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Wiers, R.W.; Larsen, H.

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Training cognitive-motivational processes underlying self-control in addiction

Reinout W. Wiers and Helle Larsen

In this chapter, we will discuss recently developed methods that directly target cognitive-motivational processes to enhance self-control in addiction. Before doing so, we first briefly discuss current theoretical models underlying this approach. In the next section, we summarize findings of different training-methods in the field of addiction. The final section presents new challenges and possible ways forward.

Cognitive-motivational processes and addiction

Lack of self-control is a central concept in definitions of addiction, including substance use disorders as well as psychological addictions, such as gambling or compulsive internet use (usually gaming or porn-watching). Many of the diagnostic criteria (DSM5 or ICD10) are manifestations of lack of self-control, such as: doing the addictive activity longer than intended; wanting to quit or cut down, without being able to do it; failing to carry out other obligations; continuation of the addictive activity despite recurring problems or despite recurrent physical or psychological problems. Hence, failure of self-control is intimately related to the borderline of when we consider a potentially addictive activity as having escalated out of hand. Many people drink moderate amounts of alcohol (or use other drugs or gamble once in a while), without a problem; it is only when the behavior is out of control despite harmful consequences that we start calling it an addiction. Note that the amount of self-control over behavior is subjective and that it is therefore perfectly well possible that two people drinking the same amount of alcohol in the same pattern differ in their perceived control, and therefore in their diagnosis (Rehm et al., 2013). What constitutes controlled drinking (or other potentially addictive activities) is largely culturally defined. What would be considered excessive drinking in one culture would be considered perfectly normal in another (sub)culture. However, damage attributable to the addictive behavior is primarily related to amount of use, at least for alcohol (Rehm et al., 2013), irrespective of the attributed subjective self-control, one of the reasons why the authors plead for the concept of “heavy use over time”, rather than addiction. This reformulation also leads the way to the appropriate behavior change (drink less), which could be less obvious when one views addiction as a chronic brain disease (typical in the biomedical literature).

Self-control processes in addiction are about not giving in to the lure of immediate gratification (repeating the addictive behavior), which would go at the expense of long-term goals (gains associated with quitting or reducing the addictive behavior). This implies that, to experience the self-control conflict, the person needs to be aware of the long-term negative consequences of the addictive behavior, and must have at least some motivation to forgo drug use, when the opportunity to return to the addictive behavior is there. As we argued elsewhere, craving is strongly related to experiencing this conflict (Wiers, Field, & Stacy, 2014): one experiences a subjective urge to engage in the addictive activity, while realizing that there are good reasons to not do so. Note, however, that craving or experiencing conflict are not necessary for the addictive behavior to occur: depending on (sub)cultural norms, it may be considered perfectly appropriate to take part in the addictive behavior (hence no conflict), as long as this behavior is considered within the boundaries of that context. Moreover, often-repeated actions become habitual, and this may be a strong driving force in addictive behaviors, as some neurobiological models of addiction have emphasized (Everitt & Robbins, 2005). In both these cases, the addictive behavior is not related to an experienced self-control conflict, and a first step in an intervention could be to create a self-control conflict. This is exactly what Motivational Interviewing (MI) attempts to do, by helping the client to make the long-term negative effects of continuation of the addictive behavior more salient, as well as activating alternative long-term goals that are incompatible with continuation of the addictive behavior (Miller & Rollnick, 2013). The cognitive training techniques described below appear to be particularly helpful in addictive behaviors when self-control problems are indeed important: when individuals have developed an addictive behavior and a desire to quit or reduce, but have experienced difficulties in doing so (Wiers, Becker, Holland, Moggi, & Lejuez, 2016). When this is not the case, the training should be embedded in an appropriate motivational context.

Many of the training modalities discussed below were developed from a dual-process perspective. From this perspective, different processes (or even systems) are responsible for the motivation to indulge in the temptation and for the processes needed to forgo the lure of the temptation, typically referred to as impulsive or automatic processes and reflective or controlled processes, respectively (e.g., Wiers & Stacy, 2006). However, dual-process models have been criticized for lack of clear mechanisms and lack of evidence for dissociable systems (e.g., Keren & Schul, 2009). More recent theoretical models, which have been inspired by cognitive and affective neuroscience have emphasized *processing-time* as a crucial factor: in many cases, first an impulsive or preconscious reaction to a stimulus is generated (e.g., an incentive response to a glass of beer in the ex-alcoholic), which subsequently unfolds, with progressively more influence from conscious goals and desires, which can down-regulate the initial response within the second (e.g., Cunningham, Zelazo, Packer, & Van Bavel, 2007). From this perspective, cognitive training could help in the down-regulation of the initial impulse, provided that alternative long-term goals are activated (e.g., Kopetz, Lejuez, Wiers, & Kruglanski, 2013; Wiers et al., 2016). The cognitive training either focuses on re-training the automatic tendencies to approach or attend to addiction-related stimuli or strengthen control capacities. This perspective is closely related to the notion of hierarchical levels of control over behavior (see further Wiers et al., 2016).

The cognitive-motivational trainings presented in the next section can be categorized with respect to the cognitive process they address: selective attention for cues related to the addictive behavior (attentional bias), memory associations (memory bias or interpretation bias), action tendencies (approach-bias), and cognitive control processes. The first three are considered maladaptive cognitive biases, which are targeted with the aim to reduce their influence on the behavior, in varieties of cognitive bias modification procedures. The final class of training paradigms are aimed at increasing cognitive control and/or its effects on the targeted behavior.

Training self-control in addiction

Attentional bias modification

Following dual-process models, attentional biases are relatively automatic processes that occur especially when the ability to control these processes is low (Wiers & Stacy, 2006). They are characterized by the tendency to allocate attention to drug-related cues in the environment. For example, craving for alcohol may be triggered by seeing a beer bottle. The first attentional bias modification procedure was developed in the domain of anxiety, by Colin MacLeod and colleagues (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). They modified an assessment instrument (the visual probe test, developed by the first author some 25 years earlier) into a modification instrument. In an assessment instrument, the probe to which people react (e.g., an arrow pointing up or down) appears equally often in the location previously occupied by target stimuli (e.g., addiction-related cues) and by neutral stimuli. Participants are required to press the up-arrow key if the arrow is pointing up and the down-arrow key if the arrow is pointing down. The attentional bias is then calculated by subtracting the reaction times from when the arrow probe appears behind the addiction-related stimuli from the reaction time when the arrow probe appears behind the neutral stimuli with positive scores indicating an attentional bias for addiction-related stimuli. In a training version of the task, a contingency is introduced, with the probe appearing more often behind the target stimulus (inducing a bias), or more often behind the neutral stimulus (reducing a bias). Attentional biases have been found for alcohol (e.g., Field & Cox, 2008; Janssen, Larsen, Vollebergh, & Wiers, 2015), smoking (e.g., Ehrman et al., 2002), and opiates (e.g., Frankland, Bradley, & Mogg, 2016). Subsequent research in this domain investigated clinical applications, typically with multiple training sessions of attentional bias modification, with successful studies in clinically anxious patient groups (Amir, Beard, Burns, & Bomyea, 2009), and in targeted prevention (See, MacLeod, & Bridle, 2009), although it should be noted that more recent (mostly internet-based) studies in this domain have been less successful (Cristea, Kok, & Cuijpers, 2015). A further analysis of these mixed results indicated that, in line with the theoretical rationale of cognitive bias modification, those studies in which the bias was successfully changed almost invariably also demonstrated clinical effects, while the studies in which the bias was not successfully changed did not (Clarke, Notebaert, & MacLeod, 2014).

In the domain of addiction, research followed with a number of “proof of principle” studies, modeled after the seminal study of MacLeod and colleagues (2002). These studies involved a single session of attentional bias modification, assessing close generalization (whether training effects transfer to different stimuli in same task) and further generalization (whether training effects transfer to different tasks, craving, and substance use). These studies showed a consistent pattern: an attentional bias for alcohol (Field et al., 2007) and smoking (e.g., Attwood, O’Sullivan, Leonards, Mackintosh, & Munafo, 2008) could be modified in both directions. However, no evidence for generalization was found for single session attentional bias modification (Field et al., 2007). More encouragingly, the first two studies using *repeated* attentional bias modification in non-clinical problem drinkers (Fadardi & Cox, 2009), and alcohol-dependent patients in treatment (Schoenmakers et al., 2010), both found more promising effects. Fadardi and Cox (2009) developed an adaptive training procedure based on a pictorial alcohol Stroop task. Across various samples, this procedure resulted in a reduced attentional bias for alcohol, which was accompanied by an increased motivation to change drinking and reduced drinking levels. However, interpretation of the findings is hindered by the lack of a control group, and in a more

recent internet-delivered study, a reduction in alcohol use was found both in the training group and in the control group (Wiers, Houben et al., 2015).

Schoenmakers and colleagues (2010) used a variation of the visual probe test in a small randomized clinical trial with alcohol-dependent patients. Patients in the experimental condition received five sessions of attentional bias modification. Results showed the expected effect of training on the attentional bias at 500 ms presentation, with patients in the experimental condition decreasing their alcohol-attentional bias, while participants in the control condition (who performed an unrelated task) showed an increase in alcohol-attentional bias, which previous research found to be associated with subsequent relapse (Cox, Hogan, Kristian, & Race, 2002). A significant effect on time to relapse was found, with patients in the attentional bias modification condition taking on average over a month longer to relapse, but this finding should be considered as preliminary, given the small sample size (Schoenmakers et al., 2010). Encouragingly, a recent study on repeated attentional re-training to support smoking cessation over the internet (Elfeddali, de Vries, Bolman, Pronk, & Wiers, 2016) found clinically relevant effects in heavy smokers (no effects in light smokers), with 47% of participants remaining abstinent in the experimental cognitive bias modification condition, compared with 23% remaining abstinent in the continued assessment control condition (but as often in internet-trials, drop-out was high). Hence, one could argue that attentional bias modification holds promise as a tool to maintain self-control over addictive behaviors, although a more critical appraisal is also possible (Christiansen, Schoenmakers, & Field, 2015). We argue below that the approach is promising when provided in the right motivational context; in people with a desire to quit but who do not succeed because of strong bottom-up reactivity to addiction-related cues, and lacking self-control abilities to deal with the resulting urge.

Action-tendency bias modification

Approach-biases are also relatively automatic processes, which are triggered tendencies to approach rather than avoid drug-related stimuli, especially when the ability to control these processes is low (Wiers & Stacy, 2006). An approach-bias can be detected using different tasks. In the stimulus-response compatibility task, participants have to move a manikin toward a substance-related picture in one block (and away from other pictures), and in another block away from the substance (and toward other pictures). With this task, an approach-bias has been found for cigarette-cues in smokers (Mogg, Bradley, Field, & De Houwer, 2003), for marijuana-cues in marijuana users (Field, Eastwood, Bradley, & Mogg, 2006), and for alcohol in heavy drinkers (Field, Kiernan, Eastwood, & Child, 2008). Relatively strong associations between alcohol and approach-words have also been found using a variety of the Implicit Association Task (IAT; Ostafin & Palfai, 2006). Wiers, Rinck, Dictus, and Van den Wildenberg (2009) developed an Alcohol-Approach Avoidance Task (Alcohol-AAT), which has subsequently been used to re-train this bias. The AAT is a joystick-task in which participants react by pushing or pulling a joystick, depending on a feature of the stimulus unrelated to the contents (e.g. picture format, landscape or portrait). The AAT contains a “zoom-feature”: upon a pull movement, the picture size on the computer screen increases, and upon a push movement, it decreases, which generates a strong sense of approach and avoidance, respectively (Neumann & Strack, 2000), and disambiguates the task because it gives a visual impression of push and pull (Rinck & Becker, 2007). Note that the Alcohol-AAT is a so-called irrelevant-feature task: participants react to a feature of the stimulus unrelated to the contents (e.g., format or tilt), while in the stimulus-response compatibility task and IAT, participants have to categorize a content-relevant aspect of the stimulus (relevant-feature task).

While irrelevant-feature versions make the task less susceptible to explicit participant control, they typically have a lower reliability than relevant-feature tasks (e.g., Field, Caren, Fernie, & De Houwer, 2011). With the AAT, heavy drinkers (Wiers, Rinck et al., 2009) and alcoholic patients (Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011) demonstrated an approach-bias for alcohol. This bias was moderated by the *g*-allele of the *OPRM1* gene: carriers of a *g*-allele demonstrated a particularly strong approach-bias for alcohol, as well as for other appetitive stimuli (Wiers et al., 2009). In line with earlier research, no approach-bias was found for normatively positive or negative stimuli, with the irrelevant-feature AAT (note that the compatibility effect is typically found using a relevant-feature instruction: pull positive and push negative is easier than the reverse instruction). The fact that an approach-bias is found for addictive substances in an irrelevant-feature paradigm, while it is not found for general emotional stimuli, may indicate that it is especially relevant for appetitive stimuli (Wiers et al., 2009). Also, there is an approach-bias for cannabis-related stimuli, assessed with the AAT predicted escalation of use in young heavy users (Cousijn, Goudriaan, & Wiers, 2011).

Using the same logic as in attentional bias modification, the Alcohol-AAT was turned into an action-tendency bias modification instrument, by changing the contingencies of the percentage of alcohol-related or control pictures that were presented in the format that was pulled or pushed. In a first study, students were randomly allocated to a training condition in which they were either trained to approach alcohol (90% of the alcohol pictures came in the format which was pulled) or to avoid alcohol (90% of the alcohol pictures in push-format). Remarkably, in light of the consistent failure to find generalized effects after a single training session in addictive behaviors, in this first application of action-tendency bias modification, generalized effects were found both in the same task with untrained pictures and in a different task, employing words instead of pictures (approach avoid alcohol-IAT, Ostafin & Palfai, 2006). In those participants who demonstrated the change in approach-bias in the expected direction, an effect on subsequent alcohol use during a taste-test was found.

In a first clinical application of action-tendency bias modification (Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011), 214 alcohol-dependent patients were randomly assigned to one of two experimental conditions, in which they were trained to make avoidance movements (pushing a joystick) in response to alcohol pictures or to one of two control conditions, in which they received no training or sham-training (which did not differ for the results). Four sessions of training preceded regular inpatient treatment. In the experimental conditions only, patients' approach-bias changed into an avoidance-bias for alcohol. This effect generalized to untrained pictures in the task and to an IAT, in which alcohol and soft-drink words were categorized with approach and avoidance words. Patients in the experimental conditions showed better treatment outcomes a year later (13% less relapse), which was significant after controlling for gender. The clinical effect was not significantly related by either the change of bias as assessed with the AAT or with the IAT, although further analyses did confirm mediation by a subset of responses in the IAT (Gladwin et al., 2015).

In a large replication study (Eberl et al., 2013), 509 alcohol-dependent patients received either twelve sessions of action-tendency bias modification or no training (sham-training was left out because no difference was found between sham-training and no training in Wiers et al., 2011). Clinical effects one year after treatment discharge were again found (9% less relapse), and in this study mediation and moderation were found: the effect on clinical outcome was mediated by a change in the approach-bias for alcohol, and the strongest training-effect was found for participants with the strongest approach-bias for alcohol. This finding is important for theoretical reasons (because it confirms the cognitive-motivational mechanism underlying the small but stable clinical effect). However, the fact that hundreds of participants are needed

to show this moderation effect indicates that at an individual level it is hard to select participants in a meaningful way for this type of training. This is undoubtedly related to the relatively poor reliability of irrelevant-feature measures (cf., Field et al., 2011). One option could be to use a relevant-feature measure to assess the initial bias, such as the manikin-task, but the two tasks are often uncorrelated, making this no viable alternative. One interesting recent alternative for re-conceptualizing and measuring cognitive biases could be to develop new variance-based measures to capture possible fluctuations and phasic bursts of cognitive biases in real-time (Zvielli, Bernstein, & Koster, 2015).

In summary, action-tendency bias modification has a small but replicable clinical effect when added to traditional treatment for alcoholism. However, in the aforementioned online study (Wiers, Houben et al., 2015), also for action-tendency bias modification no difference was found between active and control conditions (heavy drinkers reduced drinking in all conditions). Action-tendency bias modification is therefore at this moment probably the best-supported form of cognitive bias modification, *as an addition to regular treatment for alcoholism*, which does not imply that it should be considered as proven-effective treatment in itself. Given the presence of an approach-bias for other substances as well, it would seem a logical next step to investigate the effects of approach-bias re-training for other addictions as well. First pilot-studies with placebo-conditions have been undertaken for smoking cessation with indication of effects (Larsen et al., 2015). In addition, further research into neurocognitive mechanisms underlying this training is important, with first findings indicating stronger changes in emotional-motivational brain areas in real cognitive bias modification than in sham-training (C. E. Wiers, Stelzel et al., 2015), in line with the idea that cognitive bias modification may help to down-regulate the initial motivational response to an addiction-relevant cue.

Memory and interpretation bias modification

A third cognitive bias associated with addictive behaviors concerns varieties of memory biases and the related concept of an interpretation bias. Implicit memory biases reflect associations between mental representations in memory and are measures of attitudes that people may be unwilling or unable to report. Following dual-process models, similar to attentional biases and approach-biases, memory biases are relatively automatic processes that are dependent on the ability to control these processes (Wiers & Stacy, 2006). Heavy drinkers have stronger positive and arousal associations than light drinkers (meta-analysis: Rooke, Hine, & Thorsteinsson, 2008). One way to change evaluative associations is through evaluative conditioning, as shown in many studies (meta-analysis: Hofmann, De Houwer, Perugini, Baeyens, & Crombez, 2010). In this procedure, stimuli of a specific category (e.g. alcoholic drinks) are paired with an evaluative category (positive or negative). While most research into evaluative conditioning focused on creating evaluative associations with new categories, the primary question here is whether *existing* associations can be changed through this procedure. Two studies by Houben and colleagues found that this is indeed possible (Houben, Havermans, & Wiers, 2010; Houben, Schoenmakers, & Wiers, 2010). In the first study, it was found that pairing alcohol to negative pictures resulted in stronger negative alcohol associations (assessed with an IAT) and reduced drinking compared with a control condition in which alcohol pictures were paired with neutral pictures. The second study also found effects of evaluative conditioning on explicit attitudes, craving, and subsequent drinking behavior, both in a taste-test and in self-reported consumption during the week after the experiment. To the best of our knowledge, evaluative conditioning has not been tested yet in a clinical context.

In anxiety, a different type of cognitive bias modification has been used successfully, both in clinical and in non-clinical samples: interpretation bias re-training (meta-analysis: Hallion & Ruscio, 2011). In this variety of training, typically an ambiguous situation, such as “You are going to the cinema with some friends. This includes buying something yummy to eat and to drink. You buy some . . .” (alcohol or soda; Woud, Hutschemaekers, Rinck, & Becker, 2016), is sketched which can be resolved into a disorder-related interpretation or a benign interpretation. In the training variety of the task, participants are trained systematically toward the benign interpretation. Woud and colleagues have made first attempts to assess interpretation biases in addiction (Woud, Fitzgerald, Wiers, Rinck, & Becker, 2012), but initial results of training this bias in alcohol-dependent patients have been rather disappointing (Woud et al., 2016).

A final recently developed intervention relevant here concerns selective inhibition, a procedure in which a specific category of responses is behaviorally paired with a NoGo response, using an adapted version of a Go/NoGo task (Veling, Holland, & Van Knippenberg, 2008). Houben and colleagues applied this method to alcohol in heavy drinkers (Houben, Nederkoorn, Wiers, & Jansen, 2011) and found that selective inhibition of alcohol led to stronger negative alcohol associations, and to reduced alcohol intake, compared with the control condition. In a subsequent replication study (Houben, Havermans, Nederkoorn, & Jansen, 2012), the effects on implicit attitudes and short-term drinking behavior were replicated, in the absence of an effect on general response inhibition assessed with a Stop-task. This confirmed that this procedure primarily devaluates the inhibited category, and does not lead to an increased efficiency in inhibition in general.

A recent meta-analysis found a small but homogeneous effect of inhibitory control training on behavior (Allom, Mullan, & Hagger, 2016). Note that this analysis combined two different types of inhibition training: training of general inhibitory capacity (without reference to the addictive behavior, with a Stop Signal Task), and selective inhibition, where responding to one category is systematically inhibited (either with an adapted Go/NoGo task or with an adapted Stop Signal Task). A stronger effect was found for selective inhibition with the Go/NoGo task ($d = .5$) than for Stop Signal Task-based inhibition training, which combined selective and general inhibition training studies ($d = .25$). For selective inhibition training, promising effects were found both for alcohol and for overeating. This technique has not yet been tested in clinical alcohol-samples, but is one of the interventions in an online study for heavy drinkers (protocol: Van Deursen, Saleminck, Smit, Kramer, & Wiers, 2013). In summary: there are a variety of techniques that can be used to change implicit memory associations for addiction-relevant stimuli, with promising results for evaluative conditioning, counterconditioning, and selective inhibition, but no results yet in clinical samples.

Training executive control

When cue-induced impulses to give in to the temptation of the addictive behavior despite good long-term reasons not to do so play an important role, one can either try to moderate this impulse (all training varieties described above), or to increase the ability to control the impulse by training executive control capacity. This is also the objective of more general procedures to improve self-control (Muraven, 2010), not discussed here (Beames, Schofield, & Denson, Chapter 32 of this volume). Here, studies are included that target specific executive control processes, usually working memory (see Hofmann, Chapter 13 of this volume). Across a large number of studies in the field of addiction, it has been found that working memory moderates the influence of relatively automatic processes on behavior (review: e.g., Stacy & Wiers, 2010). Working memory training has been studied a lot in children with ADHD and learning

problems (review: Klingberg, 2010). While initial reports suggested that this training has generalized effects on other cognitive tasks and on behavior (Klingberg et al., 2005), recent meta-analyses did not support generalized cognitive effects (Shipstead, Redick, & Engle, 2012). In addition, two studies tested the effects of working memory training. Bickel and colleagues (2011) found that eight sessions of training reduced delay-discounting (a measure of impulsivity) in stimulant abusers, with no reported effects on addictive behaviors. Houben, Wiers, and Jansen (2011) trained problem drinkers with 25 sessions over the internet and found a stronger increase in working memory in the active training group compared with a control training group (which was trained at a continuous low level, while the training in the experimental group was adaptive and they reached higher levels). Mediation analyses showed moderated mediation, regarding the effects of training on drinking: participants with strong automatic positive alcohol associations benefited most from the training and significantly reduced their drinking. In addition to working memory training, other executive control functions have been trained, such as inhibition (without reference to the addictive behavior), but this has generally not yielded promising effects, compared with training including the relevant category (Allom et al., 2016).

Discussion and future directions

Problems with self-control are at the heart of addiction: while one knows the long-term perils of giving in, the lure of the temptation can be hard to resist. However, not all addictive behaviors qualify as self-control problems: binge-drinking can be intentional, serving social goals (e.g. in late adolescence and early adulthood in many cultures) or can be largely habitual, and in both cases minimal conflict is experienced. Cognitive training paradigms have been developed that may help individuals to overcome self-control conflicts in addiction. The large majority of studies have been preclinical, usually testing the effects of a limited amount of training in students, on drinking in a taste-test or during the week after the experiment. In addition, there are a limited number of clinical trials, which found improved clinical outcomes when cognitive training was added to treatment as usual, usually a combination of Cognitive Behavior Therapy (CBT) and MI. These findings contrast with negative findings where participants did not want to change (e.g. community smokers who did not want to quit; Kerst & Waters, 2014) or in people who wish to cut down without further treatment (and succeed, either with “real” or with “placebo” training; Wiers, Houben et al., 2015).

This implies that cognitive training benefits from being supplemented with online CBT, which is as effective as face-to-face CBT (Riper et al., 2014). An alternative is to combine cognitive training with face-to-face therapy, building both motivation to change the addictive behavior and motivation to do the training as a means to pursue the first goal (protocol: Boffo, Pronk, Mannarini, & Wiers, 2015). Current training programs are experienced as rather boring and irrelevant. They could, however, be made more motivating, by including game-elements such as direct feedback on performance and person-adjusted levels (Boendermaker, Prins, & Wiers, 2015). Importantly, however, while game-elements may increase the motivation to participate in the cognitive training, this does not in itself yield motivation to change the addictive behavior (Boendermaker et al., 2015). Another way to increase motivation to train could be to include personal goals to train not only away from substance-related stimuli but also toward alternative goals (such as exercise, traveling, time with relatives; Kopetz, MacPherson, Mitchell, Houston-Ludlam, & Wiers, 2017).

In conclusion, recently developed cognitive training programs appear to help to overcome self-control problems in addictive behaviors, under specific circumstances: in individuals with self-control problems who are motivated to change their addictive behavior. Given the rather

preliminary current state of the data combined with the promising effects in some of the lines of research described, it is needless to emphasize that more research is desired in this domain.

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