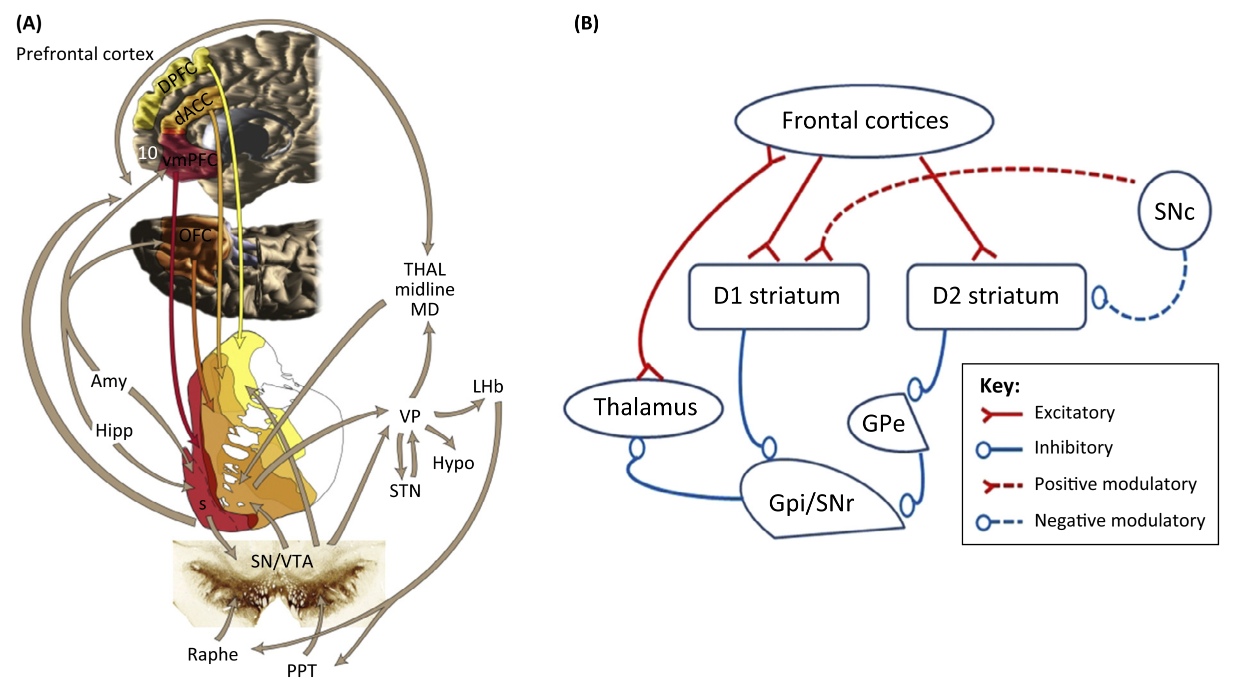

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Figure 1. Reward circuits and pathways of basal ganglia. **(A)** Key structures and pathways of the reward circuit. Arrows indicate main connections of the reward circuit. Abbreviations: Amy, amygdala; dACC, dorsal anterior cingulate cortex; dPFC, dorsal prefrontal cortex; Hipp, hippocampus; hypo, hypothalamus; LHb, lateral habenula; OFC, orbital frontal cortex; PPT, pedunculopontine nucleus; S, shell, SNc, substantia nigra, pars compacta; STN, subthalamic nucleus; Thal, thalamus; vmPFC, ventral medial prefrontal cortex; VP, ventral pallidum; VTA, ventral tegmental area. Reprinted from [74] with permission from Nature Publishing Group. **(B)** Direct and indirect pathways of the basal ganglia (BG). The principal input of BG is the striatum, receiving excitatory inputs from most cortical areas. The output nuclei of BG are the internal globus pallidus and substantia nigra reticulate (GPi/SNr), which send processed information to the thalamus to eventually feed back an excitatory projection to the cortex. Within this circuitry there are two pathways: a direct pathway that expresses dopamine D1 receptors and an indirect pathway that expresses D2 receptors. D1 striatal neurons inhibit GPi/SNr cells forming the direct pathway. D2 striatal cells inhibit an intermediate relay, the external globus pallidus (GPe), which ultimately provides inhibition to GPi/SNr. Reprinted from [75].

accompanied by some degree of craving [25,26]. Neuroimaging studies have shown that craving and craving resistance often involve similar brain networks in ACC and mPFC [26]. However, intention to avoid a thought (suppression of unwanted thoughts) often leads to thinking about the very thought one hopes to suppress [27,28]. In other words, what we resist persists. Thus, attempts to suppress thoughts about using substances may actually lead to increases in substance use [29].

Individuals at risk for substance abuse typically have deficits in self-control. Self-control deficits are related to decreased ACC/PFC activity and reduced ACC–striatum connectivity, which could enhance the risk for smoking and other addictions [17,30–35]. Our previous findings indicate that ACC/PFC and striatum activity and connectivity can be improved through a form of mindfulness meditation: integrative body–mind training (IBMT, see Glossary), described below [35–38].

Development of self-control

It has recently become common to study the brains of infants, children, and adults while they are resting to map functional networks in the brain (resting-state fMRI) [39]. Resting-state fMRI methods for mapping brain functional connectivity can be applied at any age because they do not require the person to perform a task, and are reproducible across laboratories and within subjects. They also predict an individual's brain maturity across development [40].

Resting-state studies have shown that, during infancy and early childhood, most brain networks involve short connections between adjacent areas, but the long connections important for self-control develop slowly over childhood and are not mature until young adulthood [41–43]. One of the main networks, the executive attention network, which includes the ACC and adjacent midline prefrontal cortex (mPFC), is involved in resolving conflict and relates to parental reports of the ability of their child to control their own behavior [34,41,44,45]. In addition, an fMRI study of 725 children age from 4 to 21 years showed a relationship between the ability to resolve conflict in a flanker task and the size of the right dorsal ACC in the early years of childhood [46]. It has been shown in many studies that the time to resolve conflict is related to parental reports of their children's ability to control their behavior using questionnaires designed to measure effortful control [45,46]. The study further showed that, in later years (above age 7), overall speed on the task depended on ACC connectivity to other cortical areas [46].

Development in many aspects of control continues into adolescence and young adulthood [47]. The timing of these changes in control networks is believed to underlie the dramatic increases in risk-taking behaviors (including substance use disorders, SUDs) that emerge in the transition from childhood to adolescence and in young adulthood [9,48]. Because low measures of self-control in childhood are associated with greater risk for SUDs [49], interventions that target strengthening of self-control in children might decrease risk for substance abuse [50,51].

Training self-control

In the case of smoking, participants are usually recruited who intend to reduce or quit smoking. However, some evidence suggests that the intention is not a prerequisite for overcoming addiction in drinking [4]. Moreover, given the central role of self-control in addiction, interventions that improve self-control capacity – with or without the intention to quit – have the potential to be effective in combating addiction. This section examines methods designed to improve self-control.

Brain networks and states

There are two very different methods for achieving improvements in self-control; one is network training and the other is state training [52]. Network training involves repeated practice of a specific task (e.g., attention, working memory), thus exercising its specific brain network [53–55]. Network training has been considered as a potential approach to improve executive attention and to bolster control processes that may aid attempts to quit, but to our knowledge this attempt has not been successfully applied to treating addiction [56]. State training uses practice (e.g., physical exercise, mindfulness meditation) to develop a brain state that may influence the operations of many networks. Research has shown that brain-state training can significantly improve executive function, emotion regulation, and neuroplasticity through the modulation of self-control networks [55,57].

Mindfulness meditation and addiction

A self-control framework of mindfulness meditation has three key components: attention control, emotion regulation, and improvement of self-awareness. Based on previous research, the core brain areas involved in self-control include the ACC, mPFC, and striatum [58]. These regions show reduced activity in drug users [17,58,59]. There is emerging evidence that mindfulness meditation has the potential to ameliorate negative outcomes resulting from deficits in self-control by regulating the same core regions [31,58,60–62].

A review of mindfulness training as a treatment for addiction showed a reduction in craving and smoking following training [63]. However, many of the studies were criticized because of lack of randomization and weak controls, and the review called for more rigorous and randomized controlled studies. Recently, a few rigorous and randomized studies have tested the effect of mindfulness meditation on addictions [35,64]. For example, compared to treatment as usual (12-step programming and psychoeducation), eight weekly group sessions of mindfulness-based relapse prevention resulted in significantly lower risk of relapse to substance use and heavy drinking among participants [64]. IBMT, one form of mindfulness, has been tested in several randomized controlled trials that indicate a very rapid change in brain state, including both the central and autonomic nervous systems [35–38,65]. IBMT involves systematic training of attention and self-control with an attitude of acceptance and openness to internal and external experiences [55,58,66]. The control group was given relaxation training (RT), popular in the West, as a part of cognitive behavioral therapy. A few hours of IBMT

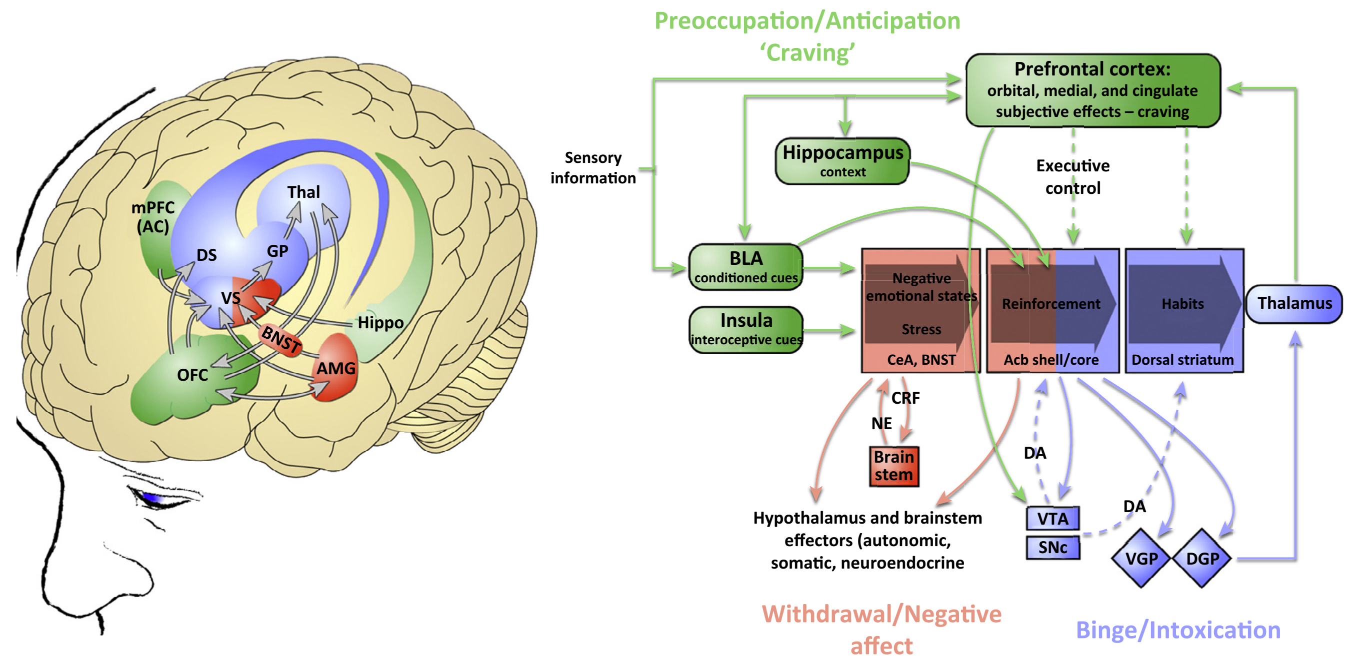

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Figure 2. Brain adaptive circuits in three stages of addiction. Schematic illustrating the combination of neuroadaptations in the brain circuitry for the three stages of the addiction cycle that promote drug-seeking behavior in the addicted state. Note the activation of the ventral striatum/dorsal striatum/extended amygdala, driven by cues through the hippocampus and basolateral amygdala, and by stress through the insula. The frontal cortex system is compromised, producing deficits in executive function and contributing to the incentive salience of drugs compared to natural reinforcers. Dopamine systems are compromised, and brain stress systems such as corticotrophin releasing factor are activated to reset further the salience of drugs and drug-related stimuli in the context of an aversive dysphoric state [59,76]. Adapted, with permission, from [59] and [76] and based on [77].

resulted in significantly greater improvement than RT in the executive attention network (shorter time to resolve conflict), and in their mood (increased positive mood and reduced negative mood). IBMT also decreased levels of the stress hormone cortisol and increased immune reactivity [65,67].

Further research revealed specific changes in brain activity and white matter structure following IBMT as assessed with neuroimaging [36–38]. The IBMT group improved functional activity and connectivity between the ACC and striatum [36,68]. Moreover, parasympathetic function changed more in the IBMT than in the RT group [36]. Further studies using diffusion tensor imaging (DTI) revealed that several white matter tracts that connect the ACC (part of the executive attention/self-control network) with other areas showed improved integrity, as measured by fractional anisotropy (FA), following IBMT compared to RT [37,38,69,70]. These results suggest that IBMT may be an effective self-control approach for reducing stress and improving emotion associated with the core symptoms of addictions.

The core clinical symptoms of addiction include an enhanced incentive for drug taking (craving), impaired self-control (impulsivity and compulsivity), negative mood, and increased stress-reactivity [59] (Figure 2). These symptoms are related to reduced activity in core areas involved in self-control and emotional reactivity. Because a few hours of IBMT appears to improve activity and connectivity in self-control areas and modulate stress and emotional reactivity, training in mindfulness meditation may be helpful for coping with addiction symptoms and the accompanying negative emotion and increased stress-reactivity [58].

Mindfulness meditation can have an automatic effect if the addicted participants are unaware that mindfulness training is an effort to reduce addiction. A recent randomized training study tested this idea [35]. Figure 3 illustrates the overall framework for the study. Participant recruitment was for stress reduction and was not specifically related to the intention to quit smoking. Before training, smokers demonstrated reduced activity in ACC, PFC, and other areas during rest compared to nonsmokers, consistent with the association between impaired self-control and addiction. Two weeks of IBMT (5 h in total) produced a significant reduction in smoking (60%), whereas no reduction was found in the RT control. Resting-state MRI showed increased activity for the IBMT group in the ACC and mPFC, key brain areas for self-control, and this was associated with a reduction in smoking behavior [35]. To test whether intention related to the reduction of smoking, we measured intention using self-report questionnaires and found that conscious intention did not make a significant difference in smoking reduction. These results suggest that brief mindfulness meditation improves self-control capacity and reduces smoking even without a conscious intention to do so [35]. It should be noted that, even though an informal study showed that smoking reduction still remained a month later, only several participants were contacted, and more research is needed on the lasting effect of mindfulness meditation.

The finding that a significant reduction in craving occurred following 2 weeks of IBMT [35] leads us to speculate

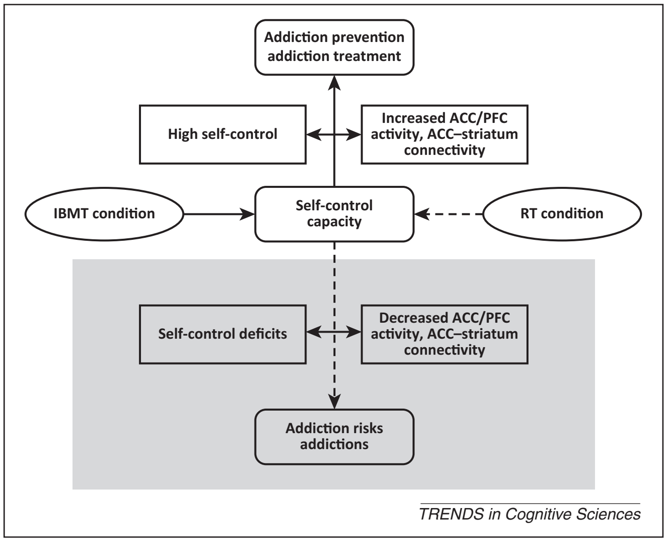

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Figure 3. Self-control networks and addictions. Self-control capacities improve following IBMT (but not RT) through increased ACC/PFC activity and ACC–striatum connectivity, and high self-control helps addiction prevention and treatment (e.g., smoking reduction or quitting). Self-control deficits are associated with decreased ACC/PFC activity and ACC–striatum connectivity, and addiction (gray area). Abbreviations: ACC, anterior cingulate cortex; IBMT; integrative body–mind training; PFC, prefrontal cortex; RT, relaxation training.

that the increased ACC activity and ACC–striatum connectivity suppressed craving even without the participants' conscious intention. There are several routes through which mindfulness could influence addiction. IBMT reduced the amount and duration of cortisol to a stressful challenge [65,67]. Human and rodent work has shown that stress, which frequently triggers relapse to drug taking in addicted individuals, disrupts connectivity of frontal and ACC brain areas [71]. Moreover, stress-induced disruption in frontal–ACC connectivity is greater in people with low working memory capacity who, in turn, are at greater risk for becoming addicted [72]. In as much as IBMT reduces stress, this may work to reduce addiction. Another possible explanation for IBMT effectiveness is based on the finding that mindfulness practice leads to a non-judgmental stance (awareness and acceptance) regarding addiction, which could reduce negative emotion, conflict, and stress, and thus lead to reduced smoking. In fact, present-moment awareness and non-judgmental acceptance through mindfulness meditation are crucial in promoting executive (cognitive) control because they increase sensitivity to affective cues in the experiential field that help signal the need for control [73]. There are clearly other possibilities. These various explanations are not mutually exclusive, and improved self-control may itself be related to both stress and judgmental changes.

Concluding remarks and future directions

Is conscious intention required for a change of addictive behavior? In most smoking studies, participants were either recruited based on their intention to quit or their awareness about the goal of reduced smoking [63]. Future research needs to study how this awareness relates to the reduction of drug taking in addiction. It remains to be seen if the conscious intention to quit, and strengthening of self-control by training, have separate additive therapeutic influences on addictions such as smoking reduction, or whether the two together reduce smoking to a greater or lesser degree than their additive effect would predict. If intention and training are additive, the neural systems involved should be studied. If intentions interact with training, the brain mechanisms responsible for this interaction need to be examined.

Some other forms of addiction, such as addiction to cocaine, involve similar pathways to those involved in addiction to tobacco. They might serve as a more general test of the relationship between intention and self-control in addiction. Moreover, various behavioral addictions such as obesity, gambling, and excessive use of the internet could potentially also be addressed with training of self-control. Combining improvements in self-control with appropriate motivation may be a particularly effective approach for treating addiction.

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