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Evaluating the Effects of Acupuncture Using a Dental Pain Model in Healthy Subjects – A Randomized, Cross-Over Trial

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Abstract: **Acupuncture is a complementary and nonpharmacological intervention that can be effective for the management of chronic pain in addition to or instead of medication. Various animal models for neuropathic pain, inflammatory pain, cancer-related pain, and visceral pain already exist in acupuncture research. We used a newly validated human pain model and examined whether acupuncture can influence experimentally induced dental pain. For this study, we compared the impact of manual acupuncture (real acupuncture), manual stimulation of a needle inserted at nonacupuncture points (sham acupuncture) and no acupuncture on experimentally induced dental pain in 35 healthy men who were randomized to different sequences of all 3 interventions in a within-subject design. BORG CR10 pain ratings and autonomic responses (electrodermal activity and heart rate variability) were investigated. An initial mixed model with repeated measures included preintervention pain ratings and the trial sequence as covariates. The results showed that acupuncture was effective in reducing pain intensity when compared to no acupuncture ($\beta = -.708$, $P = .002$), corresponding to a medium Cohen's d effect size of .56. The comparison to the sham acupuncture revealed no statistically significant difference. No differences in autonomic responses between real and sham acupuncture were found during the intervention procedures.**

Perspective: ***This study established a dental pain model for acupuncture research and provided evidence that experimentally induced dental pain can be influenced by either real acupuncture or manual stimulation of needles at nonacupuncture points. The data do not support that acupoint specificity is a significant factor in reducing experimental pain.***

Key Words: *Acupuncture, pain, toothache, nociception, Medicine, Chinese traditional.*

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Trial Registration: The study was registered at clinicaltrials.gov (registration ID: NCT02589418).

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Acupuncture might help to reduce opioid use[49] for pain management because it has been shown to have clinical effects on several prevalent chronic pain conditions[75,76] including osteoarthritis of the knee,[78] chronic back pain,[10] tension-type headache,[52] and migraine,[45] with effect sizes comparable to other common pharmacological opioid alternatives.[7] In addition, acupuncture has shown to be relatively safe,[48,79] and it is used by patients.[17] It has also been shown to be cost-effective within accepted thresholds.[30] Considering those aspects, acupuncture has the potential to contribute to the improvement of the opioid crisis and its associated chronic pain mismanagement problems.[34] However, with acupuncture also having placebo effects of relevant size,[75] it is important to get a better understanding of the biological mechanisms of acupuncture analgesia.

To date, numerous mechanistic animal and human studies have been carried out on acupuncture analgesia indicating involvement of the purinergic system,[27,70] muscle fasciae,[39] peripheral nervous,[80] and most prominently, the central nervous system (CNS).[15,21,31,39,42,57] However, human studies focusing on the central mechanisms of acupuncture analgesia are scarce. This situation may be rooted in the applied pain models and associated drawbacks in stimulation paradigms, thus hampering detectability of neurophysiologic correlates of acupuncture analgesia.

For this purpose, we propose a versatile and reliable experimental dental pain model for the study of acupuncture analgesia in the context of behavioral, psychophysical, and neurobiological studies. A dental pain model has various advantages compared to other experimental models, such as ischemic pain,[3] heat pain,[37,44] pressure pain,[36] cutaneous electrical stimulation,[53,73] and tourniquet pain.[55] First, teeth are predominantly innervated by nociceptive Aδ- and few C-fibers.[13,67] As such, electrical stimulation of dental nociceptive fibers elicits pure nociceptive sensations lacking other types of somatosensory components and is therefore clinically relevant due to the perceptual "authenticity." Furthermore, acupuncture has been suggested to be efficacious for clinical and experimental dental pain,[35] finding superior or equal efficacy when compared to control treatments.[23] This documented efficacy further supports the application of such a pain model due to its sensitivity to acupuncture treatments, supporting the ability to explore acupuncture analgesia-associated mechanisms. Lastly, the proposed dental pain model has been used and validated in psychophysical, interventional and multiple magnetic resonance (MR)-based studies[19,24,29,51] and is, therefore, applicable to a variety of study types investigating acupuncture analgesia.

In that vein, the present study applied the dental pain model in healthy young male subjects to 1) test its potential in the evaluation of its analgesic effects of a frequently applied manual acupuncture intervention using subjective pain ratings and 2) evaluate this effect by comparing it to a sham (identical stimulation of nonacupuncture points) and no acupuncture (passive control) intervention. This comparison of 3 types of interventions enables the evaluation of acupuncture point specificity. Furthermore, psychological characteristics, acupuncture sensations, and autonomic reactions to the interventional procedures were quantified in order to explore potential mechanisms of observed analgesic effects.

Methods

Subjects

Sixty healthy male subjects, aged from 18 to 40 years, were recruited for the study. The inclusion criteria were a vital, caries-free, and untreated test tooth (right upper canine); no self-reported medical knowledge about acupuncture; no acupuncture treatment in the previous 12 months; and suitable sensitivity to dental stimulation and perceptual stability (tested during the eligibility-check visit). Furthermore, due to our intention to extend this study to a functional magnetic resonance imaging (fMRI) setting in the future, we also used the common inclusion criterion of right-handedness in this study. The exclusion criteria were complaints or diseases of the oral cavity, history of pre-existing neurological and/or psychiatric conditions, history of severe dental pain, regular intake of pain medication, history of brain injury, current alcohol and drug abuse, or chronic diseases that require a permanent drug intake. No female subjects were included due to the menstrual cycle-dependent hormone level influence on pain perception[77] in order to minimize variation in the data as much as possible and thus to prevent the need for higher sample sizes.

Before the experiment, subjects confirmed that they had abstained from alcohol, drugs, and analgesics 24 hours prior to participation in any of the study appointments. If not possible, subjects were requested to contact the investigator and postpone their appointment. All subjects received detailed information about the aim of the study and the study procedures and were explicitly informed about their right to terminate participation at any time. All subjects provided their written informed consent before any study procedure was conducted. The subjects were reimbursed at the end of their participation for their required participation time (40 Swiss francs/hour). The study was conducted from November 2015 to March 2016 according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice and the Declaration of Helsinki and registered under the following number: clinicaltrials.gov NCT02589418. The study was approved by the local ethics committee (KEK-ZH-Nr. 2015-0291). From the 42 included subjects, 7 dropped out (2 subjects prematurely terminated participation, 5 subjects were excluded from the experiment due to repeatedly insufficient and/or inconstant pain intensity perception), resulting in a total of 35 analyzed data sets (mean age $\pm$ SD: 23.7 $\pm$ 4.1, see Fig 1), which corresponds to the planned sample size.

The rationale for the sample size was based on a study of manual acupuncture on experimental thermal pain[37] that also evaluated the effect on a series of experimental pain stimuli applied to healthy participants. Their

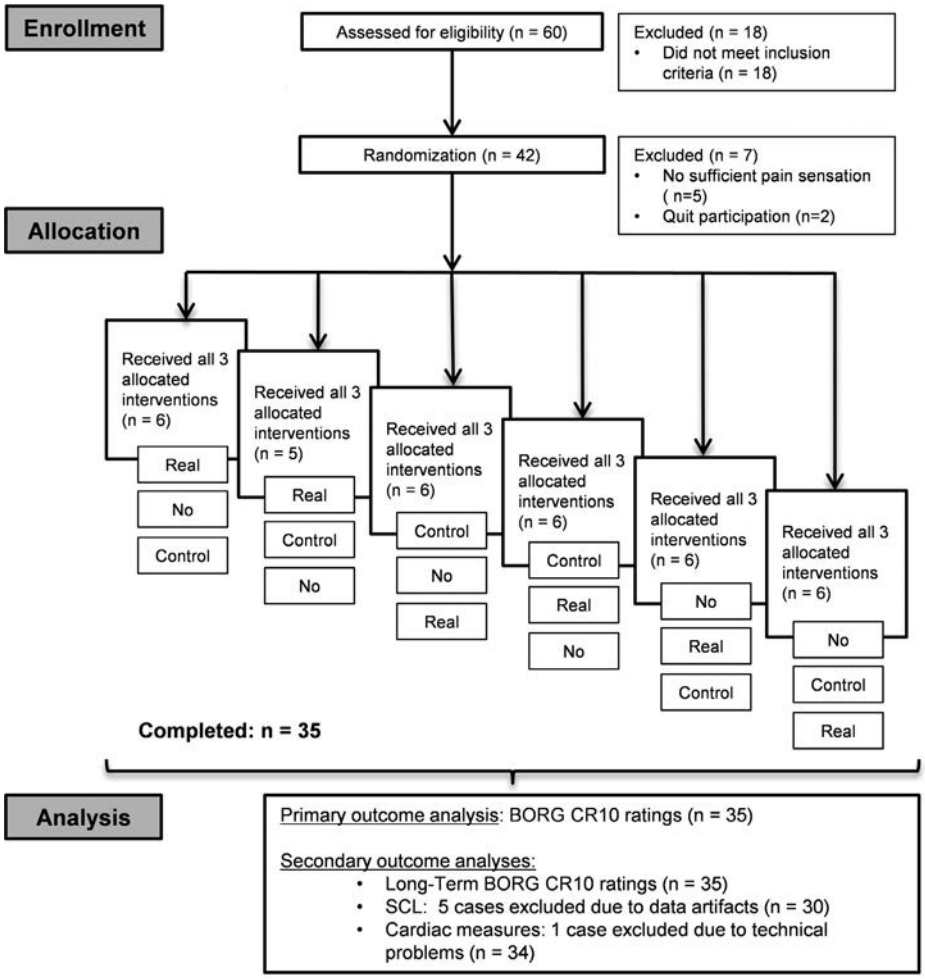

Figure 1. Flow chart illustrating the enrollment and allocation to the 6 intervention sequences and analysis procedures with the corresponding sample sizes.

study found a "medium" acupuncture-based analgesic effect of d = .50 on subjective pain intensity ratings when comparing manual acupuncture to a sham acupuncture using sham acupuncture needles over all thermal pain intensities (acupuncture (mean ± SD): 12.6 ± 1.4; sham: 11.8 ± 1.7). For our study, we therefore assumed an effect size of Cohen's d = .50 between 2 dependent means, an α-error of 5% (2-sided) and a power of 80%. Using G*Power software (version 3.1.9.2),[25] 34 subjects were needed.

Experimental Design and Procedures

We applied a randomized, single-blinded, cross-over repeated measures design. Study design and participant flow are depicted in Fig 1. To account for sequence biases inherent to the repeated measures design, subjects were randomly allocated to 1 of 6 sequence types. The randomization was performed using a randomization database programmed by a data manager not further involved in the study using Microsoft Access 2010 (Microsoft, Redmond, WA). The randomization list was concealed and not accessible for the study personnel. Subjects were registered and randomized in consecutive order and could not be deleted from the database. Subjects were blinded for the type of acupuncture. The acupuncturist could not be blinded as manual acupuncture was performed.

Study participation for a subject comprised a total of 4 study visits: an eligibility check visit and 3 experimental visits. All visits were at least 7 days apart in order to avoid carry-over effects due to the interventions.

Eligibility Check Visit

The eligibility check visit took place at the Center of Dental Medicine, University of Zurich. The aim of this visit was to 1) carefully check inclusion and exclusion criteria, including an assessment of the oral status by a dentist; 2) inform the subject about the study goal and study procedures; 3) fabricate the dental splint for dental pain stimulation; 4) test the subject's pain perception characteristics with a sensory test; and 5) familiarize the subject with the acupuncture perception.

To reduce several sources of variation in the experiment, extensive psychophysical testing was performed to evaluate the subjects' dental somatosensory characteristics and variability. The first part of the sensory

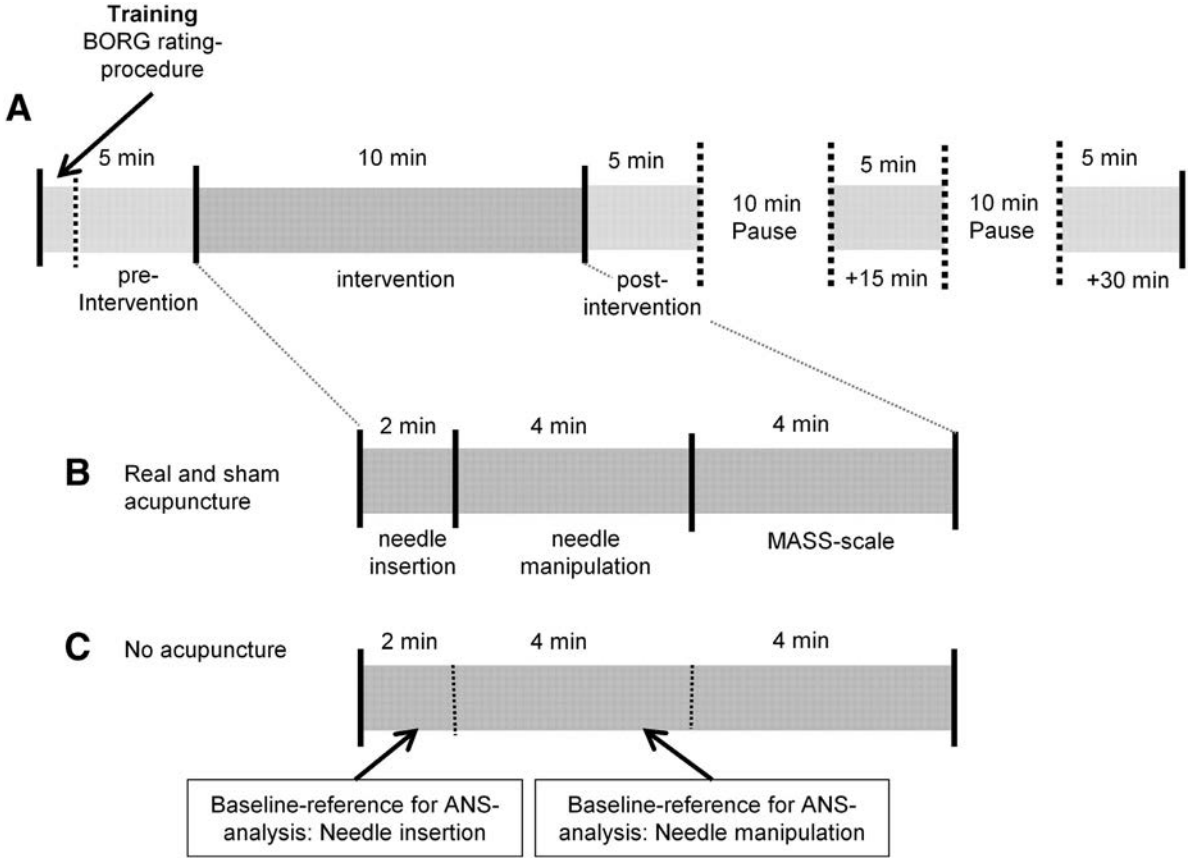

Figure 2. Overview of the experimental procedures. The experimental procedure consisted of 4 pain stimulation phases (preintervention, postintervention, 15 minutes postintervention and 30 minutes postintervention) and an intervention phase **(A)**. The intervention phase was further subdivided into 3 subphases associated with the acupuncture procedures **(B)**. The intervention phase of the no acupuncture intervention consisted of a 10-minute resting period, which was subdivided to match the subphases of the acupuncture interventions to provide valid baseline conditions for the ANS analyses **(C)**.

testing was a staircase testing procedure, in which the stimulus intensity started at an imperceptible level and was linearly increased in 1 mA steps. Subjects were instructed to report the first sensory perception (sensory detection threshold), the first pain perception (pain detection threshold) and a clearly painful but tolerable perception corresponding to a 5 on a numeric rating scale (NRS). These tests were repeated 3 times to account for novelty effects and potential initial feelings of uneasiness evoked by the stimulation procedure. Furthermore, the repetition of this test allowed for a first estimation of the volatility of the subjects' thresholds. In a second step, the electrical intensity corresponding to a 5 on the NRS, estimated in the last run, was used in a continuous stimulation block with 15 pulses and an interstimulus-interval (ISI) of 8 to 10 seconds. This continuous stimulation procedure was performed to familiarize the subject with the stimulation procedure applied in the experimental visits and to evaluate the stability of the perceptions over time. Subjects were deemed eligible for the study if 1) an intensity of 5 on the NRS was repeatedly reached using the staircase procedure, 2) the perception was described as pricking and located within the test tooth, and 3) the dental pain intensity was not subject to habituation or sensitization during the continuous stimulation procedure.

Experimental Visits

All 3 experimental visits were identical except for the intervention procedure. All visits were conducted in the Institute for Complementary and Integrative Medicine at the University Hospital Zurich. The room was kept at a stable temperature of 21°C and a humidity of 50%. To estimate the impact of the subjects' psychological status on outcome variables, the following questionnaires were completed at the beginning of the experiment: the State-Trait Anxiety Scale (STAI),[43] a brief version of the questionnaire for the Expectation Treatment Scale (ETS),[4] and the Life Orientation Test (LOT-R).[65] After subject preparation (preparation and insertion of the dental splint, attachment of electrodes), subjects were seated on a therapy bed in a semireclined position. The pain intensity threshold corresponding to a 5 on the NRS was then again determined using the same staircase sensory testing procedure applied in the eligibility visit and used as the stimulation intensity during the training/pain stimulation phases.

The experiment consisted of a short training phase, 4 pain stimulation phases (preintervention, postintervention, +15 minutes, and +30 minutes) and an intervention phase. For an overview, the sequence of the experimental phases is illustrated in Fig 2. During the training

phase, the subjects received 5 pain stimuli with respect to an optimal familiarization with the subjective pain rating procedure using a computerized BORG Category Ratio 10 Scale (BORG CR108; see "Subjective pain intensity ratings" for details). The actual pain stimulation phase lasted approximately 5 minutes and each consisted of 20 dental pain stimuli with an ISI of 8 to 10 seconds. After the postintervention and +15 minutes pain stimulation phases, a break of 10 minutes was allowed for the assessment of sustained, intervention-specific effects on pain ratings while limiting the burden on the subjects. During the breaks, the subjects were requested to lie calmly on the bed and relax. The interventions (real acupuncture, sham acupuncture and no acupuncture) were administered during the intervention phase (after the preintervention pain stimulation phase).

Dental Pain Model

Dental pain was induced by means of an experimental pain model that has been extensively validated and applied in previous studies.[11,19,29,50] Electrical stimulation was administered via individually fabricated dental splints (see Fig 3). The right upper canine was electrically stimulated using centrally embedded stainless steel electrodes on the labial and palatal surfaces of the splint. Electrical resistance between the tooth and electrodes was reduced by the placement of small portions of conductive hydrogel (size approx. 3 × 3 mm) on the electrodes before its insertion onto the subject's dentition. The electrical stimulus consisted of a short (1 millisecond), single, biphasic pulse applied with an ISI of 8 to 10 seconds to prevent sensitization effects. For detailed information regarding splint fabrication, equipment specs and hydrogel formula, please see Gutzeit et al.[29]

Subjective Pain Intensity Ratings

Subjective pain intensity perceptions from the 4 pain phases (pre, postintervention, +15 minutes, and +30 minutes) were assessed using a computerized BORG CR10 Scale.[8]

Figure 3. Exemplary dental splint for electrical dental stimulation. The electrical stimulus is applied via the embedded electrodes located at the palatal and labial surface of the right upper canine indicated by the black circle.

During the training phase (immediately before the start of the preintervention phase), subjects were extensively instructed and trained on how to use the scale. This approach had the advantage that the subjects would not anchor their ratings on the 5 from the NRS (as estimated during the sensory testing procedures) but instead had to recategorize their perceptions on a new scale, thus minimizing bias in the perceived intensity estimation at the beginning of the experiment. The BORG CR10 Scale ranged from 0 (nothing at all) to 12 (absolute maximum) and was verbally anchored by .5 (extremely weak), 1 (very weak), 2 (weak), 3 (moderate), 5 (strong), 7 (very strong), and 10 (extremely strong).

The subjects rated their subjective pain intensity of each electrical stimulus on a computerized BORG CR10 Scale. The scale was displayed on a 21" LCD-screen. The rating was chosen with a rating box (CoVAS; MEDOC, Haifa, Israel) placed on the bed on the right side of the subject.

Study Interventions

Subjects underwent 3 different interventions (real acupuncture, sham acupuncture, and no acupuncture) performed on different visits in a randomized sequence. The real and sham acupuncture regimens were the result of a consensus procedure involving an internationally recognized specialist in acupuncture (Professor Xuemin Shi and his team from the First Teaching Hospital of Tianjin University of TCM) and the research teams of the University Hospital Zürich and Charité – Universitätsmedizin Berlin. The real acupuncture regimen was based on TCM theory on the assumption that dental pain among young adults is caused by wind and heat in the large intestine and stomach meridians.[68] As a result, 2 acupuncture points located ipsilateral to the stimulated tooth on the stomach meridian and 1 distal point located on the large intestine meridian that has targeted indication for facial and oral diseases were chosen.

Our sham acupuncture had to be as similar as possible to real acupuncture to optimize participant blinding. Real and sham points were manually and identically stimulated by the acupuncturist. Points for sham acupuncture were chosen based on Chinese medicine theory, so that they did not belong to a meridian and were not acknowledged acupuncture points.[33] Two points at the shoulder and 1 point at the dorsal mid-hand were chosen. To ensure adequate blinding, subjects were instructed about the acupuncture types as follows: "In this study 2 types of acupuncture are performed. In acupuncture, both near and far points are used, whereby the distance to the pain site does not have to be related to the strength of the effect. Acupuncture Types 1 and 2 differ only in the acupunctured points on the body..." Both real and sham interventions were performed by one licensed Chinese acupuncturist from the First Teaching Hospital of Tianjin University of TCM with 5 years of training and 4 years postgraduate experience. Disposable .25 × 40 mm stainless steel needles (Seirin Corporation, Shizuoka, Japan) were used.

Real Acupuncture

Four needles were inserted in bilateral large intestine 4 (LI 4, He Gu, localized on the dorsum of the hand, between the first and second metacarpal bones, approximately in the center of the second metacarpal bone), right-side stomach 6 (ST 6, Jia Che, localized in the bone depression anterior and superior to the mandibular angle, in the masseter muscle when the teeth are clenched) and right-side stomach 7 (ST 7, Xia Guan, located on the face, in the bone depression palpable anterior to the ear and inferior to the zygomatic bone when the mouth is closed) at depths of .8 to 1.0 cun, .3 to .5 cun, and .5 to 1.0 cun, respectively, after which the "Deqi"[38] sensation was sought. Manual manipulation was done by rotating the needle according to the "reducing" method[68] and was performed for 1 minute per acupuncture point (LI 4 were simultaneously manipulated). This method is characterized by a consecutive and smooth rotation of the needle with the index finger and thumb. The forward movement of the index finger is executed with stronger force than the forward movement with the thumb.[6] Needle insertion and manipulation lasted 6 minutes (2 minutes for needle insertion; 4 minutes for needle manipulation), and the needles were retained until the end of the experiment. At the end of the acupuncture intervention, participants were asked to answer the MASS-questionnaire[38] to assess sensations associated with the acupuncture intervention.

Sham Acupuncture

Sham point 1, serving as control point for bilateral LI 4, was located on the dorsal aspect of the hand, midway along the medial side of the shaft of the second metacarpal bone. This point was acupunctured on both hands.

Sham point 2, the control point for ST 6, was located at the leading edge of the right arm inside the junction of the deltoid and biceps.

Sham point 3, the control point for ST 7, was located at the inside of the right elbow at the midpoint of the elbow tip and the armpit. The needle manipulation procedure of the sham acupuncture was identical to the procedure done in real acupuncture. After the sham acupuncture intervention, subjects completed the MASS questionnaire to assess the perceived acupuncture sensations.

No Acupuncture

To account for possible changes in dental pain perception over time independent of the interventions (due to relaxation, distraction, habituation, etc), no acupuncture was performed during the intervention phase in one of the experimental visits. Subjects were instructed to lie comfortably on the bed for 10 minutes and relax.

Autonomic Nervous System Data Recording and Preprocessing

To explore the effects of the acupuncture intervention on the autonomic nervous system (ANS), changes in heart rate (HR), heart rate variability (HRV), and electrodermal activity were quantified (PowerLab 8/35 analogue/digital converter unit recorded/analyzed with LabChart v8.1.2 (ADInstruments, Sydney, Australia)).

Electrodermal Activity Measurements

Initially, subjects were asked to wash their hands with warm water and liquid soap to ensure optimal skin conductance. Polished stainless steel dry bipolar electrodes (MLT118F) were then attached to the palmar surface of the medial phalange of the left hand index and middle fingers. The skin conductance level (SCL) signal was amplified via a fully isolated amplified galvanic skin response Amp operating with constant-voltage AC excitation (22 mV_{rms} at 75 Hz) (FE116; ADInstruments, Sydney, Australia) connected to a Powerlab 8/35 unit. The electrodermal signal was sampled with 200 Hz and a signal range of 40 μS. Prior to the start of the recording, the signal was set to zero to reduce interindividual differences in the signal amplitude. SCL analysis was performed by calculating the mean SCL signal amplitude during the acupuncture needle insertion and needle manipulation procedures of the intervention phase. The mean SCL amplitudes were baseline corrected by subtracting the mean SCL amplitude recorded during the preintervention phase. During the no acupuncture intervention, the same analyses were performed according to the corresponding time windows (see Fig 2).

Heart Rate Measures

Two electrocardiogram (ECG) electrodes (Ambu white sensor; Ambu, Bad Nauheim, Germany) were attached below the midpoint of both clavicles. An additional electrode was placed below the left pectoralis muscle and below the mammilla. The electrodes were connected to a Dual Bio Amp amplifier (FE135) via a shielded 5-lead Bio Amp Cable (MLA2540) (both from ADInstruments, Sydney, Australia). The signal recording was set to a sampling rate of 200 Hz, a range of 5 mV, low-pass filtered to 5 kHz, and high-pass filtered to 10 Hz. HR and HRV analyses were performed by means of the HRV module included in the LabChart software. The HRV module provides automated identification of R-peaks in the ECG signal and automatically provides HRV calculations in the time and frequency domains. The ECG signal was visually inspected for errors in the R-peak classification and corrected if necessary.

HR was calculated as the mean beats per minute for the acupuncture needle insertion and needle manipulation procedures of the interventions. The mean HR was then baseline corrected by subtracting the mean HR recorded during the preintervention phase. During the no acupuncture intervention, the same analyses were performed according to the corresponding time windows (see Fig 2).

HRV was quantified in the time domain by calculating the square root of the mean squared differences (RMSSD of successive NN (normal-to-normal) intervals). This measure has been suggested to reflect high-frequency signal components and is thus associated with parasympathetic

activity levels of the ANS.[14,72] We opted for a time-domain instead of a frequency-based measure due to its better reliability for short measurements such as 2 minutes[9] (duration needle-insertion phase: 2 minutes). RMSSD analysis was performed identical to the HR and SCL data. RMSSD values were calculated for the needle insertion and manipulation phases. They were baseline corrected by subtracting the RMSSD values from the pre-intervention phase. Corresponding time windows of the no acupuncture intervention were taken for the calculation of the RMSSD to allow direct comparison. It is important to note that HRV measures calculated in the time domain can only be compared when they are based on equal time windows.[72] Therefore, we want to emphasize, as needle insertion and manipulation phases had different durations, it is only valid to compare the same phases between the 3 interventions.

Acupuncture Sensations

The acupuncture sensations were characterized at the end of the acupuncture interventions using the MGH Acupuncture Sensation Scale.[38] This questionnaire consists of 13 items (scaling from 0 to 10) for diverse perceptual qualities such as soreness, tingling, and numbness. Higher values indicate a greater extent of the respective quality.

For each subject and acupuncture procedure, an index characterizing the overall acupuncture perception (MASS-index) was calculated. As recommended, the "sharp pain" and the item "other" were excluded from the MASS index calculation (for more information regarding the calculation formula, see[38]).

Statistical Analysis

All statistical analyses were conducted using SPSS (SPSS 21.0, IBM Corp., Armonk, NY). For all analyses, probability levels of $P < .05$ were deemed significant. Data distribution was tested with Kolmogorov-Smirnov tests. In case of significant deviation from a normal distribution, nonparametric procedures were applied.

Primary Endpoint Analysis

The primary endpoint of this study was the comparison of the mean BORG CR10 pain intensity ratings during the postintervention phases of the 3 intervention types. The comparisons were tested using a hierarchical test procedure: the first comparison was done between the postintervention pain ratings of the real and no acupuncture conditions. In case of significant differences, a second comparison between the postintervention pain ratings of the real and the sham acupuncture was performed. This hierarchical procedure allowed conducting of the statistical inference analyses without corrections for multiple comparisons.

The statistical inferences were done using linear mixed model (LMM) analyses, as it allows the analysis of paired data sets while including multiple covariates. In both LMM analyses, subject and subject × trial sequence interactions (the sequence of interventions) were used as random effects. Mean BORG CR10 ratings during the preintervention phase (baseline mean pain ratings), experimental condition and trial sequence type were entered as fixed effects. For covariance structure, variance components were used.

Secondary Endpoint Analyses

For secondary endpoints, the following analyses were performed: 1) sustained effect of real and sham acupuncture on subjective pain ratings, 2) associations of acupuncture sensations with effects of real and sham acupuncture, 3) comparison in HR, HRV, and SCL reactions between the following interventions: real acupuncture versus no acupuncture and real acupuncture versus sham acupuncture, and 4) differences in psychological variables (questionnaires) between the 3 interventions.

Sustained acupuncture effects on subjective pain ratings:

To assess the dynamics of analgesic effects associated with real and sham acupuncture, we extended the time frame of the primary endpoint analysis by including 3 postintervention time points (postintervention, +15 minutes, +30 minutes).

Similar to the primary endpoint analyses, an LMM analysis was conducted with subject and subject × trial sequence type as random effects and preintervention mean BORG CR10 ratings, experimental condition, trial sequence type, time (phase after intervention) and interaction between experimental condition × time as fixed effects. As the interaction of experimental condition × time was not significant, the LMM was again conducted without the inclusion of this interaction. For covariance structure, variance components were chosen.

Differences in acupuncture sensation:

We compared acupuncture sensations[38] between real and sham acupuncture with Student's t-test for paired groups.

ANS Reactions to Acupuncture

The influences of needle insertion and needle manipulation on ANS parameters (HR, HRV, and SCL) were analyzed by paired-group comparisons between 1) real and no acupuncture and 2) real and sham acupuncture. Paired-group comparisons for the HR and SCL were performed by means of Student's t-test for paired groups. HRV (calculated as RMSSD) comparisons were performed using a Wilcoxon test.

Psychological Variables (Questionnaires)

The questionnaire data collected at the beginning of the 3 experiments (real, sham, and no acupuncture) were compared using nonparametric Friedman tests for each questionnaire.

Results

Psychological Variables

None of the psychological variables (state and trait levels of anxiety (STAI-X1 and STAI-X2), expectation of

Table 1. Descriptives From the Questionnaires Recorded at the Beginning of the Experimental Visits

Intervention	Acupuncture Expectations (ETS)				Pessimism (LOT-R)				Optimism (LOT-R)			
	N	Mean	CI 95%		N	Mean	CI 95%		N	Mean	CI 95%	
			LL	UL			LL	UL			LL	UL
Real acupuncture	35	9.29	8.19	10.40	34	11.97	11.32	12.61	34	5.03	4.44	5.63
Sham acupuncture	35	8.84	7.85	9.82	34	11.97	11.32	12.61	34	5.03	4.44	5.63
No acupuncture	35	9.26	8.21	10.31	34	11.97	11.32	12.61	34	5.03	4.44	5.63

	Trait Anxiety (STAI-X1)				State Anxiety (STAI-X2)			
	N	Mean	CI 95%		N	Mean	CI 95%	
			LL	UL			LL	UL
Real acupuncture	34	31.94	29.46	34.41	34	31.26	28.26	34.26
Sham acupuncture	35	31.35	28.90	33.81	34	31.23	28.13	34.32
No acupuncture	35	30.97	28.83	33.11	34	30.35	27.58	33.13

acupuncture treatment and optimism/pessimism LOT-R) collected at the beginning of the experiment differed between the 3 interventions (STAI-X1: $\chi^2 = 1.764$ (df = 2); STAI-X2: $\chi^2 = 2.134$ (df = 2); ETS: $\chi^2 = .19$ (df = 2); LOT-R pess: $\chi^2 = .00$ (df = 2); LOT-R opt: $\chi^2 = .00$ (df = 2); Table 1).

Effect of the Interventions on Subjective Pain Ratings

According to our hierarchical test, the first comparison of the primary analysis focused on the real acupuncture and no acupuncture conditions, revealing a significant difference in mean pain rating changes of −.67 (SD = 1.35) points on the BORG-CR10 scale after real acupuncture compared to no acupuncture ($\beta = -.708$, T = −3.295 (df = 31.937), $P = .002$). This result corresponds to a mid-sized effect of Cohen's d = .56. The second comparison of the hierarchical test was nonsignificant between real acupuncture and sham acupuncture with a difference in mean pain rating changes of −.29 (SD = 1.13, $\beta = -.287$, T = −1.456 (df = 28.615), $P = .156$, d = .25).

The covariate "trial sequence" was statistically significant between experimental visits (F = 3.340; df1,2 = 2, 46.135; $P = .044$).

The following explorative analysis revealed significantly lower pain ratings over all posttreatment time points for the real acupuncture condition compared to no acupuncture ($\beta = .794$, T = 3.868 (df = 64.881), $P < .001$). The comparison between real and sham acupuncture over all time points after intervention was not statistically significant ($\beta = .252$, T = 1.228 (df = 64.885), $P = .224$). Furthermore, no interaction for condition x time was found (F = .867 (df1,2 = 2, 207.000), $P = .422$). The results are illustrated in Fig 4 and summarized in Table 2. Supplementary information about the LMM analyses are reported in supplementary material (Tables 1a-d and 4a-e).

Acupuncture Sensations

Acupuncture sensations characterized by the MASS index were not significantly different between the real and sham acupuncture interventions (real: mean [confidence interval, CI 95%] = 4.53 [3.89–5.16]; sham: 4.03 [3.43–4.63], T = 1.802 (df = 34); $P = .080$ (2-sided)).

ANS Changes to Acupuncture

The reactions of SCL, HR, and HRV to the 3 interventions are summarized in Table 3 and illustrated in Fig 5. In parallel to the primary outcome, the comparisons were performed between the 1) real and no acupuncture conditions and 2) the real and sham acupuncture conditions.

SCL

During needle insertion, the SCL signal increased more during real acupuncture compared to the no acupuncture intervention (T = 7.616 (df = 29); $P < .001$), but changes between real and sham acupuncture were not significantly different (T = .288 (df = 29); $P = .776$).

The change pattern in the SCL signal continued to be similar during the needle manipulation phase, but the overall signal changes were of smaller magnitude. Thus, a greater change in the SCL signal was observed between the real and no acupuncture interventions during needle manipulation (T = 2.768 (df = 29); $P = .010$). Again, no significant changes between real and sham acupuncture were found (T = .417 (df = 29); $P = .680$).

HR

The HR dropped during the needle insertion phase of the real acupuncture intervention compared to the no acupuncture intervention (T = −6.694 (df = 33); $P < .001$). HR reduction was not significantly different between the

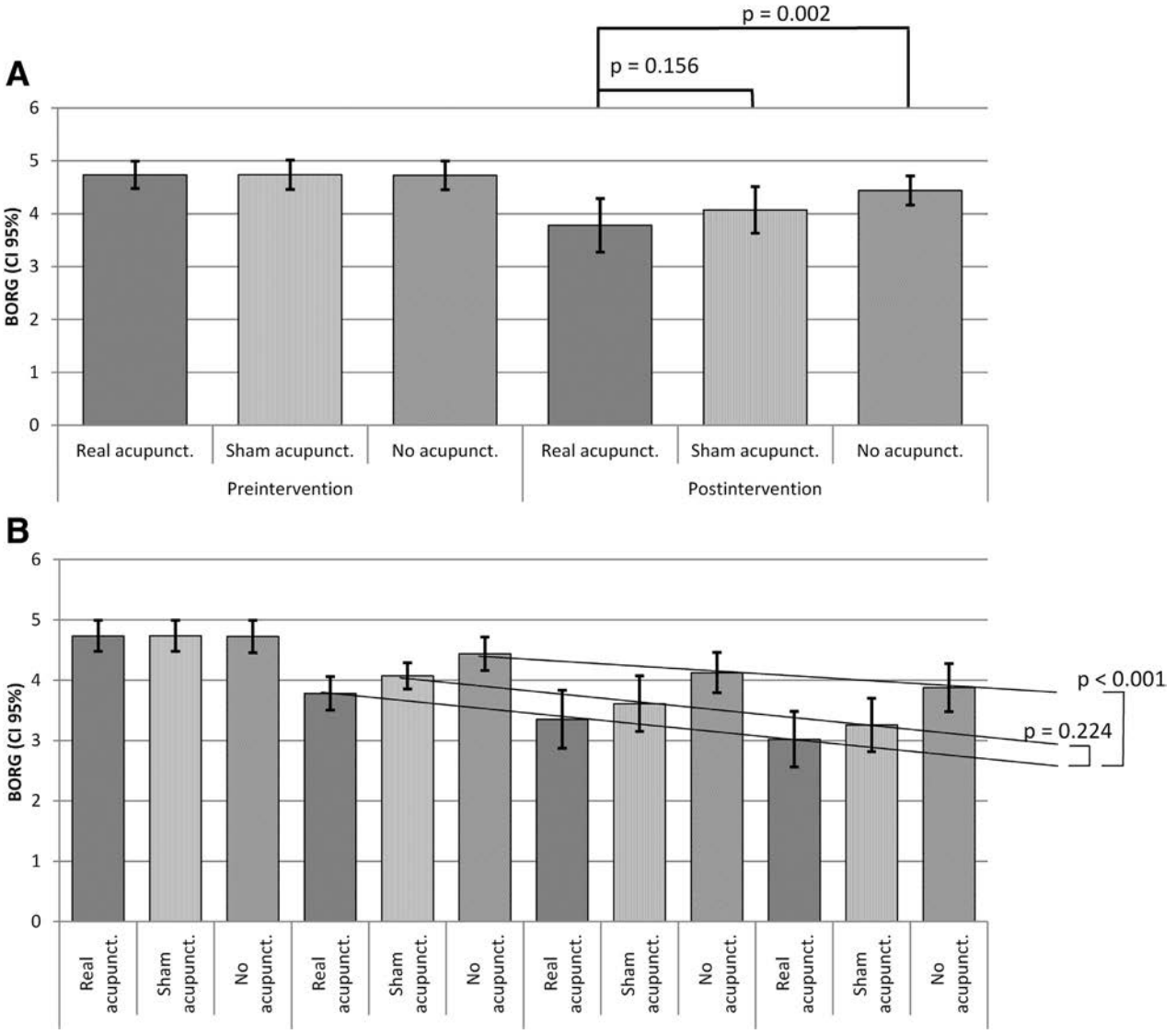

Figure 4. Pain ratings (BORG CR10, with 95% confidence intervals) **(A)** during the dental pain stimulation before and after the interventions (primary endpoint). **(B)** Sustained effects for pain intensity ratings for preintervention, postintervention, 15 minutes postintervention and 30 minutes postintervention phases. N = 35; the lines were included to visualize the slopes of the main effect analysis of condition.

real and sham acupuncture conditions during needle insertion (T = .815 (df = 33); *P* = .421).

The same pattern was observed during the needle manipulation phase with a reduction during real acupuncture compared to no acupuncture (T = −7.202 (df = 33); *P* < .001), but no difference was found between the real and sham acupuncture (T = .860 (df = 33); *P* = .396).

Table 2. Descriptives of the Acupuncture Effects on Pain Intensity Ratings (BORG CR10 Pain Intensity Ratings; n = 35)

	Real Acupuncture			*Sham Acupuncture*			*No Acupuncture*		
	Mean	*CI 95%*		*Mean*	*CI 95%*		*Mean*	*CI 95%*	
		LL	*UL*		*LL*	*UL*		*LL*	*UL*
Pre	4.74	4.48	4.99	4.74	4.46	5.01	4.72	4.45	4.99
Post	3.78	3.27	4.29	4.07	3.63	4.51	4.44	4.16	4.71
+15 min	3.35	2.87	3.83	3.61	3.15	4.07	4.13	3.79	4.46
+30 min	3.02	2.56	3.48	3.26	2.82	3.70	3.88	3.48	4.28

Table 3. Descriptives of the Baseline-Corrected ANS Reactions to the Interventions. Baseline Correction Was Performed by Subtracting the ANS Values Recorded During the Prephase (With Pain Stimulation)

	SCL (μS)			Heart Rate (BPM)			RMSSD (ms)		
Intervention	Mean	CI 95%		Mean	CI 95%		Mean	CI 95%	
	(N = 30)	LL	UL	(N = 34)	LL	UL	(N = 34)	LL	UL
Needle Insertion									
Real acupuncture	5.50	4.36	6.64	−3.56	−4.95	−2.05	6.48	−1.79	15.49
Sham acupuncture	5.19	2.94	7.43	−4.01	−5.26	−2.78	9.44	2.76	16.69
No acupuncture	−1.30	−2.86	.26	.95	.08	2.36	−3.65	−10.13	1.78
Needle Manipulation									
Real acupuncture	.77	−.90	2.43	−4.21	−5.50	−2.88	5.53	−10.77	23.41
Sham acupuncture	.27	−1.79	2.34	−4.75	−5.69	−3.73	11.17	2.92	19.58
No acupuncture	−2.20	−3.87	−.53	1.49	.43	2.60	−5.04	−12.57	2.51

HRV

For HRV, an increased RMSSD was found in real acupuncture compared to no acupuncture during needle insertion and needle manipulation ($Z = 3.145$; $P = .002$). Similar to SCL and HR, no changes in RMSSD were observed between real and sham acupuncture during needle insertion and manipulation ($Z = .262$; $P = .793$).

Discussion

In the present study, real acupuncture was associated with decreased pain intensity ratings during the postintervention pain block in comparison to the corresponding block after the no-acupuncture condition. The study found no significant differences in pain ratings between real and sham acupuncture, indicating that the location of the acupuncture needling had no discernable effect.

The pain model proved its suitability by showing stable and reproducible subjective pain perceptions over the entire time course of the preintervention pain stimulation blocks, indicated by low levels of variance and the absence of habituation/sensitization patterns (see also supplementary material). All included participants uniformly perceived the stimulus as a very short, sharp, pinprick sensation localized exclusively at the test tooth without longer lasting, secondary pain components. The pain model was susceptible to manual acupuncture indicating the reductions in the subjective pain intensity in a reproducible way.

We also found a significant effect of trial sequence, indicating stronger intervention effects during the first experimental visit (see supplementary material). Yet, the impact of this effect should not have biased our results due to the randomization of the trial sequences and the inclusion of the visit as a covariate.

Although mean subjective pain intensity ratings remained stable during the preintervention pain block, we found a continuous reduction in reported pain ratings over time after the no-acupuncture intervention. This reduction may be attributable to decreases in mental tension and/or in state anxiety over the timespan of the experiment. Another explanation could be the involvement of slight habituation effects. Other studies with this dental pain model used a longer stimulation phase (>20 minutes without break) and showed no signs of habituation.[12] Interestingly, although the subjective pain ratings after the no acupuncture intervention decreased linearly over all the postintervention pain stimulation blocks (post, +15 minutes, and +30 minutes), the pain intensity ratings after the real and sham acupuncture decreased in the same linear fashion (as indicated by the lack of significant intervention × time effects). Analogous to the findings from the primary endpoints, the overall subjective pain intensity levels were significantly lower after the real compared to no acupuncture, but not between real and sham acupuncture. The parallelism of the patterns of subjective pain decrease suggest that the induced analgesic effects were established before the start of the postintervention pain blocks and remained stable over a time span of at least 30 minutes.

Various nonspecific and specific effects could be involved in the observed acupuncture analgesia, such as psychological factors and neurophysiologic processes in the peripheral and central nervous system, respectively. First, psychological factors are capable of altering pain perception and intervention efficacy. Patients' expectations toward acupuncture treatment have been shown to be significantly linked to intervention outcome and associated pain relief.[16,20,46,61] Anxiety has also been suggested to affect perceived pain intensities in clinical and experimental studies.[1,18,32,60,62,69,74] Other psychological factors such as optimism and pessimism could contribute to the observed outcome due to their close conceptual relationship with expectation.[28,64] However, we estimated their magnitude at the beginning of the experiment using questionnaires (ETS, STAI, and LOT-R) and found no evidence of differences in these factors between the interventions.

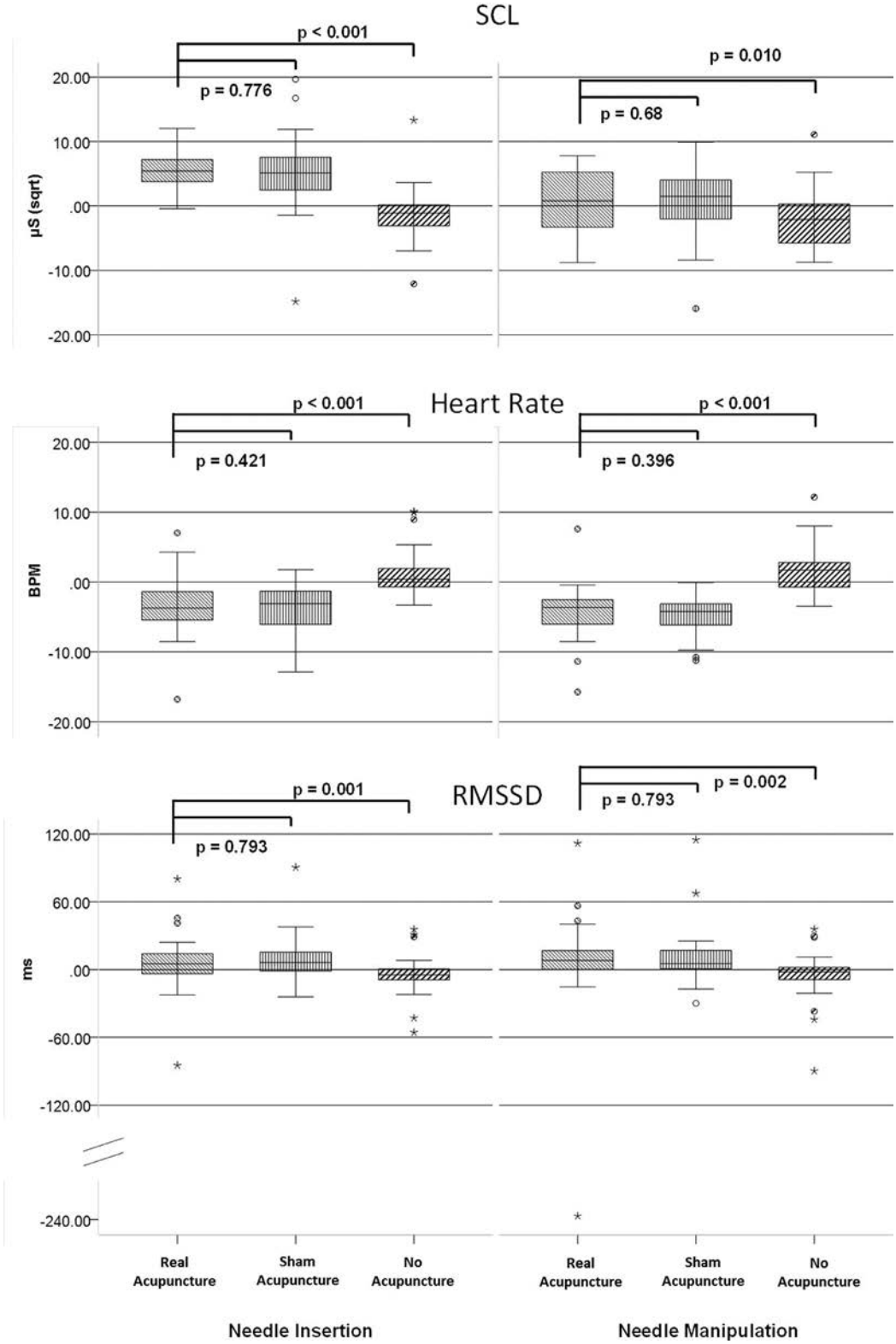

Figure 5. Comparison of ANS reactions (SCL, heart rate and heart rate variability (RMSSD)) during acupuncture needle insertion/manipulation and the corresponding time windows during the no intervention phase. The values obtained during the preintervention phase (with dental pain stimulation) were subtracted to correct for baseline differences. The whiskers of the box plots correspond to 1.5× of the interquartile range (IQR); circles represent outliers outside 1.5× IQR; stars represent outliers outside 3× IQR.

The observed influence of manual acupuncture on ANS parameters may indicate a central nervous system-mediated modulation of subjective pain perception. In this study, both real and sham acupunctures induced similar and significant increases in parasympathetic activity, as indicated by the reductions in mean HR and increments in RMSSD during the needle insertion and manipulation compared to the no acupuncture

intervention. During needle insertion, SCL of real and sham acupuncture showed higher levels compared to the no acupuncture intervention. During the needle manipulation phase, SCL decreased back to the level of the no acupuncture intervention. This initial increase in SCL levels might be attributable to short-term increases in sympathetic activity induced by the superficial sharp and pricking sensation of skin penetration. This explanation is in line with published work suggesting a relationship between superficial pain and sympathoexcitation.[5,47] Furthermore, sharp pain is not associated with the typical sensation elicited by acupuncture called "De-Qi," which has been linked to acupuncture effects and increases in parasympathetic activity.[38,81] As we found no significant differences in De-Qi sensations (MASS-Index) between real and sham acupuncture points, most likely comparable levels of ANS modulation were induced by their manipulation.

Various brain structures, such as the periaqueductal gray, locus coeruleus, and nucleus arcuatus, have been shown to be involved in acupuncture-mediated ANS responses.[5] A potential link between ANS dynamics and pain sensation modulation is further strengthened by a series of studies suggesting an oppositional relationship between experienced pain intensities and the activation level of the parasympathetic system.[2,22,56,66,82]

In addition to the central mechanisms described above, we hypothesize that the observed effects in our study might have been affected by various local effects of the acupuncture needle manipulation. Two of the real acupuncture points were located in the face and close to the site of dental stimulation. During dental stimulation, afferent nociceptive Aδ- and C-fibers of the maxillary branch of the trigeminal nerve were stimulated. The local acupuncture points ST6 and ST7 are located in the innervation area of the mandibular branch of the trigeminal nerve. Manual needle stimulation on the acupuncture points ST6 and ST7 might have acted locally by promoting local release of purines[27,70] in response to mechanical stimulation.[71] Extracellular purines activate pre- and postsynaptic P2X and P2Y receptors, and adenosine stimulates its own P1 receptor type. These receptors can modulate the effects of classic neurotransmitters.[71] Therefore, the acupuncture might have locally inhibited the dental stimulation-induced trigeminal signaling, possibly explaining the slightly higher analgesic effect elicited by the real acupuncture intervention.

Our 3-armed design is one of our study's several limitations. It cannot evaluate all potential components of the acupuncture effect and only assessed the main effect of point location. A 2×2 factorial design may have provided insights about stimulation and location components and their interactions, although at the cost of increased resources and the lack of a no-treatment condition. Still, we used the term "sham" to name our control procedure. We also did not evaluate electro-acupuncture although it might be superior to manual acupuncture.[40] Moreover, choosing proper control points is very challenging because it is not yet clear what constitutes an acupuncture point[41,59] and how best to combine the traditional concept of acupuncture with modern anatomy. Possibly, the points chosen were not inert, either from the perspective of acupuncture or from the perspective of modern anatomy. Although our sample size was comparably large for an experimental trial and was the result of a sample size calculation based on a medium effect size, we still might have overestimated the point effect of the acupuncture treatment. It is conceivable that the effect of the acupuncture procedure, especially in pain conditions, is mainly driven by the stimulation of the needles. Another possible limitation of this study is the lack of strict control for caffeine intake. An interaction of caffeine and acupuncture effect has been shown in animal models.[26,54,63]

To minimize variance in the data, we only included healthy, young male subjects in the study, whereas acupuncture is mainly used for the treatment of patients with clinical conditions and without gender limitation. These factors and the lack of the acupuncturist blinding are all potential sources of biases.

However, we also tried to avoid bias as much as possible. For example, we wanted to ensure high quality acupuncture, and for this the collaboration with First Teaching Hospital of Tianjin University of Traditional Chinese Medicine was important. We minimized carry-over effects by applying intervals of at least 1 week between measurements, which guaranteed sufficient wash-out and used a random intervention sequence. Nevertheless, the sequence of intervention had an impact on the measurements that was accounted for during analysis. A long wash-out period is especially important because the duration of the sustained acupuncture effect is still not clear.

In our study, the dental pain model showed its utility for evaluating acupuncture effects, especially since the model has already been shown to be useful in experiments using imaging methods such as fMRI and magnetic resonance spectroscopy, which are methods often used to evaluate neurological signatures of acupuncture effects in recent years.[15,31] The model might also be of use for designs using electroencephalography that is more widely available than fMRI and magnetic resonance spectroscopy and can be used for evaluating acupuncture's effect on the somatosensory system.[58] The dental pain model and these imaging methods would not only allow the evaluation of underlying mechanisms but also direct comparison of the effects of the acupuncture methods on pain.

Conclusions

This study established a dental pain model for acupuncture research and provided evidence that experimentally induced dental pain can be influenced by either real acupuncture or manual stimulation of needles at nonacupuncture points compared to a no treatment condition. The data do not support that acupoint specificity is a significant factor in reducing experimental pain.

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Contributions

Conceived and designed the experiments: N.M., D.P., C.M.W., D.E., M.B., and X.M.S. Performed oral health check: N.L. Performed the experiment: N.M., J.J.X., L.E.B., and A.K. Analyzed the data: N.M. and J.B. Discussed the data: N.M., D.P., J.B., C.M.W., and M.B. Wrote the first draft of the paper: N.M. and D.P. Revised the paper and approved the final version: N.M., D.P., C.M.W., D.E., M.B., X.MS., J.B., J.J.X., L.E.B., and A.K.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2019.08.013.

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