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Intranasal oxytocin dampens cue-elicited cigarette craving in daily smokers: A pilot study

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Abstract

Despite moderate success with pharmacological and behavioral treatments, smoking relapse rates remain high, and many smokers report that smoking cues lead to relapse. Therefore, treatments that target cue reactivity are needed. One candidate for reducing craving is the neuropeptide oxytocin (OT). Here, we investigated the effects of intranasal OT on two types of craving for cigarettes: craving following overnight abstinence and craving elicited by smoking-related cues. In this within-subject, placebo-controlled pilot study, smokers (N = 17) abstained from smoking for 12 hours before attending two sessions randomized to intranasal OT or placebo (i.e., saline nasal spray). On each session, participants received two doses of OT (20 IU) or placebo at one-hour intervals, and rated craving before and after each dose. Spontaneous cigarette craving was assessed after the first spray, and cue-elicited craving was assessed following the second spray. OT did not reduce levels of spontaneous craving after the first spray, but significantly dampened cue-induced smoking craving. These results provide preliminary evidence that OT can reduce cue-induced smoking craving in smokers. These findings provide an important link between preclinical and clinical studies aimed at examining the effectiveness of OT as a novel treatment for drug craving.

Keywords

Oxytocin; smoking; craving; placebo-controlled trial; human

Introduction

Cigarette smoking is a major health concern worldwide. In the United States alone, approximately 70 million individuals over the age of 12 are current smokers (SAMHSA 2011), and cigarette smoking accounts for nearly 480,000 deaths annually (Rostron 2013). Despite moderate treatment success with both pharmacological and behavioral treatments, nicotine dependence remains a persistent, chronic problem for many individuals. Indeed, of

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the 50% of current smokers who attempt to quit smoking per year, only 6% succeed (CDC 2011), with most relapsing within a few days of attempted cessation.

Risk for relapse can remain high for years, even after acute withdrawal has passed (Wetter et al., 2004). This persistent risk may be due in part to the power of cues (sights, smells, or places associated with smoking), to evoke learned, or conditioned, drug-seeking responses (Ferguson and Shiffman, 2009). Through repeated associations, drug-related cues become conditioned to the reinforcing effects of the drug and acquire incentive motivational properties (Robinson and Berridge, 1993). Conditioned smoking cues increase negative mood, heart rate, skin conductance, and self-reported craving (Conklin and Tiffany, 2001; Drobes and Tiffany, 1997; LaRowe et al., 2007) as well as actual smoking and relapse (Glad and Adesso, 1976; Herman, 1974; Mucha et al., 1998; Payne et al., 1990, 1991; Surawy et al., 1985) Therefore, novel treatments for smoking that target cue-induced craving are needed.

Oxytocin (OT) has received increasing interest as a potential treatment for addiction (for reviews see (Kovács et al., 1998; McGregor and Bowen, 2010; Sarnyai, 2011). OT is a neuropeptide released from the posterior pituitary that evokes a range of peripheral and central effects on reproductive/sexual behavior, mood, emotions, and socialization (Gimpl and Fahrenholz, 2001). Indeed, exogenous administration of OT has been shown to increase trust, sociability, and bonding (Kosfeld et al., 2005; Lim and Young, 2006). In addition to these well-known “pro-social” effects, there is also mounting evidence that OT also plays a role in the processes involved in drug addiction (Sarnyai and Kovács, 1994). For instance, preclinical studies have shown that OT decreases drug self-administration, and drug-primed reinstatement of drug taking (Carson et al., 2010; Sarnyai et al., 1991) and facilitates extinction of drug-paired associations (Baracz et al., 2012; Kovács et al., 1998; Qi et al., 2009). OT, and drugs that increase OT such as lithium, also reduce the severity of drug withdrawal for opiates, ethanol, and cannabis in rats (Cui et al., 2001; Kovács et al., 1998; Szabó et al., 1987; You et al., 2001).

More recently, human work has also highlighted the benefits of OT as a potential treatment agent for drug abuse. OT has been shown to relieve negative affect and anxiety (de Oliveira et al., 2012; Heinrichs et al., 2003), which are cardinal symptoms of nicotine withdrawal (Baker et al., 2004; Hughes and Hatsukami, 1986). In the first study of the effects of OT on drug craving, McRae-Clark and colleagues (2013) showed that intranasal OT significantly attenuated stress-induced craving for marijuana in marijuana dependent individuals. However, despite this evidence that OT reduces craving in response to stress, there have been no other studies examining the relationship between OT and drug reward or drug craving in humans. Taken together, the evidence suggests that OT can dampen craving in humans, perhaps due to its anxiolytic effects, and can reduce drug reward in animals. Therefore, there is a possibility that OT might reduce craving to smoking-related cues, which have acquired incentive salience in smokers.

In the current experiment, we aimed to examine the effects of OT on craving in cigarette smokers. To date, there have been no studies assessing the effects of OT on: a) cigarette craving during short-term abstinence, or b) craving elicited by drug-related cues. In the

current experiment, we tested the effect of intranasal OT (20 IU) on tonic craving following overnight abstinence and on craving following exposure to smoking-cues, in daily smokers. We hypothesized that OT would reduce both spontaneous craving and craving elicited by smoking cues.

Methods

Participants

Daily cigarette smokers (N=17; 6 female) aged 18 – 35 years participated in the study. Potential candidates completed an initial phone screen and an in-person interview, including a physical examination and electrocardiogram. Exclusion criteria were a current or past year diagnosis of a DSM-IV Axis I disorder (assessed using the non-patient version of the Structured Clinical Interview for DSM-IV), excluding nicotine dependence [assessed using the Fagerström Test for Nicotine Dependence (FTND; (Heatherton et al., 1991)], high blood pressure or a history of cardiovascular problems, less than a high school education, lack of fluency in English, and pregnancy or lactation in women. All participants provided informed consent prior to participating in the study.

Study Design

The study used a within-subjects design. Daily smokers abstained from smoking for 12h before attending two laboratory sessions, which was confirmed by assessing expired carbon monoxide (CO) levels. A criterion of 10 parts per million (ppm) or lower was used to confirm compliance with instructions (Jarvik et al., 2000; Jarvis et al., 1987; Leischow et al., 1997). Participants were randomized to receive two doses of intranasal OT (20 IU per dose) nasal spray on one testing session, and two placebo nasal sprays on the other. We chose the 20 IU dose per spray on the basis of previous studies utilizing intranasally administered oxytocin. This dose has been well tolerated by participants in our laboratory (see MacDonald et al., 2011 for a review of safety of intranasal oxytocin in humans). Participants rated their mood and smoking urge before and after the first spray. On the basis of estimates of plasma clearance time (Kirkpatrick et al, 2014) we expected that this first dose would peak after 20 min and return to near baseline levels by 75 minutes. One hour and fifteen minutes later, they received the second spray followed by exposure to smoking cues (smoking-related images followed by lighting and holding a lit cigarette) and they again rated mood and smoking urge.

Procedure

The protocol was approved by the University of Chicago Institutional Review Board. Experimental sessions were conducted in comfortably furnished rooms with a television/ VCR, magazines and a computer for administering questionnaires and images. Sessions began at 12.00h and were conducted at least 72 h apart. For women not taking hormonal birth control, sessions were conducted during the follicular phase of their menstrual cycle (between days 3 and 10) to reduce variability in endogenous oxytocin levels that occur across the menstrual cycle (Salonia et al., 2005; Shukovski et al., 1989). Participants were required to abstain from smoking, starting at midnight the night before each session. Upon arrival, they provided breath and urine samples to detect recent drug and alcohol use, and

pregnancy in women. Participants also provided expired air CO to assess compliance with instructions. After these measures, participants completed baseline mood and craving questionnaires (see below). At 12:30, they received a nasal spray containing either OT or placebo, followed by self-report mood and craving questionnaires at 10 – 20 minute intervals for 60 minutes. At 13.45, they received a second nasal spray. Thirty minutes later, they completed the 10-minute cue exposure which ended at approximately 14.30. They then provided ratings of craving and mood at subsequent 20–30 minute intervals over the next hour and a half. Once the last measures were collected, at approximately 16.00, individuals were allowed to leave. After participants had completed both testing sessions, they were debriefed and paid for their participation.

Smoking Cues

Cue exposure consisted of viewing a 5-minute set of pictures presented for 6 s each, with the pictures consisting of images of cigarettes, smoking paraphernalia, and individuals or groups of individuals smoking. These images were generated in our laboratory, and were rated by smokers, who reported the images produced a significant urge to smoke. Participants viewed a different set of images at each session. Immediately after viewing the images, participants were asked to light a cigarette provided by the researchers (Marlboro Light brand) and hold the cigarette for five minutes without smoking it.

Dependent Measures

Visual Analog Scales (VAS: 0 – 100 mm; not at all to extremely) consisted of adjectives describing OT-related effects (for a review see MacDonald et al., 2011) including *Dizzy*, *Light-Headed*, *Stimulated*, *Focused*, *Dreamy*, and *Nauseous*.

The Profile of Mood States (POMS; Johanson and Uhlenhuth, 1980) is a standardized questionnaire consisting of 72 adjectives used to describe momentary positive and negative mood states, including anxiety. Participants indicate how they feel at the moment in relation to each of the adjectives on a 5-point scale ranging from *not at all* (0) to *extremely* (4). In this study, we *a priori* chose to examine the Anxiety, Anger, and Depression POMS subscales.

The Short Tobacco Craving Questionnaire (S-TCQ: Heishman et al., 2008) is a 12-item validated questionnaire that measures subjective tobacco craving on a 7-point Likert scale and consists of four scales: Expectancy, Purposefulness, Emotionality, and Compulsivity.

The Brief Questionnaire of Smoking Urges (B-QSU: Cox et al., 2001) is a 10-item questionnaire that measures smoking urges, with each item scored on a 7-point scale. The B-QSU consists of two factor-derived subscales measuring a desire to smoke for the positive effects of a cigarette (Factor 1) and the anticipation of relief from withdrawal symptoms (Factor 2), as well as the total score (sum of the two factors; Total Composite Score).

Drug

Intranasal OT and placebo doses were prepared by the University of Chicago Hospitals investigational pharmacy. For active OT, two single doses of 20IU Pitocin (OT Injection

USB; Monarch Pharmaceuticals; concentration 10 IU Pitocin/1 ml) were transferred into two, 1 ml clear syringes fitted with an atomizer to administer the liquid in spray form (MAD300 by LMA Inc., San Diego, CA). Placebo nasal sprays consisted of Ocean Spray Nasal Spray (Valeant Pharmaceuticals, Bridgewater, NJ). Each set of nasal sprays was administered in four, 0.25 ml doses to each nare over the course of 10 minutes (1 spray in alternating nares each minute).

Statistical Analyses

Analyses were conducted using SPSS version 16.0 for Windows. Missing cases (due to equipment malfunction or other data collection problems) were deleted list-wise. Two participants' data were missing for the POMS following the first OT administration, leading to a smaller sample size for analyses using that measure. Independent 2 (dose) x 3 (time) repeated-measure analyses of variance (ANOVA) were used to assess the effects of OT on dependent measures (POMS, TCQ, and QSU) before and after cue exposure. Quadratic effects are reported following the second spray because we expected craving to rise and then fall following cue exposure. Simple-effects tests were used to compare dependent-measure ratings before and after cue exposure for both OT and placebo. For all analyses, differences were considered to be significant if $p < 0.05$. Effect sizes are reported throughout as partial eta-squared (ηp^2) for ANOVAs (where 0.01, 0.06 and 0.16 represent small, medium and large effect sizes respectively). Initially, all analyses were conducted with gender and dose order as between-subjects factors. There were no significant main effects or interactions involving sex or dose order for any of the dependent measures. Therefore, all analyses presented were collapsed across sex and dose order.

Results

Demographics and smoking habits

Table 1 shows the demographics and smoking characteristics of the sample. Participants tended to be young, of Caucasian race and smoked an average of six cigarettes per day. They had an average FTND score of 2.2, indicating a relatively low level of physical nicotine dependence.

Effects of OT on self-reported craving and mood

There were no baseline differences in craving or mood between placebo and OT sessions prior to the first spray, ps > 0.9. After the first spray, OT (vs. placebo) did not alter craving (S-TCQ and B-QSU; dose x time Fs < 1.5, ps > 0.2), mood (POMS, dose x time Fs < 0.83, ps > 0.37), or subjective effects (VAS dose x time Fs < 3.9, ps > 0.6).

Effects of smoking cues and oxytocin on self-reported craving

Craving significantly increased following exposure to the smoking cues in the placebo condition, supporting the effectiveness of the cue procedure. These increases were observed on the TCQ Expectancy scale and the QSU Total Composite and Factor 1 Subscales. OT dampened this increase in craving with significant dose x time interactions for S-TCQ Expectancy [$F(1, 16) = 4.3$, $p < 0.05$, $\eta p^2 = 0.2$], the B-QSU Factor 1 subscale [$F(1, 16) = 5.2$, $p < 0.05$, $\eta p^2 = 0.2$], and the B-QSU Composite Score [$F(1, 16) = 2.5$, $p = 0.06$, $\eta p^2 =$

0.14]. For both the S-TCQ Expectancy Scale and the B-QSU Factor 1 Subscale, simple-effects tests showed that there was a significant increase in ratings from pre-cue to post-cue exposure following placebo [pre-cue exposure (20 minutes post spray 2) versus post cue exposure (60 and 90 minutes post spray 2 on the S-TCQ Expectancy and 40, 60, and 90 minutes post Spray 2 on the B-QSU Factor 1), ps < 0.05], but not following OT for both measures (ps > 0.35) (Figures 1 and 2). There were no effects of cue or dose on ratings of B-QSU factor 2 (relief of negative affect) or the Emotionality, Compulsivity, or Purposefulness scales of the S-TCQ, ps >0.08).

Effects of OT and smoking cues on mood

Smoking cues significantly increased ratings on the POMS Anxiety subscale [Time, F(1, 16) = 8.8, p < 0.01, ηp^2 = 0.36], but there was no effect of OT on this measure [dose x time, F(1, 16) = 0.01, p = 0.9, ηp^2 = 0.001] (Figure 3). There were significantly higher ratings of Depression on the POMS following OT [Dose, F(1, 16) = 4.5, p < 0.5, ηp^2 = 0.22], however the effect of cues (main effect of time) and the dose x time interaction were not significant, ps > 0.07. There were no significant effects of cues or OT on the POMS Anger subscales (ps > 0.1).

Discussion

This study was the first to examine the effects of intranasal OT on cue-elicited craving in daily smokers. Although OT did not reduce tonic craving after the first dose administration, following overnight abstinence, it significantly dampened cigarette craving induced by smoking-related cues after the second dose administration 75 minutes later. Interestingly, the cues also increased self-reported anxiety, but OT did not dampen this effect, suggesting that the effect of OT was specific to self-reported cigarette craving and not due to a non-specific lowering of anxiety. These results extend findings in both animals and humans suggesting that OT may play a role in cue-induced craving.

One important finding in this study is that OT attenuated cigarette craving independent of any other effects on mood or affect. OT has been shown to have anxiolytic effects (de Oliveira et al., 2012; Heinrichs et al., 2003), which might make it beneficial for individuals who use drugs in response to stress. However, we found no evidence that OT altered anxiety elicited by smoking cues. Indeed, participants reported no subjective effects of OT at all, and when asked to identify what drug they had received at the end of the session, they guessed at chance level. Therefore, the effects of OT were specific to craving in this study, and not due to any calming effects that might have masked subjective craving.

Importantly, the effects of OT on craving were only seen in response to cue exposure, and not on tonic craving following the first OT administration. The participants abstained from smoking overnight before the sessions, and so their ratings of craving were moderately high at the time of the sessions. Whereas the first dose of OT did not affect these ‘tonic’ craving ratings, the second dose, administered 75 min later, decreased craving elicited by the cue. There are at least two possible explanations for this outcome. First, it is possible that different processes are involved in spontaneous craving and cue-induced craving, and that OT affects the latter but not the former. Second, it is possible that the sequential nature of the

OT doses resulted in differential plasma levels or effects during the two administrations. That is, the first dose may have been subthreshold to reduce spontaneous craving, but carryover effects from that dose added to the effect of the second dose, resulting in significant cue-induced craving reduction during the later phase of the study. Although we cannot rule out this possibility, the finding that OT attenuated cue-induced craving is consistent with preclinical work demonstrating that OT reduces drug reward in animals. For instance, in rodents, OT has been shown to attenuate self-administration of cocaine (Sarnyai et al., 1992a; Sarnyai et al., 1992b), methamphetamine (Carson et al., 2010), and heroin (Kovacs and Van Ree, 1985), and to extinguish conditioned place preference (Qi et al., 2009).

The neurochemical mechanism by which OT reduces either drug reward or conditioned reward is not known, but there is mounting evidence that OT reduces the reinforcing properties of drugs by inhibiting drug-induced activity of dopamine in mesolimbic structures (Kovacs et al., 1990; McGregor et al., 2008; Qi et al., 2009). The mesolimbic dopamine system is strongly implicated in the rewarding effects of drugs (e.g., Di Chiara and Imperato, 1988; Koob and Le Moal, 1997; Robinson and Berridge, 1993; Wise, 1980). In drug-dependent humans, drug-related cues can increase dopamine activity in the dorsal (Volkow et al., 2006) and ventral (Heinz et al., 2004) striatum, perhaps related to their ability to increase incentive salience and activate neural networks involved in craving and reward. Thus, OT might reduce drug taking behavior by dampening the dopaminergic response, in this study by reducing the dopamine response to the smoking cue. Future studies should focus on identifying how OT alters drug and cue-induced dopamine activity in humans using appropriate imaging technologies such as positron emission tomography.

There are important limitations to the present study. First, the sample size was small, and comprised of young smokers who were not highly dependent on tobacco (i.e., smoking on average 6–7 cigarettes per day). It is not known if the effects would be more, or less, pronounced in heavier smokers. Perhaps related to their low tobacco dependence, the participants reported only modest craving, and did not report craving on factors assessing relief of negative affect or feeling as if they would be unable to stop if they started smoking. These are factors that reflect more significant nicotine dependence, and we cannot determine whether OT affects these aspects of tobacco addiction. Larger or more pervasive anti-craving effects may occur in heavier smokers. Second, we tested only one dose of OT at each of the two time points (i.e., 20 IU at the measure of spontaneous craving during the first measure and 20 IU at the measure of cue-induced craving during the second measure 75 minutes later). Ideally, each of the processes should be studied at several doses. Moreover, it is possible that the first dose affected responses to the second dose. Although plasma OT levels decline by 60 min after intranasal administration (Kirkpatrick et al., 2014), it is possible that OT from the first spray was still present at the time of the second spray, resulting in a higher dose during the second phase (cue-elicited craving). Studies examining OT levels in cerebral spinal fluid (CSF) indicate that it may take up to 75 minutes for OT to reach its peak, substantially longer than the plasma OT time course (Striepens et al., 2013). Thus, we cannot be sure that OT levels were sufficiently high during our test of spontaneous craving, or whether the effects on cue-elicited craving were a result of carryover effects from the first dose. Therefore, it will be important for future work to characterize the dose-response

relationship and implement a longer measurement period to better define the dose dependency and time course of its effects on craving.

Taken together, these findings suggest that OT signaling pathways may be a target for reducing drug craving in humans. More specifically, OT may reduce subjective craving in response to smoking-related cues, possibly by reducing their incentive motivational properties. Future studies should further investigate whether OT affects other measures of craving, including physiological effects and actual smoking behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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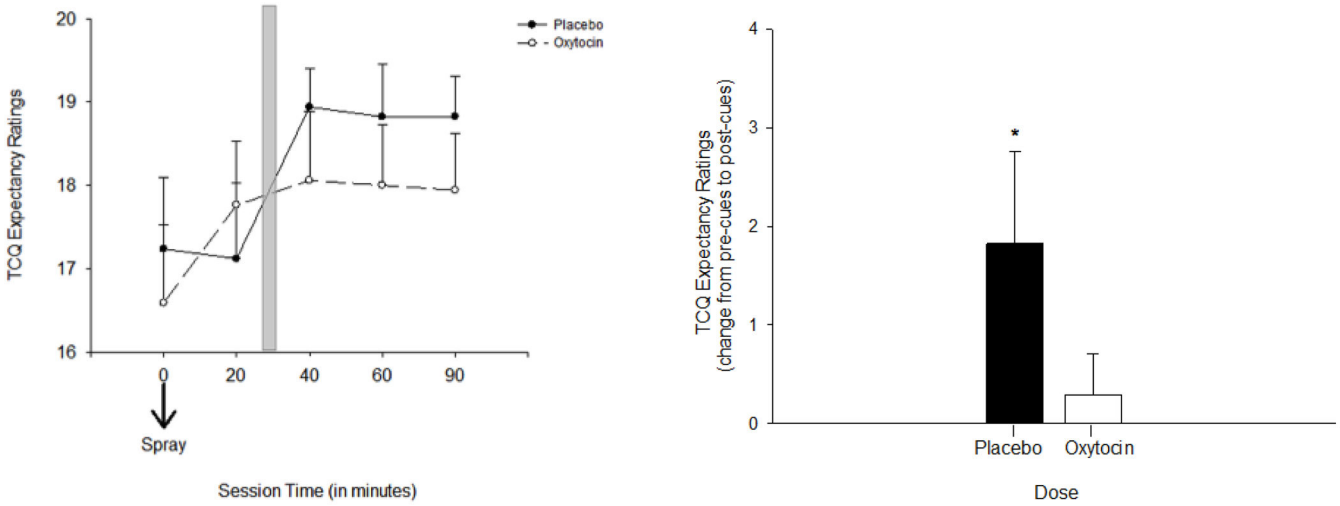

Figure 1.

Smoking Craving on the S-TCQ Expectancy Scale in response to smoking cues following OT and placebo. Left panel: subjective craving on the S-TCQ Expectancy scale following the second OT and placebo administration (time 0 minutes). Shaded bar indicates cue exposure period. Right panel: change in ratings on the S-TCQ Expectancy before and after cues. Asterisk indicates a significant increase following placebo, $p < 0.05$. Capped bars indicate SEM.

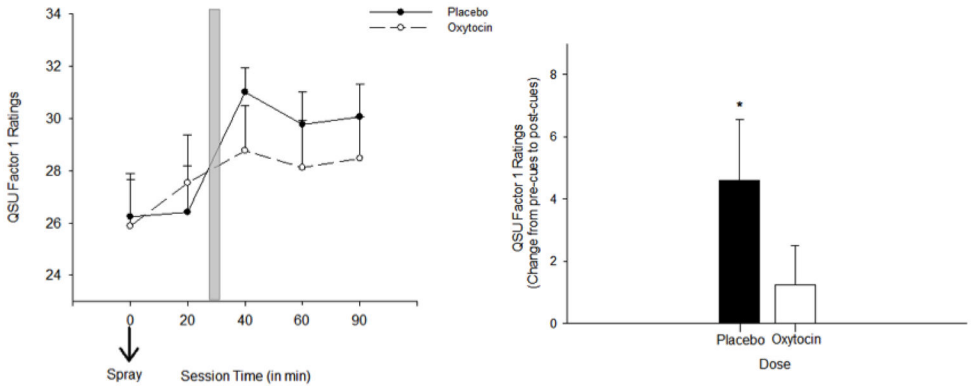

Figure 2.

Smoking Craving on the B-QSU Factor 1 Scale in response to smoking cues following OT and placebo. Left panel:subjective craving on the B-QSU Factor 1 scale following the second OT and placebo administration (time 0 minutes). Shaded bar indicates cue exposure period. Right panel: change in ratings on the S-TCQ Expectancy before and after cues. Asterisk indicates a significant increase following placebo, $p < 0.05$. Capped bars indicate SEM.

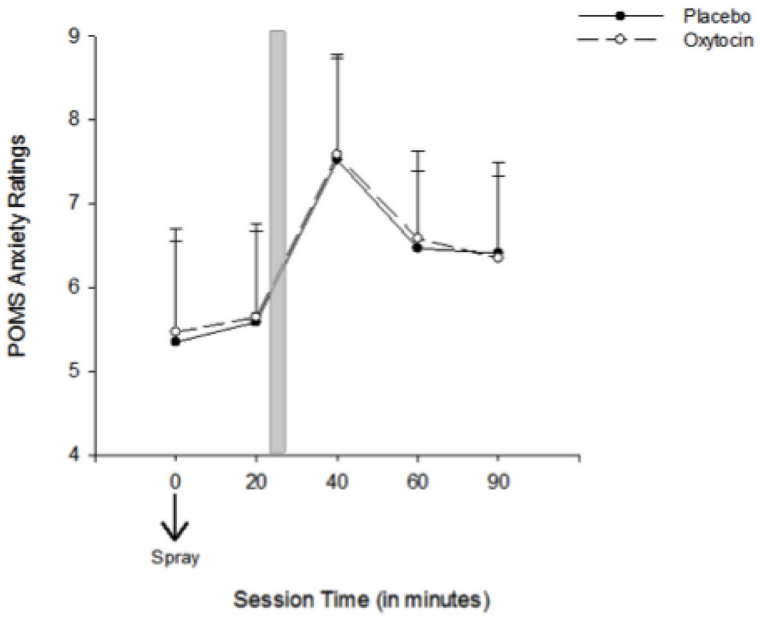

Figure 3.

POMS Anxiety ratings in response to smoking cues following OT and placebo

POMS Anxiety ratings in response to smoking cues following the second OT and placebo dose administration (time 0 minutes). Shaded bar indicates cue exposure period. Capped bars indicate SEM.

Table 1

Demographics and baseline characteristics of participants, $N = 17$

Sex (Men: Women)	11:6
Age (years)	23.5 ± 4.2
Education (years)	14.4 ± 1.1
Race *N* (%)	
Caucasian	12 (70.6)
African-American	2 (11.8)
Other	3 (17.6)
Smoking Characteristics (TLFB)	
Average Daily Cigarettes	6.6 ± 3.5
Max Daily Cigarettes	13.9 ± 6.3
Minimum Daily Cigarettes	2.5 ± 4.0
Average Weekly Cigarettes	46.3 ± 24.2
FTND Score	2.2 ± 1.6
Current Drug Use (TLFB)	
Drinking occasions per week	3.1 ± 1.4
Average number of drinks per occasion	4.4 ± 1.9
Past month cannabis use (times used in past month)	9.8 ± 12.9

FTND = Fagerström Test for Nicotine Dependence. Scores range from 0–10, and scores between 2 and 4 indicate low to minimal nicotine dependence.

TLFB – Timeline Follow-back calendar of past month drinking habits.