



Twisted memories: Addiction-related engrams are strengthened by desire thinking

Lorenzo Mattioni^{a,*}, Francesca Ferri^a, Ana V. Nikčević^b, Marcantonio M. Spada^c, Carlo Sestieri^a

^a Department of Neuroscience, Imaging and Clinical Sciences - and ITAB, Institute for Advanced Biomedical Technologies, G. d'Annunzio University, Chieti, Italy

^b Department of Psychology, Kingston University, Kingston upon Thames, UK

^c School of Applied Sciences, London South Bank University, London, UK

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ABSTRACT

Associative learning plays a central role in addiction by reinforcing associations between environmental cues and addiction-related information. Unsupervised learning models posit that memories are adjusted based on how strongly these representations are coactivated during the retrieval process. From a different perspective, clinical models of addiction posit that the escalation and persistence of craving may depend on desire thinking, a thinking style orienting to prefigure information about positive addiction-related experiences. In the present work, we tested the main hypothesis that desire thinking is a key factor in the strengthening of addiction-related associations. A group of adult smoking volunteers ($N = 26$) engaged in a period of desire thinking before performing an associative learning task in which neutral words (cues) were shown along with images (smoking-related vs. neutral context) at different frequencies. Two retrieval tests were administered, one immediately after encoding and the other after 24 h, to test how the recall of associations changed as a function of retention interval. Two control groups, smokers ($N = 21$) and non-smokers ($N = 22$), performed a similar procedure, with a neutral imagination task replacing desire thinking. Participants who engaged in desire thinking increased their performance from the first to the second retrieval test only for the most frequent smoking-related associations. Crucially, this selective effect was not observed in the two control groups. These results provide behavioral evidence in support of the idea that desire thinking plays a role in strengthening addiction-related associations. Thus, this thinking process may be considered a target for reconsolidation-based conceptualizations of, and treatments for, addiction.

1. Introduction

Substance use disorder is a complex and chronic condition characterized by continuous substance seeking and use despite harmful consequences. Smoking is one of the most prevalent addictive behaviors and a significant proportion of individuals still struggle with nicotine addiction even though the health risks associated with smoking are well known. This condition develops as smokers rely on smoking to regulate mood, arousal, and withdrawal symptoms, in a way that affects neural plasticity (Benowitz, 2010).

Addiction can be seen as an anomalous expression of the neural mechanisms supporting learning and memory, which, under normal circumstances, serve to shape survival behaviors related to the pursuit of

rewards and the detection of the cues that predict them (Hyman, 2005). In particular, a candidate mechanism for the maintenance of addiction is associative memory (Hyman, Malenka, & Nestler, 2006). According to this view, associative learning continuously enhances memory for information associated with the object of addiction (Goldfarb, Fogelman, & Sinha, 2020). For example, drug taking, including late relapses, follows exposure to cues previously associated with drug use (Courtney, Schacht, Hutchison, Roche, & Ray, 2016). Importantly, such dysfunctional adaptation processes are common to many, if not all, kinds of addiction (Kalivas & O'Brien, 2008; Nestler, 2005). The maladaptive updating of associative memory in addiction disorders is thought to depend on memory reconsolidation (Milton & Everitt, 2010), a mechanism for which the reactivation of stored memory traces makes them

* Corresponding author at: Institute of Advanced Biomedical Technologies, Department of Neuroscience, Imaging and Clinical Sciences, University G. d'Annunzio di Chieti-Pescara, Via dei Vestini 11, Chieti 66100, Italy.

E-mail address: lorenzo.mattioni@unich.it (L. Mattioni).

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Table 1

Averages of the he participants' age, Depression Anxiety and Stress Scale score, number of cigarettes smoked per day, years of smoking, Fagerström Tolerance Questionnaire, and Desire Thinking Questionnaire scores are reported (standard deviations in brackets).

Group	N	Age	DASS-21	Cigarettes	Years	FTQ	DTQ
Experimental	26	22.7(3.1)	24.4(12.9)	8.4(6.6)	6.4(3.0)	2.1(2.1)	18.8(4.8)
Smokers Control	21	21.7(2.8)	21.2(11.7)	9.3(4.5)	5.6(2.6)	2.7(2.1)	20.1(6.6)
Non-Smokers Control	22	23.5(2.6)	19.6(12.2)	-	-	-	-

transiently labile (Lee, Nader, & Schiller, 2017). In this reconsolidation window, memory associations enter a dynamic state in which it is possible to change their characteristics (Nader & Einarsson, 2010) and boost their relevance (Lee, 2009). Indeed, many studies have suggested that reconsolidation may be a key factor in the conceptualization and treatment of addiction disorders (Sorg, 2012; Milton & Everitt, 2010; Monfils & Holmes, 2018; Torregrossa & Taylor, 2013; Lee, Di Ciano, Thomas, & Everitt, 2005). It has been proposed that this kind of learning happens through unsupervised learning rules that adjust neural representations based on how strongly memories are activated during the retrieval process (Ritvo, Turk-Browne, & Norman, 2019). Unsupervised learning models are based on information that is local to the synapse, without any explicit consideration of how well the network is predicting external outcomes (Sinclair & Barense, 2019). The classic Hebbian rule “fire together wire together” is an example of such a model (Sanger, 1989). When two memories are simultaneously activated, their connection will be strengthened to reduce competition in subsequent retrieval attempts (Ritvo et al., 2019). In this view, memory associations are boosted by the strong concurrent representations of the reminder and the context rather than the ability of the reminder to predict the occurrence of that context (Alberini & LeDoux, 2013). However, to our knowledge, no study has focused on the relationship between typical addiction-related cognitive styles and memory reconsolidation.

The duration, frequency, and intensity of craving derive from a variety of external and internal triggers of automatic associations to information about a desired target or activity (May, Andrade, Panabokke, & Kavanagh, 2004). The escalation and persistence of craving are thought to depend, in part, on the activation of ‘desire thinking’, a conscious and voluntary cognitive process orienting to prefigure images, information, and memories about positive target-related experiences (Caselli & Spada, 2015) present in various forms of addiction (Caselli, Ferla, Mezzaluna, Rovetto, & Spada, 2012; Fernie et al., 2014; Caselli, Nikčević, Fiore, Mezzaluna, & Spada, 2012; Caselli, Soliani, & Spada, 2013; Mansueto et al., 2019; Marino et al., 2023). Desire thinking appears to play a crucial role in how negative emotions and thought suppression impact nicotine dependence and craving (Khosravani, Spada, Samimi Ardestani, & Sharifi Bastan, 2022). This maladaptive form of coping serves to regulate, in the short term, the discrepancies between real and ideal states caused by negative affect and the rebound effects of thought suppression, and results in the anticipation of pleasant states and relief from emotional distress. For example, when experiencing emotional distress, an individual may engage in desire thinking to cognitively prefigure the act of smoking, planning what needs to be done to obtain a cigarette, and comparing the actual sensation with the feelings associated with smoking to regulate this internal state (Caselli & Spada, 2010). Initially, this activity may have a positive effect by momentarily dampening emotional distress. However, in the longer run, it will bring an escalation of emotional distress through the biasing of memory, and consequently attention, towards smoking-related information (Spada, Caselli, Nikčević, & Wells, 2015). As a consequence, when spotting a smoking-context reminder, e.g., a place where the behavior usually takes place, salient smoke-related memories will enter consciousness, each time more strongly and automatically (Caselli & Spada, 2016). This, in the longer term, leads to the desired activity being perceived as the only, and increasingly urgent, route to regulate both emotional distress and craving in specific contexts (Khosravani et al., 2022).

The central hypothesis of the present study is that desire thinking represents a cognitive process through which memory reconsolidation abnormally updates addiction-related memory traces. In particular, we hypothesize that desire thinking can open a reconsolidation window in which those partial reminders that are simultaneously and repeatedly activated with addiction-related contexts strengthen and become more available for long-term retrieval. To test our hypothesis, we examined whether engaging in desire thinking about smoking, compared to neutral imagination, causes the long-lasting enhancement of repeated associations between smoking-related information and neutral cues. This research paves the way to broaden our comprehension of memory reconsolidation in addiction disorders by linking the theory of memory updating with the clinical construct of desire thinking. The understanding of how the mind updates specific salient information will have an important impact on the clinical treatment and the conceptualization of addiction while shedding light on everyday life factors which maintain this disorder.

2. Methods

2.1. Participants

A total of 79 Italian native speakers between 18 and 30 years of age were sampled from a list of volunteers willing to take part in behavioral experiments at the D’Annunzio University of Chieti, Italy. Participants were assigned to one of three groups (Table 1): i. an experimental group of smokers engaging in desire thinking, ii. a group of smokers engaging in a control imagination task, and iii. a group of non-smokers engaging in the same control imagination task. Exclusion criteria were the current presence of heart problems and the undergoing of treatment employing psychotropic drugs. Ten participants who could not perform the memory tests above the chance level (average error rate < 25%) were excluded, leaving a final sample of 69 participants (45 females and 24 males), 26 in the experimental group, 21 in the smoker control group, and 22 in the non-smoker control group. Participants provided informed consent and received a €21 reimbursement for their participation in the study. The present experiment was part of a larger investigation that also involved the non-invasive measurements of the electrocardiogram and electrodermal activity. The research project was approved by the Ethics Committee of the Provinces of Chieti and Pescara (Verbal #22; Oct, 8th, 2020).

2.2. Procedure

The experiment consists of a series of phases: i. a first thinking manipulation phase; ii. a word-image associative learning phase, in which participants encoded a series of word-image pairs, iii. a second thinking manipulation phase, iv a first memory test performed immediately after the encoding session, and v. a second memory test performed the day after the encoding session. Moreover, the study involved a series of manipulations to assess the specificity of the hypothesized effect. To ensure that desire thinking specifically affects strong, but not weak, smoking-related associations, we introduced two within-participant manipulations, one concerning the stimulus context (smoking-context vs. neutral images) and the other concerning the strength of the word-image association (low, medium, and high). To ensure that the hypothesized effect is specifically caused by desire thinking, the design

included a between-participant manipulation involving the nature of the pre-learning imagination tasks (desire thinking about smoking vs. neutral imagination). Finally, to test the degree to which people are aware of the hypothesized effect of desire thinking, we further collected a measure of response confidence in addition to retrieval accuracy.

Three days before the experimental session, the participants were asked to complete a series of questionnaires to control for differences in individual smoking habits and mental state. The questionnaire about smoking habits included questions about the number of cigarettes smoked per day, the number of years the participants had been smoking, and the Fagerstrom Tolerance Questionnaire (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Fekketich, Fossati, & Apolone, 2008), which measures nicotine dependence. Additionally, we administered the 21-item form of the Depression Anxiety and Stress Scales (Henry & Crawford, 2005; Bottesi et al., 2015) in all groups, to measure psychological distress, and the Desire Thinking Questionnaire (Caselli & Spada, 2011) in the two groups of smokers, to measure the participants' tendency to engage in desire thinking about smoking.

Participants were asked to abstain from smoking or drinking coffee in the morning preceding both experimental sessions. The experiment was performed while sitting at a distance of 100 cm from a 28x52cm screen. E-Prime 3.0 (Tools, 2016) was used for stimulus presentation and response collection.

2.2.1. First thinking manipulation phase

This study presented two comparable guided imagination conditions (desire thinking, control), both consisting of 16 items (Fig. 1A). In both conditions, participants were asked to concentrate on a series of items for about 8 min keeping their eyes closed. All items comprised suggestions and instructions aimed to drive the participant's cognitive elaboration. After 3 min of silence, items were presented through an audio recording with a 30sec interval between each item. In the desire thinking condition, items instructed participants to remember past episodes or plan future opportunities for smoking, e.g. "Try to imagine yourself while smoking" or "Try to plan everything you could do to obtain a cigarette as soon as possible." The items were adopted from the Desire Thinking Questionnaire (Caselli & Spada, 2011). This thinking manipulation was used in a previous study which found that craving could be increased by eliciting verbal perseveration (Caselli et al., 2013). In the control task, participants were asked to remember the road they take to reach the laboratory and to plan how to return home after the experiment, e.g., "Try to imagine yourself while you were coming here" or "Try to plan everything you should do to return home after the experiment." The rationale behind using these items was that of employing a thinking manipulation that makes participants use the same cognitive representation mechanisms of prediction and recall of the desire thinking condition but without bringing to mind the smoking-related context. The audio stimuli were administered through high-performance JBL headphones. This phase lasted approximately 12 min.

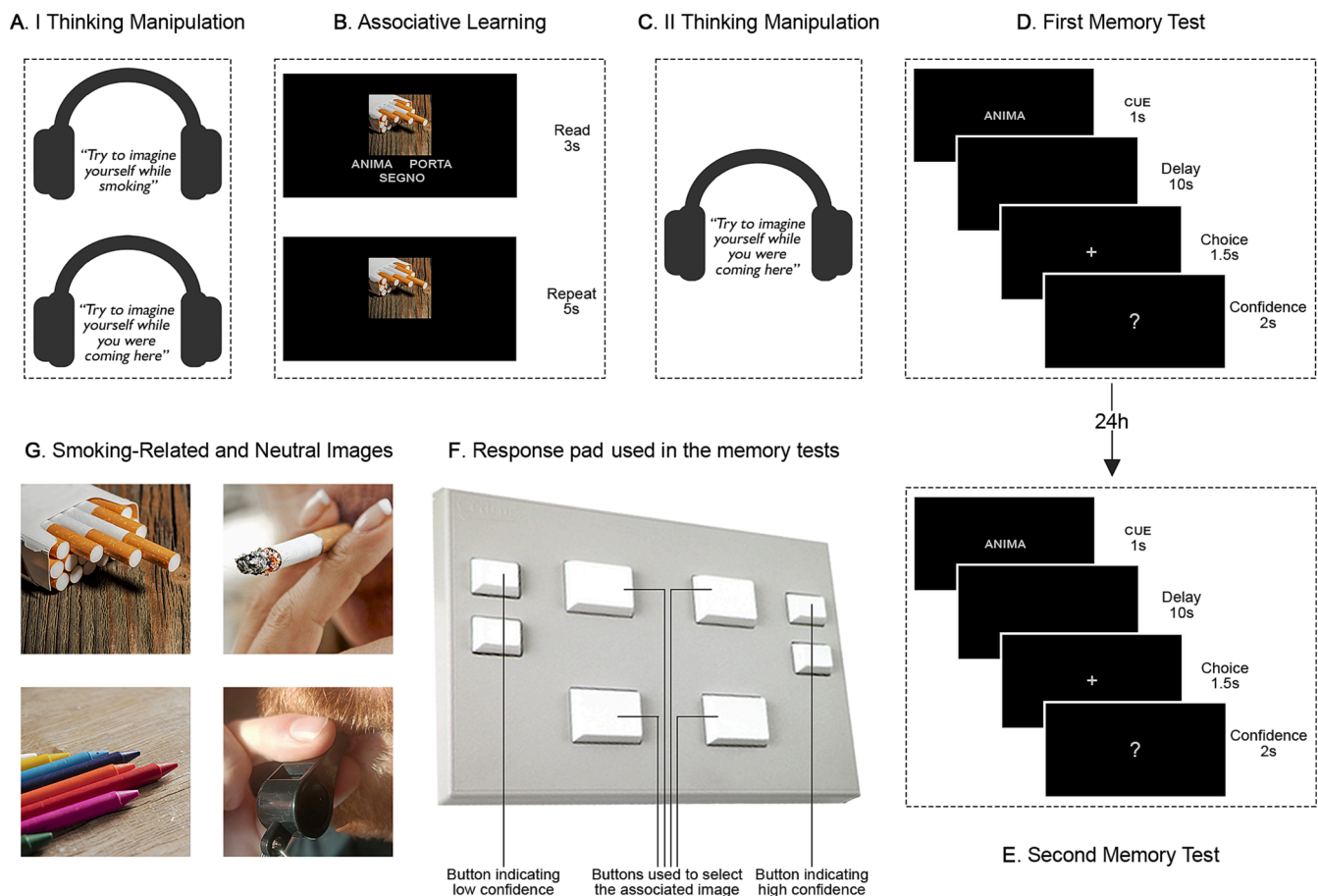


Fig. 1. Experimental paradigm. A. The first thinking manipulation phase where the experimental group underwent the desire thinking condition while the two control groups underwent the neutral imagination condition. B. The associative learning phase in which participants were instructed to focus on the words-image associations and to repeat aloud the words as soon they disappear from the screen. C. The second thinking manipulation in which all participants underwent the neutral imagination condition of the first phase. D. The first memory tests in which participants in every trial were presented with one of the words used in the associative learning phase and were asked to select which image was associated with that word and the level of confidence regarding their choice. E. The second memory test which was done 24 h after the first one. F. The Cedrus RB-844 response pad used in the two memory tests. G. The images used in the associative learning as smoking and neutral context.

2.2.2. Word-image associative learning phase

The material of the word-image association task included four images (Fig. 1G), and a set of 52 words (Italian nouns of five letters with an absolute frequency between 200 and 1000 (Bambini & Trevisan, 2012)). To manipulate the association context, two images represented smoking-context information (a pack of cigarettes and a person who smokes), and two images represented comparable neutral information (a pack of crayons and a person blowing a whistle). Thirteen words were uniquely associated with every picture in a random fashion between participants.

After a brief random presentation of the four pictures, one at a time for 3 times for 2sec with a 10sec inter-trial interval, participants underwent a series of 96 learning trials, 24 for every picture, in random order. On each trial (Fig. 1B), three words and the associated picture were presented for 3sec. Then the words disappeared and the picture remained on-screen for 5sec. At the offset of the image, participants were instructed to vocally repeat the three words that have been just shown to reinforce the association and keep their attention on the task. The inter-trial interval was 2sec and there was one resting pause of 40sec in the middle of the task. For every image, the associated words were presented at different frequencies to manipulate the strength of the association: three words were presented 33% of the time (high activation), four words 25% of the time (medium activation), and six words 17% of the time (low activation). This phase lasted approximately 20 min.

2.2.3. Second thinking manipulation phase

To prevent participants from autonomously engaging in desire thinking, all three groups undertook the same neutral thinking manipulation (control condition of the first thinking manipulation; Fig. 1C). This phase lasted approximately 9 min.

2.2.4. First memory test

In the first memory test (Fig. 1D), participants were shown each of the 52 words from the previous word-image associations learning task in random order, one at a time, and were asked to indicate the associated picture by pressing a corresponding button of a Cedrus RB-844 response pad (Fig. 1F). In every trial the word remained on the screen for 1 sec, followed by a 10sec black screen and by a 1.5sec fixation cross

indicating to press the button associated with the image. A question mark then appeared for 2 sec, prompting participants to report the confidence (low, high) in their previous response by using one of two additional buttons on the response pad. The inter-trial interval was 6sec. This phase lasted approximately 16 min.

2.2.5. Second memory test

The second memory (Fig. 1E) test was identical to the first one but trials were presented in a different random order and it was preceded by a 10 min resting state. This phase lasted approximately 26 min.

2.3. Analysis

Our primary measure of interest was the difference in performance between the first and the second memory test (error rate change), which indicates the degree to which a particular word-image association has been reconsolidated. In particular, we expected a selective reconsolidation effect (smaller negative or even positive error rate change) for high smoking-related associations, compared to the five other conditions (medium and weak smoking-related, neutral) for which a negative error rate change was expected. Moreover, we expected this particular advantage to be selectively associated with the act of desire thinking and thus to be present only in the experimental group (Fig. 2).

Paired t-tests were conducted between the error rates in the first and the second memory test for each of the six conditions (smoking and neutral contexts with three levels of presentation rate). A Friedman test (Friedman, 1937) was used to account for the presence of a significant effect of condition (six levels) within each group. A non-parametric LSD post hoc test (Conover, 1999) was used to further assess the presence of significant differences across individual conditions. Finally, a modified Wilcoxon-Mann-Whitney test (Fong & Huang, 2019) was performed on the difference between the error rate calculated in two memory tests, selectively for the condition of interest (strong smoking-related associations), to test for significant differences between each group. The second measure of interest was the difference in the response confidence between the two memory tests, in particular for what concerns the high-frequency smoking-related associations in the experimental group. This time, we expected no specific change in confidence rating, indicating

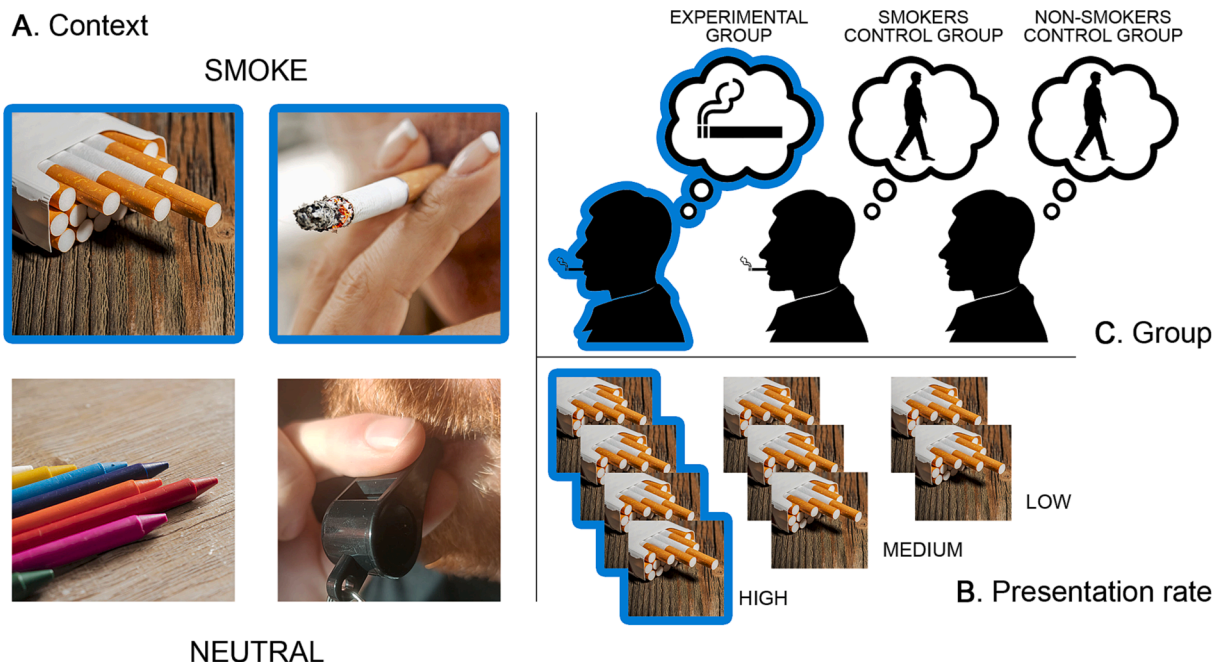


Fig. 2. The primary measure of interest. If our hypothesis is correct we should expect to find a higher error rate change in trials regarding the association between A. words and smoking-related pictures, B. with high association strength, C. only in the group of smokers who undertake the desire thinking imagination condition.

Table 2

In the table are reported the results of the modified Wilcoxon-Mann-Whitney tests for the control variables between the experimental group and the two control groups. The first line refers to the differences between the experimental group and the smoking control group expressed in Z scores, the line just below represents the p-values. In the same way, the third and the fourth lines represent the Z scores of the differences between the experimental group and the non-smoking control group and the related p-value, respectively. EG = experimental group; SG = smoking control group; NG = non-smoking control group; DASS-21 = Depression Anxiety and Stress Scale; Cigarettes = number of cigarettes smoked per day; Years = years of smoking; FTQ = Fagerstrm Tolerance Questionnaire score; DTQ = Desire Thinking Questionnaire score.

	DASS-21	Cigarettes	Years	FTQ	DTQ
EG - SG	-0.60	1.18	-0.73	1.09	0.55
p.	0.55	0.23	0.47	0.31	0.58
EG - NG	-1.21	-	-	-	-
p.	0.22	-	-	-	-

that participants were not aware of the effects of our manipulations. The confidence change for the six conditions was calculated as the difference between the rate of low-confidence responses in the first and the second memory test (confidence changes), where positive and negative values indicate a percentage increase or decrease in confidence, respectively. As before, a Friedman test assessed the presence of a significant effect of condition in each group of participants and three modified Wilcoxon-Mann-Whitney tests were performed on memory changes regarding the condition of interest (smoking-related strong associations) to account for between-group effects.

The t-tests were performed through the software IBM SPSS Statistics 25 (IBM Corp., 2017), the Friedman and the non-parametric LSD tests through the MATLAB toolbox MYFRIEDMAN (Cardillo, 2009), and the modified Wilcoxon-Mann-Whitney test through the R package robustrank (Fong, 2020).

3. Results

None of the control variables differed significantly between the experimental group and the two control groups (Table 2). The t-tests showed that smoking-related strong associations were the only type of associations that were better remembered on the second compared to the first day, showing a significant positive error rate change (Table 3), whereas the other conditions exhibited negative, albeit non-significant, error rate changes.

The Friedman tests conducted in each group of participants revealed a significant effect of condition for the experimental group both using Chi-square ($\chi^2(5) = 11.14$; $p < 0.05$) or F-statistic ($F(5) = 2.34$; $p < 0.05$) approximation, but not for the smoker ($\chi^2(5) = 3.77$; $F(5) = 0.74$; $p = n.s.$) or the non-smoker ($\chi^2(5) = 6.78$; $F(5) = 1.38$; $p = n.s.$) control groups. Consistent with our hypothesis, the post hoc tests (Fig. 3) conducted in the experimental group showed that smoking-related strong associations exhibited significantly higher error rate change compared to all the other conditions (all $p < 0.05$) apart from the neutral strong association condition. None of the control conditions was found to be significantly different from the others.

Next, as a test of the selective effect of desire thinking over strong smoking-related associations, we compared the error rate changes of the condition of interest across groups using the modified Wilcoxon-Mann-Whitney test (Fig. 4). As expected, we found that the error rate change of the experimental group was significantly greater than that of both the control groups of smokers ($Z = -1.85$; $p < 0.05$) and non-smokers ($Z = -2.17$; $p < 0.03$), whereas the two control groups did not differ from each other ($Z = -0.25$; $p = n.s.$).

Finally, we examined the presence of significant differences in the change of response confidence as a function of condition in each group. Consistent with the hypothesis that participants were not aware of the effect of the manipulation, the Friedman test revealed no main effect of condition in any group (experimental: $\chi^2(5) = 2.91$; $F(5) = 0.57$; $p = n.s.$; control smokers: $\chi^2(5) = 0.39$; $F(5) = 0.07$; $p = n.s.$; control non-smokers: $\chi^2(5) = 6.11$; $F(5) = 1.23$; $p = n.s.$). Analogously, the modified Wilcoxon-Mann-Whitney tests comparing confidence changes for

the condition of interest showed no effects between the experimental group and both the control group of smokers ($Z = 0.46$; $p = n.s.$) and non-smokers ($Z = 0.87$; $p = n.s.$), and between the two control groups ($Z = 0.52$; $p = n.s.$).

4. Discussion

The present study aimed to test if desire thinking can strengthen the associations between neutral cues and smoking-related information, making them more available for long-term retrieval. Our results indicate that the group of participants who engaged in desire thinking before the encoding phase of an associative memory test exhibited an increase in retrieval performance from an immediate to a delayed test of strong smoking-related associations. Confirming the specificity of our finding, no effect was observed for weaker or neutral associations. Crucially, the advantage for smoking-related strong associations was not observed in control groups of smokers and non-smokers that were involved in a comparable, but smoking-unrelated, imagination task. We believe that the present results represent the first demonstration that desire thinking enhances memory representations associated with the desired action and, more generally, provide support for the idea that a particular cognitive style may be the cause of the maladaptive associative memory updating characterizing addiction disorders. Furthermore, this kind of unsupervised learning is thought to be implicit (Rohrmeier & Rebuschat, 2012), in line with our data showing that the effects of desire thinking on memory performance are not reflected by similar changes in response confidence.

4.1. Strengthening addiction-related association without the need for re-exposure

It is important to stress that desire thinking is not maladaptive per se. For example, it may be helpful to motivate individuals to plan adequate actions to reach goals through virtual anticipation of pleasant results. However, desire thinking becomes dysfunctional when it assumes a perseverative and poorly regulated form (Caselli & Spada, 2015). Our results suggest that an exaggerated engagement in desire thinking may increase the probability of strengthening associations between environmental cues and addiction-related context, without the need for a re-exposure to the object of desire. In this view, memory reconsolidation is not solely reliant on external stimuli, as it can also occur without re-exposure to the original learning context (Alberini & LeDoux, 2013). For instance, retrieval cues that partially replicate the initial encoding experience can effectively promote reconsolidation through expectation and memory reactivation (Tassone et al., 2020; Forcato et al., 2020; Sinclair & Barense, 2019). Reminders serve as a trigger for the retrieval of a particular context, which subsequently leads to the involuntary recall of other memories associated with that same context (Bornstein & Norman, 2017), even in the short term (Hannula, Tranel, & Cohen, 2006). When activation spreads to related memories, it has the potential to strengthen the associations between them, thereby making them easier to recall in the future (Antony, Ferreira, Norman, & Wimber,

Table 3

Paired t-tests between error rates of the first and the second memory test for the six conditions in the three groups. SH = smoke-related associations with high presentation rate; SM = smoke-related associations with medium presentation rate; SL = smoke-related associations with low presentation rate; NH = neutral associations with high presentation rate; NM = neutral associations with medium presentation rate; NL = neutral associations with low presentation rate; * = positive two-tailed significant difference ($p < 0.05$).

Condition	Experimental Group			Smokers Controls			Non-Smokers Controls		
	MT1	MT2	MT1-MT2	MT1	MT2	MT1-MT2	MT1	MT2	MT1-MT2
SH	0.53	0.46	0.08*	0.58	0.62	-0.04	0.47	0.51	-0.04
SM	0.50	0.53	-0.03	0.53	0.62	-0.10	0.54	0.63	-0.09
SL	0.57	0.60	-0.03	0.64	0.67	-0.03	0.65	0.63	0.02
NH	0.44	0.46	-0.01	0.35	0.42	-0.07	0.35	0.40	-0.04
NM	0.40	0.44	-0.03	0.44	0.47	-0.04	0.43	0.40	0.03
NL	0.54	0.58	-0.04	0.61	0.63	-0.02	0.56	0.59	-0.03

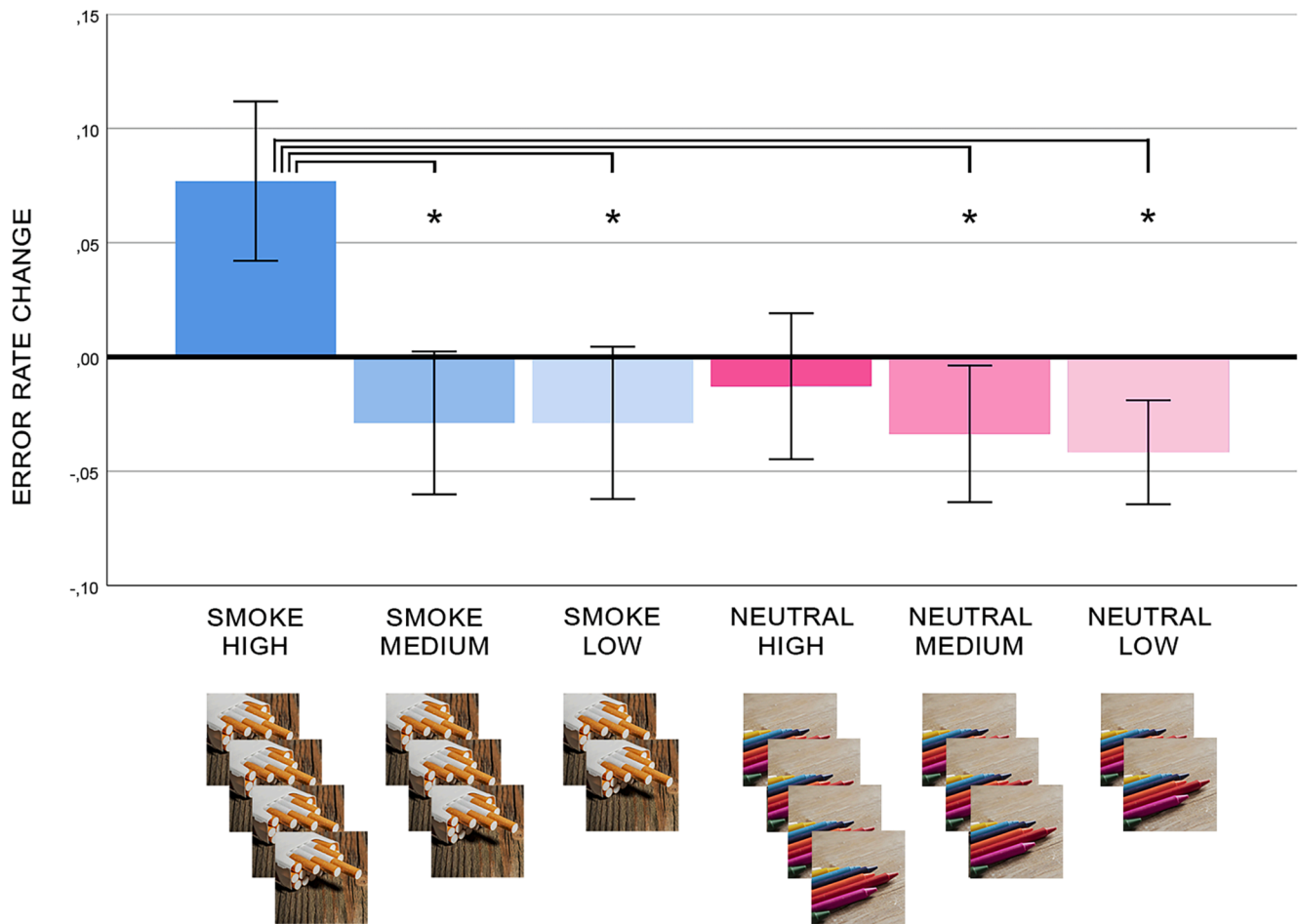


Fig. 3. Non-parametric LSD test between conditions of the experimental group. * = two-tailed significant difference between conditions ($p < 0.05$); bars = standard error.

2017). In fact, successfully retrieving memories without receiving feedback results in superior recall compared to mere restudying the material (Rowland, 2014). Therefore, when the recognition of cues linked to drug use triggers the retrieval of addiction-related information, it can further strengthen the already robust association between that cue and the addiction context (Torregrossa & Taylor, 2016). This way, desire thinking has the potential to enhance the strength of memory associations between the smoking context and diverse contextual information even in the absence of cigarette exposure, consistent with the fact that relapse risk is considered a threat to the rest of life also after many years of abstinence (Xie, McHugo, Fox, & Drake, 2005).

It has been proposed that desire thinking serves as a mediator that connects negative affect and thought suppression to craving and use in

individuals with nicotine dependence, beyond the influence of comorbidity, onset, and duration of use (Khosravani et al., 2022). Consistent with this idea, and with the fact that we artificially modulated desire thinking in the same way for all participants, none of our control measures correlated with the error rate change in our variable of interest. This negative result suggests that, at least within the present context, the maladaptive strengthening of addiction-related memory associations is not caused by the severity of the addiction or the emotional state, but rather by the degree of engagement in desire thinking. Nonetheless, we acknowledge that severity of addiction and negative affect can influence the degree of engagement in desire thinking in real life (Exton-McGuinness, Lee, & Reichelt, 2015).

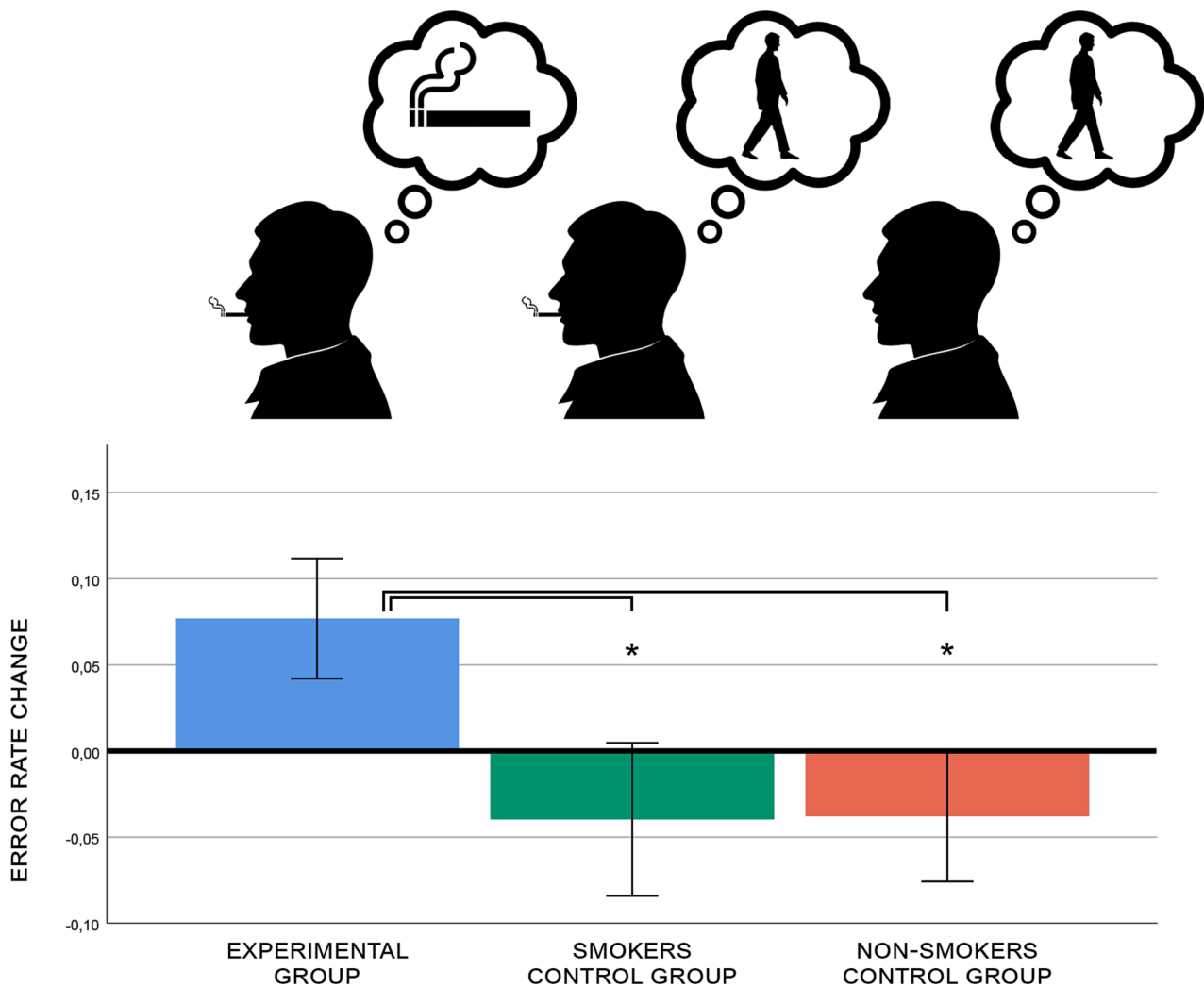


Fig. 4. Modified Wilcoxon-Mann-Whitney tests on the between-subjects changes regarding the changes between the second and the first memory test error rates for the condition of interest; * = two-tailed significant difference between groups ($p < 0.05$); bars = standard error.

4.2. Desire thinking as a link between supervised and unsupervised learning models

In computational psychiatry, addiction is understood as a complex interplay between an accelerated unsupervised learning system, promoting rapid adoption of automatic addiction-related behaviors, and a biased supervised learning system characterized by heightened drug expectations resistant to devaluation (Redish, 2020). According to this class of models, the brain supports perception and action by constantly attempting to match incoming inputs with top-down predictions (Huang & Rao, 2011). Sensory predictions prepare for upcoming perceptions (Rao & Ballard, 1999; Ernst & Bühlhoff, 2004), skeletomotor predictions prepare for movements (Shipp, Adams, & Friston, 2013; Friston, 2011), and, importantly, interoceptive predictions prepare for the sensory consequences within the body (Barrett & Simmons, 2015) to model future interactions between interoceptive and exteroceptive states and facilitate emotional processing (Allen, 2020). Neural networks remove the predictable components of the input and transmit only the unpredicted portions of incoming signals, also called prediction errors, in order to increase the efficiency of the system (Schultz & Dickinson, 2000). The overall goal is to reduce prediction errors to increment the accuracy of the internal model of the world, and this could be done by updating the prior model or by increasing prediction matching in future instances (Friston, 2010).

Our study underlies the role of desire thinking in the imbalance

between supervised and unsupervised learning and the consequent abnormal memory reconsolidation of addiction-related representation. In this respect, the present study links two important paradigms of addiction disorders which are often treated independently, i.e., the neurobiological view that considers addiction as a consequence of learning and memory mechanisms (Hyman, 2005) and the clinical view that conceptualizes it as a consequence of a repetitive way of cognitively representing addiction related information (Caselli & Spada, 2015). Our results also shed light on the connection between the two approaches, pointing out the importance of considering memory-updating mechanisms in clinical practice and of considering desire thinking as a target for studies involving the underlying mechanisms of memory reconsolidation in addiction disorders.

As we saw before, desire thinking may increase the salience of addiction-related cues, which progressively assume more importance for the organism. In this way, smokers may automatically recall the context of smoking at the sight of a reminder, e.g. a place where they usually smoke, and consequently start desire thinking. This would cause an increase in the perceived need for a cigarette, in the level of craving (Caselli et al., 2013), and in the physiological effect of stress caused by craving (Sinha, 2009), e.g., increased heart rate (Kennedy et al., 2015). Eventually, smokers will receive sensory input in accordance with their perceived need to smoke to feel better. In other words, desire thinking may issue interoceptive predictions to explain incoming sensory events that remain uncorrected by sensory cues, resulting in a decrease in the

weight of new evidence, and an increase in the weight of the interoceptive prediction, as proposed for other forms of repetitive thinking (Barrett, Quigley, & Hamilton, 2016).

4.3. Future directions

The recognition of the impact of desire thinking on memory associations may account for different aspects of addiction. Firstly, addiction is characterized by the involuntary activation of reward circuits in response to drug-associated cues accompanied by reports of drug craving, which can modulate the circuitry involved in learning (Kalivas & O'Brien, 2008). Secondly, the activation of drug-related representations is considered a fundamental factor in the maladaptive memory reconsolidation underlying substance use (Treanor, Brown, Rissman, & Craske, 2017). Furthermore, the strength of addiction-related contexts affects the motivation and the reaction toward addiction-related rewards (Goldfarb et al., 2020). Finally, addiction is characterized by a selective increase in the association between neutral cues and addiction-related information (Milton & Everitt, 2010). Identifying a mental behavior that modifies addiction-related memory associations in everyday life could be fundamental for the development of effective therapies (Monfils & Holmes, 2018). Considering the effect of desire thinking on memory could have various clinical implications. For example, using beta-blockers, it is possible to chemically inhibit the reconsolidation of specific emotional-motivational memory, changing the emotional response to subsequent stimuli (Chan & LaPaglia, 2013; Kindt, Soeter, & Vervliet, 2009; Vallejo et al., 2019). A paradigm in which patients undertake desire thinking while under the influence of beta-blockers may therefore be able to decrease the emotional-motivational characteristics of the smoking context, thereby reducing the salience of its subsequent reactivation. Future studies should aim at replicating our results not only with other addiction disorders but also with other forms of repetitive thinking, e.g. worry for anxiety-related contexts, to test if the relationship between repetitive thinking and memory reconsolidation could be a preclinical transdiagnostic factor for many other mental disorders.

4.4. Limitations

One limitation of the present study is the reliance on a university population, which has a limited age range and a predominance of females. This choice was motivated by participants' availability and efficiency of the procedures, and by the consideration that university students are particularly exposed to factors that may lead to addiction (El Ansari, Vallentin-Holbech, & Stock, 2015) and thus represent good candidates to explore the features of addiction and develop appropriate public health policies and preventive measures. However, the focus on a particular population inevitably reduces the variability of demographic characteristics in comparison with the general population. Future studies should focus on other populations to increase the generalizability of the results.

A second limitation is that participants were not objectively tested for nicotine or other substances before the two experimental sessions, as we were confident in their compliance with the instructions. We also did not ask them to abstain from smoking or drinking coffee after performing the first experimental session, and we solely relied on a measure of psychological stress to evaluate their mental health conditions. Although we acknowledge that a tighter experimental control and a more comprehensive assessment of mental health would have allowed us to exclude the effect of potentially confounding variables, it would have also required more invasive control measures and more effort from participants, potentially discouraging their participation.

Another limitation is that this study was conducted in Italy between 20/04/2021 and 27/06/2022 during the COVID-19 global pandemic. The fast-changing dynamics of the situation may have influenced the participant state by the time they were undertaking the experiment, a

variable that we did not take under explicit consideration.

5. Conclusions

Neurobiological paradigms explain addiction by considering the aspects of learning and memory that preclude the ability to interrupt a given behavior, such as smoking, treating addiction as a disease of free will. Instead, clinical paradigms consider addiction as a consequence of a dysfunctional cognitive style involving the redundant representation of the desired object or situation. In the attempt to reconcile these different approaches, our study showed that desire thinking can influence memory and learning for repeated stimulus associations between addiction-related context and neutral cues, as predicted from unsupervised learning models of memory reconsolidation. Thus, our results indicate the importance of considering desire thinking as a target for reconsolidation-based treatments of addiction.

6. Author agreement statement

We declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions, and final approval of proofs.

CRediT authorship contribution statement

Lorenzo Mattioni: Conceptualization, Investigation, Writing – original draft. **Francesca Ferri:** Supervision, Writing – review & editing. **Ana V. Nikčević:** Writing – review & editing. **Marcantonio M. Spada:** Writing – review & editing. **Carlo Sestieri:** Supervision, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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