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Honors Thesis

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PROJECT TITLE: **Painful yet Tolerable? The Effects of Oxytocin Administration on Social Influence Effects on Pain**

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ABSTRACT

This study examines how Oxytocin (OT) and a placebo (PL) contribute to analgesia during heat pain. Social conformity and associative learning effects were replicated within a placebo analgesia paradigm based on other literature. Using an intranasal OT spray and a PL spray, the main aim of this study was to examine the effects of OT on learned pain perception using three different noxious temperatures, social and experience based cues, and hand holding support from a romantic partner. In contrast to other OT literature, this particular experiment found null effects of OT on pain ratings versus PL. OT did not keep the heat pain from being painful and did not enhance placebo analgesia. We suggest that OT may still yet be responsible for inducing these desired effects through auxiliary mechanisms, further research is needed into OT's role in anxiolytic and gender effects of placebo.

INTRODUCTION

Oxytocin, a Neurohormone produced in the hypothalamus and released in both the brain and bloodstream, has long been a complicated molecule to study. There is significant research behind the influences of Oxytocin on child birth and breast feeding. Oxytocin is also associated with empathy, trust, sexual activity and relationship-building (De Dreu et al. 2009). Perhaps most strangely, Oxytocin (abbreviated 'OT') has just recently been implicated as an important modulator of pain in human trials (Zunhammer et al. 2015).

Functioning as both a neurotransmitter and a hormone, OT's targets are widespread and include the amygdala, hippocampus, brainstem, and regions of the spinal cord that regulate the autonomic nervous system (Rodrigues et al. 2009). Importantly, OT is safe to administer via an intranasal route with no known subjective changes in recipients. The synthetic version of endogenous OT, 'Syntocinon', shows no reliable side-effects or adverse outcomes when administered in 40 IUs (or about 67 µg of pure peptide in solution) for short term use in research settings (MacDonald et al. 2011). Although OT is biochemically unable to directly cross the blood brain barrier, studies that measure plasma and cerebrospinal concentrations after a Syntocinon nasal spray found that OT increases in the peripheral and central nervous system (PNS and CNS, respectively). Blood concentrations peak 30 minutes after administration and could be a coordinated response by central and peripheral OT systems to increase cerebrospinal levels (Evans et al. 2013).

Preliminary fMRI experiments using intranasal administration of OT showed decreased amygdala activity in empathic responses to pain (Singer et al. 2008).

Enhancing empathy with coinciding reductions in amygdala activity offers advantages for OT to possibly produce anti-nociceptive or anxiolytic effects. Under research conditions, OT was explored as an important variable in observations of placebo analgesia. Experimental models of placebo analgesia showed that OT enhances the placebo effect with indications that the Oxytocinergic system has a modulatory effect on nociception (Lundeberg et al. 1994). Placebo responses have been shown to contribute to positive clinical treatment outcomes, where the pharmacological enhancement of placebo responses via OT therefore has the potential to increase treatment benefits (Kessner et al. 2013).

A placebo is a treatment with no inherent physical or pharmacological effect, but which nonetheless may benefit the treated individual. The placebo response is mediated by active learning processes, is influenced by prior conditioning, and can persist over several days (Colloca & Benedetti, 2006). The placebo acts as a signal along with other cues (context, setting, white lab coat, etc.) to form a placebo or nocebo response (Colloca & Miller, 2011). Social influences have previously been demonstrated to modulate pain and autonomic responses, independent of reinforcement (Koban & Wager, 2016). OT could therefore present itself as a viable analgesic treatment if its enhancement of social influence effects are better understood.

OT has been explored in clinical studies of social behavior in both animal and human paradigms. It seems to reduce anxiety in interpersonal situations in mice (Goodin et al. 2015). Interestingly, combined treatment of OT with Estradiol enhanced these results (McCarthy et al. 1996). In humans, administered OT has been shown to
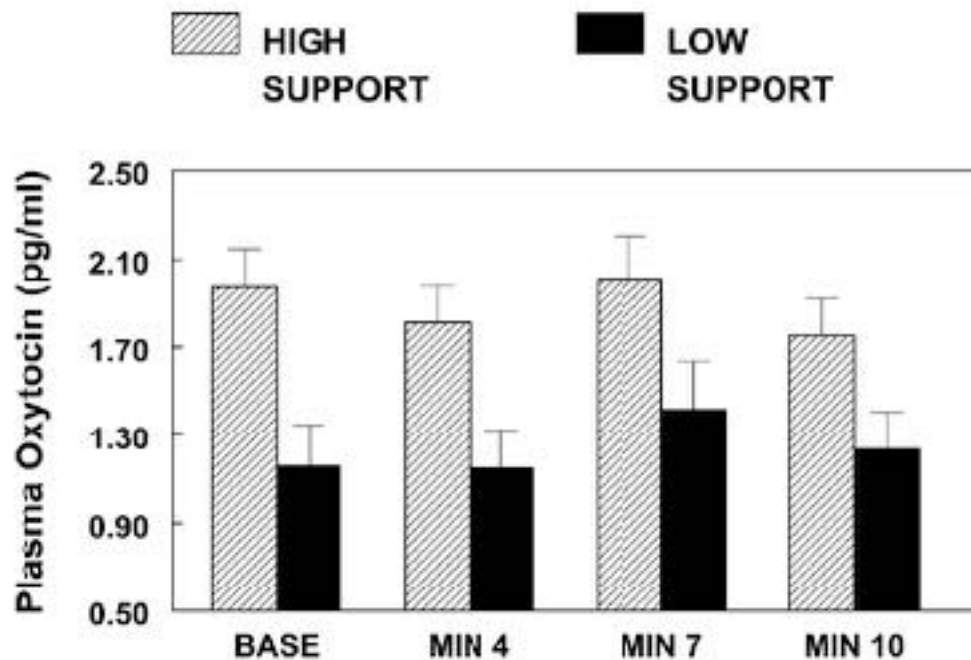
reduce salivary Cortisol levels (see figure 1), especially in conjunction with social

support. Additionally, as figure 2 illustrates below, plasma OT increases in individuals

receiving *more* support from their partner, regardless of gender (Grewen et al. 2005).

Fig 1
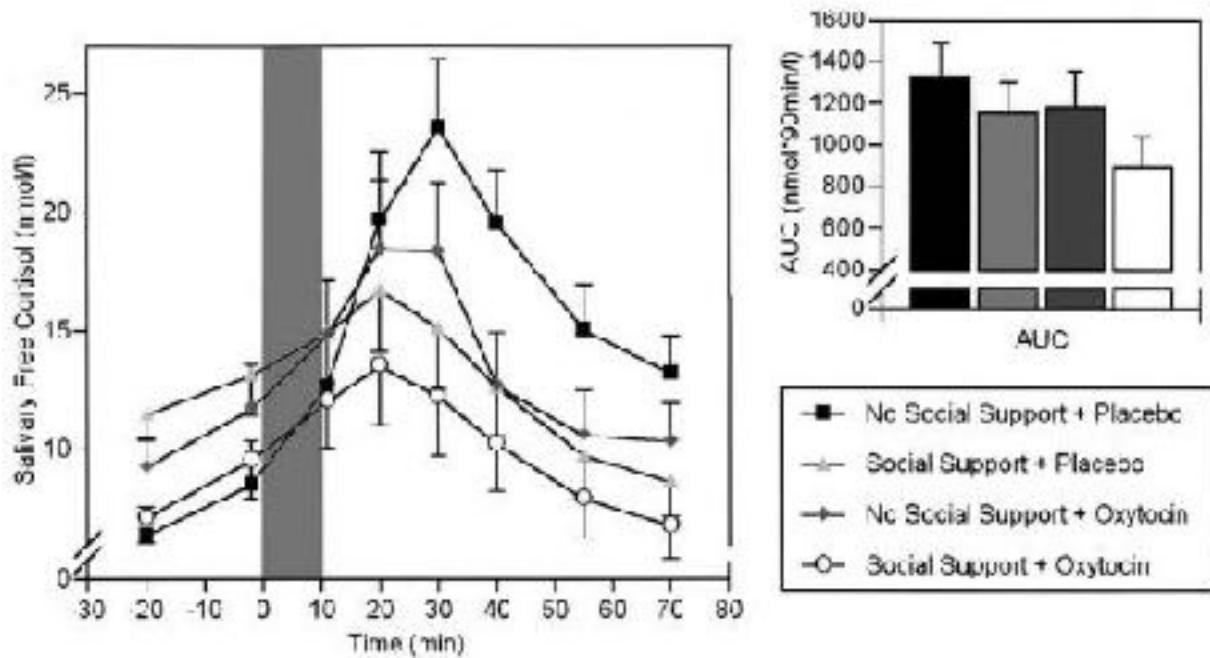
K. M. GREWEN et al.

Fig 2

Placebo effects seem to directly influence neurochemical systems, including endogenous opioids (Sauro, 2004), as well as dopamine (Fuente-Fernández, 2009), and possibly OT (Kessner et al, 2013), although these interactions have received little empirical attention. Studies have shown that placebo effects are active neurobiological phenomena that arise from an interaction with opioid systems, including the periaqueductal gray (PAG), to relieve acute pain (Gao, 2004). The PAG and the endogenous opiod system is of course the primary target of opiate-prescription drugs in relieving pain. Endogenous OT has also been correlated with increased pain thresholds (Yang et al, 2011), and production of anti-nociceptive effects after thermal pain administration; importantly, these effects were reversible with OT antagonists but *not* opioid antagonists i.e. Naloxone (Lundeberg et al, 1994), implicating OT's role in placebo analgesia as at least partly separate from the opioid system. Further, because OT produces no subjective effects, it has a relatively low risk for addiction, unlike that of opiate-prescription drugs.

The literature suggests that both conceptual (i.e. socially instructed beliefs) and associative learning processes are also critical for the genesis of placebo effects.
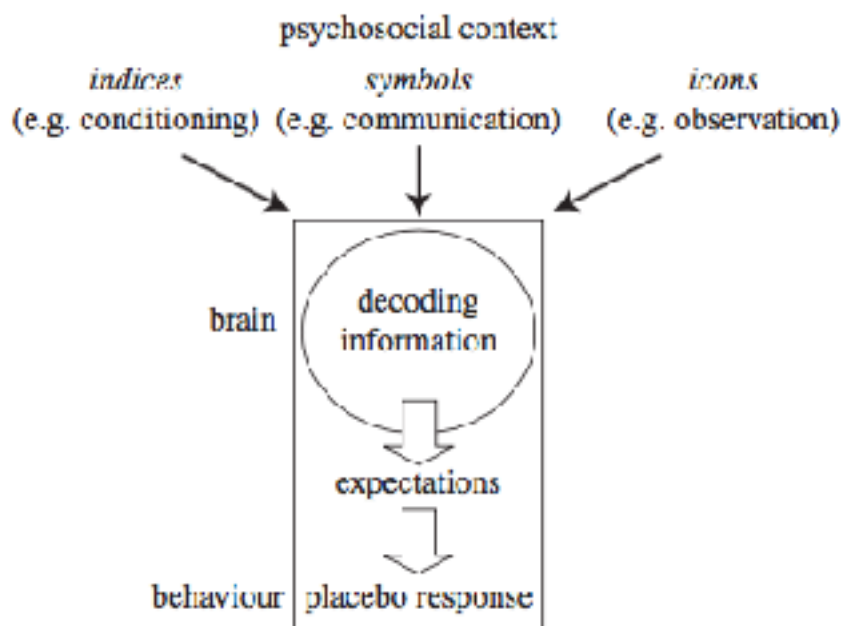
Fig 3

Figure 3. This diagram shows how placebo responses are formed from a learning perspective. Environmental cues are interpreted by the brain to form expectations and influence behavioral outcomes (Colloca & Miller, 2011).

The figure above shows the different kinds of context cues that contribute to a placebo or nocebo effect. After learning that certain cues are associated with a certain type of therapeutic benefit or injury, it is possible to generalize that effect to cues that have never been learned before. Specifically, pain can be modulated by previously not reinforced stimuli into being perceived as more or less painful.

Previous research on pain has found that learning associations to conditioned stimuli can modify the perception of pain. That is, prior experiences that pair stimuli with intense pain become more painful, and stimuli paired with lower pain become less painful (Price et. al 2008; Colloca et. al 2010; Atlas et. al 2010).

Separate OT literature suggests that OT enhances socially reinforced learning (Hurlemann et al, 2010), improves acceptance of social advice (Kendrick, 2017),

reduces anxiety in interpersonal situations (Goodin et al, 2015), and reduces salivary

cortisol levels, especially in conjunction with social support (Heinrichs et al, 2003). The

enhancement of empathic behaviors and placebo analgesia therefore provides overlap

where OT could theoretically become drastically important in understanding pain and

the treatment thereof. Previous thermal-pain experiments has demonstrated that touch

from a partner reduced pain ratings when compared to control conditions (see figure 4

below, Goldstein et al. 2016).

Fig 4

Empathy Predicts Touch-Induced Analgesia
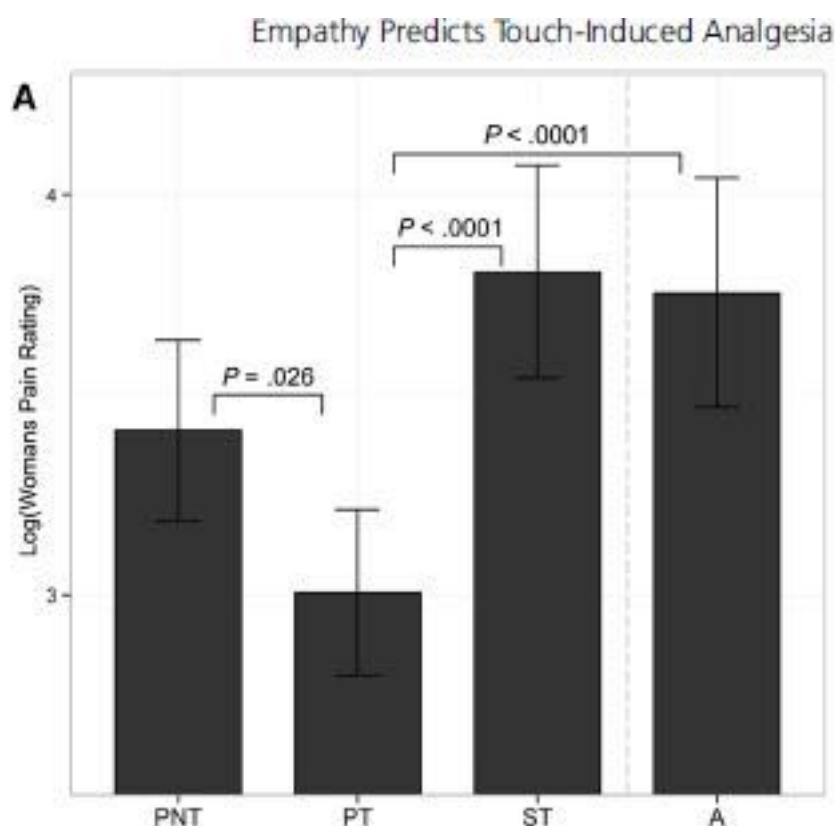
Despite its proposed importance to the manifestation of placebo analgesia and

that it can be safely administered to humans with no known subjective effects or side

effects, OT's role in placebo effects has not been explored extensively. The experiment proposed here will help clarify the roles of the OT neurochemical system and its contributions to facilitation of analgesia. The specific aim of the present study is to replicate the influence of social information and associative learning on placebo analgesia. In addition, OT will be examined as a synergistic contributor to the formation of placebo analgesia.

We expect greater social influence effects on pain and enhanced associative learning in the OT compared to the control group, i.e. a larger difference in pain ratings for high versus low cues. We further expect greater social support effects in the OT compared to control group, i.e. the effect of handholding on pain relief is stronger following OT administration. We expect that these effects are also mediated by increases in trust, as OT has been shown to increase trust in interpersonal situations (Kosfeld et al, 2005). Finally, we expect OT to decrease unpleasantness ratings *to* the pain.

Questions we asked ourselves throughout the scientific process included: Does OT directly reduce pain via enhancement of placebo analgesia, or does it indirectly increase the rate of positive pain-treatment outcomes by decreasing anxiety and enhancing empathic behavior? In other words, does OT make pain less intense, more tolerable, or both?

METHODS

To study the effect of OT on social influence and associative learning on pain, we employed a two-session cross-over design with a total of N=47 participants (N=22

couples). Half of the participants will receive OT in the first session — a single intranasal dose of Syntocinon-Spray 40-60 min before the onset of experimental tasks — and an inert saline spray in the second session. The other half of participants will receive the OT and control spray in the opposite order to control for potential order effects. Whereas studies have shown OT concentrations to peak at 30 min after intranasal administration, Cerebrospinal Fluid levels take up to 75 min to peak in humans (Evans et al, 2013). There is a 30 minute wait period after administration to allow for a 40-60 minute time period between administration and onset of experimental tasks. Roughly the first half of participants (N=25) received 24IU, while the remaining participants (N=22) received 40IU (after approval of protocol changes by the IRB).

Both experimenters and participants will be blind to the assigned condition and treatment of each participant, resulting in a double-blind cross-over design. The University of Colorado's Institutional Review Board (IRB) and Scientific Advisory and Review Committee (SARC) approved the study.

PARTICIPANTS

Recruitment for both couples and single participants included paper advertisements (posted in the general Boulder Valley County) and online advertisements (Craigslist and Facebook ads). Following a response to recruitment advertisement, participants were directed to a REDcap (online) screening form. 47 healthy volunteers took part in the experiment (N=47), 27 of which were tested with a romantic partner of at least one month (N=27 for HH task). All participants enrolled in the study were screened to ensure they were free of psychiatric, neurological, and pain

conditions in addition to being between the ages of 18-50 years old. About 54% of participants were female. The average age of participants was 24 (standard deviation of 5). Additional exclusion criteria included drug and alcohol use (occasional Nicotine use not included), women who were pregnant and women who were breastfeeding. Every participant signed an informed consent and was paid upon completion of their study session.

MATERIALS

Following preliminary screening, all participants underwent additional screening carried out by the University of Colorado Boulder's Clinical and Translational Research Center (CTRC) professional staff on the day of testing. This includes collection of medical history, general physical evaluation by a physician, EKG, blood pressure, pregnancy test, alcohol breathalyzer, and 14-panel poly-substance urine drug screen for illicit substances. We did not record data from these tests. All participants were required to pass all screening measures before administration of nasal spray and continuation of study procedures. Screening equipment was provided by the CTRC.

The CTRC pharmacologist was aware of the assigned conditions of the participants. Un-blinding of the CTRC staff and the experimenters occurred at the conclusion of data collection. The OT nasal spray was a 24 or 40 IU dose of Syntocinon-Spray (Novartis, Switzerland) while the control nasal spray was an inert saline solution. Heat pain was administered to participant's left vular forearm (and left calf in the HH task, only for those participating with a romantic partner) via ultra-short

thermal stimulation pulses (ATS II thermode, Medoc advanced medical systems, Israel).

This thermode has been used in numerous, previous pain studies (Chen et al. 2001).

EXPERIMENTAL PROCEDURES

Participants performed two tasks in each experimental session — couples

additionally performed a third hand holding task.
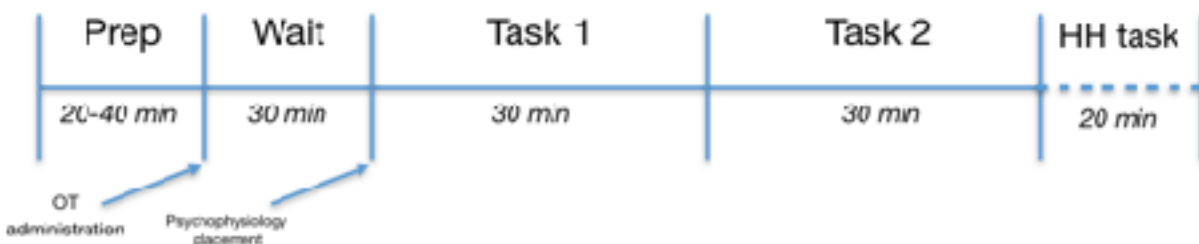
For task 1 and task 2, participants partook in a social-influence and conditioning

paradigms with heat pain to investigate the effects of OT on social instruction effects

and associative learning on pain. We used an Experience Based Learning paradigm

(EBL) and Social Conformity paradigm (SC), with the order of experimental tasks

counter-balanced.

EBL Task
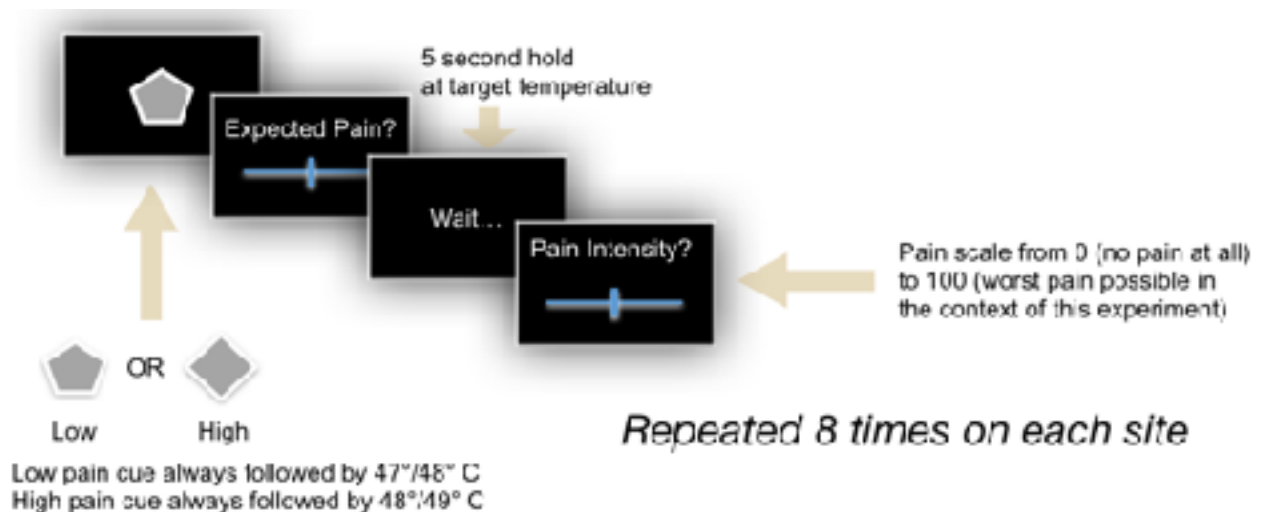
Participants experienced varying degrees of noxious heat stimuli on 4 different sites on their left solar forearm. Only three different temperatures were used: 47° C for "low pain" stimulation, 49° C for "high pain" stimulation, and 48° C for an "average pain" stimulation. Each of the 4 forearm sites was stimulated a total of 8 times, for a total of 32 "trials," for the EBL task and SC tasks.

At the beginning of each trial, participants were shown an abstract pattern. One of which was consistently followed by high pain stimulation and the other abstract pattern was consistently followed by low pain stimulation. Average pain stimulations (48° C) were preceded by high pain cues (High) for half of the trials and low pain cues (Low) for the other half. Each abstract pattern was associated with either high or low pain. After viewing a cue, participants were asked to rate their expected pain intensity on a scale from 0 (no pain at all) to 100 (worst pain possible under the experimental conditions).

Participants then received the actual pain stimulation. After receiving the pain, participants were asked to rate the intensity of the pain, again using the same 0-100 scale. The next trial began immediately following submission of actual pain intensity.
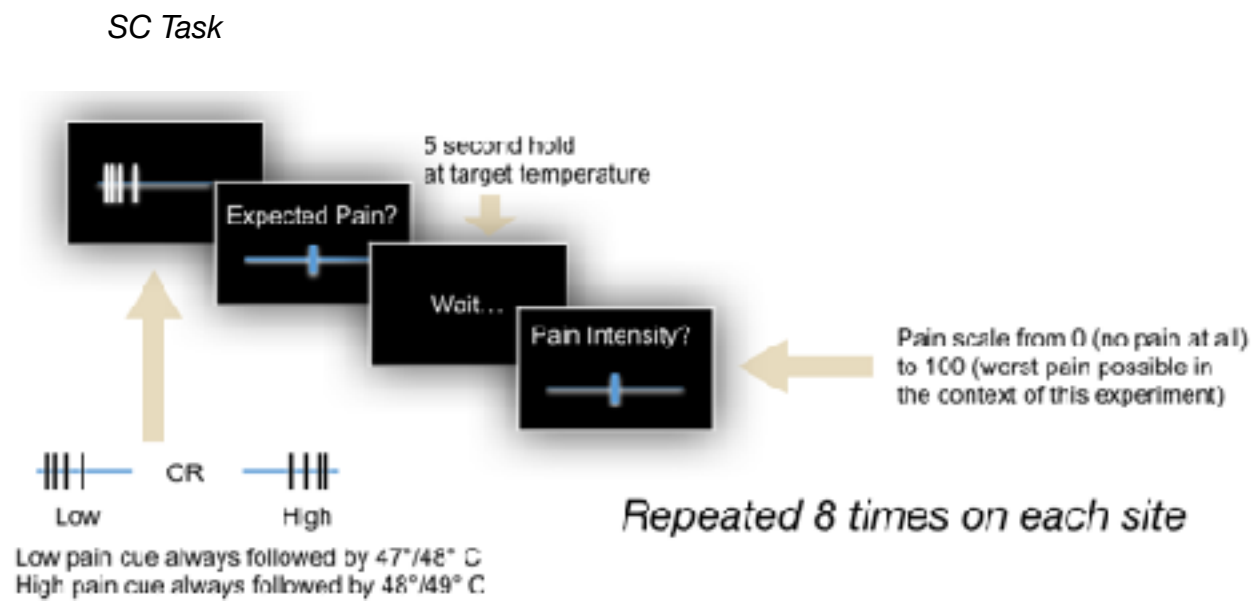
SC Task

The procedure for the SC task follows exactly with the EBL procedure, except for a few key differences: The low pain and high pain cues were symbolized by figures of pain ratings from 'several other participants in Boulder who have experienced this specific pain stimulation.' Each line on the figure represents the rating of one individual "participant" among an aggregate of other ratings (see above). The participants and social ratings displayed were actually fake, and generated to appear as realistic ratings.

For the final task, the Hand Holding (HH) paradigm, participants in a romantic relationship with a stable partner experienced thermal pain while receiving tactile social-support to test the effects of OT on the pain-alleviating effects of direct social support.

HH TASK
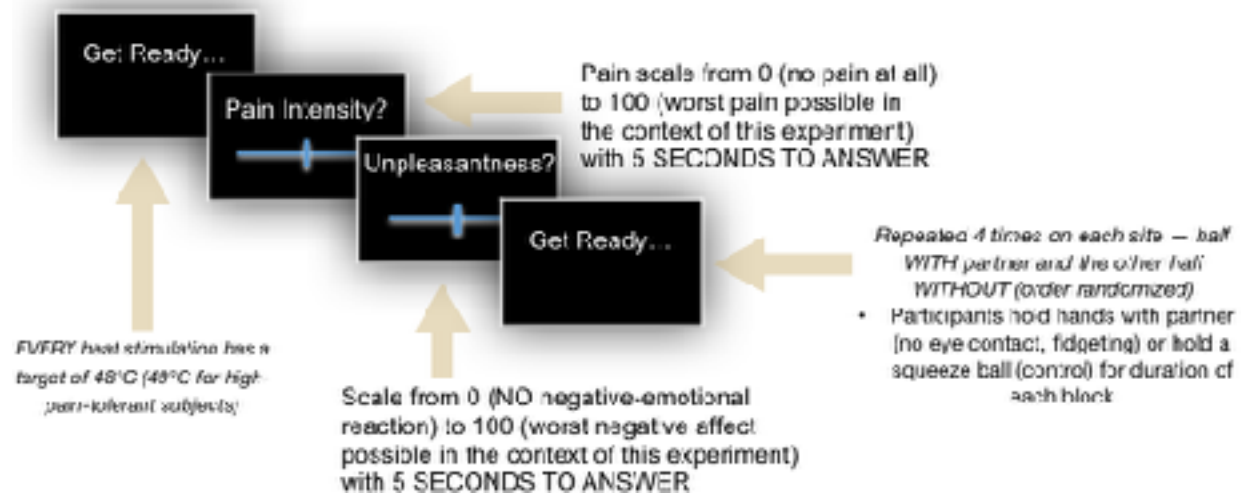
Participants experienced painful heat stimuli on 4 different sites on their left calf. Only one stimulus intensity was used for each trial. Most participants rated 48° C as

painful, yet tolerable and was used as the noxious heat stimulus temperature. However, some participants exhibited higher than average pain tolerance after experiencing a calibration temperature of 48° C. Those participants received 49° C as their temperature throughout the HH task. About 35% of participants (whom took part in the HH task) received the 49° C stimulation.

For each trial, participants received pain stimulation and then were asked to rate the level of pain intensity AND unpleasantness. The pain intensity scale was from 0-100, similar to the EBL and SC paradigms, and was meant to measure the "raw, physical intensity" of the pain stimulation. The unpleasantness scale was from 0 (the participant experienced no negative-emotional reaction to the pain) to 100 (worst negative affective response to the pain under experimental conditions). Unlike the EBL and SC paradigms, participants only had 5 seconds to answer each question. They were told that a timer would ensure spontaneous and hopefully accurate reports of pain intensity and unpleasantness.

During half of the stimulations, participants received social support from their romantic partners in the form of hand holding. Neither individual was allowed to look at or talk with the other. Hand holding required consistent contact without varying degrees of pressure or moving of the fingers and wrist. The other half of painful stimulations occurred while the participant was holding a squeeze-foam-stress ball (control).

ANALYSIS

Behavioral ratings were acquired on visual analog scales varying from 'absolutely no pain' to 'worst pain imaginable' (in the context of the experiment), ranging from 0 to 100 (where 100 indicating highest pain or pain expectancy ratings). We used a multi-level general linear model to test how learning cues affected pain expectation ratings, across all trials, and pain ratings for medium temperature trials (48°C) to control for temperature.

The code for the multi-level GLM and linear mixed model toolboxes are available at wagerlab.colorado.edu/tools. Other statistical analyses were conducted in Matlab. A significance level of $p < 0.05$ was applied to all analyses unless indicated otherwise.

RESULTS

EBL TASK

We first determined whether participants could discriminate between different heat stimuli (i.e. 3 noxious temperatures; 47°, 48°, 49° C). Pain ratings increased as a function of temperature intensity. A multi-level robust regression (see section 'Analysis') found a significant effect of temperature on pain ratings for both OT and placebo (PL) sessions (Fig 5).

Fig 5
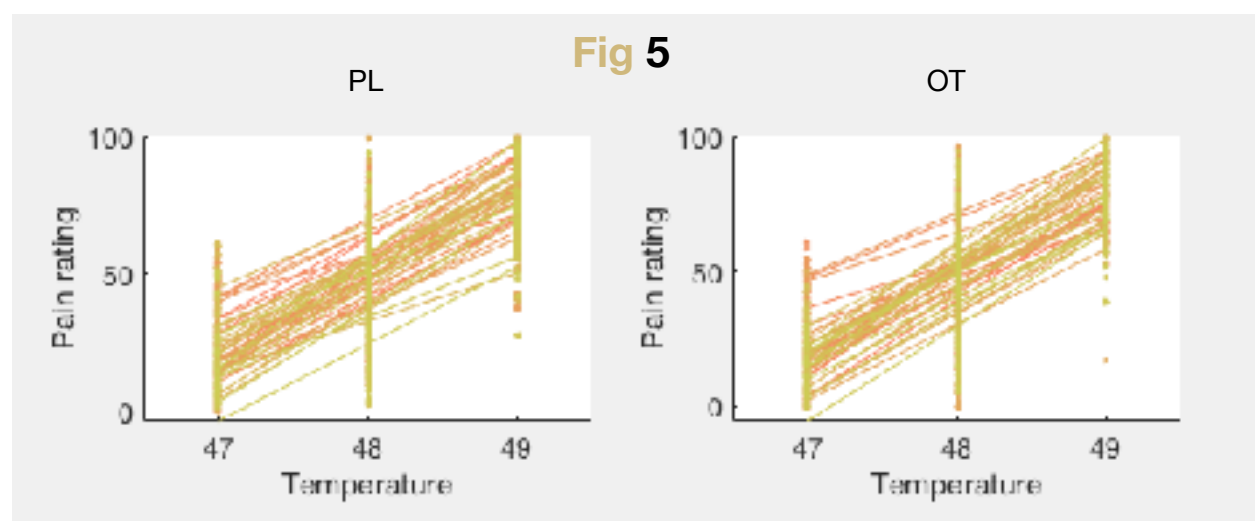
We then examined the effect of learning cues on pain. To do so, we specifically analyzed pain ratings for the 48° C (average pain) stimulation and looked for differences in ratings dependent upon their initial learning cue (High or Low=CH or CL, respectively). A significant effect of learning cues on pain rating was found for both the OT session (Fig 6) and PL session (Fig 7), where t(44)=9.18 and t(44)=8.12, respectively. OT and PL session T-test results are outlined in table 1 and provide further evidence that the cue effect of associative learning was replicated. In other words, there were significant differences in pain ratings dependent on the presented cue (CL vs CH), where participants generally rated pain as less intense when preceded with CL cue, regardless of OT administration.
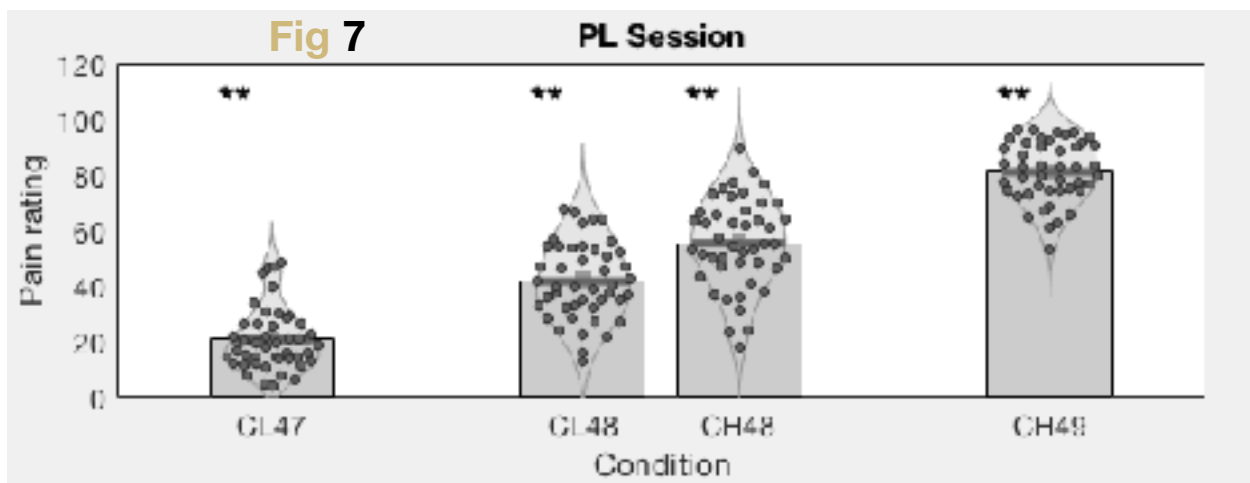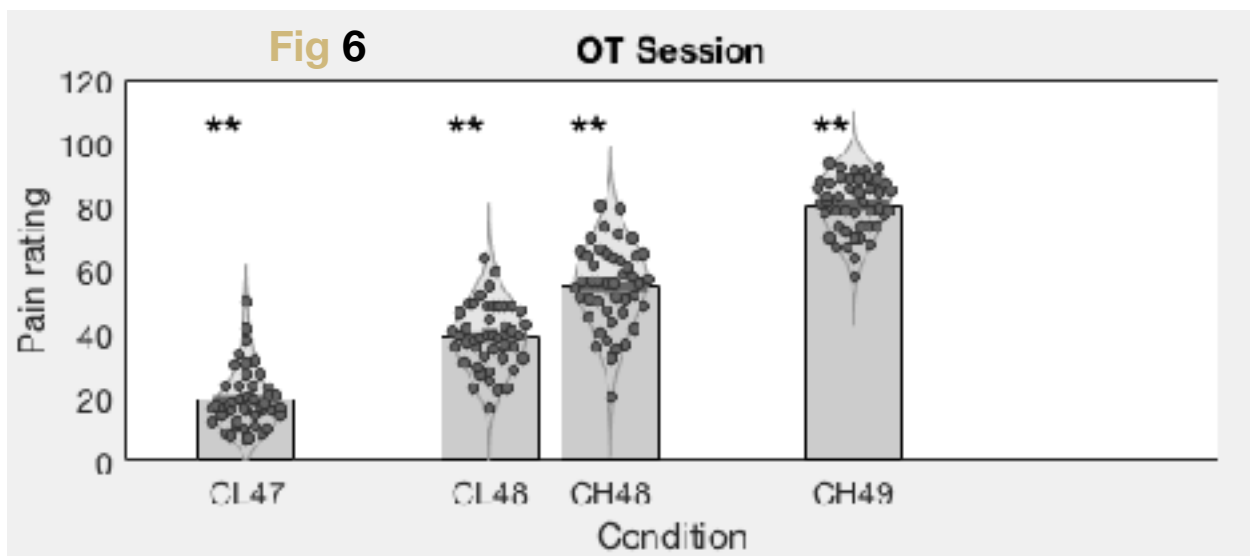

Fig 6 — OT Session

Fig 7 — PL Session

Table 1

T-test of CL48 pain & CH48 pain ratings	T-stat	Standard Deviation	P-value
OT session (Fig 6)	-8.72	12.15	>0.00005
PL session (Fig 7)	-6.93	13.26	>0.00005

No significant differences were found within subject (PL v OT) on pain ratings, as shown in Fig 8. T-tests of PL pain ratings minus OT ratings showed a clear null effect of OT on pain ratings with none of the columns being significantly different from zero.

Fig 8
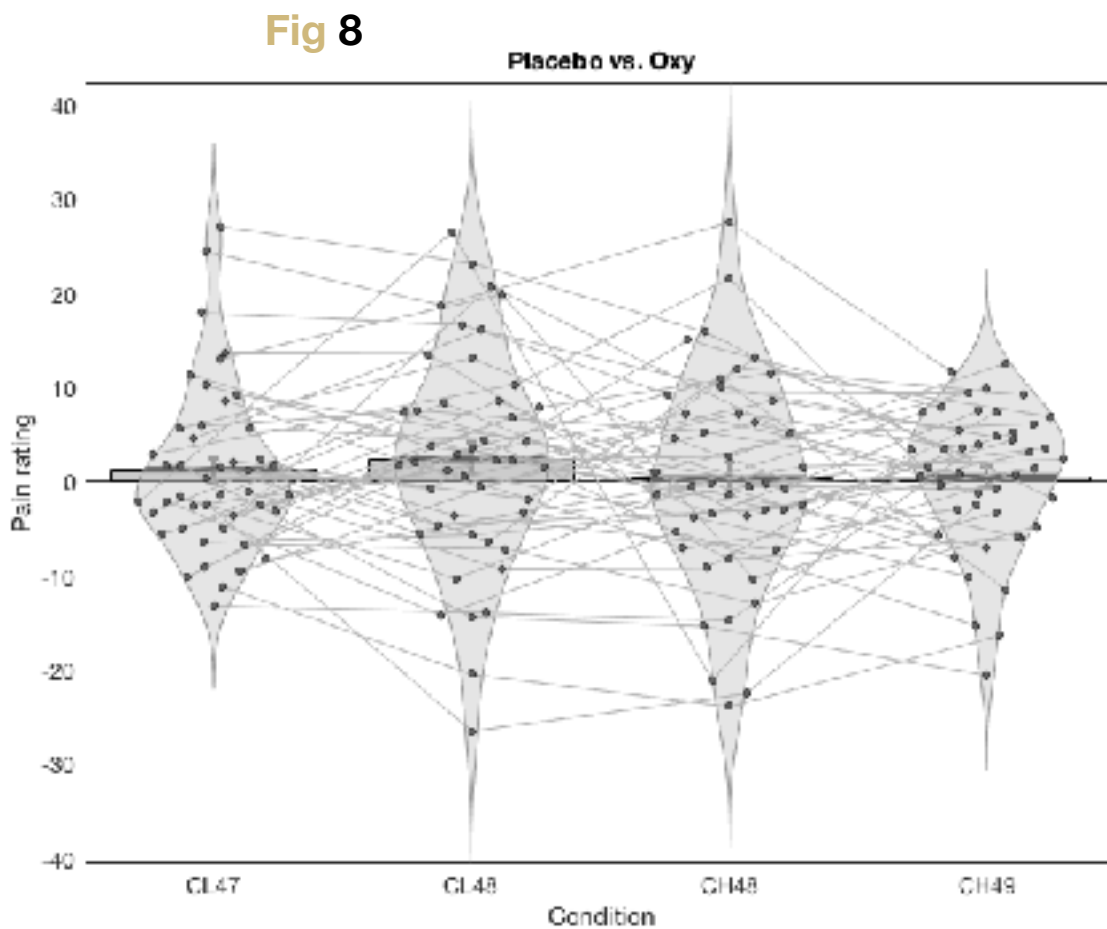
SC TASK

Similar to the EBL Task, we first determined whether participants could discriminate between different heat stimuli (i.e. 3 noxious temperatures; 47°, 48°, 49° C). Pain ratings increased as a function of temperature intensity. A multi-level robust regression (see section 'Analysis'- GLM) found a significant effect of temperature on pain ratings for both the OT session and PL session (Fig 9).

Fig 9
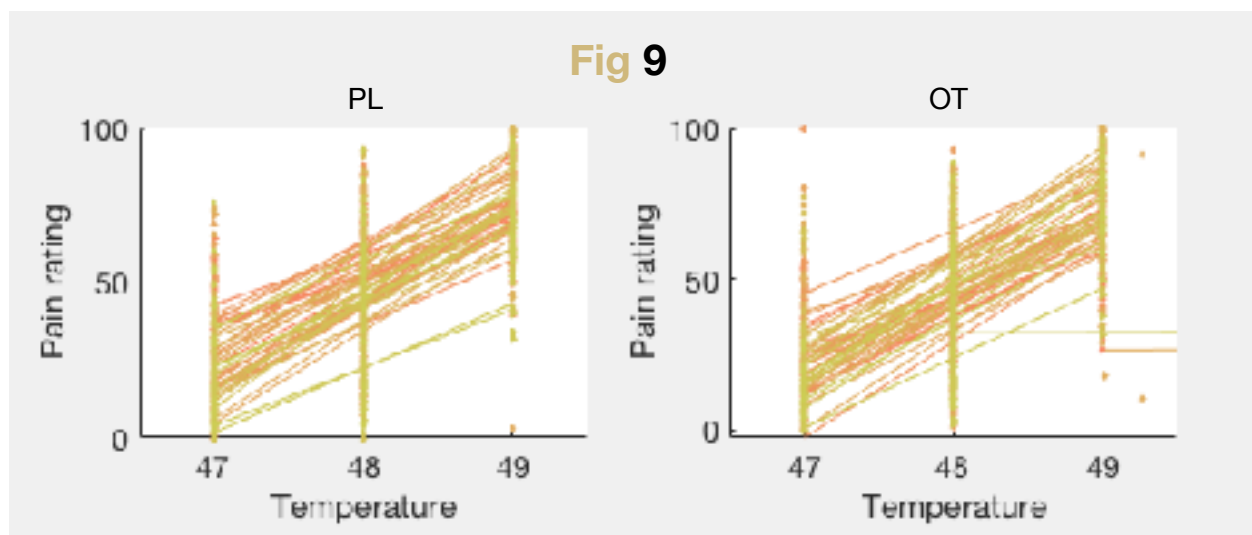
We then examined the effect of social cues on pain. To do so, we specifically analyzed pain ratings for the 48° C (average pain) stimulation and looked for differences in ratings dependent upon their initial social cue (High or Low=SH or SL, respectively). A significant effect of social cues on pain rating was found for both the OT session (Fig 10) and PL session (Fig 11), where t(44)=9.18 and t(44)=8.12, respectively. OT session T-test results are outlined in table 2 and provide further

evidence that the social influence effect was replicated. PL session T-test results are outlined in table 3 and also show significant differences in pain ratings dependent on the presented social cue.


Fig 10   OT Session

Fig 11   PL session
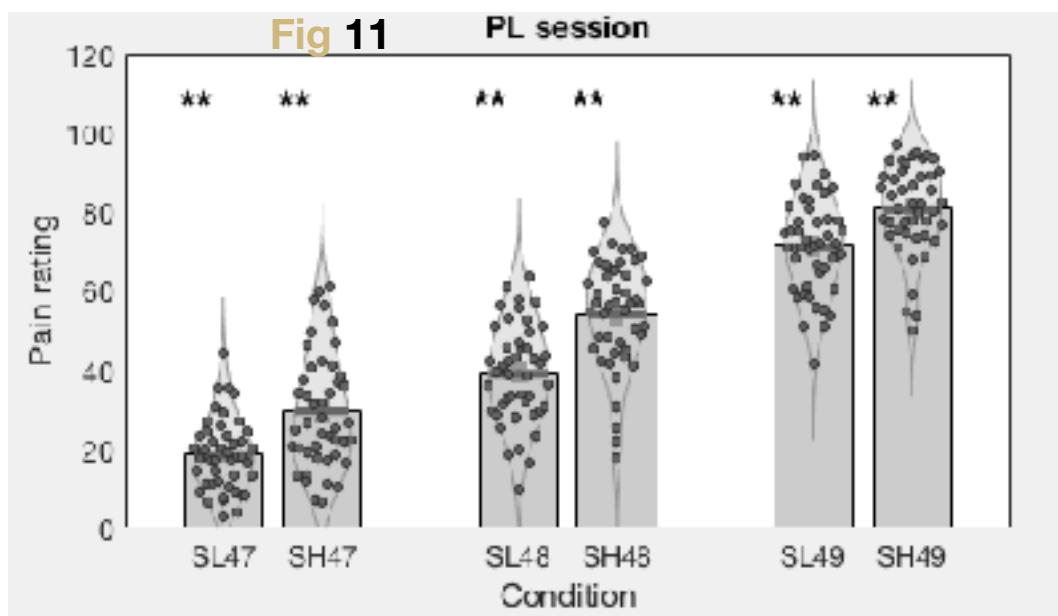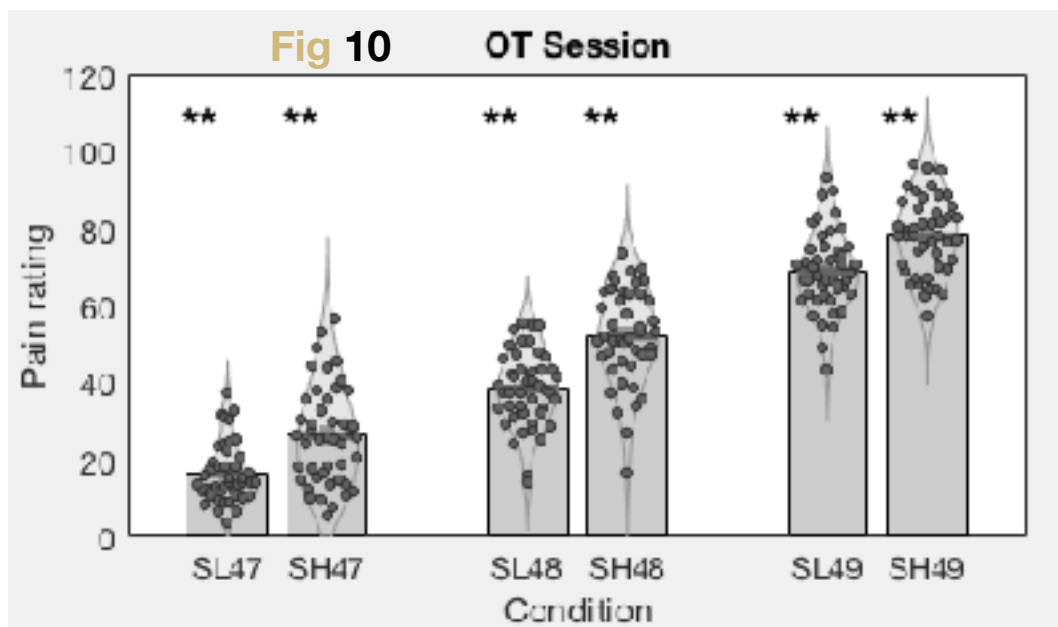
Table **2**

T-test of pain ratings for the OT session (Fig 10)	T-stat	Standard Deviation	P-value
CL47 & CH47	-5.53	11.96	<0.00005
CL48 & CH48	-9.17	10.03	<0.00005
CL49 & CH49	-6.55	9.26	<0.00005

Table **3**

| T-test of pain ratings for the PL session (Fig 11)	T-stat	Standard Deviation	P-value
CL47 & CH47	-6.03	12.46	<0.00005
CL48 & CH48	-8.72	11.40	<0.00005
CL49 & CH49	-4.99	12.65	<0.00005

Further, the plot showing the (null) effect of OT on pain ratings (labeled as PL minus OT, Fig 12) illustrates that none of the columns are sig different than zero, which means there was no OT effect on pain ratings for *both* tasks.


Fig **12**
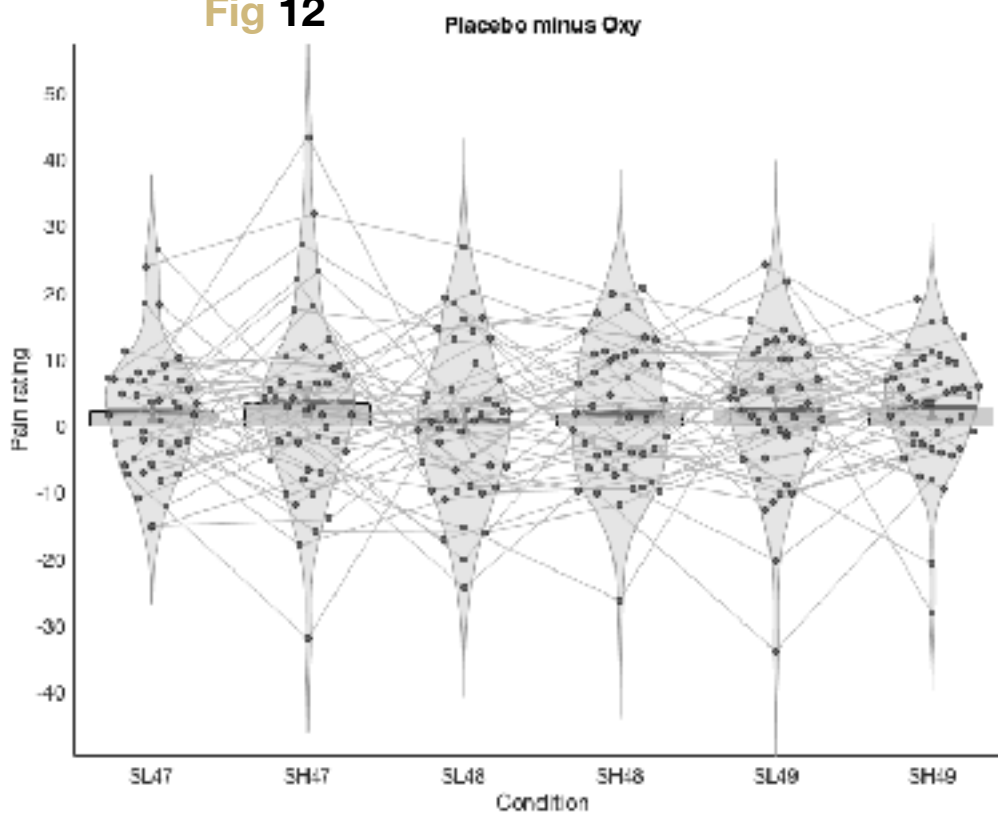
HH TASK

For the final task, the HH task, Fig 13 shows that there were no significant difference in pain intensity among all conditions (see description underneath figure for clarification of conditions, or 'Methods- experimental procedure' above).

Fig 13
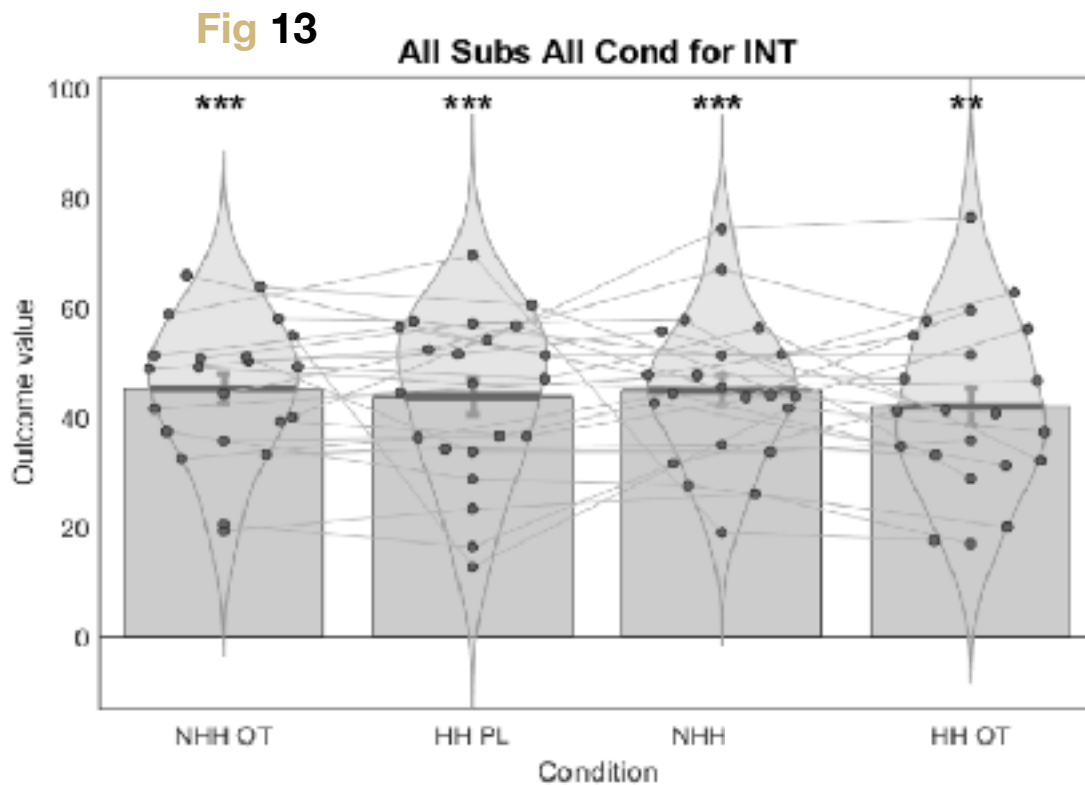
NHH OT = OT condition without holding hands
HH PL = PL condition while holding hands
NHH PL = PL condition without holding hands
HH OT = OT condition while holding hands

Further, we examined the effect of OT on unpleasantness ratings associated with pain within the hand holding paradigm. As Fig 14 shows, holding hands with a romantic partner decreased unpleasantness ratings regardless of session condition, where $t(24)= -9.19$ and $p=0.000625$.

Fig 14 **Hand Holding eff on UNP**
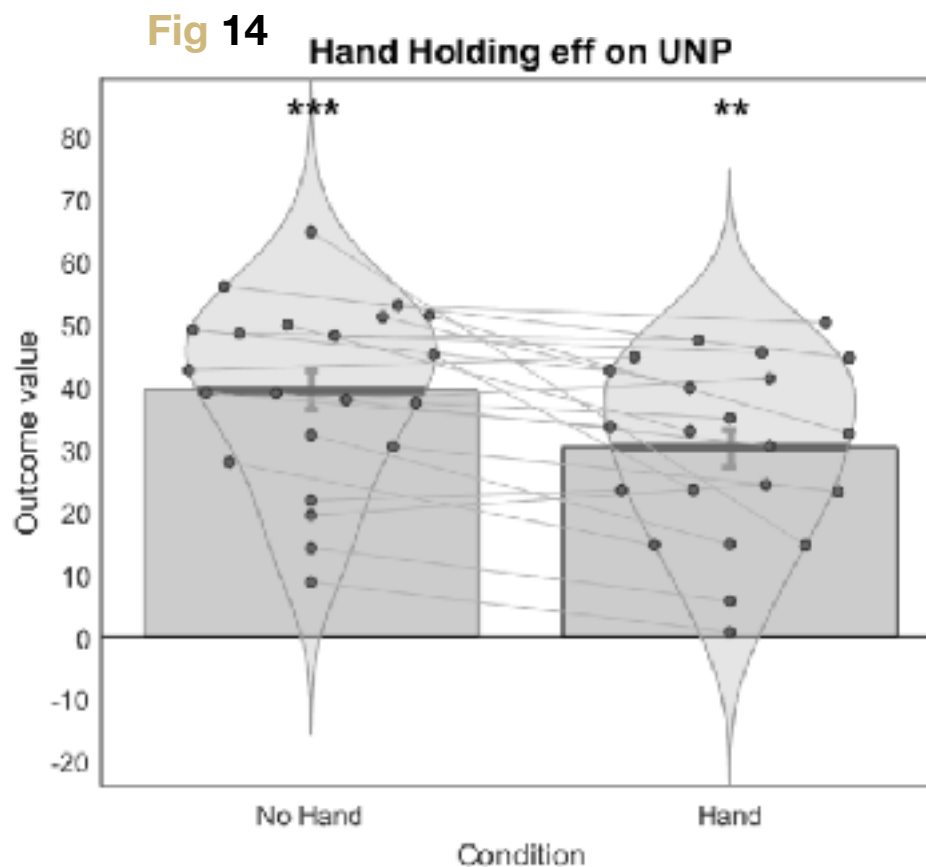
There was no significant difference between HH PL and HH OT conditions (Fig 15), indicating that OT did not show an enhancement of the effects of hand holding on unpleasantness. There was also no significant difference between NHH OT and NHH PL, indicating that OT did not show a reduction of unpleasantness ratings, regardless of hand holding conditions.

Fig 15   All Subs All Cond for UNP
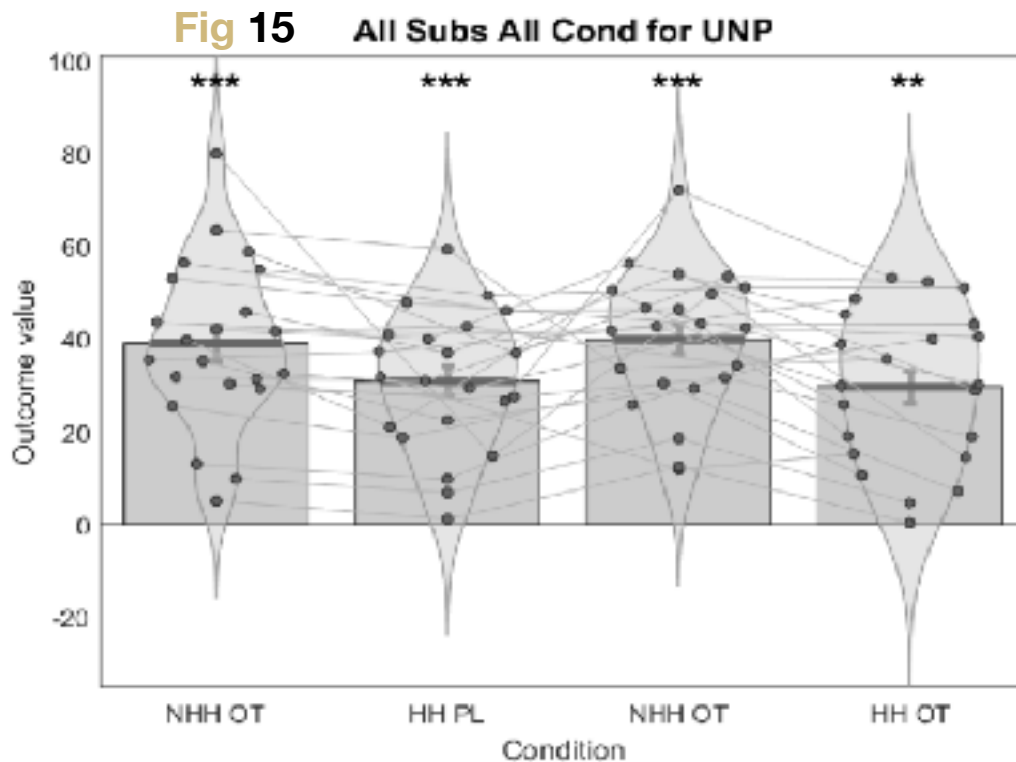
DISCUSSION

Previous research has highlighted OT's role in social learning and emotional empathy, with significant effects found in the function of the amygdala (Hurlemann et al. 2010). We found significant effects on pain perception from both social and experience based learning cues. The placebo effect can therefore be confirmed as a significant contributor to the analgesic effects seen in both EBL and SC tasks. However, we found no effect of OT on pain intensity or enhancement of the effects of cues (High vs Low; between sessions), despite the apparent importance of OT in regulating amygdala activity.

Other OT research studying its interaction with the amygdala illustrated OT's ability to attenuate autonomic responses to emotional faces regardless of valence (Domes et al. 2007). While the Amygdala's role in social cognition is still questionable, its role in pain perception and learning of pain-related cues remains significant. Not seeing an effect of OT in the study presented here may serve as a narrowing of the road for future research. Perhaps, OT provides anxiolytic effects without inherent analgesic properties. Additionally, our social cues were computer generated, meaning the participants never received valid social information such as facial expression and body language.

It remains to be seen if OT would enhance the effects of the SC task with more complex social information is presented as cues. Other OT research found that memory encoding of social experiences is enhanced with intranasal OT administration, but only *positive* memories (Guastella et al. 2008). In a paradigm involving heat pain (and no explicit techniques to encourage positive social interaction), it is possible we will never be able to see an effect of OT on pain perception.

However, OT has also been shown to increase trust in humans by affecting prosocial approaches to new information and lowering defense behaviors (Kosfeld et al. 2005; Singer et al. 2008). As the EBL results above demonstrated, participant pain ratings were significantly affected by learning cues. The effect of learning cues on pain ratings was also significant when those cues were presented as social information in the SC task. Theoretically, OT should have increased trust in participant's belief in the social cues presented and therefore shown an effect between sessions. Yet, the placebo effect was not enhanced by intranasal administration of OT.

Another factor that could explain this lack of effect comes in the form of perceived trustworthiness. That is, OT can facilitate acceptance of social advise, but is dependent upon the acquired trustworthiness of said advisor (Luo et al. 2017). The pain ratings "from other participants in Boulder" presented as cues were, again, computer generated. Conceivably, a figure on a computer screen can be perceived as *not* trustworthy and therefore disregarded, preventing OT effects from surfacing. There is support for OT being able to blur this self-other distinction, but only implicitly (Pfundmair et al. 2018). More explicit details in provided social cues could be added to future pain paradigms to verify the null effect of OT.

This all is not to say that OT should be forgotten amongst the continued research of pain and placebo. While we replicated findings from previous research on the social influence and associative learning effects on placebo analgesia (Koban & Wager, 2016) and found OT did not enhance these effects, we did find unpleasantness ratings decreased while holding hands with a romantic partner.

Couple this with the fact that OT reduces hemodynamic responses within the amygdala in response to heat (Zunhammer et al. 2015) and also decreases feelings of anxiety (Goodin et al. 2015), then perhaps OT serves a different role in pain perception than "direct" analgesia. Such mixed results on a single biomolecule suggests a complex mechanism underlies "indirect" analgesic effects previously reported (but not replicated here). These indirect analgesic effects could include psychological (anxiolytic) or physiological (amygdala modulation), but the null effects reported here suggests that OT does not enhance placebo analgesia as initially thought.

Another interaction to note is that of gender effects. OT has been speculated to influence perceived saliency of noxious thermal stimuli in conjunction with sex hormones, most specifically estrogen (Tracy et al. 2017). Future research on OT's role in pain perception and placebo analgesia should focus on implementing more social information (rather than just tactile touch or computer generated figures), exploring those indirect analgesic effects posited above, and investigate whether gender effects are present therewith.

CONCLUSION

The study presented here contributes to the Oxytocin literature by reporting a null effect of OT on placebo analgesia. While we were able to reproduce the social conformity and associative learning effects on placebo analgesia, OT did not enhance either. OT also was not found to enhance the indirect effects of analgesia previously reported in the literature. The most reliable conclusion we can draw from these results are so forth: Oxytocin does not keep heat pain from being painful, but it may just make it tolerable. Further research, is needed to verify just exactly how OT can make pain more tolerable.

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