Bilateral Acupuncture Analgesia Observed by Quantitative Sensory Testing in Healthy Volunteers

Philip M. Lang, MD, PhD,* Johanna Stoer, MD,* Gabriel M. Schober, MD,* Joseph F. Audette, MA, MD,† and Dominik Irnich, MD, PhD*

**BACKGROUND:** There is evidence that acupuncture activates different spinal and supraspinal antinociceptive systems, but the specific modulatory effects on the sensory system have not been systematically investigated. In this study, we evaluated the immediate effects of different types of acupuncture on thermal, mechanical, and vibratory sensory thresholds.

**METHODS:** Twenty-four healthy volunteers (12 men and 12 women, mean age 33.1 years) received 3 different forms of acupuncture in a single-blinded crossover design; these included manual acupuncture, acupuncture with low-frequency electrical stimulation, and acupuncture with high-frequency electrical stimulation. The time between the interventions was 1 week. All forms of acupuncture were applied unilaterally in the leg at standard acupuncture points: spleen 6, spleen 9, stomach 36, and gallbladder 39. The effects of acupuncture were evaluated by systematic quantitative sensory testing (QST) immediately after each intervention. QST was performed on bilateral lower extremities, including thermal and mechanical perception and pain and vibratory thresholds.

**RESULTS:** The heat pain threshold was increased after manual acupuncture on the treated and untreated side compared with baseline. Low- and high-frequency electrostimulation led to a higher mechanical pain threshold on the treated side compared with baseline and manual acupuncture. The pressure pain threshold was increased by all forms of acupuncture on both sides, with individual changes from baseline ranging from 25% to 52%.

**CONCLUSIONS:** There were congruent changes on QST after 3 common acupuncture stimulation methods, with possible unilateral as well as bilateral effects. (Anesth Analg 2010;110:1448–56)

Acupuncture is widely used in the treatment of chronic pain,1 and there is increasing evidence that acupuncture is effective in a number of chronic pain conditions, including migraine,2 tension-type headache,3 and osteoarthritis of the knee,4,5 when compared with untreated controls. However, our knowledge of the immediate effects of acupuncture on the sensory processing of painful stimuli is still unsatisfactory. Release of endogenous opioids, segmental inhibition, and diffuse noxious inhibitory control are possible explanations of acupuncture analgesia.

Experimental studies have shown that both manual acupuncture6,7 and acupuncture with electrical stimulation (EA)8 cause an increase in the concentration of endogenous opioids in different regions of the central nervous system. A study of human subjects suggests that the analgesia observed after low-frequency (LF)-EA is mediated by re-release of β-endorphin into the cerebrospinal fluid.9 Analgesia induced by LF-EA (2 Hz) seems to be mediated by µ- and δ-opioid receptors, whereas high-frequency (HF)-EA (100 Hz) induces its analgesic effects via the κ-receptor. EA with a stimulation of 2 to 15 Hz has combined effects on µ-, δ-, and κ-receptors in the spinal cord of rats.10 Moreover, there is evidence that EA induces the release of other neurotransmitters in the central nervous system, such as serotonin and norepinephrine.7,11

Further mechanisms of acupuncture-induced analgesia have been proposed, including segmental spinal inhibition (depression of primary afferent neurotransmission in Aδ-fibers), propriospinal heterosegmental inhibition (activation of antinociceptive heterosegmental interneurons by either noxious stimuli or supraspinal descending pathways), and supraspinal descending inhibition.12 Heterotopic nociceptive stimuli may have pain-relieving effects via the diffuse noxious inhibitory control mechanism.13 Acupuncture could be considered a heterotopic nociceptive stimulus, and therefore, diffuse noxious inhibitory control could serve as a possible explanation of acupuncture analgesia.14

There is a lack of knowledge regarding the effect of different acupuncture techniques on pain transmission in the peripheral nervous system. Hence, there is a need to further investigate the physiologic effects of acupuncture on the peripheral sensory system.

Although pathological changes in large myelinated nerve fibers can be diagnosed by determination of either conduction velocities or sensory-evoked potentials, none of the standard, objective nerve conduction studies assessed small fiber function. Thermal quantitative sensory testing (QST) has been shown to provide a sensitivity of 67% to...
100% when used to diagnose small-fiber neuropathies.\textsuperscript{15–17} When mechanical tests are added, QST can provide information on the integrity of A\textsubscript{\beta}, A\textsubscript{\alpha}, and C-fibers.\textsuperscript{18,19}

The aim of this study was to systematically evaluate the immediate effects of different acupuncture stimulation techniques on sensory perception evaluated by QST.

**METHODS**

**Subjects**

Twenty-four healthy volunteers (12 men and 12 women) participated in this study. The mean age of the participants was 33.1 ± 2.8 (SEM) years. Study participants did not receive medications or any other medical treatment for at least 4 weeks before inclusion in the study. None of the volunteers had any history of chronic pain, substance misuse, or depression. All subjects participated voluntarily and gave written informed consent. They did not receive any form of compensation. The study was performed according to the Helsinki Declaration and was approved by the local ethics committee.

Subjects were excluded if they were pregnant, had any (even suspected) disease, or reported taking any medication or herbal preparations.

**Design**

Each subject was randomly assigned to 1 of the possible 6 study arms. In each study arm, the participants underwent baseline QST measurement and 3 forms of acupuncture in a random order. The 3 acupuncture treatments were manual acupuncture, LF-EA, and HF-EA. The study design and the participants’ progress throughout the trial are illustrated in Figure 1. The QST was performed by a physician (GMS) who was trained in neurophysiologic testing. He was blinded to the acupuncture treatment and not present in the room during the treatment. In addition, the volunteers were advised not to reveal any information regarding the received acupuncture treatment. Treatments and tests were performed at the same time of the day with an interval of exactly 1 week between each visit. QST was performed immediately after a 30-minute acupuncture session.

**Acupuncture**

Acupuncture points were selected because of their frequent use in pain management: spleen 6,\textsuperscript{20,21} spleen 9,\textsuperscript{22} stomach 36,\textsuperscript{23} and gallbladder 39.\textsuperscript{24} The location of the acupuncture points and the regions where the QST was performed are illustrated in Figure 2. All subjects received acupuncture on the left leg.

Acupuncture was applied by an experienced acupuncturist (JS) with 140 hours of curricular teaching in the major German acupuncture society (DÄGfA) and 2 years of training in practical skills. Acupuncture was performed using sterile single-use acupuncture needles (0.3 × 30 mm, Seirin, Germany). In all 3 groups, a de Qi sensation was
elicited after penetration of the skin in a depth of approximately 1 cun. In the manual acupuncture group, a second stimulation was given midway through the session by rotation of the needle. EA was performed by using an electrical device (AS Super 4, Schwa-Medico, Ehringshausen, Germany) connected by insulated cables with clamps that were hooked up at the acupuncture needles. For LF-EA, a frequency of 2 Hz was used and for HF-EA, 100 Hz (pulse duration was 60 microseconds for both LF and HF). Stimulus intensity was increased, so that the patient felt the stimulation strongly, but not painfully (2–8 mA). Each acupuncture treatment lasted 30 minutes.

Test persons received standardized information about acupuncture and its possible effects and adverse effects. No other interventions were performed.

**Quantitative Sensory Testing**

The comprehensive QST protocol was developed by the German Research Network on neuropathic pain to improve the diagnostic value of QST and provide a broad basis of reproducible results.\(^{19,25}\) QST was performed under identical conditions, after providing each subject a standardized set of instructions. QST measurements were performed by an independent, blinded examiner. All subjects were tested in a comfortable position in a quiet room. Subjects were not permitted visual access to the QST computer screen and were not given visual or auditory clues to indicate the start of the stimulus. The anterolateral skin of the lower limb (sensory region of the peroneal nerve: L4) was tested bilaterally.

The QST procedure started with determination of the thermal followed by mechanical thresholds. The detailed QST protocol including reference data is reported elsewhere.\(^{25}\) In brief, the following testing procedures were performed.

**Thermal Testing**

Thermal tests were conducted by means of a Peltier-based computerized thermal stimulator (TSA II, Medoc, Ramat Ishai, Israel) with a 3 × 3 cm contact probe. All thresholds were measured using ramped stimuli (\(1^\circ\)C/s) until the subject pressed a stop button. Cutoff temperatures were 0°C and 50°C. First, cold and warm detection thresholds were assessed. Subjects were then asked whether they felt a prick or a blunt touch. Afterward, cold and heat pain thresholds were obtained.

**Mechanical Testing**

Mechanical detection thresholds were measured with a set of von Frey filaments forming a geometric series, differing by a factor of 2 from 0.25 to 512 mN (MARSTOCKnervtest, Marburg, Germany). Using the method of limits, 5 ascending and 5 descending series of stimuli were applied (1-second duration per stimulus).

Mechanical pain thresholds were measured in a similar manner to the former test using punctate mechanical stimulators (blunt pinpricks) forming a geometric series, differing by a factor of 2 from 8 to 512 mN (Department of Physiology and Pathophysiology, Mainz, Germany). The pinpricks had a sharp noninjuring tip with a diameter of 0.2 mm.\(^{26}\) Upon application of the probe, the subjects were asked to decide whether they felt a prick or a blunt touch.

Stimulus-response function for the mechanical pain sensitivity was determined using the same pinpricks already described above, which activate A\(_\delta\)-nociceptors.\(^{26,28}\) Pain in response to light touch (dynamical mechanical allodynia) was tested by light stroking with a cotton wisp (3 mN), a cotton wool tip fixed to an elastic strip (100 mN), and a brush (200–400 mN). Each of the 7 intensities of pinpricks and 3 intensities of light stroking was applied 5 times in a randomized sequence. The subjects were asked to rate pain on a numerical rating scale (0 = no pain and 100 = maximal imaginable pain). The mechanical pain sensitivity was calculated as the arithmetic mean of all pain ratings for pinprick stimuli. Dynamic mechanical allodynia was quantified as the arithmetic mean of all numerical pain ratings after light touch stimuli.

The windup ratio was examined using 10 repetitive pinprick stimuli (1 Hz) compared with a single pinprick stimulus with a force of 256 mN. Windup ratio was calculated as the mean pain rating of 5 series of repetitive pinprick stimuli divided by the mean pain rating of 5 single stimuli.

Vibration detection thresholds were examined with a Rydel-Seiffer tuning fork (64 Hz) that has a graded readout of vibration amplitude (from 0 to 8). Vibration detection threshold was assessed with 3 series of descending stimulus intensities.

Pressure pain thresholds were measured using a pressure algometer (FDK20, Wagner Instruments, Greenwich, CT) with a range between 2 and 20 kg. The algometer had a rubber tip with a contact area of 1 cm\(^2\). The algometer was pressed to the skin with an increasing ramp of 0.5 kg/s, and the patient was asked to respond verbally as soon as the pressure became painful. This procedure was performed 3 times.

**Data Analyses**

All continuous variables are given as mean ± SEM. Statistical inferences were based on mixed linear models for each QST parameter as dependent variable using the MIXED procedure of SAS 9.1 (SAS Institute, Cary, NC). The model included a random intercept for each participant and the fixed effects treatment (baseline, manual acupuncture, LF-EA, and HF-EA), side (left = treated versus right = untreated), interaction of treatment and side, age (entered numerically), and sex. Because of the exploratory nature of our analyses, no \(\alpha\) adjustment for multiple testing was undertaken. Raw \(P\) values <0.05 were regarded as statistically significant. Therefore, the test results must not be taken as absolutely confirmatory.

Formal sample size estimation (power calculation) was not performed because of the hypothesis-generating nature of the study.

**RESULTS**

Twenty-four volunteers (12 of each gender) participated in this study. All subjects completed all interventions and measurements; there were no dropouts. None of the subjects experienced any major or minor adverse event.
Sensory data obtained by QST are presented in Table 1. All sensory variables under the defined conditions (baseline, manual acupuncture, LF-EA, and HF-EA) are illustrated to indicate the treated and untreated side.

Statistical analysis was performed to test whether sensory variables are affected by acupuncture treatment (intervention), the side (treated versus untreated side), and the interaction of both. The main results of the mixed linear models are listed in Table 2. It should be noted that the presented type III analyses of effects are adjusted for gender and age. Whereas gender does not affect the investigated sensory variables (all P values > 0.15), age has an effect on the sensory variables cold detection thresholds (P = 0.0002), warm detection thresholds (P = 0.0008), thermal sensory limen (P = 0.0012), heat pain threshold (P = 0.0065), mechanical detection thresholds (P < 0.0001), and mechanical pain sensitivity (P = 0.0176), which has been described.25

**Intervention**

Thermal and mechanical thresholds were affected immediately after different types of acupuncture stimulation.

**Manual Acupuncture**

Painful heat was detected at higher temperatures shortly after manual acupuncture on both sides compared with baseline. Quantitatively, heat pain threshold increased from a value at baseline of 43.3°C ± 0.8°C (both sides) to 45.2°C ± 1.1°C (treated) and 45.0°C ± 0.6°C (untreated) after manual acupuncture. The results of heat pain threshold are illustrated in Figure 3.

---

**Table 1. Quantitative Sensory Testing at Baseline (BL), After Manual Acupuncture (MA), After Acupuncture with Electrostimulation with Low (LF) and High Frequency (HF)**

<table>
<thead>
<tr>
<th>Temperature tests</th>
<th>BL Left</th>
<th>BL Right</th>
<th>MA Left (treated)</th>
<th>MA Right</th>
<th>LF Left (treated)</th>
<th>LF Right</th>
<th>HF Left (treated)</th>
<th>HF Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold detection threshold, CDT (°C from baseline)</td>
<td>−3.6 ± 0.9</td>
<td>−3.4 ± 0.6</td>
<td>−3.6 ± 0.4</td>
<td>−4.0 ± 0.6</td>
<td>−3.4 ± 0.4</td>
<td>−4.3 ± 0.7</td>
<td>−3.9 ± 0.4</td>
<td>−4.7 ± 0.6</td>
</tr>
<tr>
<td>Warm detection threshold, WDT (°C from baseline)</td>
<td>7.0 ± 0.6</td>
<td>7.5 ± 0.6</td>
<td>7.3 ± 0.9</td>
<td>7.6 ± 0.6</td>
<td>6.5 ± 0.6</td>
<td>8.5 ± 0.6</td>
<td>7.3 ± 0.6</td>
<td>7.4 ± 0.6</td>
</tr>
<tr>
<td>Thermal sensory limen, TSL (°C)</td>
<td>8.1 ± 1.1</td>
<td>12.2 ± 3.9</td>
<td>9.4 ± 1.1</td>
<td>9.7 ± 0.7</td>
<td>9.9 ± 1.2</td>
<td>11.6 ± 1.1</td>
<td>11.1 ± 0.7</td>
<td>10.9 ± 0.8</td>
</tr>
<tr>
<td>Paradoxical heat sensation, PHS (×/3)</td>
<td>1.1 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>Cold pain threshold, CPT (°C)</td>
<td>20.3 ± 2.2</td>
<td>21.2 ± 2.0</td>
<td>17.8 ± 2.4</td>
<td>20.4 ± 2.0</td>
<td>18.7 ± 2.0</td>
<td>18.1 ± 2.2</td>
<td>19.1 ± 2.1</td>
<td>18.5 ± 2.2</td>
</tr>
<tr>
<td>Heat pain threshold, HPT (°C)</td>
<td>43.3 ± 0.8</td>
<td>43.3 ± 0.8</td>
<td>45.2 ± 1.1</td>
<td>45.0 ± 0.6</td>
<td>44.3 ± 0.8</td>
<td>44.8 ± 0.8</td>
<td>45.6 ± 0.7</td>
<td>44.3 ± 0.9</td>
</tr>
</tbody>
</table>

**Mechanical tests**

| Mechanical detection threshold, MDT (mN) | 19.1 ± 8.1 | 9.5 ± 2.1 | 12.6 ± 3.1 | 5.8 ± 1.1 | 11.5 ± 2.8 | 11.2 ± 5.7 | 14.8 ± 2.9 | 7.0 ± 1.1 |
| Mechanical pain threshold, MPT (mN)      | 23.2 ± 4.9 | 40.3 ± 12.6 | 26.8 ± 6.0 | 49.8 ± 14.5 | 60.0 ± 20.8 | 61.3 ± 17.3 | 52.1 ± 13.1 | 63.5 ± 17.3 |
| Mechanical pain sensitivity, MPS (rating 0–100) | 6.0 ± 2.0 | 5.5 ± 1.7 | 7.5 ± 2.1 | 6.0 ± 1.6 | 5.8 ± 1.5 | 5.5 ± 1.5 | 4.5 ± 1.2 | 5.0 ± 1.4 |
| Allodynia, ALL (rating 0–100)             | 0.3 ± 0.2 | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 |
| Wind up, WUR (ratio)                      | 2.2 ± 0.3 | 2.0 ± 0.3 | 1.8 ± 0.2 | 2.0 ± 0.3 | 2.0 ± 0.3 | 2.4 ± 0.4 | 1.8 ± 0.1 | 1.9 ± 0.1 |
| Vibration detection threshold, VDT (×/8)  | 6.1 ± 0.3 | 6.2 ± 0.4 | 6.3 ± 0.4 | 5.5 ± 0.5 | 5.9 ± 0.3 | 5.8 ± 0.5 | 6.5 ± 0.3 | 5.8 ± 0.4 |
| Pressure pain threshold, PPT (kPa)         | 369 ± 24 | 345 ± 20 | 516 ± 42 | 523 ± 43 | 460 ± 36 | 458 ± 28 | 530 ± 49 | 483 ± 38 |

Data are presented as mean ± SEM.

---

**Table 2. Statistical Analysis: P Values from the Type III Analyses of Effects from the Random Intercept Models**

<table>
<thead>
<tr>
<th>Temperature tests</th>
<th>Intervention</th>
<th>Side</th>
<th>Intervention</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold detection threshold (CDT)</td>
<td>0.0034</td>
<td>0.2001</td>
<td>0.9062</td>
<td></td>
</tr>
<tr>
<td>Warm detection threshold (WDT)</td>
<td>0.9828</td>
<td>0.0104</td>
<td>0.2220</td>
<td></td>
</tr>
<tr>
<td>Thermal sensory limen (TSL)</td>
<td>0.0010</td>
<td>0.0221</td>
<td>0.2633</td>
<td></td>
</tr>
<tr>
<td>Paradoxical heat sensation (PHS)</td>
<td>0.4683</td>
<td>0.9379</td>
<td>0.7679</td>
<td></td>
</tr>
<tr>
<td>Cold pain threshold (CPT)</td>
<td>0.2652</td>
<td>0.5301</td>
<td>0.5334</td>
<td></td>
</tr>
<tr>
<td>Heat pain threshold (HPT)</td>
<td>0.0119</td>
<td>0.5482</td>
<td>0.4959</td>
<td></td>
</tr>
<tr>
<td>Mechanical tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical detection threshold (MDT)</td>
<td>0.0992</td>
<td>&lt;0.0001</td>
<td>0.3092</td>
<td></td>
</tr>
<tr>
<td>Mechanical pain threshold (MPT)</td>
<td>0.0026</td>
<td>0.0575</td>
<td>0.8555</td>
<td></td>
</tr>
<tr>
<td>Mechanical pain sensitivity (MPS)</td>
<td>0.0284</td>
<td>0.3623</td>
<td>0.9691</td>
<td></td>
</tr>
<tr>
<td>Allodynia (ALL)</td>
<td>0.3885</td>
<td>0.2598</td>
<td>0.2946</td>
<td></td>
</tr>
<tr>
<td>Wind up (WUR)</td>
<td>0.1349</td>
<td>0.1512</td>
<td>0.2786</td>
<td></td>
</tr>
<tr>
<td>Vibration detection threshold (VDT)</td>
<td>0.6543</td>
<td>0.0685</td>
<td>0.3389</td>
<td></td>
</tr>
<tr>
<td>Pressure pain threshold (PPT)</td>
<td>&lt;0.0001</td>
<td>0.4303</td>
<td>0.7101</td>
<td></td>
</tr>
</tbody>
</table>

The results are adjusted for age and sex. Interaction of side and treatment (intervention). Measurements (quantitative sensory testing) may depend on the side and on the type of treatment (intervention). In addition, there may be an interaction of side and treatment (intervention × side).

---

**May 2010 • Volume 110 • Number 5**

© International Anesthesia Research Society. Unauthorized Use Prohibited.
After manual acupuncture, the volunteers rated mechanical pain sensitivity on the treated side higher than at baseline ($P = 0.0282$).

A bilateral increase in pressure pain threshold after all types of acupuncture stimulation is illustrated in Figure 4. Manual stimulation resulted in a 40.2% (treated) and 51.7% (untreated) increase in pressure pain thresholds.

**Low-Frequency Electrostimulation**

The thermal sensory limen increased on the treated side from the baseline measurement of $8.1^\circ C \pm 1.1^\circ C$ to $9.9^\circ C \pm 1.2^\circ C$ ($P = 0.0289$) after LF-EA.

The mechanical pain threshold was increased after LF-EA on the treated side only. The mechanical pain threshold after LF-EA was higher ($60.0 \pm 20.8 \text{ mN}$) than at baseline ($55.0 \pm 19.9 \text{ mN}$).
baseline (23.2 ± 4.9 mN) and also higher compared with the mechanical pain threshold after manual acupuncture (26.8 ± 6.0 mN). Figure 5 shows these effects on mechanical pain threshold after electrostimulation.

**LF-EA** resulted in an increase of pressure pain thresholds: 24.9% increase on the treated side and 32.8% increase on the untreated side.

**High-Frequency Electrostimulation**

The cold detection threshold (difference to baseline temperature of 32°C) was slightly changed from 3.6°C ± 0.9°C to 3.9°C ± 0.4°C (P = 0.0275) on the treated side and from 3.4°C ± 0.6°C to 4.7°C ± 0.6°C on the untreated side (P = 0.0035) after HF-EA. Correspondingly, the thermal sensory limen increased on the treated side from the baseline measurement of 8.1°C ± 1.1°C to 11.1°C ± 0.7°C (P < 0.0001) after HF-EA. Painful heat was detected at higher temperatures after HF-EA on the treated side compared with baseline. Quantitatively, heat pain threshold increased from a baseline value of 43.3°C ± 0.8°C (both sides) to 45.6°C ± 0.7°C on the treated side after HF-EA.

The mechanical pain threshold was increased after HF on the treated side only. The mechanical pain threshold after HF-EA was higher (52.1 ± 13.1 mN) than at baseline and after manual acupuncture (Fig. 3).

After HF-EA, mechanical pain sensitivity on the treated side was rated lower than at baseline (P = 0.0403).

**Treated Versus Untreated Side**

After LF-EA, warm detection threshold differed between the left side (treated; 6.5°C ± 0.6°C) and the right side (untreated; 8.5°C ± 0.6°C; P = 0.0030). A difference was also observed on thermal sensory limen testing at baseline between the treated side (8.1°C ± 1.1°C) and untreated side (12.2°C ± 3.9°C; P = 0.0231).

Mechanical detection thresholds tested by von Frey hairs differed from treated to untreated side after each of the investigated acupuncture interventions (manual acupuncture, P = 0.0017; LF-EA, P = 0.0114; and HF-EA, P = 0.0016). In general, higher stimulation intensities were needed on the left (treated) side.

**DISCUSSION**

This study demonstrated the immediate effects of different acupuncture interventions on perception and pain thresholds in healthy adults observed by QST. In general, there was bilateral inhibition of sensory thresholds with unilateral needling. The type of acupuncture stimulation applied was found to influence whether the changes in pain thresholds were unilateral or bilateral.

**Manual Acupuncture**

The literature is inconclusive about acupuncture effects on thermal thresholds and pressure pain. Prior studies found a nonsignificant increase in cold detection and pain thresholds and heat pain threshold after manual acupuncture, whereas Ashton et al. concluded that acupuncture increased cold detection thresholds. Our data show that heat pain threshold is increased immediately after manual acupuncture. This suggests that transduction and/or transmission of thermal (noxious) stimuli via C-fibers (heat pain threshold) might be affected by acupuncture stimulation.

To explain the observed effects of acupuncture on pressure...
pain thresholds, we hypothesize that the underlying analgesic effect may be attributable to an inhibitory action of acupuncture on nociceptive C-fibers; however, the relative contribution of Aδ- and C-fiber nociceptors to pressure pain thresholds is still unclear. There are additional potential mechanisms regarding the effect of acupuncture on pressure pain thresholds, which will be discussed below.

Low-Frequency Electrostimulation
Our data suggest that LF-EA affects only mechanical thresholds. The analgesic effect of EA on pressure pain thresholds was observed before: LF-EA (4 Hz) with high intensity increased pressure pain thresholds bilaterally in a significant manner compared with placebo. A mechanism explaining these effects could be the induction of long-term depression of nociception in the spinal cord after Aδ- and C-fiber stimulation. Another possible mechanism that would explain our findings is the release of endogenous opioids after EA. Both mechanisms would allow us to understand the bilateral effects of acupuncture stimulation on pressure pain thresholds.

Our results show a remarkable bilateral increase in pressure pain thresholds after LF-EA. In contrast, mechanical pain threshold using blunt pinpricks was increased only on the treated side. This change in mechanical pain threshold was not observed after manual acupuncture. EA with low and high stimulation may lead to local activity-induced hyperpolarization of the axon because of the effect of electrical stimulation on Na⁺/K⁺ pumps. Potentially, the contrast in probe size of the different stimuli (mechanical pain threshold: blunt tip of 0.2 mm diameter; pressure pain thresholds: tip of 1 cm²) leads to a distinct activation pattern of sensory nerves, with the response to pressure pain thresholds being mediated by the summation of a number of sensory afferents whereas mechanical pain threshold more likely represents the excitability of a small number or even a single small nerve fiber. Whereas Aδ-fiber function is represented by mechanical pain threshold, the relative contribution of Aδ- and C-fiber nociceptors to pressure pain thresholds is less clear. It was found that homotopic acupuncture stimulation induced moderate depressive effects of the C-fiber reflex in an animal study. The results obtained by different mechanical pain tests lead us to the assumption that local, segmental, and systemic factors are involved in the antinociceptive action of acupuncture.

High-Frequency Electrostimulation
Thermal perception was affected in a bilateral way by HF-EA: cold detection thresholds and the thermal sensory limen were altered. Bilaterally increased warm detection thresholds have been shown after EA, whereas the heat pain score decreased during EA. Heat pain threshold was increased immediately after HF-EA only on the treated side. EA provided analgesia against noxious heat, suggesting that longer stimulation is more effective. Alteration in C-fiber activity caused by HF-EA might be a possible mechanism.

The effects of HF-EA on mechanical thresholds are similar to those resulting from LF-EA: pressure pain thresholds increased bilaterally, whereas mechanical pain threshold changed only on the treated side. Again, possible mechanisms are long-term depression, release of endogenous opioids, and a peripheral effect on Aδ- and C-fibers.

Mechanisms Underlying Acupuncture Stimulation
There continues to be a lack of clarity regarding the nerve fibers affected by acupuncture stimulation. Initially, acupuncture stimulation was thought to stimulate Aβ-fibers, which, based on the modified gate-control theory, could act to inhibit nociceptive transmission. More recently, there is evidence to suggest that acupuncture activates Aδ- and C-fibers, which might alter pain transmission at the spinal cord, midbrain, and hypothalamus. Hypothalamic activation can then lead to systemic, pain-modifying effects by the release of substances such as β-endorphin. The diffuse noxious inhibitory control mechanism should also be considered as a possible explanation for the analgesic action of acupuncture. Finally, there is experimental evidence that neuropeptides (nociceptin/orphanin) may be involved in the antinociceptive mechanism of acupuncture electrostimulation.

Information from acupuncture stimulation might be conducted by nociceptive afferents and low-threshold mechanoreceptive afferents entering the dorsal horn. The low-threshold mechanoreceptive might then activate an inhibitory interneuron resulting in postsynaptic inhibition of both the projection neuron and presynaptic inhibition of its own activity.

Tissue trauma after acupuncture needle might liberate adenosine triphosphate (ATP) from damaged cells. ATP and adenosine (degraded from ATP) have both inhibitory and excitatory effects on unmyelinated human C-fibers by the activation of purinergic receptors. This could serve as an explanation for the effects on the treated side; a systemic effect from ATP release seems unlikely but cannot be excluded.

The presented results are in accordance with findings that demonstrated bilateral or mirror-image electromyographic activity associated with unilateral needle stimulation of active myofascial trigger points.

Implications for Future Trials
The lack of dramatic changes in the sensory data might be explained by the fact that all participants were healthy. Acupuncture might have a greater effect in altering sensory thresholds in individuals with various disease states, such as those with neuropathic pain. Future studies should observe the acupuncture effects on sensory thresholds in patients with various medical conditions. Those observations might give further insight into how acupuncture may modulate antinociceptive systems.

The presence of bilateral effects of unilateral acupuncture stimulation strengthens our discussion of the effect of acupuncture on segmental inhibition with possible activation of descending pain inhibitory systems. A systemic acupuncture-induced effect can be assumed but not verified by our study. To differentiate between segmental and systemic effects, it might be desirable to conduct trials that include a further sensory test site, such as the arm, which is outside the influence of potential segmental inhibition.

Technical Considerations
The results obtained in this study could be influenced by mechanisms other than acupuncture. It cannot be excluded...
that habituation or learning might have had an effect on the acquired results. In addition, QST is a psychophysical test and therefore depends on patients’ cooperation. However, although these nonspecific effects cannot be excluded completely, it is less likely given the use of a crossover study design.

Some of the results obtained by QST should be interpreted with caution. Significant results found on thermal sensory limen may reflect additive changes observed in cold detection thresholds and warm detection thresholds. The significant differences found between treated and untreated sides on thermal testing (warm detection thresholds, thermal sensory limen, and mechanical detection thresholds) may have arisen by chance, given the relatively small number of subjects. Our data are not influenced by a gender effect. However, in the literature, there is evidence that healthy female volunteers have lower pressure pain thresholds than male subjects.

We measured the effects for only a few minutes after the cessation of acupuncture stimulation; therefore, we cannot make a statement regarding the change in pain thresholds after acupuncture over time. In a mouse model of cutaneous cancer pain, the analgesic effect reached its maximum within 15 to 30 minutes and decreased afterward to a minimum at 50 minutes after electroacupuncture stimulation. Given these results in an animal model, we may have missed the optimal time to study the sensory thresholds in our participants. However, this possibility only strengthens our results. A washout phase of 1 week seems sufficient after a single acupuncture treatment according to several trials.

In this crossover design, we did not use a placebo control. However, the results of 1 study demonstrate that expectation about pain and analgesia influence cognitive control of central sensitization. It is unlikely that our results are attributable to expectancy of the participants, in that one would expect that this kind of cognitive effect would alter all the sensory thresholds but we found that only 1 thermal and 2 mechanical pain thresholds changed. In addition, studies in humans evaluating thermal thresholds showed no evidence of a placebo effect with acupuncture.

CONCLUSION
Different types of acupuncture stimulation modify pain thresholds with relation to Aδ- and C-fibers. This study indicates that there are local as well as segmental and/or systemic inhibitory effects involved in antinociception mediated by acupuncture.

ACKNOWLEDGMENTS
Intellectual support was provided by the German Medical Association of Acupuncture (DÄGfA). The authors thank Dr. Alexander Crispin for the statistical analyses, helpful discussions, and critical reading of the manuscript. Parts of the presented results are topics of the thesis by JS.

REFERENCES
Quantitative Sensory Testing Detects Acupuncture Analgesia


27. Greenspan JD, McGillis SL. Stimulus features relevant to the perception of sharpness and mechanically evoked cutaneous pain. Somatosens Mot Res 1993;8:137–47


34. Zhu B, Xu WD, Rong PJ, Ben H, Gao XY. A C-fiber reflex inhibition induced by electroacupuncture with different intensities applied at homotopic and heterotopic acupoints in rats selectively destructive effects on myelinated and unmyelinated afferent fibers. Brain Res 2004;1011:228–37


