Study Protocol with SAP

Official Title: An Investigation of the Effects of Opioid Receptor Blockade on Changes in Self-esteem and Attentional Bias Toward Social Cues

ClinicalTrials.gov ID: A02-B12-11B

Date: February 11, 2021

Background

Given the evolutionary importance of social ties for survival, humans are thought to have evolved psychobiological mechanisms to monitor and safeguard the status of their social bonds. At the psychological level, self-esteem is proposed to function as a gauge—*sociometer*—reflecting one's social belongingness status (Leary & Baumeister, 2000). Thus, negative self-referential cognitions (e.g., "I am worthless") and their accompanying negative feelings signal failure to maintain an adaptive level of closeness to other people. In support of Sociometer Theory, it is well established that events threatening one's sense of social connection, or social value in the eyes of others, evoke decrements in self-esteem, both in the laboratory (Gruenewald, Kemeny, Aziz, & Fahey, 2004; Leary et al., 2003; Leary, Haupt, Strausser, & Choket, 1998; Leary, Tambor, Terdal, & Downs, 1995) and daily life (Denissen, Penke, Schmitt, & van Aken, 2008; Harris & Orth, 2019); further, there is a direct correlation between feelings of inclusion and in-the-moment self-esteem (Leary et al., 1995).

At the biological level, the endogenous opioid system, which plays a key role in mediating pain and pleasure (Fields, 2007; Leknes & Tracey, 2008), appear to be an important substrate for the hedonic signalling needed to regulate social behaviour. According to the Brain Opioid Theory of Social Attachment (Herman & Panksepp, 1978; Machin & Dunbar, 2011; Panksepp, 1998), endogenous opioids (specifically, μ-opioids) contribute to feelings of reward, safety, and warmth experienced in the presence of supportive others, thus positively reinforcing the social bond, whereas declines in opioidergic activity precipitated by loss of social contact evoke feelings of separation distress, and drive consequent attempts to regain closeness. Therefore, opioidergic activity is suggested to underpin the workings of an "emotional barometer" monitoring the availability of social support (Panksepp, 1998). In support of this

idea, research has shown that administration of opioid receptor antagonists such as naltrexone reduces feelings of social connection induced by the presentation of affiliative stimuli, such as warm written messages from participants' close others (e.g., friends, family, and romantic partners) (Inagaki, Hazlett, & Andreescu, 2019; Inagaki, Ray, Irwin, Way, & Eisenberger, 2016), and increase feelings of disconnection in daily life (Inagaki et al., 2016).

Noting the parallels between Sociometer Theory (Leary & Baumeister, 2000) and the Brain Opioid Theory of Social Attachment (Panksepp, 1998), we investigated whether endogenous opioids may serve as the biological correlate of the sociometer. Specifically, we hypothesized that opioid receptor blockade with the drug naltrexone would produce a state that is analogous to the experience of social disconnection. Just as opioid receptor blockade potentiates separation distress in non-human animals, we reasoned that it may similarly promote reductions in self-esteem, considered to be a cognitive derivative of separation distress in humans (Watt & Panksepp, 2009).

In addition to investigating the effects of opioid receptor blockade on self-esteem, we also took this opportunity to examine a possible behavioural consequence of opioid receptor blockade. The Brain Opioid Theory of Social Attachment argues that a low endogenous opioid state heightens social need and motivates affiliative behaviour to restore well-being (Panksepp, 1998), although there are boundary conditions for this effect. For example, non-human animal studies suggest that the effects of naltrexone on social motivation are often selective for more "safe" targets (e.g., increasing affiliation with Mom but not peers) (Martel et al., 1995). Notably, similar boundary conditions have been observed in work investigating the effects of acute psychological rejection on human social motivation; that is, social exclusion increases pursuit of social acceptance, but only from those individuals who appear to represent viable sources of

social connection (Maner, DeWall, Baumeister, & Schaller, 2007). This "cautious interest" makes sense considering that recently rejected people must balance their need for social connection against the risk of further rejection (Finkel & Baumeister, 2018). Thus, borrowing from DeWall et al. (Dewall, Maner, & Rouby, 2009), we focused on early-stage perceptual processes that are thought to maximize opportunities for social connection. Specifically, DeWall and colleagues showed that recently rejected (vs. control) participants oriented more quickly to faces signalling acceptance (in the form of a smile), but not disapproval. Similarly, we hypothesized that naltrexone (vs. placebo) would result in heightened social need manifested as increased attentional bias to smiling faces.

To test these hypotheses, we administered naltrexone and placebo on two occasions, approximately one week apart, and then assessed self-esteem and attentional bias to accepting (vs. neutral and rejecting) faces. Given our focus on changes in self-esteem, we elected to use a within-subjects design because it allows us to control for individual differences in trait self-esteem across drug conditions; moreover, a within-subjects design offers considerably greater statistical power, given the same number of participants, than does a between-subjects design.

Study Objectives

This study examined the effects of endogenous opioids on self-esteem and attentional bias toward social cues. This was accomplished by temporarily blocking endogenous opioid activity with the administration of an opioid receptor antagonist.

Study Design and Methods

All research procedures were approved by the McGill University Medical Institutional Review Board (protocol #A02-B12-11B). The study used a randomized, within-subjects, placebo-controlled design in which participants received 50 mg oral naltrexone and matching

placebo on two occasions approximately one week apart (to provide a wash-out period for the drug); order of drug administration was counterbalanced and participants and experimenters were blind to drug condition (see "Drug/Placebo Information" below for details). After providing informed consent and confirming that they met the pre-conditions for the study (e.g., no alcohol within 24 hours, no drug use within 10 days, not pregnant), eligible participants were administered either naltrexone or placebo, by random assignment and in double-blind conditions, and were asked to wait for one hour before testing began; during this time they were allowed to perform quiet activities (e.g., reading).

Approximately two hours after drug/placebo ingestion, we assessed self-esteem with the Rosenberg Self-Esteem Scale and attentional bias to accepting vs. rejecting faces with a Visual Probe Task. Participants remained in the lab for another hour so that side effects could be monitored. During the second testing session, participants were administered the alternate compound and then underwent identical procedures as described above.

Participants/Eligibility Criteria

Applicants were screened for normal health status. Exclusion criteria included: (1) allergy to naltrexone, (2) kidney or liver injury or disorder, (3) bipolar, panic, or psychotic disorders, (4) epilepsy, (5) smoking more than 15 cigarettes per day, (6) pregnancy, (7) substance abuse, (8) use of opioid analgesics, cocaine, recreational drugs (e.g., marijuana, LSD, ecstasy, etc.), or prescription medication (except oral contraceptives) within the past 10 days, (8) use of over-the-counter drugs (e.g., analgesics, anti-inflammatories, sleeping aids, etc.) or alcohol within the past 24 hours. Participants were also excluded if they reported that they were currently in pain (e.g., headache), or if they had used anti-diarrheal medications (e.g., Immodium, Kaopectate, Pepto-Bismol) in the seven days prior to the study, as these substances may interact with naltrexone.

Because naltrexone is metabolized by the liver and kidneys, participants were required to provide medical records from within the past year reporting normal kidney and liver function results. If interested potential participants were not able to provide these records, we administered blood tests for kidney and liver function through an independent laboratory (Medisys, Montréal, QC); we compensated potential participants $15 for taking part in this process. Individuals with evidence of abnormal kidney or liver function were excluded from the study.

All participants who passed initial kidney and liver screening were scheduled for participation in the experiment, and completed further screening on the two days of testing for drug use and pregnancy. Screening for drugs of abuse was conducted with a DrugCheck® Urine Drug Test - 5 panel (DTK, Barrie, ON). The test detects cocaine, opiates, δ^9-tetrahydrocannabinol, amphetamine, and methamphetamine. Urine pregnancy screening was conducted with the BFP hCG test strips (Fairhaven Health, Bellingham, WA, USA) *in vitro* test. There were no positive results on these tests and thus no participants were excluded at this stage.

Thirty-five participants met the eligibility criteria and provided informed consent. However, seven participants were excluded from analyses because they did not complete all phases of the study (i.e., experienced side effects and/or did not return for the second testing session); moreover, self-esteem data was missing from two participants. Due to computer error, two participants were missing attentional bias data and two additional participants were excluded from attentional bias analyses because of outlying high error rates (Mogg, Bradley, De Bono, & Painter, 1997). Thus, the final sample for self-esteem analyses consisted of 26 participants (11 men), aged 18-45 years old (M=22.83*; SD*=5.53), and the final sample for the attentional bias analyses consisted of 24 participants (11 men, M_{age}=23.00, SD_{age}=5.75, $Range_{age}$=18-45). All participants

were fully debriefed at the conclusion of the study and compensated $100 (plus up to $40 for transportation and/or parking).

Naltrexone and Placebo Information

Participants were given 50mg of naltrexone hydrochloride (Revia, Bristol-Myers Squibb) or a matching placebo. Drug/placebo administration order was counterbalanced and participants and experimenters were both blind to drug condition. To ensure double-blind conditions, a compounding pharmacy (Paylan Pharmacy, Montréal, QC) prepared the naltrexone hydrochloride in an opaque blue, unmarked capsule packed with cellulose filler, and used identical capsules with the same cellulose filler as the placebo. An independent set of judges was unable to tell the capsules apart by inspection.

Measures

The Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem Scale (Rosenberg, 1965) is a widely used 10-item self-report measure of global self-worth. Participants provide an assessment of both positive and negative feelings about the self by responding to items such as "On the whole, I am satisfied with myself," and "I feel that I'm a person of worth, at least on an equal plane with others" on a 4-point Likert scale ranging from "strongly agree" to "strongly disagree." The scale was scored such that higher scores reflect higher levels of self-esteem. For exploratory purposes, we also calculated separate subscale scores for *self-liking* and *self-competence* as in (Tafarodi & Milne, 2002).

The Visual-Probe Task

The Visual Probe Task (VPT; 39) is a visual cuing task widely used to assess attentional bias (Fox, Russo, Bowles, & Dutton, 2001; MacLeod, Mathews, & Tata, 1986). We used the

VPT as a measure of early-stage interpersonal attention (Dewall et al., 2009): specifically, attentional bias to social acceptance. Participants were seated in front of a PC laptop computer and instructed to stare at a fixation point (a black cross) on the screen. After 500 ms, two faces simultaneously appeared on the computer screen, separated by the fixation point. The stimuli consisted of smiling (accepting), neutral, or disapproving (rejecting) faces (see (Dandeneau et al., 2007) for a complete description of the VPT). Specifically, two face stimuli, one neutral and one emotionally salient (i.e., accepting or rejecting) were presented on the computer screen, one on the left and the other on the right, for 500 ms; the faces were then replaced by a probe (either two dots aligned vertically [:] or two dots aligned horizontally [..]), which appeared on the side of either the neutral or accepting/rejecting face with equal probability. The probe remained on screen until participants identified its location by pressing the correct key on the keyboard (the letter *q* for the vertically aligned dots and the letter *z* for the horizontally aligned dots; both keys were labelled with the symbol of their corresponding probe). Participants were instructed to respond as quickly and accurately as possible in identifying the probe location; their response times (RTs) were recorded on each trial. The assumption is that, if participants' attention is directed toward the emotional stimulus, then they should be faster to respond (i.e., will have smaller RTs) on trials in which the probe replaces the emotional stimulus versus trials where the probe replaces the neutral stimulus. Conversely, participants should be slower (i.e., will have larger RTs) when responding to a probe that replaces the stimulus they were *not* selectively attending to.

The stimuli consisted of 64 pictures of 32 different individuals (50% females, 50% males), with 16 making neutral and accepting facial expressions and 16 making neutral and rejecting facial expressions (Dandeneau et al., 2007). Each neutral picture was matched with the

rejecting or accepting pose of the same person, thereby making 16 rejecting-neutral pairs and 16 accepting-neutral pairs for the critical experimental trials. The task included two blocks, and each expressive-neutral pair was presented twice per block (once with the emotional face on the right and once on the left), making for a total of 64 neutral-accepting and 64-neutral-rejecting trials. Of note, the version of the VPT we used (39) was preprogrammed to also include 64 neutral-neutral trials for the testing of other research questions (these trials consisted of 8 neutral poses for each expressive-neutral pair). Although we did not have specific hypotheses for the neutral-neutral trials, we used these trials to assess the effects of naltrexone (vs. placebo) on reaction time in general. Thus, the entire task consisted of 16 practice trials, and 2 blocks of 96 trials each for a total of 208 trials (16 practice, 64 neutral accepting, 64 neutral-rejecting, and 64 neutral-neutral).

Following (44), we discarded all inaccurate VPT trials (i.e., trials on which subjects did not press the key that corresponded to the probe location). Importantly, drug condition did not influence error rate (placebo=2.80% vs. naltrexone=2.69%). In addition, following (Dandeneau et al., 2007), we discarded individual trials on which participants responded faster than 200 ms or slower than two standard deviations above their overall mean RT. Attentional bias scores (acceptance bias scores and rejection bias scores) from both the naltrexone and placebo sessions were computed for each participant. Specifically, to obtain individual acceptance bias scores, we used RT data from trials on which an accepting-neutral stimulus pair was presented. Next, we subtracted each participant's mean RT on "valid" trials (where the probe replaced the accepting face) from their mean RT on "invalid" trials (where the probe replaced the neutral face). Likewise, rejection bias scores were obtained by subtracting each participant's mean RT on valid trials from their mean RT on invalid trials using data from the rejecting-neutral trials. In this

way, higher positive scores indicate greater attentional bias to the emotional (vs. neutral) face, and negative scores indicate disengagement from, or inhibition of attention to, the emotional face.

Statistical Analyses

To test our hypotheses, we conducted a series of repeated measures analyses of variance (ANOVA) with drug condition (naltrexone or placebo) as the within-subjects factor, and self-esteem and VPT scores as the outcome measures; separate analyses were conducted for acceptance bias, rejection bias, and neutral-neutral trial RTs. To ensure that changes in the variables of interest were a function of the drug and not order of drug administration or the tasks participants completed prior to ours, we included order (naltrexone vs. placebo on Day 1), study participation (music pleasure vs. music cognition), and the interaction between these two variables as between-subjects factors in our statistical analyses. For full transparency, we also provide results without these control variables included in the model.

Results

Self-Esteem

The repeated measures ANOVA revealed a significant effect of drug on self-esteem, $F(1, 22)=5.18$, $p=.033$, $\eta^2=0.19$). As seen in *Figure 1,* mean self-esteem scores were lower on the naltrexone day ($M=3.27$, $SE=0.07$) compared to the placebo day ($M=3.39$, $SE=0.09$).[1] There were no effects of drug administration order or prior study on self-esteem, nor were there any significant interactions between these variables and drug condition (all ps > .050). Of note, we also observed a significant drug order by prior study interaction, $F(1, 22)=5.60$, $p=.027$ on self-

[1] When the order of drug administration and prior study variables were removed from analysis, the test statistics for the drug effect were as follows: $F(1, 25)=6.45$, $p=.018$, $\eta^2=0.20$.

esteem; however, none of the contrasts were significant (all *p*s >.050), rendering this effect uninterpretable.

As an exploratory analysis, we also examined the effect of naltrexone vs. placebo on the self-liking and self-competence subscales of our self-esteem measure separately (Tafarodi & Milne, 2002). Results showed that participants reported significantly lower self-liking on the naltrexone day, M=3.05, SE=0.10, relative to the placebo day, M=3.21, SE=0.11, $F(1, 22)=6.54$, p=.018, η^2=0.23, whereas there was no effect of naltrexone on the self-competence subscale, $F(1, 22)=1.56$, p=.225, η^2=0.07.[2] Results also showed the same drug order by prior study interaction that was observed for overall self-esteem on self-liking ($F(1, 22)=8.72$, p=.007), but not self-competence (p > .050); other than this one interaction, there were no significant effects of drug administration order or prior study, nor were there any significant interactions between these variables and drug condition on either self-liking or self-competence component scales (all *p*s > .050) .

Acceptance Bias

The repeated measures ANOVA yielded a significant effect of drug on acceptance bias, $F(1, 20)=4.42$, p=.048, η^2=0.18. As illustrated in *Figure 2,* acceptance bias scores were significantly higher following naltrexone (M=15.03, SE=7.23) vs. placebo (M=-6.52*,* SE=6.35), indicating that participants showed greater attention to accepting faces following naltrexone (vs. placebo) administration.[3] There were no main or interaction effects of drug administration order or prior study on acceptance bias (all *p*s >.050).

[2] When the order of drug administration and prior study variables were removed from analysis, the test statistics for the drug effect were as follows: (1) self-liking: $F(1, 25)=7.58$, p=.011, η^2=0.23; (2) self-competence: $F(1, 25)=1.23$, p=.278, η^2=0.05.

[3] When the order of drug administration and prior study variables were removed from analysis, the test statistics for the drug effect were as follows: $F(1, 23)=2.29$, p=.143, η^2=0.09.

Rejection Bias

In contrast to the findings for acceptance bias, there were no significant effects of drug on rejection bias scores, $F(1, 20)=1.33$, $p=.262$, $\eta^2=.06$.[4] In fact, the pattern of results was in the opposite direction from the acceptance bias score with nominally (but not significantly) less attention to rejecting faces following naltrexone (M = -6.02, SE = 4.32) vs. placebo (M = 1.35, SE = 5.12). There were no main or interaction effects of drug administration order or study on rejection bias (all ps >.050).

Neutral-Neutral Trial RT

The repeated measures ANOVA showed no significant effect of drug on neutral-neutral trial RTs, $F(1, 20) = 0.34$, $p=.566$, $\eta^2=0.02$, although there was a significant drug by drug order effect, $F(1, 20) = 11.84$, $p = 0.003$: for participants who received naltrexone on Day 1, reaction times were greater in the naltrexone vs. placebo condition, $M_{diff}=35.90$, $F(1, 20)=12.69$, $p=.002$, whereas there was no difference between drug condition for participants who received placebo on Day 1, $M_{diff}=-25.48$, $F(1, 20)=3.00$, $p=.099$. Importantly, even though there may have been a slowing down of RTs in general (at least for those who received naltrexone on Day 1), this would not explain the primary effect of interest—i.e., faster RTs to accepting faces following naltrexone—in fact, this general slowing down would, if anything, work against this effect.

[4] When the order of drug administration and prior study variables were removed from analysis, the test statistics for the drug effect were as follows: $F(1, 23)=0.80$, $p=.380$, $\eta^2=0.03$.

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