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Methadone maintenance patients show a selective deficit to reverse positive outcomes in drug-related conditions compared to medication free prolonged opiate abstinence

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ABSTRACT

Background: Drug addiction is a chronic relapsing disease. Most users will relapse back to using drugs over and over again throughout their life. These relapses may become more frequent in the presence of contextual reminders. We aimed to examine associations between the ability to maintain a medication-free life-style and the capability to learn and reverse positive and negative stimulus–outcome associations in the presence of neutral and drug-related contextual reminders.
Methods: We conducted a highly unique comparison of former opiate-dependent individuals who are either medication free or methadone maintenance patients for the last ten years. Groups were matched for age, gender and education. Participants were tested on a novel partial reversal paradigm, which tests the ability to acquire and reverse stimulus–outcome associations in neutral and drug-related context.
Results: Both groups were equally able to acquire and reverse positive and negative outcomes in conditions of neutral context. However, methadone maintenance patients showed a selective deficit in reversing the outcomes of positive stimulus in drug-related context. Hence, after learning a positive stimulus–outcome association in one drug-related context, methadone maintenance patients struggled to learn that the same stimulus predicts negative outcome when presented later in a different drug-related context.
Conclusions: Methadone maintenance patients demonstrate a selective difficulty to learn negative outcomes when exposed to a drug, but not neutral, related environment. The results may reflect the core mechanisms of addiction and provide a possible explanation for the inability of methadone maintenance patients to illicit drug abuse without the need of agonist treatment.

1. Introduction

Drug addiction is a chronic relapsing disease. Most drugs users will relapse back to using drugs over and over again throughout their life. These relapses may become more frequent in the presence of contextual reminders (see Chase et al., 2011 for meta-analyses of studies in substance abuse populations; Engelmann et al., 2012 for meta-analyses of studies in nicotine abusers). For instance, places where an individual used to inject or abuse drugs, equipment (syringe, needles), or people that were present during drug abuse may become classically conditioned, evoke craving and withdrawal symptoms, and lead to drugs usage (for a review of studies in substance abuse populations see O'Brien et al., 1998).

The majority of opioid-dependent individuals require long-term opioid agonist maintenance treatment like full agonist methadone (for a review see Kreek and Vocci, 2002) or the partial agonist buprenorphine (for a review see Bart, 2012) to minimize repeated

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relapsing. Yet, 20–30% of opioid dependent individuals are able to successfully discontinue abusing drugs and take on a drug free life style (Haastrup and Jepsen, 1984; DSM-IV-TR, 2000). It is possible that repeated relapsing is associated with impaired reversal learning. The goal of the present study is to test differences in reversal learning in individuals who discontinued drug use and methadone maintenance patients. Specifically, we aim to test whether a sample of individuals who discontinued drug use with no need of opioid maintenance have an advantage in learning and reversing stimulus–outcome associations in drug-related conditions, compared to a sample of individuals on long-term methadone treatment. To that end, we concentrate on a unique population of DSM-IV-TR previous opiate dependence, who were either successfully discontinued their drug abuse for more than 10 years (prolonged abstinence participants) with no need of agonist treatment or patients in methadone maintenance treatment for at least 10 years. These groups were tested on a novel partial reversal paradigm, which test the ability to acquire and reverse stimulus–outcome associations in neutral and drug-related context.

Studies on cocaine abusers have shown that exposure to drug-related reminders may activate the reward brain circuit, providing temporary positive feelings (Volkow et al., 2006, 2008). These positive feelings are sooner or later replaced with negative feelings and outcomes (e.g., drugs dependency, which is associated with inability to maintain stable social and occupational life and its accompanying costs). However drug users usually do not alter their behavior accordingly (for a review of substance abuse populations, see Jasinska et al., 2014).

One factor that may contribute to maintaining this mechanism is impaired reversal learning in drug users. Animal and human studies have shown that cocaine usage is associated with impaired reversal learning (Camchong et al., 2011; Izquierdo et al., 2010; Jentsch et al., 2001). Hence, after learning that a specific stimulus has a certain outcome, cocaine abusers may struggle to learn that the same stimulus is later associated with a different outcome. Another factor that may facilitate such mechanisms relates to deficits in the brain reward circuit among drug users (Volkow et al., 2010 for review see Volkow et al., 2011; for animal study see Smith et al., 2011). Specifically, drug users may continue to attribute positive outcomes to specific stimuli even in situations when it is no longer adequate. These findings may suggest that drug users have a selective impairment in reversing positive outcomes in drug-related conditions.

In order to test this assumption we developed a novel partial reversal learning paradigm. In a common reversal paradigm, participants acquire a stimulus–outcome association (S → Positive) and later need to reverse the outcome of the same stimulus (S → Negative). Such a paradigm does not take into account that stimulus dimensions regularly occur in a specific context (Mayes et al., 1992; Murnane et al., 1999). Our paradigm has three innovative aspects; first, we manipulate partial reversal learning while using different contextual conditions. Hence, participants learn stimulus–outcome associations in one contextual condition (S in Context A → Positive). Later they see the same stimulus in a new context. However now it is associated with the opposite outcome (S in Context A → Positive, while S in Context B → Negative). Second, we manipulate the type of context, using neutral and drug-related contexts. While impaired ability to reverse the outcome of stimuli

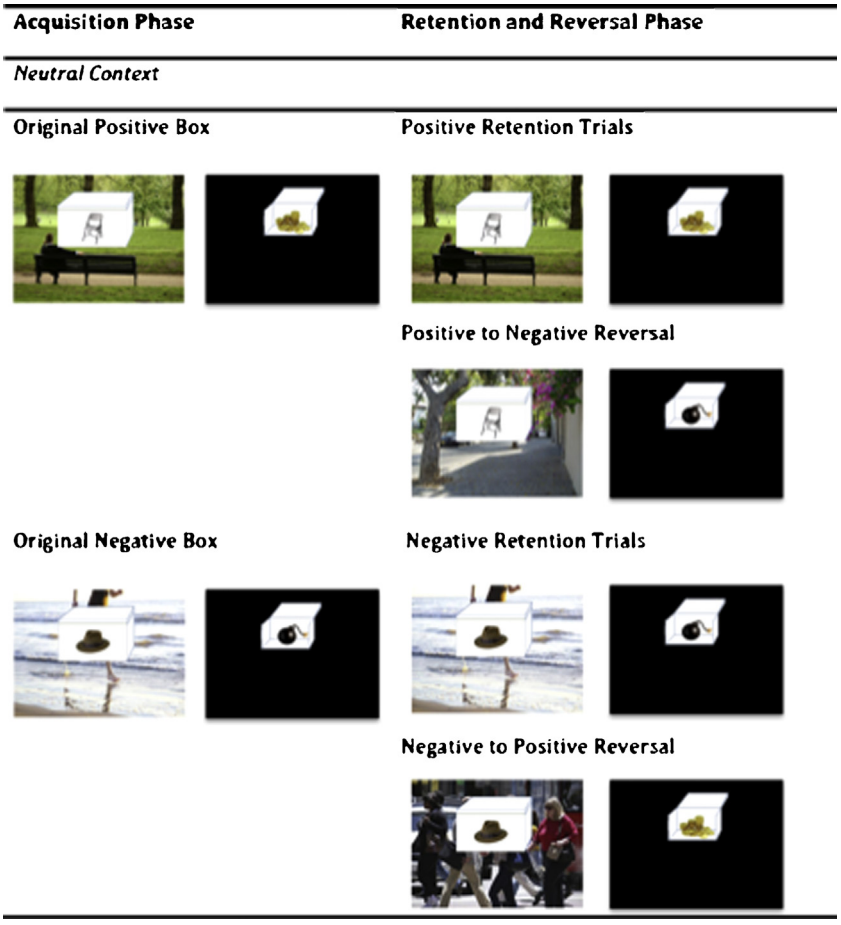

Fig. 1. Example of the stimuli in the two phases of the drugs reversal paradigm – neutral context.

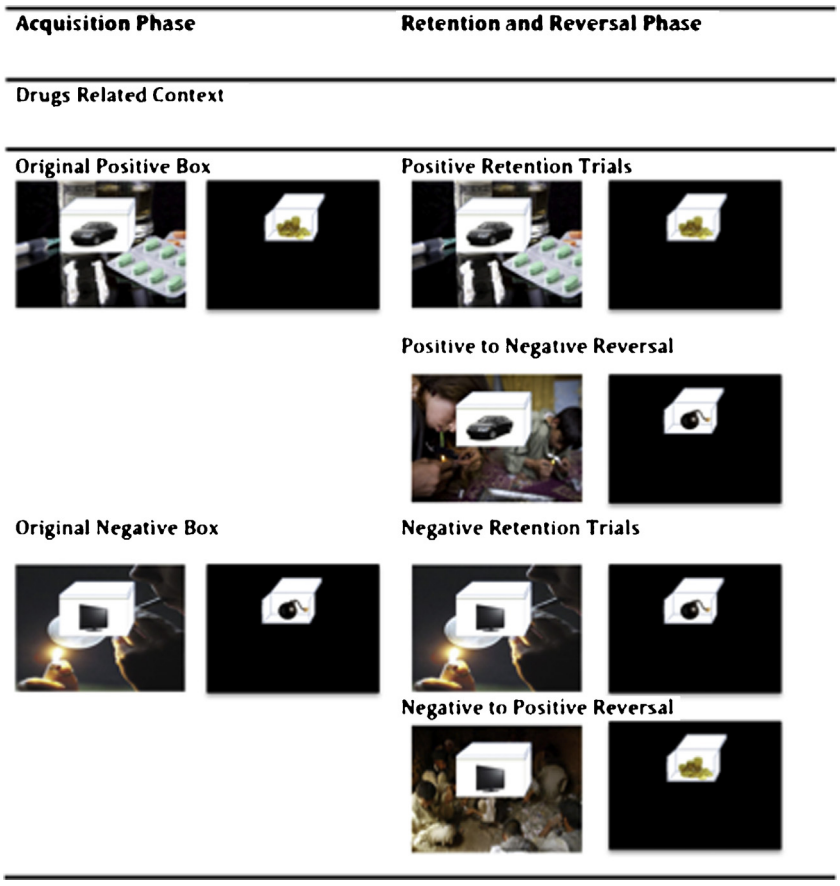

Fig. 2. Example of the stimuli in the two phases of the drugs reversal paradigm – drug-related context.

presented in neutral context (Fig. 1) may reflect a general cognitive impairment, selective impairment in drug-related context (Fig. 2) might suggest a more complex mechanism. Finally, we compared performance in conditions in which a previously positive stimulus becomes negative to conditions in which previously negative stimulus becomes positive. This paradigm enables us to test possible effects of valance (positive vs. negative outcomes) and contextual condition (neutral vs. drug-related context) on the ability to reverse previously learned information.

Based on the literature cited above we predict that participants from both methadone maintenance treatment and medication free abstinent groups would equally be able to learn and retain positive and negative stimulus–outcome associations that are presented in drug and neutral context. However, we anticipate that while medication free abstinent would show intact reversal learning in both neutral and drug-related contexts, methadone maintenance patients would show a selective impairment to reverse positive outcome in a drug-related context.

2. Method

2.1. Participants

We tested two groups of former opiate dependence individuals, who volunteered to participate in this study with no compensation and were matched for age, gender and education (Table 1). Inclusion criteria were based on DSM-IV-TR definition of opiate dependence. The first group included prolonged abstinence for at least 10 years representing a non-selective subgroup that was recruited consecutively to participate in a separate genetic study. None of these participants had any history of opioid agonist or other medication-assisted drug therapy in the abstinence duration that last a minimum of 10 years. Participants in this group were either instructors–counselors worker from various addiction-treatment institutes or active Narcotic Anonymous participants. The second group included current methadone maintenance patients from the Adelson clinic in Tel-Aviv Medical Center, who are in methadone maintenance treatment for at least 10 years (Mean methadone dose 117.4 ± 44.1 mg/day ranged 45–175 mg/day). We have screened a total of 26 methadone maintenance patients and 24 former opiate users. Four participants from the methadone users were excluded due to traces of drugs in urine in the day of testing. Two participants (one from each group) quit in the middle of the experiment. Two (one from the former opiate users and one from the methadone maintenance group) were excluded due to technical problems. The remaining 42 participants (20 methadone maintenance patients and 22 prolonged abstinence participants) were included in the study. There were no differences between the groups in past opioids usage and all had at least one institutional detox from illicit opioids (see Table 1 for a detailed description of the sample). The majority of the methadone maintenance patients (18 out of 20) presented negative urine results for any substance for at least 2 years and up to 14 years. However, two patients had one sporadic positive urine test for substance 3 months prior to study. These participants did not differ from the other participants in any of the study measures. Moreover, when we analyzed the data without these participants we reached the same pattern of results. Therefore we did not exclude them from the study. Importantly, all the participants in the methadone maintenance group fulfilled the American Society of Addiction

Table 1
Demographic characteristics of the sample (means and standard deviations/percentage).

	Prolonged abstinence ($N = 22$)	Methadone maintenance patients ($N = 20$)	Significance (p values)
Age (years, SD)	47.1 (6.7)	47.5 (5.7)	>.05
Female (%)	13.6	10.0	>.05
Education (years, SD)	10.4 (3.5)	10.2 (1.5)	>.05
Abstinence/methadone maintenance (years, SD)	13.8 (5.0)	12.7 (4.6)	>.05
Opiate onset (year, SD)	18.3 (3.6)	22.3 (7.0)	<.05
Opiate lifetime scores	9.7 (1.9)	10.7 (1.9)	>.05

Opiate lifetime scores were calculated based on KMSK score (Kellogg et al., 2003).

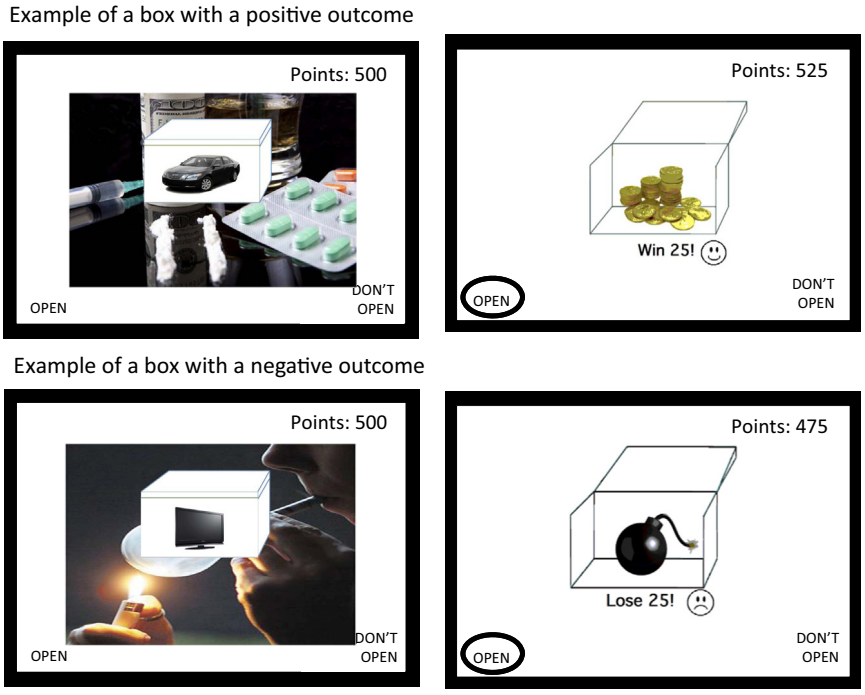

Fig. 3. Example of experimental trials in which participants chose to (a) open a positive-outcome box and (b) open a negative-outcome box.

Medicine (ASAM) criteria for take-home dose privilege, which include 3 month of abstinence together with an indication that the patient is stable, and responsible to keep the dose safe at home and drink it at due time (Peles et al., 2011). Exclusion criteria included age above 55 and positive urine for any drugs in the last 3 months. Participants were randomly tested before or after methadone administration (Peles et al., 2013), with 15–120 min interval (average time = 57.6 ± 28.4 min) between administration and testing for those who were tested after methadone administration. The experiment was done in accordance with the Declaration of Helsinki for the protection of human participants (Tel Aviv Sourasky Medical Center Ethics, IRB number 251-13). All participants provided a written informed consent at the beginning of the experiment.

2.2. Drugs in urine

Methadone maintenance participants had random observed urine tests as part of the clinic routine at least twice a month. The urine test is analyzed for opiates, cocaine metabolite (benzoylecgonine), benzodiazepine, cannabis (THC), amphetamines and methadone metabolite using enzyme immunoassay systems (DRI® and CEDIA® for the two latter substances; Hawks, 1986). The prolonged abstinence participants were tested for drugs in urine on the day of testing.

2.3. Self-report questionnaires and cognitive assessment

All participants completed self-report questionnaires to measure childhood trauma (CTQ; Pennebaker and Susman, 1988), depression (BDI-II; Beck et al., 1996) and anxiety symptoms (STAI; Spielberger et al., 1983). This was done in order to eliminate possible alternate explanations of impaired cognitive functions that may relate to the mental state and traumatic history of the participants (Spann et al., 2012). Finally, we used the Wechsler Adult Intelligence Scale III (WAIS-III) vocabulary subtest to estimate IQ levels (Wechsler, 1997). The results of the two groups are presented in Table 3. There were no significant differences between the groups on these measures. In addition there were no significant correlation between performance on the reversal paradigm and these measures.

2.4. Context reversal paradigm

In this paradigm, participants view a series of boxes against either a neutral (Fig. 1) or a drug-related context (Fig. 2). Neutral and drug-related context was manipulated using different pictures. These pictures were validated in a preliminary study among 30 former opiate users who rated 40 neutral and drug-related pictures on a 1–7 scale (1 – neutral; 7 – highly drug related). We chose the 4 pictures, which received the total higher and lower rates for the drug and neutral manipulation respectively (see Figs. 1 and 2). Boxes are presented with a target stimulus (one of various objects, e.g., a *hat*). When opened, each box is associated with a specific outcome (positive or negative). Participants receive the following instructions: "In this experiment you will be shown various boxes. For each box you have the option to open it or to leave it closed. If you open a box you will either win or lose 25 points. If you do not open the box you will not win or lose any points. Your job is to earn as many points as possible. Through trial and error you will learn to open the boxes that earn you points and not open the boxes that cost you points. Note that in order to learn which box earns you points and which box costs you point you should open each box the first time you see it". The experimenter verifies that the participants understand the instructions. Afterwards, the participants take part in a practice phase with close supervision of the experimenter. This phase demonstrates the task using two boxes; one associated with a positive outcome, and the other associated with a negative outcome (see Fig. 3 for example of the different trials). The experiment starts at the end of the practice phase. We created new boxes for the experiment, different from those presented in the practice phase, using four different objects and eight pictures; four drug-related pictures and four neutral pictures (for a schematic description see Table 2). The outcome of each box was counterbalanced across participants. The task has two phases. In the acquisition phase, participants learn by trial and error to predict the outcome of four different boxes (i.e., open the two positive boxes and skip the two negative boxes). The acquisition phase contains a minimum of 40 trials. However, in order to ensure learning of the stimulus–outcome associations in this phase, participants have to reach a criterion of six consecutive correct responses before they move on to the next phase. Participants who do not reach this criterion within 64 trials are automatically opted-out from the experiment. Correct responses refer to conditions

Table 2
Schematic description of the drugs reversal task.

Acquisition	Retention and reversal
Neutral context	
A(1) → Positive	A(1) → Positive A(3) → Negative
B(2) → Positive	B(2) → Positive B(4) → Negative
Drug-related context	
C(3) → Negative	C(5) → Negative C(7) → Positive
D(4) → Negative	D(6) → Negative D(8) → Positive

A–D represent 4 different stimuli (chair, hat, car, TV).
1–8 represent 8 different types of context, 4 are neutral pictures and 4 are drug-related pictures. In both the acquisition and retention-reversal phases, each stimulus was presented 10 times. This constitutes a total of 40 acquisition trials, 40 retention trials and 40 reversal trials.

Table 3
Questionnaires and cognitive assessment (means and standard deviation) of our sample.

	Prolonged abstinence	Methadone maintenance patients	Significance (*p* values)
BDI-II	9.2 (8.6)	10.2 (5.7)	>.05
STAI-State	35.9 (5.4)	35.6 (7.9)	>.05
STAI-Trait	36.5 (9.76)	37.2 (8.8)	>.05
CTQ	59.3 (22.9)	47.6 (18.7)	>.05
MMSE Score	27.6 (2.4)	28.2 (1.4)	>.05
IQ Score	7.8 (2.1)	7.2 (2.5)	>.05

We conducted *t*-tests for independent samples and found no significant differences in these variables.

in which participants open positive boxes or leave negative boxes closed. Similarly, incorrect responses refer to conditions in which participants open negative boxes or leave positive boxes closed. A subsequent retention and reversal phase starts immediately after the acquisition phase without any signaled switch or delay. In this phase participants receive retention trials with the original boxes that keep the same learned outcome. In addition, for each original box we added a new box. This box shares the same stimulus with the original box, but presented against a different new context (Figs. 1 and 2). The new box is associated with the opposite outcome relative to the original boxes (i.e., if the original box has gold inside, then new box will have bomb inside and vice versa). Therefore, in order to successfully learn these new stimulus–outcome associations, participants need to reverse the association rule of the original stimulus. Boxes in this phase are presented in 10 blocks of 8 boxes each (two boxes from each of the following conditions: positive/negative retention, positive/negative stimulus reversal). This sums up to a total of 80 trials; 20 trials per condition. At the end of the task, participants see their total earned points; however, the experiment includes no actual payment.

2.5. Data analysis

We used SPSS (version 19) software (SPSS Inc., Chicago, IL) to analyze the data. All data were checked for normality of distribution using Kolmogorov–Smirnov tests. Mixed models analyses of variance (ANOVAs) were used in order to detect differences between the groups and within the performance of each participant. Follow-up pair comparisons with Bonferroni correction were used in order to detect the source of significant interactions.

3. Results

There were no differences between the groups in lifetime opioids scores indicating amount of past opioids usage (Kellogg et al., 2003). However, the prolonged abstinence group displayed a significantly younger age of opioids onset (Table 1). In addition, there were no significant differences between the groups in levels of depression and anxiety symptoms, levels of childhood trauma, cognitive function and estimated IQ (Table 3). Finally, since there were no differences between the groups in reaction time (all $Fs < 1$), we report the percentage of correct responses only.

3.1. Acquisition and retention of stimulus–outcome associations

All the participants were able to learn the stimulus–outcome associations in the acquisition phase (number of trials in this phase $M = 41.1$; $M = 41.2$ for the methadone and abstinent groups respectively). In order to test whether participants are equally able to retain neutral and drug-related associations we conducted a group (methadone and abstinent participants) by retention type (neutral vs. drug related) by retention outcome (positive vs. negative) mixed model ANOVA on the percentage of correct responses. As can be seen in Fig. 4 the results revealed no significant main effects and no significant interaction between group, retention type and retention outcome ($F(1,40) = .13$, $p = .72$). The results confirm that participants from both groups were equally able to retain neutral and drug-related stimulus–outcome associations.

3.2. Reversal learning

In order to test possible differences in reversing positive and negative outcomes in neutral and drug-related context, we conducted a group (methadone and abstinent participants) by context (neutral vs. drug related) by outcome (positive vs. negative) mixed model ANOVA on the percentage of correct responses. The results are depicted in Fig. 5. We found a significant triple interaction between group, stimulus reversal learning and type of context ($F(1,40) = 7.09$, $p < .05$, $\eta_p^2 = .15$). Follow-up analyses showed significant differences between the groups in drug-related context, but not in neutral context ($F(1,40) = 7.91$, $p < .01$, $\eta_p^2 = .17$; $F(1,40) = .22$, $p = .64$; for drug-related and neutral context respectively). Pairwise comparisons with Bonferroni correction ($\alpha = .01$) in conditions of drug-related context revealed that while there were no differences between the groups in negative to positive reversals ($t(40) = .45$, $p = .65$), methadone maintenance patients were significantly more impaired in positive to negative reversals ($t(40) = 5.34$, $p < .001$). Hence, after they learned that a specific stimulus has a positive outcome, they struggled to learn that the same stimulus, when presented in a different context has a negative outcome. There were no significant correlations between timing of methadone administration and performance on any of the experimental conditions (all $ps > .26$).

4. Discussion

In the present study, we conducted a unique comparison of former opiate-dependent individuals, who were either successfully discontinued their drug abuse for more than 10 years with no need of agonist treatment or patients in methadone maintenance treatment for at least 10 years. Participants were tested on a novel paradigm which examines the ability to reverse positive and negative outcomes in neutral and drug-related context. As predicted, the results revealed a selective impairment of methadone maintenance patients in reversing positive outcomes of associations that were presented in a drug-related context. Specifically, after they learned that a certain stimulus is associated with a positive outcome, methadone maintenance patients struggled to learn that the same stimulus is associated with a negative outcome when presented later in a different drug-related context.

The results may reflect the core mechanisms of addiction and provide a possible explanation for frequent relapses. Accordingly, drug usage is initially associated with positive outcomes such as pleasure and euphoria but quickly leads to negative consequences (for a review see de Wit and Phillips, 2012; Koob, 2013; White, 2004). Our findings suggest that former drug users who succeeded maintaining prolonged abstinence are able to update their associative learning. Hence, they may be able to change their behavior according to the negative consequences. On the other hand, methadone maintenance patients show a selective impairment to reverse positive associations, which were acquired in a drug-related context. Therefore, even if drug usage is no longer associated with positive outcomes they may struggle to change their behavior accordingly.

Importantly, these differences do not seem to reflect a more severe past drug usage of the methadone maintenance patients. As can be seen in Table 1, not only that there were no differences in lifetime opioids scores between the groups, the age of onset was significantly younger among the prolonged abstinence participants. Similar results were found in a recent study (Peles et al., 2014, under-review), which compared a larger sample of prolonged abstinence and methadone maintenance participants and show no differences in lifetime opiate usage. Moreover, prolonged abstinence individuals in this study reported younger age of onset

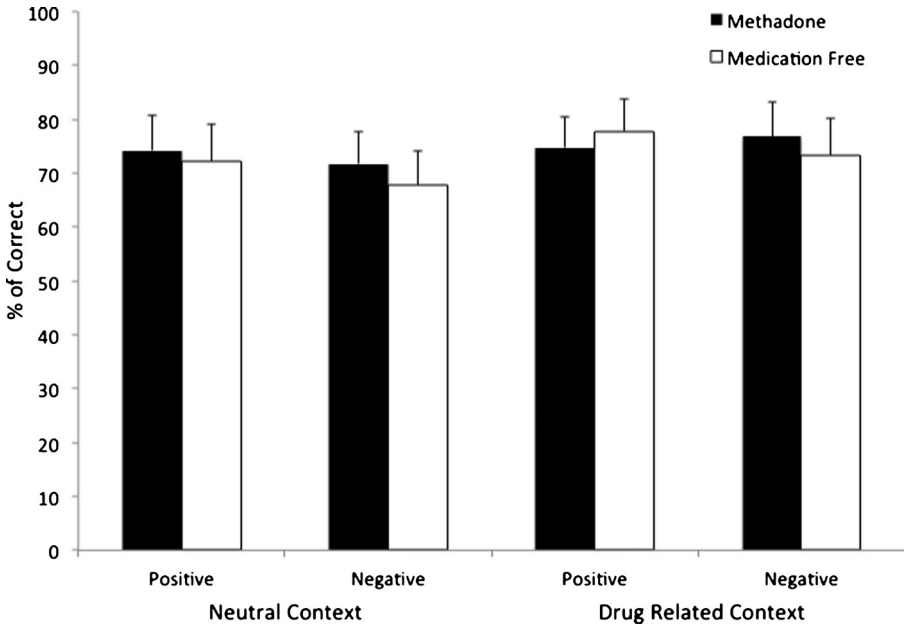

Fig. 4. Percentage of correct retention (means and standard error bars) of the four original boxes as a function of Outcome (positive vs. negative), Context (neutral vs. drug related) and Experimental Group (methadone maintenance patients vs. prolonged abstinence medication free individuals).

and longer duration of usage of other drugs such as cocaine and marihuana.

Our findings are in line with other studies, which tested alcohol dependent patients (Máttyássy et al., 2012; Rustemeier et al., 2012). Similarly, these studies have shown that both alcohol dependent patients and healthy controls were equally able to acquire stimulus–outcome associations. However, alcohol dependent patients showed a selective impairment when they had to modify their learning according to changing circumstances. Although these studies did not distinguish between different types of context, the comparable results in the two populations may reflect a similar impairment in the midbrain dopamine system, which is involved in learning from positive feedback (for reviews see Schultz and Dickinson, 2000; Schultz et al., 1997). It is well established that cocaine abusers (for a review see Volkow et al., 2004) as well as alcohol dependent patients (Martinez et al., 2005) suffer from reduced dopamine transmission in the striatum. However, they show a significant increase in the striatum dopamine in response to contextual reminders of the drugs (Volkow et al., 2006 for review see Everitt and Robbins, 2013; Volkow et al., 2011). It is

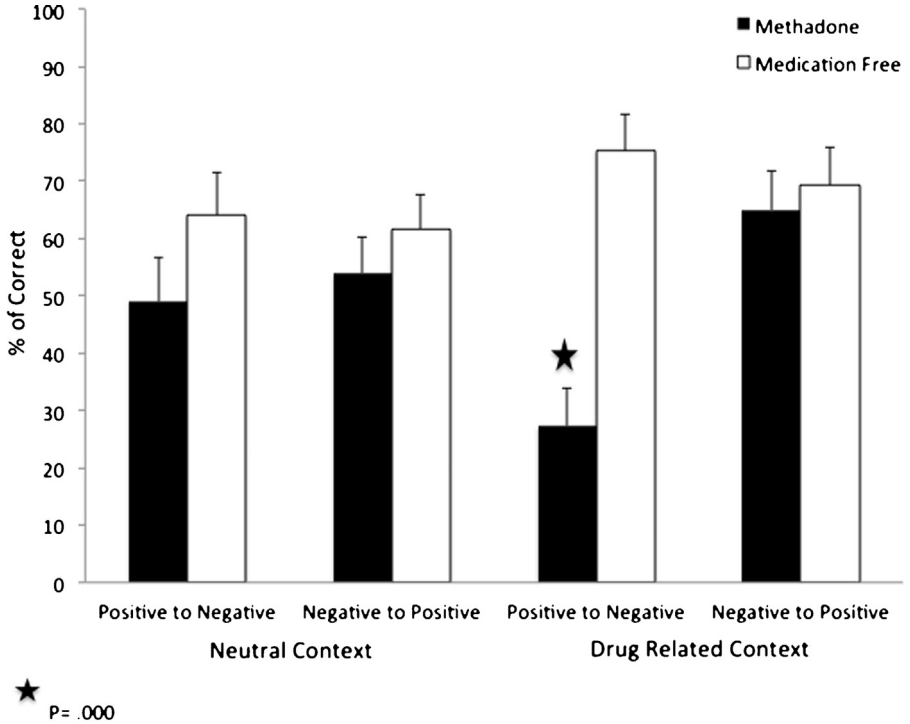

Fig. 5. Percentage of correct responses (means and standard error bars) for the new associations as a function of Reversal (negative to positive vs. positive to negative), Context (neutral vs. drug related) and Experimental Group (methadone maintenance patients vs. prolonged abstinence medication free individuals).

possible that this dopamine incline results in stronger positive associations in drug-related conditions, which may be harder to reverse. Similar mechanisms may explain why methadone maintenance patients are able to learn that stimulus with negative outcome that are presented in a drug-related context becomes positive (for a review see Everitt and Robbins, 2005; Kalivas and O'Brien, 2008). However, future studies using similar task in different populations together with neurobiological measures are needed in order to further explore these possible connections.

It is important to emphasize that the impairment in reversing positive associations was selective to drug-related conditions, and does not reflect a general impairment in associative learning. In conditions of neutral context both prolonged abstinence and methadone maintenance patients preformed equally well. This selective impairment may revoke possible alternate explanation. Specifically, one may claim that the impaired performance of the methadone maintenance patients is due to timing of methadone administration. Rass et al. (2014) have found that methadone negatively affects physiological and cognitive functioning. These effects are evident 1 h after dose administration and reach peak at approximately 2 h post dose. Indeed, most of the methadone maintenance patients in this study (18 out of 20) completed the reversal paradigm 15–120 min after methadone administration (average time = 57.6 ± 28.4 min), and therefore might be subjected to its deteriorating effects. However, there are several reasons that may revoke such claim. First, in a previous unpublished study we found no differences in cognitive performance between patients as a function of administration timing (before/after testing). Moreover the fact that the methadone maintenance participants performed equally well as prolonged abstinence in neutral conditions suggests that this selective impairment is not a result of general poorer performance or general cognitive decline due to timing of methadone administration. Finally and most importantly, there was no significant correlation between performance on any of the experimental conditions and timing of methadone administration. Taking together it may suggest that methadone administration timing does not significantly affects the cognitive functions that are needed in order to complete our task. Alternatively, it is possible that its effects become more substantial only later in time. A future study that compares the performance on our task as a function of methadone administration timing is needed in order to clarify this point.

The intact performance of methadone maintenance patients in neutral conditions may challenge previous findings, which compared opiate abusers and methadone maintenance patients (e.g., Curran et al., 2001; Rogers et al., 1999; Wang et al., 2013), and revealed that methadone maintenance patients have several cognitive impairments. However, it is important to note that other studies did not find such impairments (Darke et al., 2000; Rapeli et al., 2011). A possible explanation for these apparently contradicting results is the unique characteristics of our methadone maintenance sample. Although methadone maintenance patients usually represent a very heterogeneous group, in the present study we carefully selected participants in order to provide a comparable and homogenous group. The range of ages across all participants was relatively small, and level of education was similar. Most importantly all of our methadone participants were stabilized on methadone, have been in treatment for at least 10 years and tested negative in their urine for any drug usage. Alternatively, it can be claimed that the simple nature of our task allowed participants from both groups to learn it, independent of possible other cognitive impairments. Indeed, similar to findings in other clinical populations (Levy-Gigi and Richter-Levin, 2014; Levy-Gigi et al., 2012, 2014), we found no associations between IQ level and performance on the different phases of the task. Future studies may aim to test a larger sample of methadone maintenance patients in order to test individual differences within this group. For example it would be interesting to test how general cognitive impairment (e.g., lower IQ scores and diminished mental state) affects the performance in this task, whether people who experience occasional relapsing to drug abuse show greater positive reversal impairment, and whether there are individual differences as a function of abstinence duration.

Another possible claim is that methadone administration has an accumulative effect that may alter the salience of drug-related cues, induce craving and result in distraction and impaired learning in drug-related conditions. However, it is well established that the methadone maintenance treatment has the opposite effect. Specifically, it has a therapeutic effect since it reduces drugs craving and minimizes the effects of drugs-related stimuli (e.g., Kling et al., 2000). In addition, the pattern of the results shows that this impairment is unique to conditions of positive to negative reversals. Specifically, methadone maintenance patients struggled to learn that a positive cue presented in a drug-related context becomes negative. Nevertheless, they could learn that a negative cue presented in a drug-related context becomes positive. In order to further clarify this point future study may aim to test drug users before they start methadone treatment and follow them for several years to see changes in their performance and its possible association with their ability to reach and maintain medications free lifestyle.

Finally, it is still in question whether the impaired performance in the positive to negative condition among methadone maintenance patients is due to the use of long acting opioid methadone, or due to a pre-existing different psychobiology behavior (Paulus, 2007). In order to test it future longitudinal study may aim to test drug users as close as possible to their first drug episode and see whether positive and negative associative learning in drug-related context can help to predict their ability to successfully withdraw drugs in the future.

It is important to note that as found in narcotic, cocaine and heroin abusers, as well as in methadone maintenance patients, relapse may be related to several parameters such as disturbed stress responsivity (Kreek et al., 1983; Levran et al., 2014), addiction severity, or genetic vulnerability. Moreover, each of these factors may be associated or interact with the reported deficit and with the two treatment approaches that are represented by our participants. However, the differences between these two treatment approaches are not as important as the ultimate goal of successful treatment of drug abuse. Notwithstanding the clinical and cognitive implications of our results, the conditions of intervention is less important in comparison with the aim to decrease relapses that illicit drug use and improve the overall well-being and quality of life of the individual.

To summarize, the results of the present study show that methadone maintenance patients have a selective deficit in reversing the outcome of positive stimulus that were presented in a drug-related context, compared to prolonged abstinence participants. This impairment may reflect drug abuse brain mechanisms and emphasize possible cognitive challenges faced by these individuals when trying to maintain a medication free life.

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Nothing declared.

Contributors

ELG – design of the paradigm, design of the study, responsible for recruiting and testing participants, analyzing data, writing and finalizing the manuscript; SK – design of the paradigm, analyzing data; ARS – testing participants, preparation of the manuscript. AS

– responsible for recruiting and testing participants; MA – responsible for recruiting and testing participants. EP – design of the study, responsible for recruiting and testing participants, writing and finalizing the manuscript. All co-authors took part in preparing and reviewing the manuscript.

Conflict of interest

No conflict declared.

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