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Improved memory for reward cues following acute buprenorphine administration in humans

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Abstract In rodents, there is abundant evidence for the involvement of the opioid system in the processing of reward cues, but this system has remained understudied in humans. In humans, the happy facial expression is a pivotal reward cue. Happy facial expressions activate the brain's reward system and are disregarded by subjects scoring high on depressive mood who are low in reward drive. We investigated whether a single 0.2 mg administration of the mixed mu-opioid agonist/kappa-antagonist, buprenorphine, would influence short-term memory for happy, angry or fearful expressions relative to neutral faces. Healthy human subjects ($n \equiv 38$) participated in a randomized placebo-controlled within-subject design, and performed an emotional face relocation task after administration of buprenorphine and placebo. We show that, compared to placebo, buprenorphine administration results in a significant improvement of memory for happy faces. Our data demonstrate that acute manipulation of the opioid system by buprenorphine increases short-term memory for social reward cues.

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1. Introduction

The opioid system mediates core positive affective responses to pleasurable stimuli, and forms a major reward system in the brain. Data from animal work indicates that activation of opioid receptors in the nucleus accumbens (NAcc), a principal component of the brain's reward circuit, specifically increases positive affective reactions by ''shifting affective responses towards a positive affective pole'' (Berridge, 2003). Conversely, drugs that block opioid receptors make pleasurable stimuli seem less pleasant in both rats (Nizhnikov et al., 2006), and humans (Yeomans and Gray, 1997). The observation that depression in humans is marked by a lack of pleasure or lust for life points to hypo-function of the brain reward systems and insensitivity for reward cues (Pizzagalli et al., 2009), thereby providing a strong theoretical rationale for the development of drug therapies for depression that target neuropeptide systems (Panksepp and Watt, 2011).

As food forms a basic appetitive reward stimulus, much of the work on the effect of opioid manipulations on the reward system has examined the hedonic modulation of responses to food by the opioid system in both rodent and human models (Barbano and Cador, 2006). However, given the role of the opioid system in affective reward, it seems plausible that opioid administration would also influence the processing of other reward cues. Indeed, positron emission tomography (PET) studies in humans also show opioid system involvement in response to food and social reward cues (Hsu et al., 2013; Rabiner et al., 2011). In humans, happy facial expressions are pivotal indicators of social approval and have been successfully used as social reward cues in numerous studies. Furthermore, previous data from our group has shown that short term memory for facial happiness is negatively associated with both self-reported and hormonal measures of depression (Van Honk et al., 2003a), which also indicate hyposensitivity of the reward system (Van Honk et al., 2003b).

It was shown that administration of the mu-opioid agonist remifentanil increases pleasantness ratings of neutral pictures, suggesting that the opioid system modulates how visual emotional stimuli are perceived (Gospic et al., 2007). However, the role of the opioid system in emotion processing (e.g. emotion perception, motivated attention and emotional memory) in humans has remained understudied. A recent study from our group that examined emotion perception found that acute manipulation of the opioid system via buprenorphine administration reduced fear recognition sensitivity (Ipser et al., 2013a,b). Buprenorphine is a high affinity partial mu-opioid agonist/kappa-opioid antagonist with analgesic properties (Vadivelu and Hines, 2007), but there is also evidence that buprenorphine may assist in the treatment of depression (Emrich et al., 1982; Bodkin et al., 1995). In the work presented here, we again used buprenorphine to study the role of opioid system in short-term emotional memory for social reward and threat cues (facial happiness and fear). We hypothesized that buprenorphine administration would enhance short-term memory for happy face reward cues in humans. Additionally, given our earlier findings of reduced fear sensitivity following buprenorphine administration (Ipser et al., 2013a,b), we also expected to find decreased memory for fearful faces. We administered a single dose of buprenorphine to healthy adult volunteers in a randomized, double blind, placebo controlled study. Participants then completed an object relocation task that tested their memory for happy, as well as angry and fearful faces using a modified version of the object relocation task, which uses emotional facial expressions as stimuli.

2. Method

2.1. Subjects

A total of 38 subjects (18 female), aged 18–33 (Mean = 21.92, SD = 4.42) completed the object relocation task and were included in this study. These participants represented a subset of 800 subjects participants who were recruited as part of a larger online study at the University of Cape Town looking at the effects of opioid administration on cognitive and affective function in a population with childhood trauma exposure, and who were free of psychotropic medication, psychopathology (as assessed on the Mini-International Neuropsychiatric Interview (MINI), and depressive symptoms (as defined by a score of 13 or less on the Beck's Depression Inventory). Sixteen subjects in our cohort reported ''moderate to severe'' ratings on one subscale of the short form of the childhood trauma questionnaire (CTQ-SF). All subjects gave written informed consent prior to participating in this study. The Human Research Ethics Committee of the Health Sciences Faculty, University of Cape Town, approved the study.

2.2. Drug administration

Subjects were given 0.2 mg of buprenorphine or placebo orally on separate testing days in a double-blind, randomized and counter-balance fashion. One of the reasons to use buprenorphine is that it can be orally administered, which is important in the light of the objectives of this acute administration study. Intravenous administrations are known to acutely produce adverse stress associated effects. The object relocation task and mood questionnaires were completed 2 h after administration, in order to coincide with peak levels of drug metabolism. A low dose of buprenorphine (0.2 mg) was used in order to minimize nausea. Five participants who were eligible to participate and completed one of the two behavioral testing sessions withdrew due to adverse responses to medication (nausea).

2.3. Experimental task

Selective memory for happy faces was investigated using the object relocation task (Van Honk et al., 2003b). Each display consisted of a set of eight previously validated emotional faces of different persons, presented for 30 s on a grey background. Four faces had a neutral expression and the other four had an emotional expression (either happy, fear or anger, see Fig. 1A for an example). After the display was emptied, the faces re-appeared at the top of the screen in random order, and subjects were instructed to relocate the faces to their original positions. Each combination of faces with neutral expressions and one of the emotion

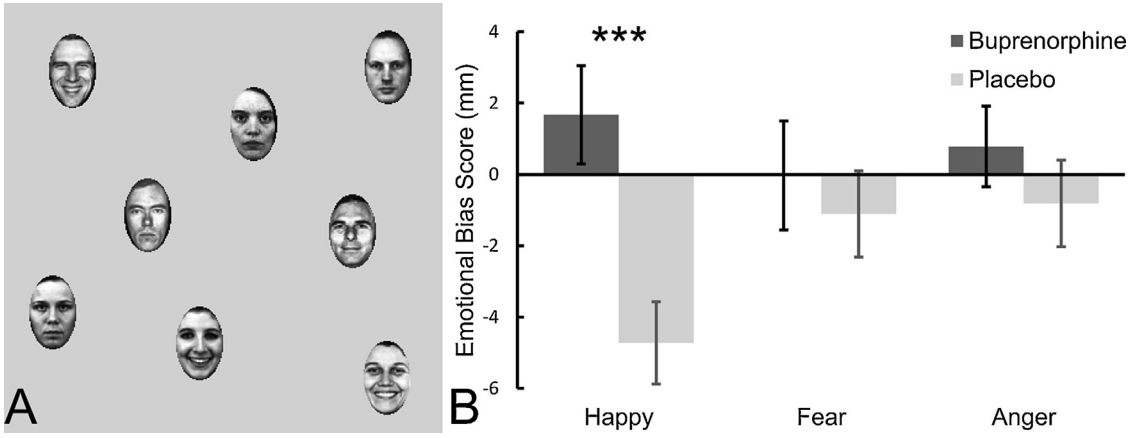

Fig. 1 (A) Example of a trial in the happy condition of the object relocation task. (B) Emotional bias scores averaged for the buprenorphine and placebo conditions. Error bars represent standard error of the mean, and *** ≡ $p < 0.001$.

types was presented twice during the experiment. In order to avoid memory bias for specific actor's faces, the deviation in millimeters between the indicated position for each emotional face and the original location of the emotional face for the same actor was calculated. Indices for emotional memory bias were derived by subtracting the average deviation scores for the four emotional faces from the corresponding figure for the four neutral faces (Van Honk et al., 2003b).

2.4. Mood measurements

Mood was assessed using the visual analogue mood scales (VAMS). The VAMS (Freitas-Ferrari et al., 2010a,b) consists of seven scales composed of 100 mm vertical lines and simple, schematic faces, representing the following mood states: sad, afraid, angry, tired, energetic, happy, and confused, and has been shown to possess excellent discriminant and convergent validity.

3. Results

3.1. Object relocation task

A 2(drug conditions: buprenorphine or placebo) X 3(emotion: happy, angry or fearful) repeated measures general linear model (GLM) with trauma status and gender as the between subjects factors was used to assay the effect of buprenorphine on emotional memory. Our analyses revealed a significant main effect of drug condition $F(1, 34) \equiv 10.414$, $p \equiv 0.003$, $\eta^2_{partial} \equiv 0.23$ as well as an interaction between drug condition and emotion $F(2, 68) \equiv 3.446$, $p \equiv 0.038$, $\eta^2_{partial} \equiv 0.18$. No effects were observed for trauma ($F(1, 34) \equiv 0.194$, $p \equiv 662$) or for interactions between trauma and either drug condition ($F(1, 34) \equiv 0.3$, $p \equiv 0.587$) or emotion ($F(2, 68) \equiv 0.0$, $p \equiv 1.0$). Similarly, there was no evidence of a gender effect ($F(1, 34) \equiv 2.283$, $p \equiv 0.140$) nor any interactions of gender with either drug condition ($F(1, 34) \equiv 0.562$, $p \equiv 0.458$) or emotion ($F(2, 68) \equiv 1.213$, $p \equiv 0.304$). Crucially, planned comparisons using paired samples *t*-tests revealed that participants had significantly enhanced memory for happy faces after administration of buprenorphine compared to placebo ($t(37) \equiv 3.913$, $p < 0.001$, Cohen's-$d \equiv 0.63$, see Fig. 1B). No such effect was noted for fearful ($t(37) \equiv 0.711$, $p \equiv 0.482$), or angry ($t(37) \equiv 0.950$, $p \equiv 0.348$) faces.

3.2. Mood

VAMS data were available for 31 participants. To test whether drug administration affected mood, we conducted a 2 (drug; placebo and buprenorphine) × 8 (mood; afraid, confused, sad, angry, energetic, tired, happy, and tense) repeated-measures ANOVA. There was no evidence of an effect of drug ($F(1, 30) \equiv 0.559$, $p \equiv 0.460$), nor a significant drug by mood interaction ($F(7, 210) \equiv 1.736$, $p \equiv 0.102$). Drug administration did not influence self-reported mood on the VAMS.

3.3. Trauma

Post-hoc calculations supported our conclusion that our emotional bias results are not related to trauma status and that the noted effects of buprenorphine on selectively enhanced memory for happy faces can be generalized to a healthy population. Specifically, we correlated emotion bias delta scores (computed by subtracting the Emotional Bias scores in the Placebo condition from the Emotional Bias scores in the Medication condition) with participant scores on the different subscales of the CTQ-SF that index different types of trauma (Emotional Abuse, Sexual Abuse, Physical Abuse, Emotional Neglect, or Physical Neglect). There was no significant relationship between any type of trauma and emotional bias difference scores.

Further, there was no relationship between overall CTQ-SF scores and Emotional Bias scores (for Happy or Angry or Fearful faces), and this was also the case when a correlation was run between these variables only within the traumatized subjects.

4. Discussion

The main aim of this study was to assess if manipulation of the opioid system by buprenorphine alters short-term

memory for social reward and threat cues: happy and fearful facial expressions. We found that a single dose of buprenorphine, as compared to placebo, significantly increased short-term spatial memory for happy faces. This effect was emotion specific — there was no effect of buprenorphine administration on the memory for fearful or angry faces. This effect was furthermore independent of early trauma assessed by self-report, thus experienced trauma in healthy subjects did not change the effect of buprenorphine administration. The significant increase in memory for social reward cues was based upon a positive emotion processing shift: poorer memory for happy compared to neutral faces after placebo (negative happy face bias) turned to better memory for happy relative to neutral faces after buprenorphine (positive happy face bias). The negative happy face bias independent of trauma after placebo was unexpected, and can only be explained by demand characteristics of stress induction by the experiment. Indeed, high levels of the stress hormone cortisol were previously shown to be inversely related to memory performance for happy facial expressions (van Honk et al., 2003). The placebo condition can however not be evaluated as a pure baseline, thus this explanation is speculative.

Previously we reported reduced fear recognition sensitivity as a result of opioid manipulation with buprenorphine (Ipser et al., 2013a,b), however, presently we did not find an effect of buprenorphine administration on short memory for fearful faces. A possible explanation for this lies in the different properties of the tasks used across our two studies. Emotion perception and attention tasks such as the one used in Ipser et al. (2013a,b), tap most strongly into fear and anxiety, by indexing hypersensitivity or hyperreactivity for threat. As a result, findings on these types of facial expression perception tasks typically concern threatening facial expressions (anger and fear faces). On the other hand, emotional memory tasks as used in the current study do not specifically assess hypersensitivity or hyperreactivity for threat or reward cues, because of the critical involvement of a memorizing component (van Honk et al., 2003).

Impaired memory for reward cues is a marker for depression, thus our current findings of improved memory for happy face reward cues correspond to the previously noted antidepressant properties of buprenorphine (Dillon et al., 2013). This memory improvement for reward cues after a single buprenorphine administration was not accompanied by any change in mood reports. This is not surprising given that hormone manipulation studies using single doses of oxytocin, testosterone, and cortisol do not report any changes in mood, but do report changes in emotional and motivational behavior, corresponding to the present study and our earlier study with buprenorphine (Bos et al., 2012; Ipser et al., 2013a,b). Importantly, our current data suggest that the effects of buprenorphine on social reward processing/enhanced memory for social reward cannot be attributed to a secondary, mood generated change, but involve core reward processing system of the human brain (van Honk and Schutter, 2007). Such changes in emotional and motivational behavior after acute manipulation of the hormonal systems seem to precede changes in mood, which likely depend on more chronic administration (Bos et al., 2012). Taken together, these findings indicate that buprenorphine exerts a potent effect on the reward processing system of the human brain, and chronic administration of buprenorphine can translate these early reward-processing enhancements into improvements in mood and depressive symptomology. As noted, the original focus of our study was trauma, and a subgroup of our subjects reported moderate to severe childhood trauma, and all of the subjects were selected on low levels of depression. Our results of enhanced memory for reward cues are independent of childhood trauma, which is appealing in suggesting a general population effect. However, given the selection on low levels of depression the direct clinical relevance of our data with respect to depressive symptomatology is limited. Nonetheless, ultra-low doses of buprenorphine have previously been used as effective antidepressants for individuals not helped by traditional medications (Bodkin et al., 1995), and studies report rapid mood improvement (5—8 days) using low dose buprenorphine (0.2 mg, which is the same as the acute dose used in our study) in non-opiate users with refractory depression (Emrich et al., 1982), and improvement (after 1 month) in depressive symptoms during an open trial of buprenorphine (Kosten et al., 1990).

Buprenorphine is a mixed mu-opioid agonist and kappa antagonist, and pharmacological fMRI research in rodents and humans shows that buprenorphine acts on the limbic/mesolimbic circuitry of the brain (Seah et al., 2014). An important region of interest in the limbic system is the NAcc in the striatum. Research shows that positive affective reactions are increased by activation of mu-opioid receptors in the NAcc, which then feed into mesocorticolimbic circuits to activate dopaminergic reward (Perez-Torres et al., 2000a,b; Spanagel et al., 1990). However, blockade of the kappa-receptor also increases basal dopamine (Fujita et al., 2012a,b), and kappa-receptor antagonists have also been shown to produce anti-depressant like effects in rodent models. NAcc activation is associated with a wide range of pleasant or rewarding stimuli such as monetary reward (Knutson et al., 2001), listening to music (Menon and Levitin, 2005) or looking at beautiful (Aharon et al., 2001) or happy (Monk et al., 2008) faces. The opioid system has been specifically linked to the processing of reward cues in the NAcc (Peciña, 2008), providing one plausible mechanism for enhanced memory for happy faces after buprenorphine administration.

Overall, our data are in agreement with animal data that indicate that mu-opioid agonists increase the hedonic value of reward stimuli (e.g. food) (Peciña and Smith, 2010), which in turn lead to increased incentive salience motivation. Incentive salience has been studied using the Pavlovian-instrumental-transfer test in animal research wherein animals are trained to associate a Pavlovian cue with a reward such that the cue itself becomes rewarding. Opioid microinjections in the rat NAcc increase both hedonic liking and motivated behaviors towards Pavlovian reward-predicting stimuli (Smith et al., 2011). In humans, the happy face forms the pivotal cue that is predictive of social reward. The happy face cue might therefore trigger motivated behavior towards the reward predicting stimuli, enhancing the learning and memory of that cue. Further neuroimaging research is necessary to parse the neural mechanisms underlying these hypotheses.

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Conflict of interest statement

Dr. Stein has received research grants and/or consultancy honoraria from Abbott, Astrazeneca, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson and Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah, and Wyeth.

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