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# Specifying the nonspecific components of acupuncture analgesia

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ABSTRACT

It is well known that acupuncture has pain-relieving effects, but the contribution of specific and especially nonspecific factors to acupuncture analgesia is less clear. One hundred one patients who developed pain of $\geqslant 3$ on a visual analog scale (VAS, 0 to 10) after third molar surgery were randomized to receive active acupuncture, placebo acupuncture, or no treatment for 30 min with acupuncture needles with potential for double-blinding. Patients' perception of the treatment (active or placebo) and expected pain levels (VAS) were assessed before and halfway through the treatment. Looking at actual treatment allocation, there was no specific effect of active acupuncture ($P = .240$), but there was a large and significant nonspecific effect of placebo acupuncture ($P < .001$), which increased over time. Interestingly, however, looking at perceived treatment allocation, there was a significant effect of acupuncture ($P < .001$), indicating that patients who believed they received active acupuncture had significantly lower pain levels than those who believed they received placebo acupuncture. Expected pain levels accounted for significant and progressively larger amounts of the variance in pain ratings after both active and placebo acupuncture (up to 69.8%). This is the first study to show that under optimized blinding conditions, nonspecific factors such as patients' perception of and expectations toward treatment are central to the efficacy of acupuncture analgesia and that these factors may contribute to self-reinforcing effects in acupuncture treatment. To obtain an effect of acupuncture in clinical practice, it may therefore be important to incorporate and optimize these factors.



## 1. Introduction

It is well known that acupuncture may have a pain-relieving effect [32]. It is, however, less clear to what extent specific factors (eg, needle penetration), nonspecific placebo factors (eg, expectation of treatment efficacy), and confounding factors (eg, spontaneous remission) contribute to the reported efficacy of acupuncture [15,20,43]. Recent meta-analyses show equivocal effects of active vs placebo acupuncture [15,42], but moderate effects of placebo acupuncture vs no treatment. This observation suggests that placebo factors may play a role for the observed effect in acupuncture analgesia [7,8,13,18,29].

Because of the apparently large placebo component of acupuncture analgesia, there is a growing interest in specifying these nonspecific placebo factors [3,8,15,43]. Some studies show that patients' overall belief about acupuncture treatment may influence treatment outcome [19,22,43], and one study has directly documented that the perception of the treatment allocation (active vs placebo acupuncture) influences pain levels to a higher extent than actual treatment allocation [3]. Patients' perceived treatment allocation has, nevertheless, never been studied under optimized blinding conditions nor in relation to expectation, which is a key factor in placebo analgesic effects [21,24,27,39,40].

Recently acupuncture needles with optimized practitioner and patient blinding properties have been developed [34–36]. By using these needles, it may be possible to get a less biased understanding

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of how specific and nonspecific factors contribute to acupuncture analgesia. Also, a recent systematic review of expectancy and acupuncture analgesia has called for better ways of assessing expectancy [8]. Most studies use crude measures of expectancy (interviews, questionnaires, or 5-point Likert scales) and turn them into high vs low expectancy [2,5,6,16,17,19,22,31,33]. However, it may be more precise to record expected pain ratings on a visual analog scale (VAS) and compare these to actual pain ratings [21,27,39,40].

Expected pain levels are likely to change throughout the course of acupuncture treatment [8], but so far, to our knowledge, no studies have directly examined this aspect in the context of acupuncture. Expected pain levels have been shown to account for larger amounts of the variance in the late compared to the early phase of pharmacologically active or placebo treatments, thereby suggesting that expectancy may contribute to self-reinforcing placebo effects [10,38,40]. It would therefore be of interest to test the influence of expectancy on pain levels over time after active and placebo acupuncture treatments.

Patients undergoing surgical removal of 1 mandibular third molar were randomized to (1) active acupuncture, (2) placebo acupuncture, or (3) no treatment with acupuncture needles with potential for double blinding [34–36]. The patients' perception of the treatment (active vs placebo acupuncture) was recorded, and the patients' expected and actual pain levels were obtained to answer the following questions:

- Do specific (active minus placebo acupuncture) and nonspecific (placebo acupuncture minus no treatment) factors contribute to acupuncture analgesia?
- Does patients' perception of the treatment (active vs placebo acupuncture) influence the treatment outcome?
- Do expected pain levels contribute to the pain-relieving effect after active and placebo acupuncture, respectively?
- Do expected pain levels account for higher amounts of variance in pain levels in the late vs early phase of the treatment, thereby suggesting a self-reinforcing effect?

## 2. Methods

### 2.1. Patients

A total of 111 patients referred to surgical removal of 1 mandibular third molar at the Section of Oral and Maxillofacial Surgery and Oral Pathology, Department of Dentistry, Aarhus University, from September 2008 to July 2009, participated in the study. In order to be included in the study, patients had to have pain due to tooth removal, be $\geqslant$18 years of age, and be in good health, which was defined as risk groups I, II, or III according to the American Society of Anesthesiologists. The indications for surgical removal of 1 semi-impacted mandibular third molar were (1) recurring episodes of pericoronitis ($\geqslant$2 episodes), (2) caries or resorption of the second molar (distal surface), (3) unrestorable caries of the third molar, (4) progressive periodontitis of the second molar (distal surface) or third molar, or (5) other pathologic conditions related to the third molar.

Patients were excluded if they (1) had previous experience with acupuncture, (2) experienced pain < 3 on a VAS (0 to 10) [9] 4 h after surgery, (3) had to take rescue medication during the study period, (4) had a pain disorder that may interfere with the measurement of pain, (5) were medicated 24 h before the experiment, (6) were pregnant or breast-feeding, or (7) had local dental or other medical or psychiatric disorders that prevented them from participating in the study. All patients provided signed informed consent and were compensated with 70€ (500 DKK) for participating in the study. The study was approved by the local ethical committee for the Central Denmark Region (M-20070270).

### 2.2. Procedure

The study took place at the Department of Dentistry, Aarhus University, Denmark. Before the study, a research assistant (SB) informed the patients about the study and introduced them to the pain rating scales. The surgery started at 9 AM. Immediately after surgery, the patients were asked to rate their pain intensity and pain unpleasantness, after which the experimenter, wearing a white coat, escorted them to an examination room at the research clinic. The patients' pain intensity and pain unpleasantness were monitored every 15 min. No external stimuli other than orange juice and ice cream were allowed during the study. Patients were informed that they would be randomized to 1 of 3 groups: active acupuncture, placebo acupuncture, or a message of no treatment. Patients were then randomized to one of these treatments by drawing a number that corresponded to a sealed envelope containing either of these treatments (treatment group could not be recognized by handling the sealed envelope).

During the treatment, 2 examiners were involved: an acupuncturist and a research assistant. Both were blinded to the type of acupuncture given. In the 2 treatment groups, the patients were introduced to the acupuncturist and invited to lie down comfortably in a horizontal dental chair. The acupuncturist spent approximately 15 min establishing rapport with each patient, inquiring about his or her pain and general well-being. During this conversation, the acupuncturist stated, *"Acupuncture treatment has been shown to effectively reduce pain after surgical removal of mandibular third molars in some patients."*

At the beginning of the treatment (−2 min, ie, right before the treatment was initiated), the research assistant asked the patients about their current pain intensity and pain unpleasantness, and subsequently about the patients' expected pain intensity and pain unpleasantness during the treatment (Fig. 1). At time point 0, the acupuncturist applied the needles in the designated points and rotated the needles manually. Halfway through the study (at 13 min), the research assistant again asked the patients about their current pain intensity and pain unpleasantness, and subsequently about the patients' expected pain intensity and pain unpleasantness levels during the remainder of the session. At the time point of 15 min, the acupuncturist rotated the needles manually. Near the end of the study (28 min), the research assistant asked the patients about their current pain intensity and pain unpleasantness. At the time point of 30 min, the acupuncturist rotated the needles manually and removed the needles.

The period from −2 to 13 min were conceptualized as the early part of the study, whereas the period from 13 to 30 min were conceptualized as the late part of the study, which is in agreement with previous studies [40]. Once the treatment was terminated,

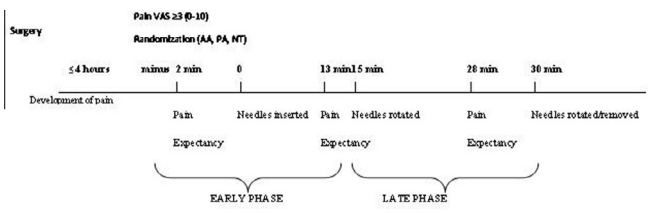


**Fig. 1.** Experimental design. Patients who developed pain levels of $\geqslant$3 (0 to 10) up to 4 h after surgical removal of 1 mandibular third molar were randomized to receive active acupuncture (AA), placebo acupuncture (PA), or no treatment (NT) for 30 min. Before the treatment (−2 min), halfway through the treatment (13 min), and at the end of the treatment (28 min), actual pain levels and expected pain levels for subsequent time points were measured. Needles were rotated at insertion, at 15 min, and at 30 min when they were removed.

the patients were asked which treatment they believed they had received (active or placebo acupuncture). If the patients found it necessary, they were offered rescue medication (ibuprofen, 600 mg, or paracetamol, 1000 mg).

The research assistant, the acupuncturist, and the patients were not informed whether active or placebo acupuncture was administered. In the no-treatment group, the patients were also asked to lie down comfortably in a horizontal dental chair, and the research assistant obtained the same measures at the same time points. Because no treatment was given, the acupuncturist was not present, and it was evident for everyone that the patients had been assigned to the no-treatment group.

### 2.3. Materials and methods

#### 2.3.1. Local analgesia and surgery

Before surgery, the patients received local analgesia with lidocaine (20 mg/mL) with adrenaline (12.5 μg/mL) (Xyloplyin Dental Adrenalin, Dentsply, Surrey, England). The standard dose was 2 mL for the inferior alveolar and lingual nerves, 1 mL for the buccal nerve, and 1 mL for infiltration buccally. If the patients found it necessary, they received additional local analgesia during the surgical procedure.

The third molar was removed using a standardized surgical approach. In brief, a full-thickness mucoperiosteal flap was elevated and buccal/distal bone was removed with a burr under sterile saline irrigation. The tooth was removed in one piece or several pieces after sectioning with a burr, also under sterile saline irrigation. Inflammatory tissue and sharp bony edges were removed before meticulous irrigation of the socket and the operation field. Finally, the flap was repositioned and sutured using 2 or 3 resorbable sutures (Vicryl 4-0, Ethicon, Norderstedt, Germany). Most teeth (96%) were removed by dental students under supervision of oral and maxillofacial surgeons or dentists with special training in oral surgery. A few teeth (4%) were removed by oral and maxillofacial surgeons or dentists with special training in oral surgery.

#### 2.3.2. Active acupuncture

Active acupuncture was performed with potentially double-blind penetrating needles (Hanada College, Japan School of Acupuncture) (Fig. 2) [35].

#### 2.3.3. Placebo acupuncture

Placebo acupuncture was performed with potentially double-blind nonpenetrating needles (Hanada College, Japan School of Acupuncture) (Fig. 2) [35].

#### 2.3.4. Acupuncture points

The acupuncture needles (both active and placebo acupuncture) were inserted in the following positions: ST44, LI4, ST7, ST6, and TE17 (Fig. 2). The acupuncture points LI4, ST7, ST6, and TE17 have previously been used in studies on dental pain after surgical removal of mandibular third molars [3], and ST44 is considered helpful for toothache and facial pain [23,37,44]. All acupuncturists agreed with the selection of acupuncture points.

#### 2.3.5. Acupuncturist and interaction with patients

The majority of the acupuncture sessions (63 of 67) were performed by 4 acupuncturists trained at the Aarhus Acupuncture Academy, Aarhus, Denmark, and licensed as registered alternative practitioners. The remaining 5 sessions were performed by 2 acupuncturists from the same academy and with the same qualifications. All acupuncturists had at least 5 years of experience practicing acupuncture. Before the study, the acupuncturists, the research assistant, and the principal investigator (LV) agreed on and practiced standardized ways of interacting with the patients in an empathic and professional manner [15]. The acupuncturists interacted with the patients at the beginning of the study where they established rapport and inserted the needles, halfway through the study when the needles were rotated, at the end of the study when the needles were rotated and removed. In between these time points, the acupuncturists stepped outside the room, which is in accordance with standard practice and minimizes potential bias.

### 2.4. Measures

#### 2.4.1. Pain measures

Perceived pain intensity and pain unpleasantness were rated on a mechanical visual analog scale (M-VAS) [25]. Patients were instructed how to rate both pain intensity and pain unpleasantness according to standardized written statements described in detail elsewhere [25]. The experience of pain consists of a sensory (intensity) and an affective (unpleasantness) dimension, which may be experienced differently [26]. Verbal anchors serve to establish the distinction between these 2 pain dimensions. To the left, the M-VAS sensory scale was anchored by the descriptors "no pain sensation" and to the right by "the most intense pain sensation imaginable." Likewise, the M-VAS unpleasantness scale was anchored by the descriptors "not at all unpleasant" and "the most unpleasant imaginable."

#### 2.4.2. Expectancy measures

Ratings of expected pain intensity and pain unpleasantness were obtained using the same M-VAS scales that were used for measuring actual pain intensity and unpleasantness. Expected pain intensity was measured by asking the patients, *"What do you expect your level of pain intensity to be?"* Expected pain unpleasantness was measured by asking the patients, *"What do you expect your level of pain unpleasantness to be?"* The scales for rating expected pain intensity and unpleasantness have been validated and have previously been used in studies of placebo analgesia [4,21,27,28,39].

#### 2.4.3. Perception of treatment allocation

Measurement of perceived treatment allocation was obtained by asking patients, "*Which treatment do you believe that you received (active or placebo acupuncture)?*"

### 2.5. Statistical analyses

#### 2.5.1. Comparisons of patients and surgery

To test whether the 3 groups (active acupuncture, placebo acupuncture, and no treatment) were comparable with respect to gender, ethnicity (white, Asian), work status (receiving public benefits, unskilled worker, student, "medium-cycle" higher education, or "long-cycle" higher education), and the surgeon removing the third molar (student or oral and maxillofacial surgeon/dentist), chi-square analyses were conducted. To test whether the 3 groups were comparable with respect to age, dose of preoperative analgesia, dose of intraoperative analgesia, and time until development of pain intensity and pain unpleasantness (VAS $\geqslant$3), 1-way analysis of variance (ANOVA) analyses were conducted with group as factor and the remaining variables as dependent variables.

#### 2.5.2. Comparisons of treatment groups

In order to examine whether there was a specific effect of acupuncture as well as a nonspecific placebo effect, repeated-measure analyses of variance (ANOVA) were conducted with pain at the different time points (pain intensity and pain unpleasantness at −2, 13, and 28 min) as within-subject variables and group (active acupuncture, placebo acupuncture, and no treatment) as between-subject variable. Least significant difference (LSD) served as post hoc

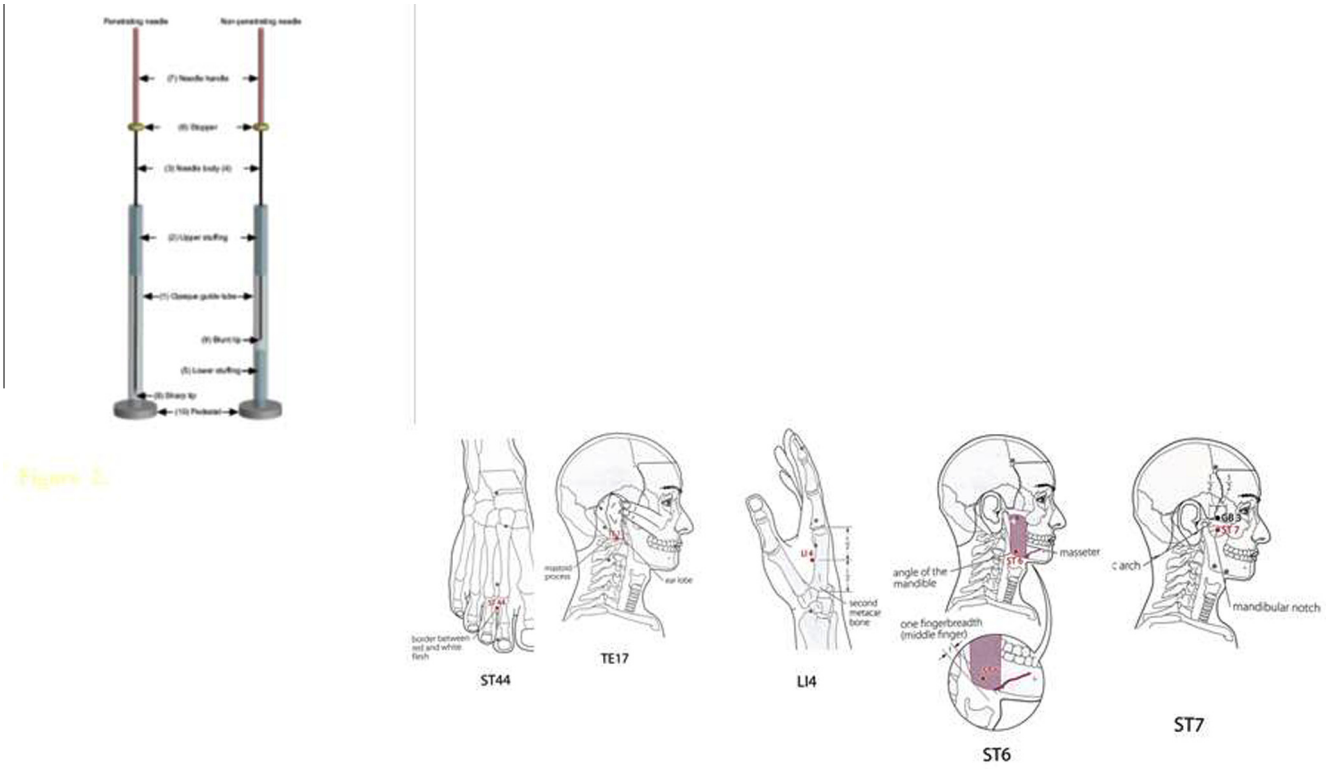


**Fig. 2.** Active and placebo acupuncture needles as well as the acupuncture points. Each needle assembly comprises an opaque guide tube (1) and upper stuffing (2) to provide resistance to the needle body during its passage through the guide tube. The body of penetrating needle (3) is longer than the guide tube by an amount equal to the insertion depth, but the body of the nonpenetrating needle (4) is only long enough to allow its blunt tip to press against the skin when the needle body is advanced to its limit. The nonpenetrating needle contains stuffing at the bottom as well (5) to give a sensation similar to that of skin puncture and tissue penetration. Both needles have a stopper (6) that prevents the needle handle (7) from advancing further when the sharp tip of the penetrating needle (8) or the blunt tip of the nonpenetrating needle (9) reaches the specified position. The pedestal (10) on each needle is adhesive, allowing it to adhere firmly to the skin surface. The diameter of the needles used in this study was 0.16 mm.

test, and the interaction between pain at different time points and groups was tested. In case of an interaction between pain at different time points and groups, *t* tests for independent samples were used to compare groups (active and placebo acupuncture) at different time points of pain (−2, 13, and 28 min) and *t* tests for paired samples were used to compare time points of pain (−2 to 13 min as well as 13 to 28 min) within the active acupuncture and the placebo acupuncture groups, respectively. Bonferroni corrections ($P = .05/3 = 0.017$ and $P = .05/2 = 0.025$ for independent and dependent *t* tests respectively) were used to control for multiple comparisons.

The data were analyzed according to the *actual* group allocation (patients who received active acupuncture, placebo acupuncture, and no treatment) as well as according to the *perceived* group allocation (patients who believed they received active acupuncture or placebo acupuncture, respectively). The perceived group allocation did not include the no-treatment group because these patients knew that they were not receiving any treatment.

*2.5.3. Expected pain levels*

Means and standard deviations were calculated for expected pain intensity and expected pain unpleasantness at all time points (−2, 13, and 28 min). Paired-sample *t* tests were used to test if expected pain levels were different at different time points (−2 to 13 min and 13 to 28 min) in the active acupuncture group and in the placebo acupuncture group. Bonferroni correction ($P = .005/2 = 0.025$) was applied to control for multiple comparisons.

To test whether expected pain levels contributed to pain, linear regression analyses were conducted with expected pain intensity and expected pain unpleasantness at the different time points as the independent variable and pain intensity and pain unpleasantness scores at the different time points as dependent variables. The analyses were conducted in 3 ways: (a) overall: expected pain levels at −2 min vs average pain during the entire session, (b) early phase: expected pain levels at −2 min vs pain at 13 min, and (c) late phase: expected pain levels at 13 min vs pain at 28 min. All analyses were conducted for both active acupuncture and placebo acupuncture groups as well as in relation to actual treatment allocation and perceived treatment allocation.

To test whether expected pain levels contributed differently to active and placebo acupuncture, regression coefficients were compared using a traditional normality test using pooled standard deviations.

*2.5.4. Acupuncturists*

To test whether the 4 acupuncturists differed with respect to the patients' mean pain intensity and pain unpleasantness after active acupuncture and placebo acupuncture a 2-way ANOVA was performed where the dependent variable was mean pain and the factors were group and acupuncturist. The analysis was conducted both for pain intensity and pain unpleasantness.

There were only few missing data (less than 2%), and in case of missing data only patients who had missing data for the actual analyses were excluded.

The SPSS program version 19 was used, and $P < .05$ was considered significant. The results are expressed in mean values ± SD.

## 3. Results

*3.1. Characteristics of patients and surgical procedure*

Ten patients did not develop pain (VAS $\geqslant 3$) 4 h after the surgical procedure, and they were therefore not included in the study.

Consequently, 101 were enrolled in the study and none of these patients were subsequently excluded. There were no significant between-group differences for gender, age, ethnicity, work status, category of surgeon, dose of local analgesia before the surgery, dose of local analgesia intraoperatively, time to development of pain intensity, and time to development of pain unpleasantness (all $P > .113$). Thus, the 3 groups seem comparable.

Almost all patients were white (98%), and there was a close to equal distribution of men and women (52.5% women). The majority of the patients were students (66.3%), and the average age was 25.5 (4.6) years. The average dose of the local analgesia before surgery was 4.35 (1.0) mL and the average intraoperative dose was 2.66 (1.3) mL. The average time to development of pain intensity $\geqslant 3$ was 59.6 (33.8) min, and the average time until development of pain unpleasantness $\geqslant 3$ was 59.0 (33.4) min.

### 3.2. Magnitude of active and placebo acupuncture analgesia

#### 3.2.1. Actual treatment allocation

For pain intensity, there was a significant interaction between pain at different time points (−2, 13, and 28 min) and treatment groups ($F(4,196) = 16.31$, $P < .001$). The post hoc test and visual inspection of Fig. 3a showed a significant difference between the no-treatment group on the one hand and the active and placebo acupuncture groups on the other (all $P < .001$). A similar analysis involving only active and placebo acupuncture groups showed no interaction effect ($F(1,65) = 0.784$, $P = .784$), no effect of pain at the different time points ($F(2,130) = 0.436$, $P = .648$), and no difference between active and placebo acupuncture ($F(1,65) = 1.409$, $P = .240$). Effect sizes in Table 1 and visual inspection of Fig. 3a showed that the nonsignificant effect of active acupuncture (active vs placebo acupuncture) was moderate (just above small) throughout the test period whereas the significant analgesic effect of placebo acupuncture (placebo acupuncture vs no treatment) increased from small to large during the test period.

Similar results were obtained for pain unpleasantness for which there was a significant interaction between pain (−2, 13, and 28 min) and treatment group ($F(4,196) = 16.89$, $P < .0005$). The post hoc test and visual inspection of Fig. 3b showed a significant difference between the no-treatment group on the one hand and the active and placebo acupuncture groups on the other (all $P < .002$). A similar analysis involving only active and placebo acupuncture groups showed no interaction effect ($F(2,130) = 0.036$, $P = .965$), no effect of pain at the different time points ($F(1,65) = 0.193$, $P = .662$), and no effect of group ($F(1,65) = 0.193$, $P = .662$). Effect sizes in Table 1 and a visual inspection of Fig. 3b showed that the nonsignificant effect of active acupuncture (active vs placebo acupuncture) was small throughout the test period, whereas the significant effect of placebo acupuncture (active vs placebo acupuncture) increased from small to large during the test period.

#### 3.2.2. Perceived treatment allocation

For pain intensity there was a significant interaction between pain at the different time points (−2, 13, and 28 min) and group ($F(2,128) = 9.21$, $P < .001$). Independent sample $t$ test showed that there was no significant difference between active acupuncture and placebo acupuncture at −2 min ($t(64) = -1.362$; $P = .178$), whereas there were significant differences between the 2 groups at 13 min ($t(64) = -2{,}849$; $P = .006$) and 28 min ($t(64) = -3.500$, $P = .001$). Paired-sample $t$ test for the active acupuncture group showed a significant difference in pain intensity levels from −2 to 13 min ($t(35) = 2{,}542$, $P = .016$), whereas there were no significant difference in pain intensity levels from 13 to 28 min ($t(35) = 0.494$, $P = .624$). In the placebo acupuncture group there was no significant difference in pain intensity levels from 2 to 13 min ($t(29) = -1.604$, $P = .120$) or from 13 to 28 min ($t(29) = -1.777$, $P = .086$). Effect sizes in Table 1 and a visual inspection of Fig. 3c showed that the significant effect of perceived active acupuncture (perceived active vs perceived placebo acupuncture) increased from medium to large during the test period.

Similar results were obtained for pain unpleasantness in so far as there was a significant interaction between pain (−2, 13, and 28 min) and group ($F(2,128) = 7.95$, $P = .001$). Independent sample $t$ test showed that there was no significant difference between active acupuncture and placebo acupuncture at −2 min ($t(64) = -1.872$, $P = .066$), whereas there were significant differ-

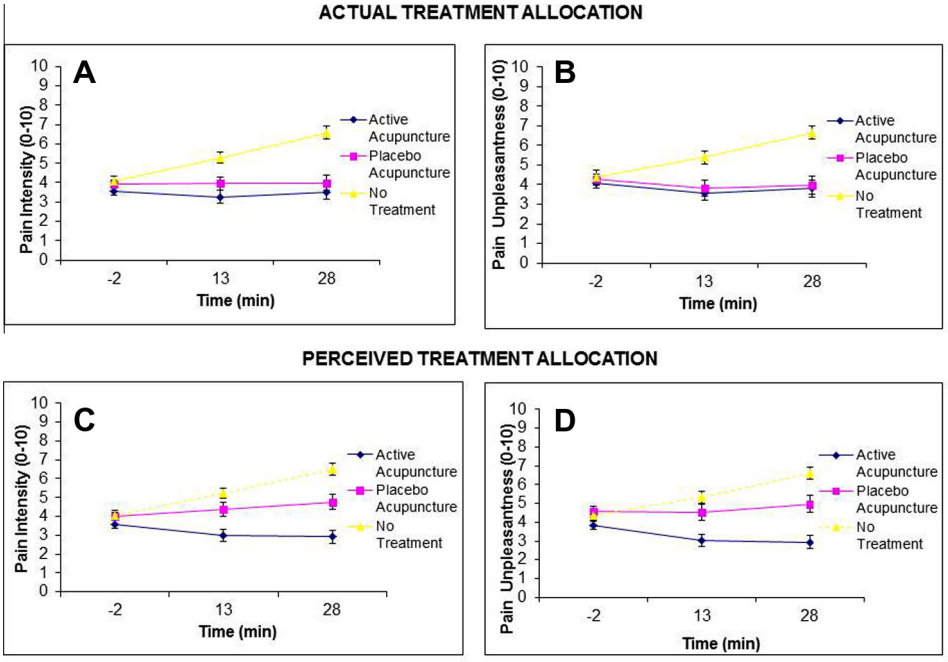


**Fig. 3.** Comparisons of treatment groups. Comparison of pain intensity and pain unpleasantness in active acupuncture, placebo acupuncture, and no-treatment groups during the 30 min of treatment. Data are shown for both actual and perceived treatment allocation. (A) actual treatment, pain intensity. (B) Actual treatment, pain unpleasantness. (C) Perceived treatment, pain intensity. (D) Perceived treatment, painunpleasantness.

**Table 1**
Pain ratings in the treatment conditions as well as effect sizes of active and placebo acupuncture.

| Condition | −2 min Mean | SD | 13 min Mean | SD | 28 min Mean | SD | | −2 min d | 13 min d | 28 min d |
|---|---|---|---|---|---|---|---|---|---|---|
| Actual group allocation | | | | | | | | | | |
| *Pain intensity* | | | | | | | | | | |
| Active acupuncture | 3.57 | 1.16 | 3.27 | 1.93 | 3.53 | 2.27 | Effect of active acupuncture | 0.30 | 0.34 | 0.39 |
| Placebo acupuncture | 3.91 | 1.13 | 3.95 | 2.12 | 4.00 | 2.32 | Effect of placebo acupuncture | 0.12 | 0.72 | 1.18 |
| No treatment | 4.08 | 1.58 | 5.29 | 1.58 | 6.57 | 2.00 | | | | |
| *Pain unpleasantness* | | | | | | | | | | |
| Active acupuncture | 4.05 | 1.31 | 3.55 | 2.00 | 3.80 | 2.51 | Effect of active acupuncture | 0.14 | 0.12 | 0.06 |
| Placebo acupuncture | 4.27 | 1.73 | 3.81 | 2.43 | 3.96 | 2.66 | Effect of placebo acupuncture | 0.06 | 0.71 | 1.14 |
| No treatment | 4.38 | 2.00 | 5.40 | 2.00 | 6.65 | 2.01 | | | | |
| Perceived group allocation | | | | | | | | | | |
| *Pain intensity* | | | | | | | | | | |
| Active acupuncture | 3.57 | 1.25 | 3.01 | 1.88 | 2.93 | 2.10 | Effect of active acupuncture | 0.34 | 0.70 | 0.85 |
| Placebo acupuncture | 3.99 | 1.23 | 4.38 | 2.04 | 4.77 | 2.22 | | | | |
| *Pain unpleasantness* | | | | | | | | | | |
| Active acupuncture | 3.85 | 1.51 | 3.02 | 1.87 | 2.94 | 2.19 | Effect of active acupuncture | 0.46 | 0.71 | 0.81 |
| Placebo acupuncture | 4.55 | 1.53 | 4.53 | 2.37 | 4.98 | 2.62 | | | | |

d = Cohen's *d:* <0.02 = 0.05 > 0.08
In the actual group allocation, pain intensity and pain unpleasantness ratings are reported for active acupuncture, placebo acupuncture, and no treatment groups at −2 min, 13 min, and 28 min. Also, the effect sizes for active acupuncture and placebo acupuncture, respectively, for the 3 time points are presented.
In the perceived group allocation, pain intensity and pain unpleasantness ratings are reported for active acupuncture and placebo acupuncture (ratings in the no treatment group are similar to the actual group allocation) at −2 min, 13 min, and 28 min. In addition, the effect size for active acupuncture at all 3 time points is presented.

ences between the 2 groups at 13 min ($t(64) = -2.890$, $P = .005$) and 28 min ($t(64) = -3{,}440$, $P = .001$). Paired-sample $t$ test for the active acupuncture group showed a significant difference in pain unpleasantness levels from −2 to 13 min t(35) = 0.5745, $P < .001$, whereas there was no significant difference in pain unpleasantness levels from 13 to 28 min ($t(35) = -1.860$, $P = .071$). In the placebo acupuncture group there was no significant difference in pain unpleasantness from 2 to 13 min ($t(29) = 1{,}034$, $P = .310$), but there was a significant difference from 13 to 28 min ($t(29) = -2{,}654$, $P = .013$). Effect sizes in Table 1 and a visual inspection of Fig. 3d showed that the significant effect of perceived active acupuncture (perceived active acupuncture vs perceived placebo acupuncture) increased from medium to large during the test period.

### 3.3. Expected pain levels

#### 3.3.1. Description of expected pain ratings

Means and standard deviations for expected pain intensity and expected pain unpleasantness levels at all time points (−2, 13, 28 min) are shown in Table 2. Paired-sample $t$ test, corrected for multiple comparisons, generally showed that expected pain ratings did not increase significantly over time (from −2 to 13 min and from 13 to 28 min) in neither the active acupuncture nor the placebo acupuncture group (all $P > .019$, data not shown). The only exceptions were: expected pain unpleasantness from 13 to 28 min in the active acupuncture group for actual group allocation ($P = .008$) and expected pain intensity from −2 to 13 min in the placebo acupuncture group for perceived group allocation ($P = .004$).

#### 3.3.2. Regression analyses between expected pain levels and pain in actual treatment allocations

Expected pain intensity levels contributed significantly to pain intensity levels in all 3 analyses: (1) overall—expected pain at −2 min vs average pain, (2) early phase—expected pain at −2 min vs pain at 13 min, and (3) late phase—expected pain at 13 min vs pain at 28 min. Expected pain intensity accounted for larger amounts of the variance in the late phase compared to the early phase of the study (Table 3).

Expected pain unpleasantness levels also contributed significantly to pain unpleasantness levels in all 3 analyses: (1) overall—expected pain at −2 min vs average pain, (2) early phase—expected pain at −2 min vs pain at 13 min, and (3) late phase—expected pain at 13 min vs pain at 28 min. Expected pain unpleasantness accounted for larger amounts of the variance in the late phase compared to the early phase of the study (Table 3).

#### 3.3.3. Regression analyses between expected pain levels and pain in perceived treatment allocations

Expected pain intensity levels contributed significantly to pain intensity levels in all 3 analyses: (1) overall—expected pain at −2 min vs average pain, (2) early phase—expected pain at −2 min vs pain at 13 min, and (3) late phase—expected pain at 13 min vs pain at 28 min. Expected pain intensity accounted for larger amounts of the variance in the late phase compared to the early phase of the study (Table 3).

Expected pain unpleasantness levels also contributed significantly to pain unpleasantness levels in all 3 analyses: (1) overall—expected pain at −2 min vs average pain, (2) early phase—expected pain at −2 min vs pain at 13 min, and (3) late phase—expected pain at 13 min vs pain at 28 min. Expected pain unpleasantness accounted for larger amounts of the variance in the late phase compared to the early phase of the study (Table 3).

There were no significant differences between the contribution of expected pain levels after active and placebo acupuncture treatments in actual or perceived group allocations ($P > .893$).

### 3.4. Acupuncturist and patients' pain levels after active and placebo acupuncture

With respect to pain intensity, there was no significant interaction between acupuncturists and treatment groups ($F(3,54) = 0.312$, $P = .816$). Also, there was no significant effect of group (active vs placebo acupuncture) ($F(3,54) = 0.778$, $P = .382$) or acupuncturists ($F(3,54) = 0.170$, $P = .916$).

Similar results were obtained for pain unpleasantness where there was no significant interaction between acupuncturist and treatment groups ($F(3,54) = 0.190$, $P = .903$). Also there was no effect of group ($F(3,54) = 0.043$; $P = .836$) and acupuncturists ($F(3,54) = 0{,}699$, $P = .556$). Apart from confirming the main finding of no significant difference between active and placebo acupuncture, the results indicate that the different acupuncturists had similar effects of active and placebo acupuncture.

## 4. Discussion

To our knowledge, this is the first study to show that under optimized blinding conditions, no specific effect of acupuncture could be identified, but a rather large nonspecific placebo effect that increased over time was revealed. Interestingly, it was possible to specify at least some of the nonspecific factors contributing to pain relief after active or placebo acupuncture treatment. Patients who believed they received active acupuncture had significantly lower pain levels than those who believed they received placebo acupuncture. Also, expected pain levels accounted for large and significant amounts of the variance in pain ratings after both active and placebo acupuncture. Furthermore, expected pain levels accounted for larger amounts of the variance in pain ratings in the late vs early phase of the study, thereby suggesting that expectations may contribute to a self-reinforcing analgesic effect in relation to acupuncture treatment.

### 4.1. Actual vs perceived effect of acupuncture

In the *actual* treatment allocation, no significant difference was found between active and placebo acupuncture which corroborates previous findings [7,8,13,18,20,29] and shows that even when needles with optimized doubling-blinding properties are used [34–37], there is no specific effect of acupuncture. This finding suggests that the pain-relieving effect of acupuncture does not come from penetration of acupuncture needles into specific acupuncture points as it has been suggested in acupuncture treatment [14,36]. However, a large and significant nonspecific placebo effect was found.

Interestingly, in the *perceived* treatment allocation a significant difference was found between active and placebo acupuncture, thereby indicating that patients who believed they received active acupuncture reported significantly lower pain levels compared to patients who believed that they received placebo acupuncture. In fact, patients who believed they received active acupuncture experienced a significantly decreased pain intensity and pain unpleasantness over time, whereas patients who believed they received placebo acupuncture experienced an increase in pain unpleasantness over time. These results corroborate findings by Bausell et al. [3] by showing that beliefs about treatment allocation seem to be more important for pain relief than the actual treatment and by illustrating that these beliefs may influence the temporal development of pain.

In the present study, patients were asked about perceived treatment allocation once the treatment (and not just the insertion of needles) was completed in order not to interfere with the psychological measures obtained throughout the study. Hence, it is possible that patients who experienced low pain levels believed that they received active acupuncture, whereas patients who experienced high pain levels believed they received placebo acupuncture. However, this interpretation is contradicted by the finding that the patients' pain levels (measured at −2, 13, and 28 min) and their experience of the needle (measured immediately after insertion of the needles) did not significantly influence the assessment of treatment allocation (personal communication). Furthermore, in the study by Bausell et al. [3], patients were asked about perceived treatment allocation right after the administration of the experimental condition and similar results were obtained. Thus, the present study suggests that nonspecific factors such as patients' perception of the treatment influence treatment outcome to a higher extent than specific factors such as needle penetration.

**Table 2**
Expected pain levels in active and placebo acupuncture conditions.

| Condition | −2 min | | 13 min | | 28 min | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| Actual group allocation | | | | | | |
| *Active acupuncture* | | | | | | |
| Expected pain intensity | 2.73 | 1.48 | 3.11 | 1.90 | 4.33 | 1.16 |
| Expected pain unpleasantness | 2.78 | 1.71 | 3.20 | 2.04 | 3.86 | 2.57 |
| *Placebo acupuncture* | | | | | | |
| Expected pain intensity | 3.12 | 1.54 | 3.34 | 2.67 | 3.00 | 1.79 |
| Expected pain unpleasantness | 3.08 | 1.77 | 3.35 | 2.48 | 3.87 | 2.64 |
| Perceived group allocation | | | | | | |
| *Active acupuncture* | | | | | | |
| Expected pain intensity | 2.79 | 1.43 | 2.52 | 1.83 | 3.00 | 1.79 |
| Expected pain unpleasantness | 2.58 | 1.55 | 2.49 | 1.72 | 2.92 | 2.16 |
| *Placebo acupuncture* | | | | | | |
| Expected pain intensity | 3.16 | 1.61 | 4.07 | 2.12 | 4.33 | 1.16 |
| Expected pain unpleasantness | 3.37 | 1.90 | 4.22 | 2.54 | 5.00 | 2.67 |

Expected pain intensity and expected pain unpleasantness levels in active and placebo acupuncture groups are listed at -2 min, 13 min, and 28 min for both actual and perceived group allocation.

### 4.2. Expected pain levels

Expected pain levels accounted for large and significant amounts of the variance in pain levels after both actual and perceived active and placebo acupuncture treatment. This is in agreement with some previous studies [16,17,19,22,33] and in contrast with others [2,5,6,31]. The main difference between the previous and the current findings is the use of specific VAS measures of expected pain levels allowing a precise and quantifiable estimation of the contribution of expected pain levels. In the present study, expected pain levels accounted for 25.7% and 23.1% of the variance in pain intensity and pain unpleasantness, respectively, after active acupuncture, and for 27.7% and 38.4% of the variance in pain intensity and pain unpleasantness, respectively, after placebo acupuncture. No significant difference was found in the contribution of expected pain levels to active and placebo acupuncture treatment, and consequently no significant interaction was seen between expected pain levels and active vs placebo acupuncture treatment. These results are in agreement with findings in relation to pharmacological studies in which expected pain levels have also been shown to contribute equally to lidocaine and placebo treatments [10,39,40]. Furthermore, the findings illustrate that placebo factors contribute to the efficacy of both active and placebo treatments not only in traditional biomedical treatments [1,4], but also in complementary and alternative treatments.

To our knowledge, this is the first study to investigate the contribution of expected pain levels throughout the course of the treatment. Strikingly, expected pain levels accounted for larger amounts of the variance in the late phase of the study (active acupuncture: 69.8% and 65.4% of the variance in pain intensity and pain unpleasantness, respectively; placebo acupuncture: 49.3 % and 69.0% of the variance in pain intensity and pain unpleasantness, respectively) compared to the early phase of the study (active acupuncture: 16.2% and 19.3% of pain intensity and pain unpleasantness, respectively; placebo acupuncture: 21.2% and 34.2% of pain intensity and pain unpleasantness, respectively). This is in agreement with previous studies showing that expected pain levels may contribute to self-reinforcing placebo effects in relation to pharmacological treatments [10,40,41]. In line with previous studies, these findings suggest that verbal suggestions given for pain relief at the beginning of the study *("Acupuncture treatment has been shown to effectively reduce pain after surgical removal of mandibular third molars in some patients")* may lead patients to generate expectations of low pain levels. This psychological mindset

**Table 3**
Contribution of expected pain levels to pain in active and placebo acupuncture conditions.[a]

| Condition | Overall | | | Early | | | Late | | |
|---|---|---|---|---|---|---|---|---|---|
| | *B* | $R^2$ | *P* | *B* | $R^2$ | *P* | *B* | $R^2$ | *P* |
| Actual group allocation | | | | | | | | | |
| *Active acupuncture* | | | | | | | | | |
| Expected pain intensity | 0.569 | 0.257 | .003 | 0.525 | 0.162 | .022 | 0.999 | 0.698 | <.001 |
| Expected pain unpleasantness | 0.515 | 0.231 | .005 | 0.509 | 0.193 | .012 | 0.993 | 0.654 | <.001 |
| *Placebo acupuncture* | | | | | | | | | |
| Expected pain intensity | 0.602 | 0.277 | .001 | 0.633 | 0.212 | .005 | 0.719 | 0.493 | <.001 |
| Expected pain unpleasantness | 0.744 | 0.384 | <.001 | 0.802 | 0.342 | <.001 | 0.893 | 0.690 | <.001 |
| Perceived group allocation | | | | | | | | | |
| *Active acupuncture* | | | | | | | | | |
| Expected pain intensity | 0.547 | 0.238 | .003 | 0.448 | 0.116 | .042 | 0.824 | 0.593 | <.001 |
| Expected pain unpleasantness | 0.456 | 0.167 | .013 | 0.402 | 0.111 | .047 | 0.963 | 0.571 | <.001 |
| *Placebo acupuncture* | | | | | | | | | |
| Expected pain intensity | 0.578 | 0.311 | .001 | 0.664 | 0.276 | .003 | 0.731 | 0.488 | <.001 |
| Expected pain unpleasantness | 0.675 | 0.392 | <.001 | 0.762 | 0.371 | <.001 | 0.848 | 0.671 | <.001 |

*B*, unstandardized beta coefficient; $R^2$, regression coefficient; $P < .05$.

[a] Regression analyses show the contribution of expected pain intensity and expected pain unpleasantness levels at a given time point to experienced pain intensity and unpleasantness levels at a subsequent time point. Overall indicates expected pain levels at −2 min seen in relation to the average pain ratings during the 30-min test period; early, expected pain levels at −2 min in relation to pain levels at 13 min; and late, expected pain levels at 13 min in relation to pain levels at 28 min.

may in itself contribute to actual low pain levels measured halfway through the study. The actual experience of low levels of pain may then further stimulate expectations of low pain levels and thereby contribute to continued low pain levels in the late part of the session.

The important question is the amount of time the increasing analgesic effect will continue. Some studies have shown that the effect of acupuncture peaks 1 to 2 days after the actual treatment [32]. In the present study, we followed the patients' expected pain levels, pain levels, and use of rescue medication for 7 days after surgery, but the heterogeneous use of rescue medication complicated the interpretation of the data. In future studies, it will be relevant to test to which extent expected pain levels contribute to the pain-relieving effect several days after administration of active and placebo acupuncture, preferably within a design with a minimum use of rescue medication.

Recent studies show that the acupuncturist's expression of empathy as well as verbal suggestions provided for pain relief may influence the magnitude of active and placebo acupuncture treatments [15,17,33,43]. In the present study, the above factors were not directly manipulated; however, the acupuncturists were trained in expressing empathy, and patients were given positive verbal suggestions for pain relief, which, taken together, may have facilitated the patients' perception of the treatment and expectations toward the treatment. In contrast to a recent study [43], there was no difference in treatment efficacy across the 4 acupuncturists in the present study, which may at least in part be explained by the joint training and the homogeneous education of the acupuncturists participating in the study.

In this study with optimized blinding conditions and rigorous measures of expected pain levels, it was evident that expectancy is central to the efficacy of acupuncture analgesia. Thus, along the lines of previously published studies [11–13,30], it may be speculated to what extent patients' expectations may have biased the apparent analgesic effect of acupuncture reported in studies where patients' expectations are not considered in the selection of patients, measured during the study, or accounted for in the interpretations of the results.

### 4.3. Clinical implications

The present study suggests that patients' perception of a treatment together with their expectations toward treatment efficacy may be the best way to optimize analgesia in relation to acupuncture treatment. This finding is in agreement with recent studies showing that manipulation of nonspecific factors may markedly increase the effect of acupuncture analgesia [3,8,15,43].

The fact that a treatment effect can be optimized by focusing on patients' overall perception of the treatment and expectations toward the treatment is well known from the pharmacological literature [1,4]. Nevertheless, one important difference between pharmacological and acupuncture treatment may be that needle penetration produces small or no specific effects [15,42]. Hence, if acupuncture needling is implemented in a traditional biomedical treatment setting, as it has been done to a higher extent in present years, awareness of patients' perception of the treatment and their expectations toward the treatment may be pivotal in order to obtain an effect of the treatment.

## Conflict of interest statement

The authors report no conflict of interest.

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