Dopaminergic tone does not influence pain levels during placebo interventions in patients with chronic neuropathic pain

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Summary: Dopamine does not contribute to placebo effects in patients with neuropathic pain after thoracic surgery.

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Abstract

Placebo effects have been reported in patients with chronic neuropathic pain. Expected pain levels and positive emotions are involved in the observed pain relief, but the underlying neurobiology is largely unknown. Neuropathic pain patients are highly motivated for pain relief, and as motivational factors such as expectations of reward, as well as pain processing in itself, are related to the dopaminergic system, it can be speculated that dopamine release contributes to placebo effects in neuropathic pain. Nineteen patients with neuropathic pain after thoracic surgery were tested during a placebo intervention consisting of open and hidden applications of the pain-relieving agent lidocaine (2 mL) and no treatment. The dopamine antagonist haloperidol (2 mg) and the agonist levodopa/carbidopa (100/25 mg) were administered to test the involvement of dopamine. Expected pain levels, desire for pain relief, and ongoing and evoked pain were assessed on mechanical visual analog scales (M-VAS, 0-10). Significant placebo effects on ongoing ($P \leq 0.003$) and evoked ($P \leq 0.002$) pain were observed. Expectancy and desire accounted for up to 41.2% and 71.1% of the variance in ongoing and evoked pain, respectively, after the open application of lidocaine. We found no evidence for an effect of haloperidol and levodopa/carbidopa on neuropathic pain levels ($P = 0.071$-0.963). Dopamine seemed to influence the levels of expectancy and desire, yet there was no evidence for indirect or interaction effects on the placebo effect. This is the first study to suggest that dopamine does not contribute to placebo effects in chronic neuropathic pain.

1. Introduction

Placebo effects have been reported in chronic neuropathic pain [32,54,55]. Expected pain levels contribute to the observed pain relief, and studies have shown that these expectations are embedded in positive emotions such as hope and excitement [54]. However, the underlying neurobiological mechanisms remain unclear.

Pain has been described as a motivational factor that encourages actions to reduce pain, and the experience of pain relief has been associated with feelings of reward [41,42,49,50]. Patients with chronic pain are particularly motivated to obtain pain relief [5,40,61,64,75], and patients with neuropathic pain have reported expectations of pain reduction at the onset of treatment and feelings of excitement during the pain-relieving effect of a placebo intervention [54]. Hence, the prospect of pain relief during placebo treatments may evoke expectations of reward.

Motivational factors such as expectation of reward [11,19,24,35,45,65,66] and pain processing in itself [1,28-30,33,53,56,67,76-78] have been associated with the dopaminergic system. Therefore, it can be speculated that endogenous dopamine release may contribute not only to placebo effects in Parkinson's disease [14-16,47,71], but also to placebo effects in patients with neuropathic pain. This has been put forward in the so-called placebo-reward hypothesis proposing that dopamine is related to the expectation of reward and precedes other neurobiological events leading to the clinical benefits such as pain relief during placebo treatments [14].

Three studies have directly examined the involvement of the dopaminergic system in placebo analgesia effects [68,69,79], but the findings were inconclusive. Two of the studies reported dopamine activity in reward-sensitive brain areas during placebo interventions [68,69], whereas the third study found that a dopamine antagonist did not block placebo analgesia effects [79]. Importantly, these studies were conducted in healthy volunteers who may not have been particularly motivated for pain relief [64], so it is important to investigate this further in chronic pain patients.

In the present study, the dopamine antagonist haloperidol and agonist levodopa/carbidopa were administered to test whether endogenous dopamine release contributes to placebo effects in chronic neuropathic pain. This administration paradigm has been used previously to either decrease [48,52,79] or increase [37,51,52] the dopaminergic tone. This is the first study to investigate the role of dopamine in placebo effects in chronic pain patients on the basis of both up- and downregulation of dopamine. The effect of dopamine was examined in relation to actual ongoing and evoked pain levels and to expected pain levels and desire for pain relief. Expectations and desire are closely linked to motivation for pain relief [61,62,64] and have been associated with placebo effects in chronic pain [73,74]. We propose the following hypotheses:

1) Large placebo effects can be obtained in neuropathic pain, and administration of haloperidol blocks the placebo effects while administration of levodopa/carbidopa increases the magnitude of the placebo effects.

2) Expectancy and desire contribute to the pain relief following a placebo intervention in neuropathic pain, and these factors may be influenced by haloperidol and levodopa/carbidopa.

2. Methods

2.1. Patients

The study included 19 patients aged 18 years or above with a confirmed diagnosis of probable or definite neuropathic pain [22,32] after unilateral thoracotomy or video-assisted thoracoscopic surgery. Neuropathic pain was defined in accordance with the International Association for the Study of Pain as "Pain caused by a lesion or disease of the somatosensory system" [32] and should be located in an area of sensory abnormalities compatible with nerve injury after thoracic surgery. A trained neurologist screened the patients for neuropathic pain characteristics and symptoms using a Danish version of the Douleur Neuropathique 4 (DN4) questionnaire [12]. Patients were recruited from the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Denmark, where they had undergone surgery between 2004 and 2015 (14 patients were operated after 2010). Patients were screened for inclusion if they reported ongoing neuropathic pain corresponding to a minimum pain intensity of 3 on an 11-point numerical rating scale (NRS; 0 = no pain to 10 = worst imaginable pain) [18,54]. Patients were excluded from the study if they had psychiatric or competing neurological disorders, glaucoma, uncontrolled low potassium values in plasma, skin diseases in the upper part of the body, or if they had known allergies to any medications, including local anesthetics. Patients treated with antidepressants, class 1 antiarrhythmic, antipsychotics, or anti-Parkinsonian agents were excluded from the study. Electrocardiogram and tests of blood pressure were performed, and patients were excluded if the tests revealed unknown heart diseases, including long QT_c-interval, and/or venous thromboembolism, and/or risk of orthostatic hypotension. Patients receiving medication on an irregular basis were asked to withdraw from the medication 24 hours before each test day, and patients receiving medication on a regular basis were asked to maintain their fixed doses during the study period. Patients were asked to withdraw from analgesics 12 hours prior to each test day, if tolerable. The patients were asked only to ingest natural yoghurt and water short of iron 3

hours before each test day as the absorption of levodopa/carbidopa is inhibited by high levels of iron. Noncompliance with the above-mentioned criteria led to exclusion from the study. Patients received reimbursement for their travel expenses. The study was approved by the Central Denmark Region Committees on Health Research Ethics (1-10-72-188-14) and registered at ClinicalTrials.gov (Identifier: NCT03109860).

2.2. Conditions and verbal suggestions

The study used a within-subject design, and each patient went through 5 different test days, each consisting of a baseline session and a test session (Fig. 1). The placebo effect was investigated via an open-hidden design, as previously described [54,55]. On the first 3 test days, the patients randomly received an open application of lidocaine (in full view of the patient), a hidden application of lidocaine (without the patient's knowledge), or no treatment (control condition). Lidocaine was applied topically using a disinfection napkin, as previously described [54,55]. A disinfection napkin is typically used to cleanse the patient's skin before evoked pain tests so the open and hidden applications of lidocaine could easily be embedded in this procedure. On 2 subsequent test days, haloperidol or levodopa/carbidopa was administered before the open application of lidocaine to test if dopamine contributed to the placebo effect [2,6,7,10,25,43,44,80]. The administration of haloperidol and levodopa/carbidopa took place after the examination of the placebo effect on the first 3 test days to ensure that any effects of the drugs (eg, blocking of the placebo effect) did not influence the initial examination of the placebo effect. To control for order effects, the administrations of haloperidol and levodopa/carbidopa were block randomized.

In the baseline-open conditions: open lidocaine, open lidocaine with administration of haloperidol, and open lidocaine with administration of levodopa/carbidopa, lidocaine was applied to the disinfection napkin in full view of the patient and applied to the test area with verbal suggestions

for pain relief: “The agent you have just been given is known to powerfully reduce pain in some patients.”

In the baseline-hidden condition, lidocaine was applied to the napkin just before the session and without the patient’s knowledge. The investigator pretended to use the napkin for disinfection only, and the patients were told that: “This is a control condition for the active medication, and we will test your response to different types of stimuli to get a better understanding of how your pain is processed.” In the baseline-control condition, the disinfection napkin was used for disinfection only, and no treatment was administered, and the patients received the same verbal information as in the baseline-hidden condition.

2.3. Test area

A 2 x 2 cm test area in the most painful area close to the surgical site outside the cicatricial tissue was identified and marked with a pencil. A picture was taken to document the location to ensure that the test area was placed in the approximate same area on all 5 test days. Lidocaine was applied in the center of the test area and evenly dispersed over the painful area (as described in Section 2.2). Evoked pain was measured in the test area.

2.4. Medications

2.4.1. Lidocaine

Lidocaine (Xylocain®; cutaneous solution, 5%, 2 mL) was used to investigate the placebo effect. Lidocaine was chosen as the active pain-relieving treatment because it has been successfully used in previous placebo studies [54,55]. Our research group have previously performed pilot tests to explore if the patients were able to detect the lidocaine on the disinfection napkin or the skin [54,55]. These tests revealed that the patients were not able to detect the lidocaine on the napkin, as the lidocaine

solution was transparent and easily applied to the skin. Furthermore, the lidocaine solution did not cause any numbness, skin irritation, or coolness, which might have led to unblinding of the procedure. Thus, it is possible to apply lidocaine in an open and hidden manner completely unbeknownst to the patient.

2.4.2. Haloperidol and levodopa/carbidopa

The dopamine antagonist haloperidol (Serenase®; 2-mg tablets) and the dopamine agonist levodopa/carbidopa (Sinemet®; 100/25-mg tablets) were dissolved in strawberry milk (Arla; Mathilde Mini Strawberry; 100 mL) and administered orally to patients [7,10]. The dosages and administration of haloperidol and levodopa/carbidopa were guided by previous studies demonstrating that a single dose of haloperidol (2 mg) decreased dopamine activity in reward-sensitive areas of the brain (eg, the ventral striatum and nucleus accumbens) [48,52,79], and that levodopa/carbidopa (100/25 mg) increased dopamine activity in the brain [37,51,52]. The dissolution of haloperidol and levodopa/carbidopa in strawberry milk was performed by an independent research assistant, insuring that both the investigator and the patient were blinded for the procedure. Regarding the administration of haloperidol and levodopa/carbidopa, the following details were provided to the patients: “On each test day you will be asked to drink 100 mL of strawberry milk. The strawberry milk will sometimes be mixed with the drugs haloperidol and levodopa/carbidopa. These drugs may increase or decrease your ability to modulate pain and will provide us with information on how the pain-relieving treatment works. There are no known adverse events or risks associated with the administration of these drugs.”

2.5. Pain measures

Perceived pain intensity and unpleasantness were measured using a mechanical visual analogue scale (M-VAS; 0-10, 0 = no pain intensity/unpleasantness, 10 = worst imaginable pain intensity/unpleasantness) in accordance with guidelines described elsewhere [59]. Patients were instructed to distinguish between the sensory (intensity) and affective (unpleasantness) dimensions of pain [63].

2.5.1. Ongoing pain

Ongoing pain was assessed by asking patients to rate their current levels of pain intensity/unpleasantness in the painful chest area on the M-VAS. Ongoing pain levels constituted the primary outcome measures.

2.5.2. Evoked pain

A handheld Semmes-Weinstein nylon monofilament (Stolting, IL; No. 5.88) was used to assess evoked pain. When applied to the skin, this monofilament exerts a constant force at 75.86g/588.24 mN as it bends. The evoked pain tests were selected based on previous studies demonstrating large placebo effects on these measures [54]. In order to control for tactile allodynia, the evoked pain tests started with the gentlest stimulation [27,36]. Hence, the order of the tests was: 1) the area of hyperalgesia, 2) pinprick-evoked pain, and 3) wind-up-like pain.

The area of pinprick hyperalgesia was mapped by moving the monofilament from the periphery outside the painful area towards the center of the painful skin area in steps of 1 cm at a rate of 1 cm s^{-1}. Patients were instructed to look away during the stimulation and to report when the sensation changed to pain. This spot was marked with a pencil, and the investigator started the stimulation from another part of the periphery. The procedure was continued until the entire area of hyperalgesia was mapped. The area was transferred to plastic wrap and then to white paper. The area

of hyperalgesia was finally calculated in square centimeters (cm^2) using the computer program ImageJ (https://imagej.nih.gov/ij/).

Pinprick-evoked pain intensity and unpleasantness were measured via a single stimulation with the monofilament in the test area. Patients rated pinprick-evoked pain intensity and unpleasantness on the M-VAS.

Wind-up-like pain was measured in the test area via repeated stimulation with the monofilament (2 Hz for 30 s, including a total of 60 stimuli). Patients were asked to continuously rate their pain on an electrical visual analogue scale (E-VAS; 0-100, 0 = no pain, 100 = most imaginable pain). Pain was rated until the wind-up-like pain had waned, and the total time period was recorded. The area under curve (AUC) was calculated in order to evaluate how the patients' pain varied during repetitive stimulation. Additionally, patients rated their worst pain intensity and unpleasantness on the M-VAS. Patients were told that they could discontinue the stimulation at any time if the pain became unbearable, but all patients completed the 30 s stimulation.

2.6. Psychological measures

2.6.1. Expected pain levels

Immediately after lidocaine was applied and before it had taken effect (approximately 1 min after the application), the patients were asked: "What do you expect your level of ongoing pain intensity/unpleasantness to be during the session?" Before measuring the area of hyperalgesia, the patients were asked: "Do you expect the area of hyperalgesia to be smaller, larger, or the same after the treatment?" Before the pinprick and wind-up tests, the patients were asked: "What do you expect your level of pain intensity/unpleasantness to be during the pinprick/wind-up test?"

Expected pain intensity and unpleasantness was measured using the M-VAS described above. This scale has been validated previously and has been used in numerous studies to measure expected pain levels in relation to placebo treatments [54,55,57,58,64,73,74].

2.6.2. Desire for pain relief

Immediately after the treatment was given, the patients were asked: "How strong is your desire for relief of ongoing pain?" Before measuring the area of hyperalgesia, the patients were asked: "How strong is your desire for a reduction of the area of hyperalgesia?" Before the pinprick and wind-up tests, the patients were asked: "How strong is your desire for a reduction of the pinprick-evoked/wind-up-like pain?"

Desire for pain relief was assessed on an M-VAS (1-10, 0 = no desire for pain relief, 10 = the most strong desire for pain relief). This procedure has been validated in former studies investigating placebo effects [57,58,64,73,74].

2.7. Procedure

The study took place in a hospital setting at the Danish Pain Research Center, Aarhus University Hospital, Denmark. On the first test day, the patients were greeted by the investigator (IS) and a medical doctor (KM), who screened the patients for inclusion and verified the neuropathic pain in accordance with standardized clinical guidelines [12]. Detailed information about the patients' medical history, including their pain development, was collected and the investigator took time (approximately 30 min) to establish a good patient-practitioner relationship [34]. Patients were informed about the study and time was given to answer any additional questions. All patients signed informed consent prior to the start of the study.

At the beginning of each test day, the investigator, who wore a white laboratory coat, conversed empathically with the patients about their pain and general well-being. Patients were then placed in a hospital bed, and the baseline session was conducted to control for natural fluctuation in pain [20]. First, the test area was identified on the painful chest area and the investigator cleansed the patient's skin with a disinfection napkin. Second, measures of ongoing and evoked pain were assessed. After the baseline session, strawberry milk (with or without haloperidol or levodopa/carbidopa) was administered orally, and the patients were asked to wait in the test room for 2 hours while being regularly monitored by the investigator. After the 2-hour break, patients were asked about any side effects and the test session began. In the open conditions, the investigator applied the lidocaine to the test area via a disinfection napkin in full view of the patient and gave verbal suggestions for pain relief. In the hidden condition, lidocaine was surreptitiously applied to the disinfection napkin, and the investigator pretended to use the napkin for disinfection only without giving any verbal suggestions for pain relief. In the control condition, no medication was administered, and the investigator just cleansed the test area with the disinfection napkin without giving any verbal suggestions for pain relief. Immediately after the application of the napkin (with or without lidocaine), the patients were asked about their expected pain levels and desire for pain relief. After a 10-min interval in order for the treatment to take effect, measures of ongoing and evoked pain were obtained following the same procedure as in the baseline session. Additional measures of expectancy and desire were assessed before each of the evoked pain tests. Measures of expected pain levels and desire for pain relief were obtained in the test session in the open conditions and in the hidden and control conditions. Finally, the investigator conversed with the patient about the day's session and then took leave of the patient.

2.8. Statistical analyses

The placebo effect was calculated as the difference in pain levels between the open and hidden conditions, controlled for the no-treatment control condition [3,9,43,44] as previously described [54,55]. Specifically, the 3 conditions: open, hidden, and control, were compared using repeated measures ANOVAs. Omnibus *F* tests were followed by post hoc Bonferroni corrections for multiple comparisons. Thus, the post hoc Bonferroni tests showed the difference in pain between the open and hidden conditions, when controlled for the no-treatment control condition. To control for natural fluctuations in pain, the calculations were based on difference scores between the baseline-open (ΔBO-O), baseline-hidden (ΔBH-H), and baseline-control (ΔBC-C) conditions. Separate analyses were conducted for ongoing pain intensity and unpleasantness and evoked pain tests. When the assumption of Sphericity was violated, the Greenhouse-Geisser correction was applied.

Effect sizes were calculated using Cohen's *d*: the difference between two means divided by the pooled standard deviation of the data [13]. The means and standard deviations were based on difference scores between the baseline-open and baseline-hidden conditions (Δ(BO -O)-(BH-H)) for all pain measures. Hence, in the open condition, Cohen's *d* was calculated as: (d = ($X_{(\Delta BC-C)}$ - $X_{(\Delta(BO-O)-(BH-H))}$)/(pooled standard deviation)).

Multiple regression analyses were used to assess if expected pain levels and desire for pain relief contributed to the reduction in ongoing and evoked pain levels after the open application of lidocaine. Pain levels were used as outcome variables, and levels of expected pain and desire for pain relief served as multiple predictor variables. Levels of expected pain and desire for pain relief were compared in the open, hidden, and control conditions using repeated measures ANOVAs to further verify the contribution of each.

In the baseline-open condition with administration of haloperidol, the placebo effect was calculated as the difference in pain levels between the baseline-open with haloperidol (ΔBOHP-OHP), baseline-hidden (ΔBH-H), and baseline-control (ΔBC-C) conditions using repeated measures

ANOVA. In the baseline-open condition with administration of levodopa/carbidopa, the placebo effect was likewise calculated as the difference in pain levels between the baseline-open with levodopa/carbidopa (ΔBOHP-OLD), baseline-hidden (ΔBH-H), and baseline-control (ΔBC-C) conditions. As specified above, the omnibus *F* tests were followed by post hoc Bonferroni corrections for multiple comparisons in order to calculate the difference in pain between the open and hidden conditions, when controlled for the no-treatment control condition.

In order to identify possible modulatory effects of dopamine, the changes in pain levels between the baseline and the test session were compared in the baseline-open (ΔBO-O), baseline-open with administration of haloperidol (ΔBOHP-OHP), and baseline-open with administration of levodopa/carbidopa (ΔBOLD-OLD) conditions using repeated measures ANOVAs. Omnibus *F* tests were followed by post hoc Bonferroni corrections for multiple comparisons to test the difference between single comparisons. To further test the data and to strengthen the results, this was tested post hoc using multilevel modeling. The results of the multilevel modeling mirrored those of the repeated measures ANOVAs and are therefore not shown.

Additionally, levels of expected pain and desire for pain relief were compared across the open conditions: open lidocaine, open lidocaine with administration of haloperidol, and open lidocaine with administration of levodopa/carbidopa, using repeated measures ANOVAs to explore if dopamine influenced these variables. These data were post hoc analyzed using paired samples *t* test.

Whether dopamine moderated the effect of expectancy and desire on the placebo effect was explored post hoc. The following interactions were tested via multilevel modeling: 1) dopamine*expectancy, and 2) dopamine*desire.

In addition, any indirect effects of dopamine on the placebo effect via modulation of expectancy and desire were tested post hoc, ie, whether expectancy and desire acted as mediators of the relationship between dopamine and the placebo effect. In order to test this, we investigated

whether the dopamine modulation (haloperidol and levodopa/carbidopa) had an equal influence on the placebo effect and levels of expectancy and desire. Specifically, the difference in the magnitude of the placebo effect as well as levels of expectancy and desire in the open lidocaine with administration of haloperidol and open lidocaine with administration of levodopa/carbidopa conditions were calculated and correlated. A positive correlation between the placebo effect (difference scores) and levels of expectancy/desire (difference scores) would indicate an indirect effect, as the dopamine modulation influenced the magnitude of the placebo effect and levels of expectancy/desire in an equal manner.

$P < 0.05$ was considered statistically significant. Bayesian statistics were calculated post hoc for the repeated measures ANOVAs to indicate the relative strength of evidence for one theory over the other (the alternative over the null hypothesis or vice versa) [17]. Bayes Factors (BF_{01}) were calculated using the program JASP (https://jasp-stats.org/) and interpreted according to Jeffrey's conventional cut-offs: A Bayes Factor greater than 3 or less than 1/3 represents substantial evidence. Conversely, a Bayes Factor between 1/3 and 3 is considered anecdotal evidence [31]. Specifically, larger numbers for the Bayes Factor (BF_{01}) generate more support in favor of the null hypothesis, whereas smaller numbers generate more support in favor of the alternative hypothesis.

3. Results

3.1. Patient characteristics

Ten men and 9 women (all Caucasian) with an average age of 62.26 years (range: 39-74 years) participated in the study. All patients went through all 5 test days. The vast majority of patients had undergone thoracic surgery as part of their treatment for lung cancer. In a single patient, benign lung cyst removal had led to neuropathic pain. Sixteen patients were operated at the right side of the thorax. All patients fulfilled the inclusion criteria of ongoing neuropathic pain corresponding to a minimum pain intensity of 3 on the NRS (average pain intensity: 3.83 (1.39); average pain unpleasantness: 3.67 (1.12)). The duration of neuropathic pain ranged between 1 and 12 years (mean: 4.11).

3.2. Placebo effects

There was a significant reduction in ongoing pain intensity ($P = 0.002$) and unpleasantness ($P = 0.003$) and in all evoked pain tests ($P \leq 0.002$) after the open vs the hidden application of lidocaine controlled for the no-treatment control condition (Table 1). The Bayes Factor was < 1/3 for all pain measures, which indicates substantial evidence. The Cohen's *d* for ongoing pain intensity and unpleasantness was 1.54 and 1.40, respectively, and for evoked pain tests, it ranged between 1.45 and 2.09. Hence, large placebo effects were observed in relation to ongoing and evoked types of neuropathic pain [13] (Fig. 2A). Generally, there was a non-significant reduction in ongoing and evoked pain after the hidden application of lidocaine compared to the no-treatment control condition (Table 1).

3.3. Expected pain levels and desire for pain relief in the open, hidden, and control conditions

Patients expected significantly lower pain levels in the open vs hidden condition controlled for the no-treatment control condition ($P \leq 0.001$). Seventeen patients expected the area of hyperalgesia to

be smaller after the open application of lidocaine. In addition, the patients reported a stronger desire for pain relief in the open vs hidden condition controlled for the no-treatment control condition ($P \leq 0.035$). These findings indicate that the placebo intervention was successful as shown in Figs. 3A and 4A. Zero-order correlations between ongoing baseline pain and expectancy/desire and between expectancy and desire in relation to the open lidocaine condition are reported in Tables 1 and 2 in the supplementary materials.

3.4. Expected pain and desire for pain relief predict pain levels in relation to open lidocaine

Expected pain levels and desire for pain relief accounted for up to 41.2% and 71.1% of the variance in ongoing and evoked types of neuropathic pain, respectively, after the open application of lidocaine. Examination of the beta weights indicated that expected pain levels were the only unique predictor. Findings from the regression analyses are summarized in Table 2.

3.5. Effects of haloperidol and levodopa/carbidopa on the placebo effect

Significant reductions in ongoing and evoked pain after the open vs hidden application of lidocaine controlled for the no-treatment control condition were observed in both the open lidocaine with administration of haloperidol ($P \leq 0.002$) and open lidocaine with administration of levodopa/carbidopa ($P \leq 0.003$) conditions. Hence, significant placebo effects were obtained regardless of decrease or increase of the dopaminergic tone (Fig. 2B).

There was no evidence of a statistically significant difference in the reduction in ongoing and evoked neuropathic pain between the open lidocaine, open lidocaine with administration of haloperidol, and open lidocaine with administration of levodopa/carbidopa conditions (P values ranged between 0.071 and 0.963) (Table 3). As reported in Table 3, the Bayes Factor was > 3 in 4 out of 8 pain measures, which indicates substantial evidence. Although there was only anecdotal evidence

for the remaining measures, the overall picture points to a relatively strong evidence for the null hypothesis. Thus, these findings suggest that endogenous dopamine release did not contribute to the analgesic effects during the placebo intervention.

Further examination of the post hoc Bonferroni corrections for multiple comparisons (Table 3) and the magnitude of the placebo effects (Table 3 in the supplementary materials) revealed that the lower *P* values for some of the repeated measures ANOVAs were likely a result of the placebo effect being larger in both the open lidocaine with administration of haloperidol and the open lidocaine with administration of levodopa/carbidopa conditions compared to the open lidocaine condition. This supports the finding that higher levels of dopamine in the brain were not linearly related to larger placebo effects.

3.6. Expected pain levels and desire for pain relief in the open lidocaine, open lidocaine with administration of haloperidol, and open lidocaine with administration of levodopa/carbidopa conditions

As illustrated in Figs. 3B and 4B, expected pain levels and desire for pain relief varied across the 3 open conditions. Repeated measures ANOVAs showed no significant differences in expectancy and desire for most measures (7 out of 10 analyses were non-significant) (see Table 4 in the supplementary materials). Paired samples *t* tests showed that patients expected significantly lower pain levels when levodopa/carbidopa was administered than when haloperidol was given for the majority of pain measures (Table 4). Moreover, paired samples *t* tests revealed a significantly stronger desire for pain relief in the levodopa/carbidopa condition compared with the haloperidol condition for most pain measures (Table 4). As levodopa/carbidopa increases the dopamine activity in the brain, the observed rise in expectancy and desire after the administration of levodopa/carbidopa is in accordance with research showing that dopamine release contributes to motivational factors [11,19,24,35,45,65,66].

3.7. Interaction effects between dopamine, expectancy, and desire on the placebo effect

Results from the multilevel modeling testing the interactions: 1) dopamine*expectancy, and 2) dopamine*desire, are summarized in Table 5. Generally, there was no evidence for statistically significant interaction effects, thereby suggesting that dopamine did not moderate the effect of expectancy and desire on the placebo effect.

3.8. Indirect effects of dopamine on the placebo effect via modulation of expectancy and desire

As seen in Table 6, there was no evidence for statistically significant positive correlations between the magnitude of the placebo effect (difference scores) and levels of expectancy and desire (difference scores) in the open lidocaine with administration of haloperidol and open lidocaine with administration of levodopa/carbidopa conditions. Thus, the present study did not find any indirect effects of dopamine on the placebo effect via modulation of expectancy and desire, ie, expectancy and desire did not act as mediators of the relationship between dopamine and the magnitude of the placebo effect.

4. Discussion

4.1. Major findings

The present study demonstrated large placebo effects in patients with chronic neuropathic pain after thoracic surgery (Cohen's $d > 0.8$) [22]. Expected pain levels and desire for pain relief contributed to the pain reduction following the open application of lidocaine. The administration of haloperidol or levodopa/carbidopa did not affect pain levels following the open application of lidocaine, suggesting that endogenous dopamine release did not contribute to the analgesic effect. Yet, the results suggest that dopamine may have influenced expected pain levels and desire for pain relief. Nevertheless, there was no evidence for either an indirect effect of dopamine on the placebo effect via modulation of expectancy and desire or that dopamine moderated the effect of expectancy and desire on the placebo effect, adding support to the finding that dopamine did not contribute to the placebo effect.

4.2. Expectancy and desire contribute to large placebo effects in neuropathic pain

This study corroborates previous findings by demonstrating large and significant placebo effects in ongoing and evoked types of neuropathic pain [54,55]. Hence, patients experienced significantly lower pain levels after the open vs hidden application of lidocaine controlled for the natural history of pain. The finding that placebo effects are seen in relation to 3 measures that are likely to be associated with hyperalgesia and central sensitization: (1) maximum wind-up-like pain, (2) area of secondary hyperalgesia, and (3) ongoing clinical pain [4,39,46,70], adds to an increasing body of evidence suggesting that at least some types of placebo analgesia effects reflect antihyperalgesic mechanisms [54,55,60,73,74]. The reduction in pain after the hidden application of lidocaine was non-significant, most likely because lidocaine only has a minor effect on neuropathic pain following thoracotomy, which is in line with a recent meta-analysis showing that lidocaine generally has a small

effect on different types of neuropathic pain [21]. As this suggests that the observed pain relief was due to placebo factors, it is not considered a limitation in the current study.

In line with previous studies, expected pain levels and desire for pain relief contributed to the pain reduction after the open application of lidocaine [54,55,73,74]. Although expectancy was the only unique predictor, it should be noted that patients generally had a strong desire for pain relief, and the contribution of desire may have been undermined by a ceiling effect. Expectancy and desire contribute to emotions such as hope and excitement [57,58,61,62,72] and are closely linked to motivation [61,62,64]. Hence, this study can be seen as supporting the notion that expectations of reward may be involved in placebo analgesia effects. Still, further studies are needed to specifically understand how expectations of pain relief interact with emotional factors and, more generally, with motivation in mediating placebo analgesia effects.

4.3. Endogenous dopamine release does not contribute to the analgesic effect following placebo interventions in neuropathic pain

Contrary to our hypothesis, the administration of haloperidol and levodopa/carbidopa did not affect pain levels following the open application of lidocaine. These findings suggest that endogenous dopamine release did not contribute to the observed placebo effect. This is consistent with a study showing that the same dose of haloperidol did not block placebo effects in healthy volunteers [79], yet studies using position emission tomography have observed endogenous dopamine release in the nucleus accumbens during placebo interventions, which supports a role of dopamine in placebo analgesia effects [68,69].

We do not think that the negative findings from the current study are due to methodological limitations. Firstly, antagonism of neurotransmitter systems has been successfully used to identify neurobiological placebo mechanisms in numerous studies [2,6-8,25,26,43,44] and secondly, the

effect of both up- and downregulation of the dopaminergic system were tested in the present study. Although the administration paradigm used here was similar to that used by others to decrease [48,52,79] or increase [37,51,52] the dopaminergic tone, it should be mentioned that no direct measurements of dopamine activity were performed to ensure that haloperidol and levodopa/carbidopa had the intended effects on the dopamine activity in the brain structures involved in pain processing and expectations of reward.

4.4. Is there a role of dopamine in the anticipation of pain relief following placebo interventions?

A clear difference between studies indicating that endogenous dopamine release does not contribute to placebo analgesia effects [79], including the current study, and studies supporting the role of dopamine in placebo analgesia [68,69] is that the former tested the effect of dopamine in relation to actual pain levels, whereas the latter measured dopamine activity during the anticipation of a placebo effect. This is illustrated by one study observing dopamine activity while introducing a placebo treatment but in the absence of actual pain [68]. One possible explanation to this is that dopamine is involved in the anticipation of a treatment effect but not in the actual analgesia following placebo treatments. Interestingly, expectations and desire for pain relief were higher when dopamine levels were pharmacologically enhanced in the present study. This might be explained by the association between dopamine release and motivational factors such as expectations of reward [11,19,24,35,45,65,66]. Specifically, the patients reported higher levels of desire and expected lower pain when levodopa/carbidopa was administered than when haloperidol was given. These findings reflected tendencies only, possibly as a result of the relatively low number of participants, and should accordingly be interpreted with caution. Nevertheless, as expected pain levels and desire for pain relief are most likely related to expectations of reward, this might support a role of dopamine in the anticipation of a placebo effect, although dopamine does not seem to contribute to the analgesic effect

following placebo interventions. Such an interpretation would be in agreement with the placebo-reward hypothesis [14]. Yet, although the dopaminergic tone seemed to influence levels of expectancy and desire, there was no evidence for either an indirect effect of dopamine on the placebo effect via expectancy and desire, or that dopamine moderated the effect of expectancy and desire on the placebo effect. Given that expectancy and desire contributed to the placebo effect, a dopaminergic modulation of these factors would be expected to also influence the magnitude of the placebo effect if, at least, the observed modulation of expectancy and desire is considered evidence for a role of dopamine in the anticipation of a placebo effect. Thus, these findings speak against the hypothesis that dopamine is involved in the anticipation of a placebo effect. Instead, the modulation of expectancy and desire might simply be an expression of the association between dopamine and psychological factors such as reward [66], without necessarily being related to the placebo effect. Importantly, however, the present study included a relatively low number of participants, and we cannot rule out the possibility of insufficient statistical power when testing such indirect effects. Therefore, in order to conclusively deduce that dopamine is not involved in the anticipation of a placebo effect and affects pain levels in an indirect way, it is important that future studies investigate this in a larger sample. As the existing studies are based on different methods, it may be helpful to combine pharmacological antagonist and agonist studies and brain imaging techniques with the aim of investigating the role of dopamine in placebo analgesia in future research.

4.5. Conclusion and future directions

To our knowledge, this is the first study indicating that increasing or decreasing the dopaminergic tone in the brain does not influence pain levels following placebo interventions in chronic neuropathic pain patients. Although dopamine seemed to influence levels of expectancy and desire, the study did not support a role of dopamine in the anticipation of a placebo effect, as suggested elsewhere [14]. It

is important, though, that future studies investigate any such possible indirect effects of dopamine on the placebo effect in a larger sample of chronic pain patients. In addition, future studies should test whether other neurotransmitter systems contribute to the analgesic effect following placebo interventions in patients with chronic pain. Importantly, a few studies indicate that the endogenous opioid system is not involved in placebo effects in chronic pain [38,74]. In general, no studies have so far been able to pharmacologically block placebo effects in chronic pain conditions, and as placebo effects in healthy volunteers might differ from those in chronic pain patients [23,64], it is important that the neurotransmitter systems involved in placebo effects in chronic pain is further investigated.

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Conflict of interest

The authors report no conflicts of interest.

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Figure legends

Figure 1. Study design. Each test day included a baseline session and a test session consisting of no-treatment control, hidden lidocaine, open lidocaine, open lidocaine with administration of haloperidol, and open lidocaine with administration of levodopa/carbidopa conditions.

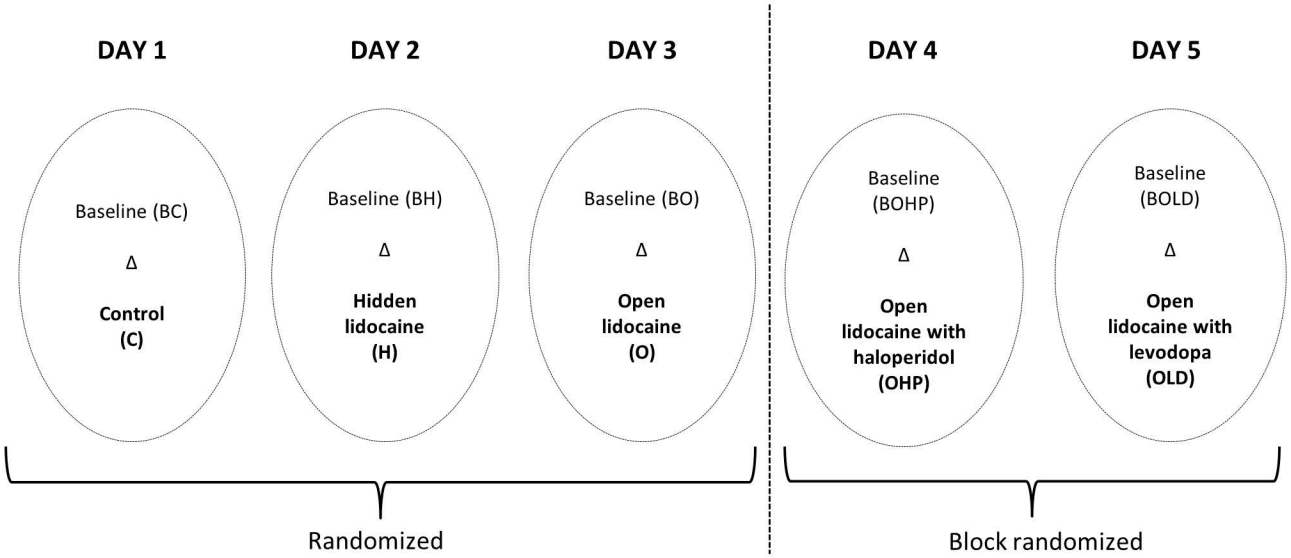
Figure 2. Placebo effects on ongoing pain intensity. Pain levels (Mean/SD) across baseline and test session in all conditions. **A:** Baseline-open lidocaine, baseline-hidden lidocaine, baseline-control. **B:** Baseline-open lidocaine with administration of haloperidol, baseline-open lidocaine with administration of levodopa/carbidopa.

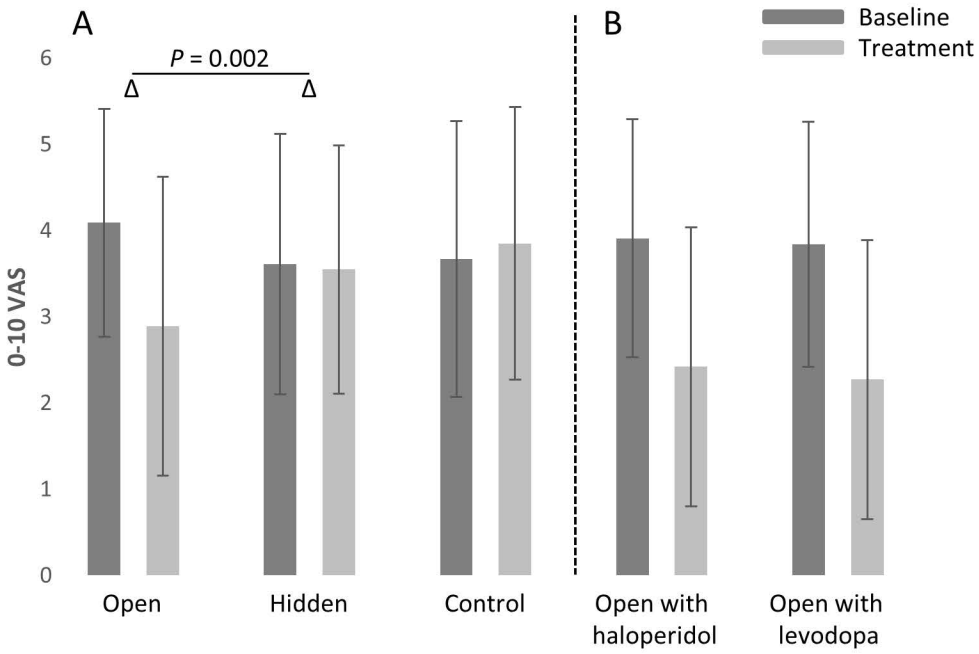
Figure 3. Expected pain intensity (Mean/SD) in relation to ongoing pain intensity across all conditions. **A:** Open lidocaine, hidden lidocaine, no-treatment control. **B**: open lidocaine with administration of haloperidol, open lidocaine with administration of levodopa/carbidopa.

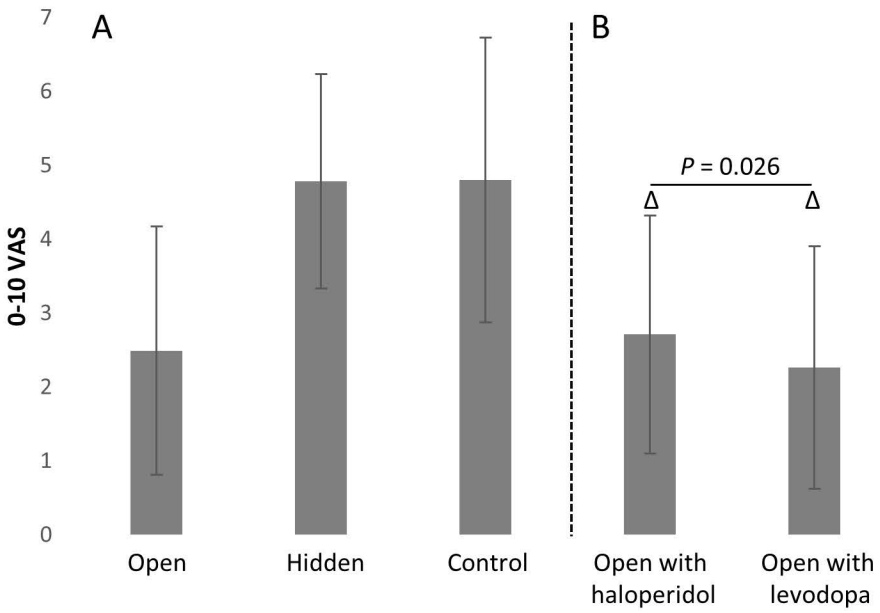
Figure 4. Desire for pain relief (Mean/SD) in relation to ongoing pain levels across all conditions. **A:** Open lidocaine, hidden lidocaine, no-treatment control. **B**: open lidocaine with administration of haloperidol, open lidocaine with administration of levodopa/carbidopa.

Baseline sessions
Application of disinfection napkin
Ongoing pain
Area of hyperalgesia
Pinprick-evoked pain
Wind-up-like pain

Test sessions
Application of disinfection napkin
Expectancy and desire
Ongoing pain
Expectancy and desire
Area of hyperalgesia
Expectancy and desire
Pinprick-evoked pain
Expectancy and desire
Wind-up-like pain




A
B
Baseline
Treatment
P = 0.002
Δ
Δ
0-10 VAS
6
5
4
3
2
1
0
Open
Hidden
Control
Open with haloperidol
Open with levodopa


A
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7
6
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0-10 VAS
P = 0.026
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Open
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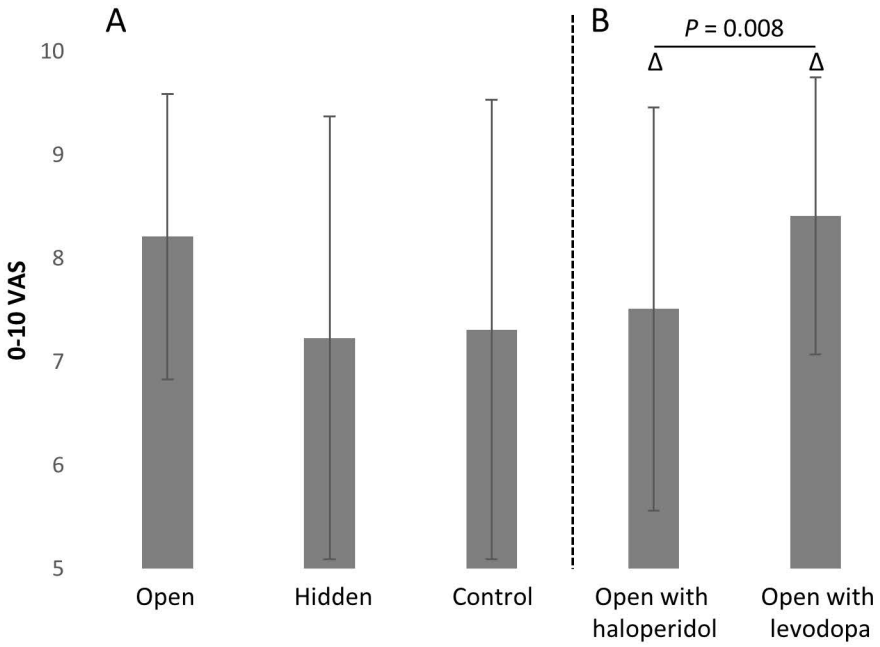
Open with haloperidol
Open with levodopa


A
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P = 0.008
Δ
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10
9
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7
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5
0-10 VAS
Open
Hidden
Control
Open with haloperidol
Open with levodopa

Table 1

Placebo effects (M-VAS) in ongoing and evoked pain in relation to the open lidocaine condition (N = 19).

Repeated measures ANOVA	***df***	***(error)***	***F***	P^1	P^2	P^3	BF_{01}
Ongoing pain intensity**	1.355	24.385	23.557	<0.001*	0.002*	0.279	3.984e-7
Ongoing pain unpleasantness	2	36	17.689	<0.001*	0.003*	0.338	8.405e-6
Area of hyperalgesia	2	36	29.645	<0.001*	<0.001*	1.000	5.750e-8
Pinprick-evoked pain intensity**	1.450	26.103	42.443	<0.001*	<0.001*	0.048*	1.404e-10
Pinprick-evoked pain unpleasantness	2	36	35.491	<0.001*	<0.001*	0.035*	1.848e-9
Wind-up-like pain, AUC**	1.533	27.590	22.346	<0.001*	0.002*	0.241	4.445e-7
Wind-up-like pain, worst pain intensity**	1.330	23.943	19.332	<0.001*	0.001*	0.753	2.290e-6
Wind-up-like pain, worst pain unpleasantness**	1.253	22.561	19.759	<0.001*	0.001*	0.648	4.458e-6

P^1 = *P* value omnibus test, P^2 = *P* value for comparison between the open and hidden conditions when controlled for no treatment, P^3 = *P* value for comparison between the hidden and no treatment control condition. All *P* values are reported with Bonferroni corrections.

*Statistically significant ($P < 0.05$).

**Greenhouse-Geisser correction.

Table 2

Prediction of ongoing and evoked pain (M-VAS) in relation to the open lidocaine condition (N = 19).

Expectancy + Desire	R^2	F		B	t	P
Ongoing pain intensity	0.379	4.876, $P = 0.022$*	Expectancy	0.461	2.311	0.034*
			Desire	0.340	1.703	0.108
Ongoing pain unpleasantness	0.412	5.599, $P = 0.014$*	Expectancy	0.502	2.580	0.020*
			Desire	0.322	1.657	0.117
Pinprick-evoked pain intensity	0.180	1.754, $P = 0.205$	Expectancy	0.431	1.744	0.100
			Desire	-0.018	-0.071	0.944
Pinprick-evoked pain unpleasantness	0.293	3.311, $P = 0.063$	Expectancy	0.556	2.518	0.023*
			Desire	0.058	0.261	0.797
Wind-up-like pain, AUC	0.498	7.451, $P = 0.006$*	Expectancy	0.709	3.849	0.002*
			Desire	0.139	0.752	0.464
Wind-up-like pain, worst pain intensity	0.607	12.354, $P < 0.001$*	Expectancy	0.773	4.922	<0.001*
			Desire	0.061	0.390	0.702
Wind-up-like pain, worst pain unpleasantness	0.715	20.061, $P < 0.001$*	Expectancy	0.847	6.270	<0.001*
			Desire	-0.010	-0.073	0.943

Outcome variables: ongoing and evoked pain levels, predictor variables: expected pain levels and desire for pain relief.

*Statistically significant ($P < 0.05$).

Table 3

Comparisons of placebo effects (M-VAS) in the open lidocaine conditions (N = 19).

Repeated measures ANOVA	*df*	*df(error)*	*F*	P^1	P^2	P^3	P^4	BF_{01}
Ongoing pain intensity**	1.326	23.873	1.896	0.180	0.753	0.341	1.000	1.907
Ongoing pain unpleasantness	1.534	27.611	3.145	0.071	0.260	0.179	1.000	0.804
Area of hyperalgesia	2	36	2.247	0.120	1.000	0.454	0.190	1.467
Pinprick-evoked pain intensity**	2	36	0.717	0.495	1.000	0.441	1.000	4.242
Pinprick-evoked pain unpleasantness	2	36	0.947	0.397	1.000	0.381	0.917	3.552
Wind-up-like pain, AUC	2	36	0.038	0.963	1.000	1.000	1.000	7.040
Wind-up-like pain, worst pain intensity**	1.236	22.242	1.563	0.229	0.383	0.514	1.000	2.345
Wind-up-like pain, worst pain unpleasantness**	1.271	22.871	1.208	0.297	1.000	1.000	0.561	3.040

P^1 = *P* value omnibus test, P^2 = *P* value for comparison between the open lidocaine and open lidocaine with administration of haloperidol conditions, P^3 = *P* value for comparison between the open lidocaine and open lidocaine with administration of levodopa/carbidopa conditions. P^4 = *P* value for comparison between the open lidocaine with administration of haloperidol and open lidocaine with administration of levodopa/carbidopa conditions. All *P* values are reported with Bonferroni corrections.

*Statistically significant ($P < 0.05$).

**Greenhouse-Geisser correction.

Table 4

Comparisons of expectancy and desire in the open lidocaine with administration of haloperidol and open lidocaine with administration of levodopa/carbidopa conditions (N = 19).

Paired samples *t* test	***df***	***t***	***P***
Expected pain (M-VAS)			
Ongoing pain intensity	18	2.430	0.026*
Ongoing pain unpleasantness	18	2.285	0.035*
Pinprick-evoked pain intensity	18	2.657	0.016*
Pinprick-evoked pain unpleasantness	18	1.945	0.068
Wind-up-like pain, worst pain intensity	18	2.715	0.014*
Wind-up-like pain, worst pain unpleasantness	18	2.285	0.035*
Desire (M-VAS)			
Ongoing pain	18	-3.002	0.008*
Area of hyperalgesia	18	-2.429	0.026*
Pinprick-evoked pain	18	-0.794	0.437
Wind-up-like pain	18	-2.173	0.043*

*Statistically significant ($P < 0.05$).

Table 5

Interaction effects between dopamine, expectancy, and desire on the placebo effect (M-VAS) (N = 19).

	Numerator df	*Denominator df*	*F*	*P*
Dopamine*expectancy				
Ongoing pain intensity	2	37.985	1.512	0.233
Ongoing pain unpleasantness	2	36.425	2.434	0.102
Pinprick-evoked pain intensity	2	38.210	1.162	0.324
Pinprick-evoked pain unpleasantness	2	37.908	1.570	0.221
Wind-up-like pain, AUC	2	37.767	1.501	0.236
Wind-up-like pain, worst pain intensity	2	38.818	3.805	0.031*
Wind-up-like pain, worst pain unpleasantness	2	38.840	7.811	0.001*
Dopamine*desire				
Ongoing pain intensity	2	39.145	0.387	0.682
Ongoing pain unpleasantness	2	39.199	0.629	0.539
Area of hyperalgesia	2	39.152	1.087	0.347
Pinprick-evoked pain intensity	2	39.574	2.051	0.142
Pinprick-evoked pain unpleasantness	2	40.436	0.753	0.477
Wind-up-like pain, AUC	2	38.634	0.474	0.626
Wind-up-like pain, worst pain intensity	2	40.054	0.456	0.637
Wind-up-like pain, worst pain unpleasantness	2	40.161	0.456	0.637

Outcome variables: ongoing and evoked pain levels.

*Statistically significant ($P < 0.05$).

Table 6

Correlations (Spearman's r_s) between the difference in the placebo effect and expectancy/desire between the open lidocaine with administration of haloperidol and open lidocaine with administration of levodopa/carbidopa conditions (N = 19).

	Spearman's r_s	***P***
Expectancy (M-VAS)		
Ongoing pain intensity	0.213	0.381
Ongoing pain unpleasantness	0.309	0.197
Pinprick-evoked pain intensity	0.088	0.719
Pinprick-evoked pain unpleasantness	-0.089	0.718
Wind-up-like pain, worst pain intensity	-0.265	0.272
Wind-up-like pain, worst pain unpleasantness	-0.055	0.823
Desire (M-VAS)		
Ongoing pain intensity	-0.077	0.754
Ongoing pain unpleasantness	-0.105	0.668
Area of hyperalgesia	-0.141	0.565
Pinprick-evoked pain intensity	-0.004	0.986
Pinprick-evoked pain unpleasantness	0.119	0.628
Wind-up-like pain intensity	0.043	0.861
Wind-up-like pain unpleasantness	-0.109	0.658

As data were not normally distributed, the non-parametric Speaman's rho (r_s) test was calculated.

*Statistically significant ($P < 0.05$).