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Research Article



Being Adaptive to Pain Enhances Sham Acupuncture Analgesia: A Crossover Healthy Human Study

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Abstract

We have reported a model that distinguishes pain adaptive individuals (PA) from those who are pain non-adaptive (PNA). The present randomised, cross-over, participant-assessor blinded study aimed to determine the impact of pain adaptability on individuals' response to real and sham acupuncture. Healthy volunteers (nine PA and 13 PNA) were randomly allocated to receive real and sham acupuncture on the left hand and forearm in two separate acupuncture sessions. Pressure pain thresholds (PPTs) were measured at bilateral forearms and right leg before, immediately after and 20 minutes after the end of acupuncture. Ratings to pinprick and suprathreshold PPT were also recorded. The two groups were comparable in their demographic and baseline data. Analgesia induced by real or sham acupuncture did not differ on any outcome measures. PA responded to acupuncture needling better than PNA, and to sham needling (20% increase in PPT) better than to real acupuncture (7.9%). Those differences were at 20 min after

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end of acupuncture in the areas distant to the needling sites. PNA reported little changes in PPT. Being adaptive to pain was associated with enhanced distant analgesia in response to sham acupuncture. Our finding might partly explain varied acupuncture analgesia in clinical practice and trials.

1. Introduction

Acupuncture is increasingly used for pain relief. Many clinical trials have been conducted to assess the efficacy of acupuncture for various clinical pains, including headache [1], low back pain [2], osteoarthritis [3], neck pain [4], and shoulder pain [5,6]. The commonly used control is sham acupuncture, where needles are inserted shallowly into sites that are nonacupoints (but close to the site of real acupoints), and De Qi sensation is avoided. De Qi, a complex sensation of aching, soreness, heaviness, and others [7], indicates the appropriate dose having been achieved. This form of invasive sham acupuncture has been criticized for being noninert as it has real physiological effect [8–10], therefore contributing to the small differences between real and sham acupuncture observed in many clinical trials [11].

It is known that acupuncture exerts its analgesia through activating endogenous pain inhibitory systems. The systems include segmental inhibition, where analgesia is exhibited at the bilateral nerve segmental distributions around the site of the needling [12], and conditioned pain modulation, where analgesia is exhibited at multiple sites over the body away from the needling site [12,13]. For instance, needling Hegu (LI4), increases pressure pain thresholds (PPT) in healthy volunteers on multiple parts of the body, such as the contralateral arm, legs, and abdomen [14]. Electroacupuncture on one of the legs increases pain threshold on the same and opposite legs, but has little effect on pain threshold on the arm [15]. Those studies support the view that acupuncture analgesia relies on the functionality of the endogenous pain controls.

In addition to inhibition, a recent study identifies the dichotomy of pain adaptability, that is, pain adaptive (PA) and pain nonadaptive (PNA) individuals [16]. When undergoing a 5-minute cold pressor test, PA individuals reported a fast increase in pain, then a significant reduction of pain intensity by at least two of 10 at end of the test, whereas PNA had a slower increase of pain to cold pressor and the pain remained high throughout the test. Furthermore, being adaptive to pain was associated with the potency of local pain inhibition, but was not correlated with the potency of conditioned pain modulation. Pain adaptability could be a representation of a facilitation-inhibition circuitry that has rarely been explored before.

This randomized, double-blind (participant and assessor), sham-acupuncture controlled, crossover study involved healthy participants and aimed to investigate (1) if pain adaptability impacted on individual responses to real and sham acupuncture and (2) the spatial distribution of acupuncture analgesia in PA and PNA individuals.

2. Materials and methods

The present study was conducted at the Aalborg University, Denmark, with the approval of the Research Ethics Committee of the North Denmark Region (20120079) and endorsement by the RMIT Human Research Ethics Committee (19156). From March to October 2013, healthy volunteers whose pain adaptability status were previously determined [16] were invited to take part in this study. Twenty-two of them gave written consent to be part of this study. Briefly, the selection criteria were aged between 18 and 50 years, without any ongoing pain or other health issues, fluent in English and without acupuncture experience in the last 3 years. Nine of them were PA with a better pain reduction at the end of the cold pressor test (≥ 2 from their maximum pain from the cold pressor), and 13 were PNA with less pain reduction at the end of the cold pressor test (< 2 from their maximum pain). In the present study, they were randomly allocated to receive real and sham acupuncture in two separate sessions (Fig. 1), with half receiving real first then sham, and the other half receiving sham first then real acupuncture. Before the first session, each participant drew a sealed envelope out of a stack of 22, each containing a number corresponding to a random number sequence generated using Excel by an independent researcher (ZZ). This researcher enrolled and allocated the participants. During the tests and interventions, participants were positioned comfortably in a reclining position in a dental chair with arms rested on the armrests and legs elevated to just below hip level.

At baseline, participants were asked to complete questionnaires about their demographics, mental and physical health (SF-36) [17], and level of anxiety (State Trait and Anxiety Test) [18]. Before each acupuncture session, participants were asked about their sleep quality from the night before on a numerical rating scale of 0–10, where 0 means the worst sleep and 10 the best sleep quality, and whether or not they had done any strenuous exercise or taken coffee in the past 24 hours. Female participants were asked about their menstrual cycle. These factors were considered as they are known to affect pain sensitivity [19–21].

2.1. Acupuncture

The real and sham acupuncture protocols followed a credible blinding procedure [22]. LI4 and LI10 were chosen in real acupuncture because of their pain-reduction effect. After insertion, needles were manipulated for 1 minute to achieve De Qi, and this procedure was repeated for a total of three times every 10 minutes. In sham acupuncture, needles were shallowly inserted into sham LI4 and LI10 to

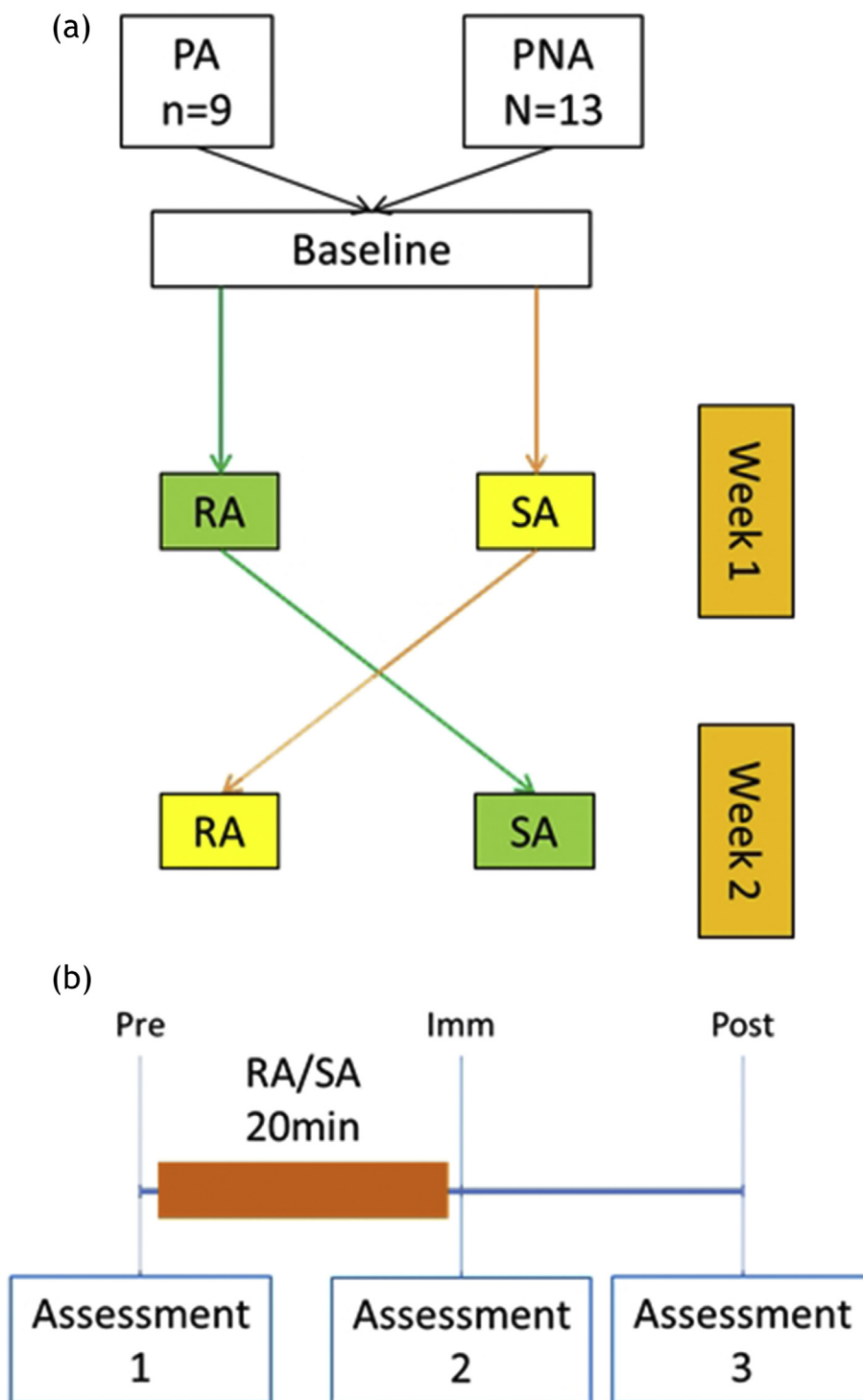


Figure 1 Study procedure (A) and assessments during each session (B). Assessment includes pressure pain threshold, rating to suprathreshold pressure stimulus and pinprick, and rating to real or sham acupuncture stimulation during the treatment. Imm = immediately after acupuncture; PA = pain adaptive; PNA = pain nonadaptive; Post = 20 minutes after the end of acupuncture; Pre = preacupuncture; RA = real acupuncture; SA = sham acupuncture.

avoid De Qi (see [Supplementary file S1](#) for locations of those points). The acupuncturist moved the needles gently and briefly every 10 minutes. The needle retention time was 20 minutes for both modes of acupuncture.

Disposable stainless steel needles of size 0.25×25 mm were used (Phoenix Medical Direct Ltd, Chelmsford Essex,

UK). A pillow was used to block the view of the participants so that they could not see the needling procedure. The acupuncturist (GI) had over 1-year experience in clinical practice.

Sensation to needling was recorded using a modified 0–10 electronic visual analogue scale (0 being no sensation

at all, 5 being just painful, and 10 being the worst pain possible; Aalborg University) and the Massachusetts General Hospital acupuncture sensation scales [7]. Side effects of acupuncture needling were also recorded. The acupuncturist's interaction with participants was minimal to reduce potential bias.

2.2. Outcome measures

The primary outcome measure was PPT measured using an algometer (Somedic Production AB, Norra Mellby, Sweden) at three locations (Fig. 2), including bilateral extensor carpi radialis (testing local and segmental pain inhibition) and the right soleus (testing conditioned pain

modulation). Secondary outcome measures included ratings to pinprick (PIN; 512 mN, 0.2 mm diameter) and to 150% PPT, suprathreshold pressure stimulus (SUPRA) delivered using a force gauge (FG-5020, Lutron Electronic Enterprise Co, Ltd, Taipei, Taiwan; 0.01–20 kg) on a modified numerical rating scale (0 being no sensation, 5 being just painful, and 10 being the worst possible pain), as described in a previous study [16]. All the psychophysical tests were performed before, immediately after and 20 minutes after the acupuncture session (Fig. 1) at the three previously mentioned locations in a randomized order. The average of three readings was recorded for each site. The skin temperature at the acupuncture points was measured using an infrared camera (Guangzhou SAT Infrared Technology Co., Ltd) before acupuncture.

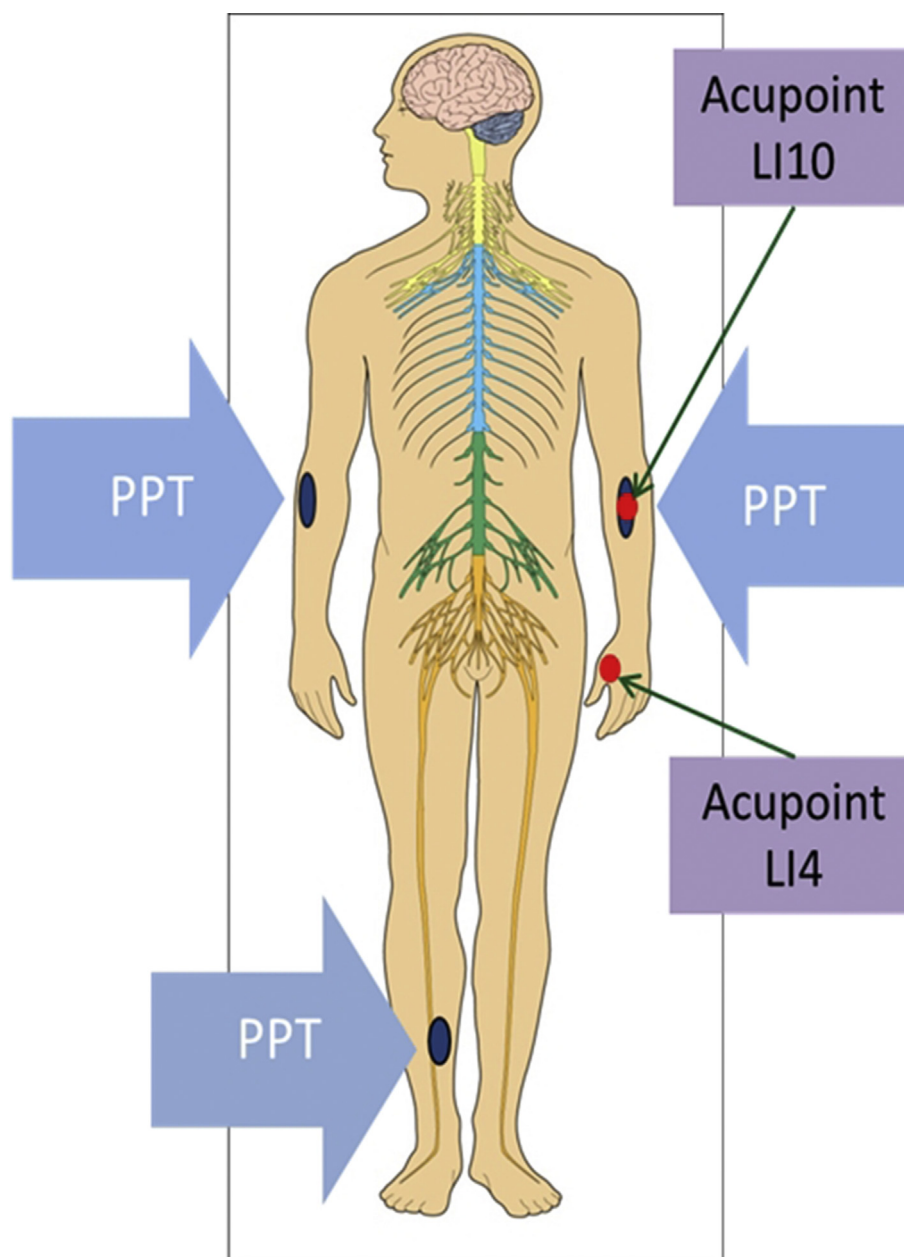


Figure 2 Sites for PPT measurement and acupoints LI10 and LI4. (PPT = pressure pain threshold).

Table 1 Baseline characteristics of PA and PNA (mean \pm SD).

| Baseline characteristics | PA (<i>n</i> = 9) | PNA (<i>n</i> = 13) | χ^2/t_{20} tests | <i>p</i> -Value | Adjusted significance [#] |
|----------------------------------|--------------------|----------------------|-----------------------|-----------------|------------------------------------|
| Age | 28.11 \pm 9.97 | 25.92 \pm 6.40 | 0.63 | 0.54 | 0.01 |
| Gender M/F | 3/6 | 5/8 | 0.06 | 0.81 | 0.03 |
| SF-36 physical component summary | 85.22 \pm 6.53 | 86.69 \pm 7.02 | -0.50 | 0.63 | 0.02 |
| SF-36 mental component summary | 75.00 \pm 15.86 | 81.31 \pm 12.45 | -1.05 | 0.31 | 0.01 |
| SF-36 total | 81.22 \pm 10.59 | 85.23 \pm 9.39 | -0.94 | 0.36 | 0.01 |
| RA—STAI (State) | 31.44 \pm 7.83 | 38.85 \pm 10.57 | -1.78 | 0.09 | 0.00 |
| RA—sleep quality | 8.39 \pm 0.70 | 7.85 \pm 1.41 | 1.20 | 0.25 | 0.00 |
| RA—coffee intake Y/N | 7/2 | 8/5 | 0.65 | 0.42 | 0.01 |
| RA—exercise Y/N | 2/7 | 3/10 | 0.00 | 0.96 | 0.05 |
| SA—STAI (State) | 32.56 \pm 8.53 | 37.46 \pm 8.10 | -1.37 | 0.19 | 0.00 |
| SA—sleep quality | 8.39 \pm 0.86 | 7.23 \pm 1.83 | 1.99 | 0.06 | 0.00 |
| SA—coffee Y/N | 8/1 | 10/3 | 0.51 | 0.47 | 0.01 |
| SA—exercise Y/N | 3/6 | 3/10 | 0.28 | 0.60 | 0.01 |

PA = pain adaptive; PNA = pain nonadaptive; RA = real acupuncture; SA = sham acupuncture; SD = standard deviation; SF-36 = short form 36 items survey, to measure the quality of life; STAI, state-trait anxiety inventory; Y/N = yes or no.

[#] Holm-Bonferroni-adjusted significance.

Table 2 Pain sensitivity measured before each acupuncture session (mean \pm SD).

| Sessions | Outcome measures before acupuncture | Sites | PA (<i>n</i> = 9) | PNA (<i>n</i> = 13) | <i>t</i> ₂₀ | <i>p</i> -Value | Adjusted significance [#] |
|-------------------------|-------------------------------------|-------------|---------------------|----------------------|------------------------|-----------------|------------------------------------|
| Before real acupuncture | PPT (kPa) | Left arm | 231.30 \pm 81.11 | 189.06 \pm 79.15 | 1.22 | 0.24 | 0.03 |
| | | Right arm | 266.78 \pm 82.40 | 198.85 \pm 75.66 | 2.00 | 0.06 | 0.02 |
| | | Right leg | 389.26 \pm 150.68 | 347.38 \pm 135.11 | 0.68 | 0.50 | 0.05 |
| | SUPRA (NRS) | Left arm | 6.56 \pm 1.57 | 5.96 \pm 1.38 | 0.94 | 0.36 | 0.03 |
| | | Right arm | 6.78 \pm 1.33 | 5.58 \pm 1.59 | 1.86 | 0.08 | 0.02 |
| | | Right leg | 6.94 \pm 1.42 | 6.31 \pm 1.69 | 0.92 | 0.37 | 0.05 |
| | PIN (NRS) | Left arm | 4.17 \pm 1.97 | 3.46 \pm 1.45 | 0.97 | 0.34 | 0.02 |
| | | Right arm | 3.83 \pm 2.18 | 3.77 \pm 1.48 | 0.08 | 0.94 | 0.05 |
| | | Right leg | 3.67 \pm 2.18 | 3.58 \pm 1.19 | 0.11 | 0.91 | 0.03 |
| | Skin temperature (°C) | Point LI 10 | 33.58 \pm 1.71 | 32.49 \pm 1.52 | 1.54 | 0.14 | 0.02 |
| | | Point LI 4 | 31.81 \pm 2.98 | 31.86 \pm 2.71 | -0.04 | 0.97 | 0.05 |
| | | Thumb | 30.90 \pm 4.02 | 29.91 \pm 4.39 | 0.53 | 0.60 | 0.03 |
| Before sham acupuncture | PPT (kPa) | Left arm | 205.48 \pm 74.02 | 216.51 \pm 97.55 | -0.29 | 0.78 | 0.02 |
| | | Right arm | 236.59 \pm 84.83 | 241.21 \pm 96.81 | -0.12 | 0.91 | 0.05 |
| | | Right leg | 348.96 \pm 142.84 | 361.09 \pm 134.77 | -0.20 | 0.84 | 0.03 |
| | SUPRA (NRS) | Left arm | 6.06 \pm 1.18 | 6.19 \pm 1.20 | -0.26 | 0.79 | 0.05 |
| | | Right arm | 6.67 \pm 0.97 | 6.23 \pm 1.26 | 0.88 | 0.39 | 0.03 |
| | | Right leg | 6.89 \pm 1.52 | 6.31 \pm 1.38 | 0.93 | 0.36 | 0.02 |
| | PIN (NRS) | Left arm | 4.06 \pm 1.91 | 3.35 \pm 1.82 | 0.88 | 0.39 | 0.02 |
| | | Right arm | 3.33 \pm 2.00 | 3.62 \pm 1.70 | -0.36 | 0.73 | 0.03 |
| | | Right leg | 3.39 \pm 2.26 | 3.35 \pm 1.77 | 0.05 | 0.96 | 0.05 |
| | Skin temperature (°C) | Point LI 10 | 33.38 \pm 1.15 | 33.68 \pm 1.45 | -0.53 | 0.60 | 0.03 |
| | | Point LI 4 | 32.43 \pm 2.25 | 32.65 \pm 1.51 | -0.28 | 0.79 | 0.05 |
| | | Thumb | 32.59 \pm 1.99 | 31.91 \pm 2.73 | 0.64 | 0.53 | 0.02 |

[#] Holm-Bonferroni-adjusted significance.

p values lower than the adjusted significance are considered significant; NRS = numerical rating scale 0–5–10, 0 meaning no sensation at all, 5 being just painful, and 10 the worst pain possible; PA = pain adaptive; PIN = pain rating to pinprick; PNA = pain nonadaptive; PPT = pressure pain threshold; RA = real acupuncture; SA = sham acupuncture; SD = standard deviation; SUPRA = pain rating to suprathreshold pressure stimulus.

Table 3 Needling sensation in PA and PNA during real and sham acupuncture (mean \pm SD).

| Needling sensation | Real acupuncture | | Sham acupuncture | | Session effect (RA vs. SA session) | | Group effect (pain adaptability) | | Group by session effect | |
|------------------------|-------------------|-------------------|-------------------|-------------------|------------------------------------|---------|----------------------------------|---------|----------------------------|---------|
| | PA (n = 9) | PNA (n = 13) | PA (n = 9) | PNA (n = 13) | F _(1,20) -value | p-Value | F _(1,20) -value | p-Value | F _(1,20) -value | p-Value |
| Peak sensation (e-VAS) | 4.31 \pm 2.22 | 5.80 \pm 1.84 | 2.06 \pm 2.91 | 2.47 \pm 2.16 | 29.40 | 0.00* | 0.96 | 0.34 | 1.33 | 0.26 |
| End sensation (e-VAS) | 2.97 \pm 2.27 | 4.78 \pm 2.58 | 1.36 \pm 2.01 | 1.89 \pm 1.92 | 17.35 | 0.00* | 1.70 | 0.21 | 1.59 | 0.22 |
| Total De Qi (MASS) | 26.56 \pm 16.39 | 27.62 \pm 14.14 | 14.61 \pm 18.42 | 14.54 \pm 12.42 | 16.85 | 0.00* | 0.01 | 0.93 | 0.04 | 0.85 |

e-VAS = electronic visual analogue scale; 0 meaning no sensation at all, 5 being just painful, and 10 the worst pain possible; MASS = Massachusetts General Hospital acupuncture sensation scale; PA = pain adaptive; PNA = pain nonadaptive; RA = real acupuncture; SA = sham acupuncture; SD = standard deviation.
*Significant *p* value.

2.3. Blinding and assessment of expectancy and blinding

Participants were blinded from the type of acupuncture they were receiving. The assessor, responsible for the psychophysical tests (DWLW), was blinded from the type of acupuncture the participants received at each session. Both the assessor (DWLW) and acupuncturist (GI) were blinded from the status of pain adaptability of the participants.

Before each intervention, participants were asked to answer whether they expected their pain thresholds to increase, decrease, not to change, or they did not know what to expect after the acupuncture sessions. At the end of each intervention, participants were given a validated Acupuncture Credibility Scale [15] to indicate their guess of if they received real or sham acupuncture and on what they based their decision.

2.4. Data analysis

All analyses were conducted in SPSS version 23, IBM, USA. Independent *t* tests and Chi-square tests were used to analyze the baseline data. Three-way (site, acupuncture session, and pain adaptability) with two repeated-measures (site and acupuncture session) analysis of variance (ANOVA) were used to assess the main effect of mode (real and sham acupuncture), site and adaptability type (PA and PNA), and their interactions in the percentage changes of PPTs, SUPRA, and PIN. Appropriate *post-hoc* analyses, such as two-way ANOVA or independent *t* tests, were used when necessary. Data were presented as mean and standard deviation in the texts and tables and as mean and standard error of mean in the figures. A *p* < 0.05 was considered to be statistically significant. The Holm-Bonferroni correction was used for multiple comparisons. A *p*-value that was smaller than the Holm-Bonferroni-adjusted significance was considered statistically significant.

3. Results

3.1. Baseline data

All 22 participants completed the two-session experiment. The two groups (PA and PNA) were comparable in their demographic data and key baseline data (Table 1), in PPT, SUPRA, and PIN at the three sites, and in skin temperature at the needling site before acupuncture (Table 2). For women, there were no differences in their menstrual cycle phases (Table A).

3.2. Needling sensation perceived by PA and PNA groups

Both PA and PNA groups rated the peak sensation induced by acupuncture as mild pain (5.2 \pm 2.1), and significantly stronger than the nonpainful sensation induced by sham acupuncture (2.3 \pm 2.5). PA and PNA did not differ on this measure (Table 3). Consistently, there were no differences between PA and PNA in their rating to the needling sensation at the end of the session. De Qi

sensation as assessed with the Massachusetts General Hospital acupuncture sensation scales was considered to be stronger during the acupuncture session than the sham acupuncture session, with no differences between PA and PNA groups (Table 3). Sensations induced by acupuncture were consistently rated stronger than sham acupuncture on aching, soreness, deep pressure, heaviness, fullness, numbness, sharp pain, and dull pain, but not on cold, warmth, tingling, or throbbing (Table B).

3.3. PPT changes after real and sham acupuncture

Immediately after acupuncture, there were no statistically significant changes in PPT between two acupuncture sessions ($F_{(1,20)} = 0.05, p = 0.82$), at all three sites (left arm, right arm, and right leg; $F_{(1,20)} = 0.56, p = 0.58$), or between pain adaptability groups ($F_{(1,20)} = 0.37, p = 0.55$). There was no acupuncture session by pain adaptability group interaction (Fig. 3a).

Twenty minutes after acupuncture, the percentage PPT changes did not differ between real or sham acupuncture, but differed statistically significantly between PA and PNA groups (acupuncture session by pain adaptability interaction: $F_{(1,40)} = 4.81, p = 0.04$), reflecting that the PPT increase was significantly higher in the PA group than in the PNA (13.1% vs. 3.94%). Two-way ANOVA was used for *post-hoc* analysis and showed that there was a trend that the PA responded to sham acupuncture (20.3% increase) better than PNA did (2.1%) ($F_{(1,40)} = 4.06, p = 0.06$), whereas PA responded to real acupuncture (5.9% increase) similarly as PNA did (5.8%) (Fig. 3b).

The two groups also tended to respond differently among the three sites (site by pain adaptability interaction: $F_{(2,40)} = 2.80, p = 0.07$). As shown in Fig. 3b, the PPT increase was higher at the right leg (19.7%) and right arm (13.5%) than on the left arm (6.2%), the site of acupuncture. PA reported a stronger analgesia induced by either real or sham acupuncture on the right arm and right leg,

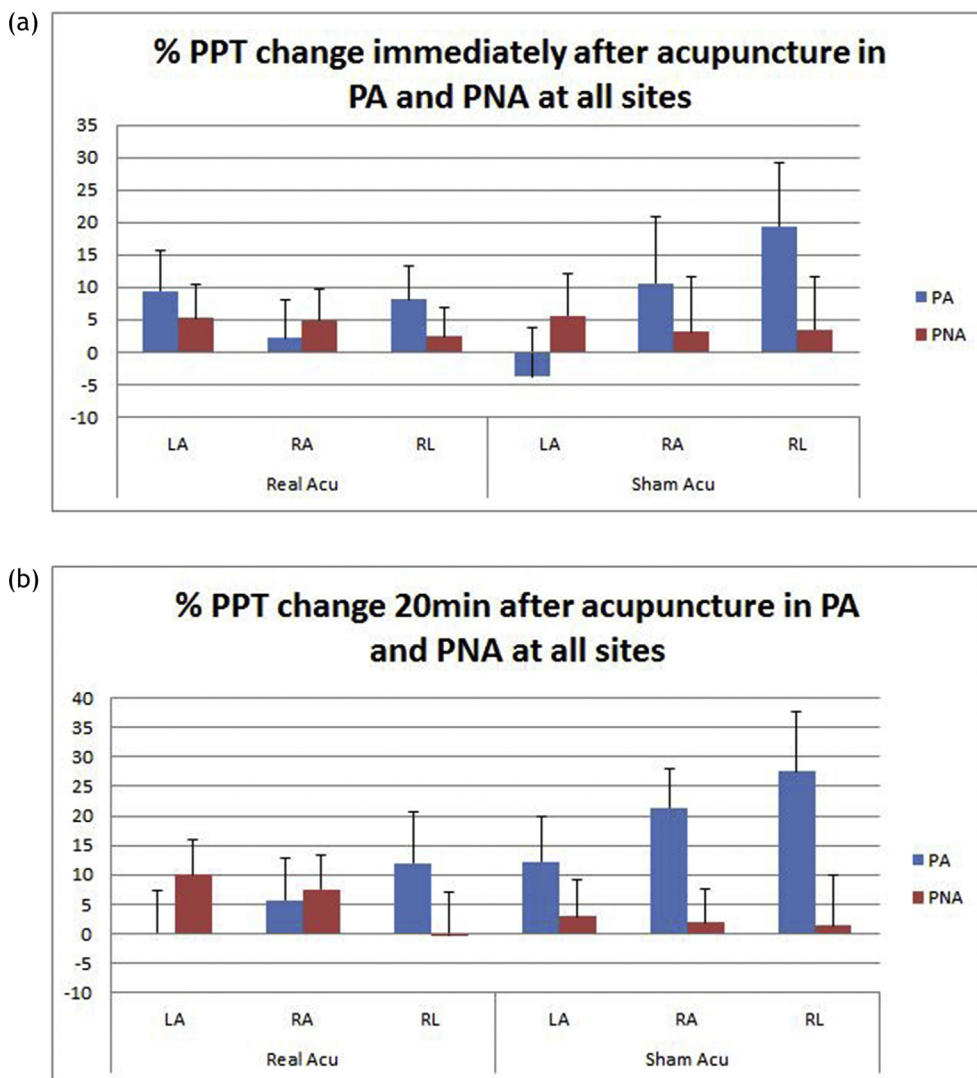


Figure 3 % PPT changes immediately (a) and 20 minutes after acupuncture (b) in PA and PNA at all three sites (mean ± SEM). LA = left arm; PA = pain adaptive; PNA = pain nonadaptive; PPT = pressure pain threshold; RA = right arm; Real Acu = real acupuncture; RL = right leg; SEM = standard error of the mean; Sham Acu = sham acupuncture.

whereas PNA had the strongest analgesia on the left arm, the needling site (6.5%).

3.4. Ratings to SUPRA or PIN after real and sham acupuncture

Immediately after either sessions of acupuncture, SUPRA did not differ between the PA and PNA groups. However, there was acupuncture session by site interaction ($F_{(2,40)} = 4.18, p = 0.02$). *Post-hoc* analysis with two-related sample *t* test indicated SUPRA increased during real acupuncture session when that reduced in the sham acupuncture session on the left or right arm, and SUPRA on the right leg did not differ between acupuncture sessions (real: 5%, 11%, and 6%; sham: -2%, -3%, and 9% for left arm, right arm, and left leg, respectively), indicating an overall pain enhancing effect to real acupuncture intervention at the segmental level immediately after acupuncture.

Twenty minutes after either sessions of acupuncture, the PA and PNA groups differed in SUPRA (group effect $F_{(1,20)} = 6.51, p = 0.02$), because of that the PA group consistently reported reduced SUPRA at all three sites, whereas PNA group reported increased pain rating (PA -4% vs. PNA 5.4%). There was no other difference between either PA and PNA groups or real and sham acupuncture sessions (Table C).

There was no PA and PNA group difference in PIN either immediately or 20 minutes after either session of acupuncture ($F_{(1,20)} = 0.95, p = 0.34$; Table D).

3.5. Expectation of acupuncture and blinding

Chi-square analyses showed that there were no differences between PA and PNA in expectancy before each acupuncture session (Table E).

After real acupuncture session, eight of nine participants in PA thought they had real treatment, more than that in the PNA group did (real acupuncture 7/13; do not know 6/13; $\chi^2 = 6.56, p = 0.04$; Table F). This is largely due to the needling sensation perceived by the PA group ($\chi^2 = 5.16, p = 0.08$; Table G). After sham acupuncture session, there was no difference between PA and PNA groups in their guess of which type of acupuncture they received ($\chi^2 = 1.04, p = 0.59$; Table F).

No serious side effects associated with either real or sham acupuncture was detected.

3.6. Internal consistency and session effect

Pearson *r* correlations were used to assess internal consistency in PPT measured before each session of acupuncture of participants. PPTs measured at three sites over the two sessions before intervention were highly correlated (left arm: $r = 0.81, p < 0.01$; right arm: $r = 0.80, p < 0.01$; right leg: $r = 0.71, p < 0.01$).

To examine if there was session effect, PPTs before acupuncture were compared between the first and second sessions using two-way repeated ANOVA. There were significant main effects of time ($F_{(1,40)} = 13.30, p < 0.01$). This is due to the fact that the PPTs measured at the second

session before acupuncture was consistently higher than that at the first session of acupuncture.

4. Discussion

In this crossover study, real and sham acupuncture induced a similar magnitude of analgesia. PA individuals reported statistically significantly higher PPT changes (20%) to sham acupuncture 20 minutes after acupuncture, whereas PNA individuals had a small increase in PPT after either real (6%) or sham acupuncture (2%). Furthermore, the enhanced PPT in PA group was better on the areas away from the needling site. Our observation that pain adaptability, but not types of acupuncture, determined the analgesic effect of acupuncture was also supported by reduced ratings to SUPRA. For the first time, we demonstrated that pain adaptability could determine how individuals responded to acupuncture.

4.1. Strengths of the study: controlling of confounding factors

We controlled a number of confounding factors. Age, gender, body mass index, anxiety, quality of life, coffee and tea intake, and sleep quality the night before the tests have been reported to impact on pain threshold [23–26]. There were no differences between PA and PNA in those measures. We also did not find any group differences in their expectancy, a factor considered to modulate acupuncture analgesia [27].

We controlled the performance bias of participants by including a sham acupuncture session. Blinding was successful during sham acupuncture session, but not in the real acupuncture session. A high proportion of PA groups guessed their group allocation correctly during real acupuncture session when compared with the PNA. This did not seem to impact on their response to acupuncture. Indeed, the PA group reported better analgesia to sham than real acupuncture. We also controlled performance bias of researchers. Studies showed that a high expectancy of trial acupuncturists led to a better pain reduction [28]. In our study, both the outcome assessor and the acupuncturist were unaware of the status of PA and PNA; and the assessor was blinded to acupuncture allocation.

PPTs measured at the second session were consistently higher than the first session. This could not be the effect of acupuncture as one-session acupuncture analgesia usually does not last more than 1 week [29]. This is likely to be training effect. It is well-established that in studies involving repeated tests, participants tended to have a high pain threshold on the second or later sessions [30,31]. This order effect could not impact on our finding as participants were randomly allocated to have real or sham acupuncture first, and percentage changes in relevance to the session baseline were used for data analysis.

We also measured the intensity of needling to ensure that any group difference was not due to varied strengths of acupuncture stimulation. Indeed, PA and PNA reported a similar level of needling sensation. It could, however, be argued that the needling sensation in present study was at the just painful level and might not be optimal for inducing acupuncture analgesia. The optimal acupuncture stimulation is, however, unknown. The notion of the stronger needling

stimulation the better analgesia is not supported. Schliessbach et al [32] found that electroacupuncture provided the best analgesia as indicated with an increase in PPT, when compared with manual acupuncture and two forms of sham acupuncture, yet the pain intensity rating of electroacupuncture was mild pain (2.7/10), much less than moderate pain (4.1/10) induced by manual acupuncture. Similarly, a positive correlation between acupuncture inhibition on heat pain and the intensity of needling stimulation of real acupuncture was not found in a recent study [33]. Both studies, however, found real acupuncture being better than sham acupuncture and caused stronger needling sensation than sham acupuncture did. The present study shows that the optimal needling sensation might be varied, depending on individual status of pain adaptability as discussed below.

4.2. A small difference between real and sham acupuncture

A recent meta-analysis including 29 high-quality randomized controlled trials with 17,922 patients found a small but statistically significant difference between real and sham acupuncture [11]. The difference in pain reduction between the two was too small (0.18 standard mean difference) to be clinically meaningful. The difference between acupuncture and no acupuncture was, however, nearly three times better at 0.51 standard mean difference. The meta-analysis supports that real acupuncture is better than sham acupuncture. The small difference between the two could only be detectable when the sample size is sufficiently large. This could explain the negative results of a number of sham-acupuncture controlled trials [34–36], as well as the findings in the present study.

However, those findings have not lent any help to researchers and practitioners on why the differences are so small.

4.3. Acupuncture analgesia, sham acupuncture, and the status of the nervous system

The effect of acupuncture is considered to be dependent on the status of the nervous system [8,9]. It is hypothesized that under central sensitization, the receptive fields of the central neurons are expanded and the neurons are highly sensitized and responsive, therefore gentle stimulation used in sham acupuncture procedure could induce adequate analgesia [9]. Using a well-established and validated heat-capsaicin model, researchers induced primary heat and secondary mechanical hyperalgesia. They found that sham electroacupuncture was equally effective in reducing secondary mechanical hyperalgesia as real electroacupuncture did [37]. The existence of central sensitization might have enhanced the effect of sham acupuncture. Central sensitization exists in many chronic pain, such as low back pain [38], headache and fibromyalgia [39], and might explain nil to a very small difference between real and sham acupuncture observed in many clinical trials [40].

Our study demonstrates that whether one is adaptive to pain or not could be another important factor determining not only the response to acupuncture, but also to which form of acupuncture that individual might respond to. Our

current research provides an initial step to link the individual variations in response to pain with how they respond to acupuncture. Clinically gentle and shallow needling as a form of acupuncture is practiced widely for a subset strong reactors. They often respond to gentle needling and the results can be long-lasting [41]. It is unknown what could mediate such an effect.

Previously, we found that PA did not differ from PNA on many measures, including the intensity of pain rating to cold pressor, PPT, and potency of conditioned pain modulation [16]. They differed, however, on time to peak pain. PA reached peak pain within 2 minutes of a cold pressor test, whereas PNA took much longer. It is possible that PA has a robust nervous system so that a fast-ascending facilitation induces a fast-descending inhibition, whereas PNA has a slower ascending facilitation therefore the inhibition system might be activated too slowly to show an effect. As a result, although the pain rating to cold pressor reduces in PA, it maintains in PNA. Such a robust pain inhibition may be activated with gentle stimulation, such as that in sham acupuncture, in PA individuals. How this mechanism is related to acupuncture analgesia is yet to be explored. From the temporal aspect, this system could explain acupuncture analgesia, as both seem to be potent at 20 minutes after the end of cold pressor [16] or acupuncture. Our study demonstrates that a fast-acting nervous system is perhaps responsible for the analgesia induced by sham acupuncture in PA. This effect is less likely due to placebo as PA did not have the same response to real acupuncture. On the other hand, it is possible that the PA and PNA responses could have been influenced by psychological factors yet to be explored. Furthermore, sensitivity to cold pressor has been reported to be largely dictated by genetics and moderately by environment [42].

4.4. Spatial distribution of acupuncture analgesia

Our limited data show that the PA individuals reported 5% increase of PPT at the site of needling and 14–20% increase of PPT at the contralateral site and distant site, reflecting a trend for stronger segmental inhibition and conditioned pain modulation in this group. This is consistent with a previous study, in which acupuncture on the hand increased PPT at a number of areas spreading over the body [14].

The current findings seem to be contradictory to our previous findings that PA presented a stronger local inhibition than PNA, but two groups did not differ on segmental inhibition or conditioned pain modulation after cold pressor. This could be due to that acupuncture analgesia is not the same as cold pressor. Indeed, cold pressor induced strong pain (8.2/10, with 0 being just painful) [16], whereas the rating to acupuncture in the present study was not painful to just painful (2–5/10, with 5 being just painful). Two recent studies also show that acupuncture analgesia is not the same as conditioned pain modulation [32,43]. It is possible that how pain inhibition exhibits in PA individuals depends on the strength of stimulation.

4.5. Limitations

This study included 22 healthy participants. The sample size is relatively small. Although the crossover design

enhances the power of the study, it is preferable to repeat this study in a large sample. Healthy participants were tested, and it is unknown if those findings are applicable to those who have chronic pain.

4.6. Implications of this study

In this study, about 40% of the participants were PA. This is in agreement with two studies in healthy humans reporting 39% of PA [16] and 35% of PA [44], respectively. Thus, if 35–40% of the healthy population could be PA, and if gentle stimulation as that in sham acupuncture can induce potent analgesia in this group of people, its implication for current trial design and clinical practice is significant. We recently found that the dichotomy of PA and PNA also exists in people with chronic pain [45]. It is necessary to replicate the present study in a clinical sample.

4.7. Conclusions

Individuals who are adaptive to pain might benefit more from gentle needling stimulation used in sham acupuncture. The effects are likely to be segmentally and distally distributed. Pain adaptability may determine individual's response to real and sham acupuncture. Our finding might partly explain varied potencies of acupuncture analgesia in clinical practice and trials.

Disclosure statement

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jams.2017.10.002>.

References

- [1] Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for tension-type headache. *Cochrane Database Syst Rev* 2009;1:CD007587.
- [2] Furlan AD, van Tulder MW, Cherkin DC, Tsukayama H, Lao L, Koes BW, et al. Acupuncture and dry-needling for low back pain. *Cochrane Database Syst Rev* 2005;1:CD001351.
- [3] Ezzo J, Hadhazy V, Birch S, Lao L, Kaplan G, Hochberg M, et al. Acupuncture for osteoarthritis of the knee: a systematic review. *Arthritis Rheum* 2001;44(4):819–25.
- [4] Fu LM, Li JT, Wu WS. Randomized controlled trials of acupuncture for neck pain: systematic review and meta-analysis. *J Altern Complement Med* 2009;15(2):133–45.
- [5] Molsberger AF, Schneider T, Gotthardt H, Drabik A. German Randomized Acupuncture Trial for chronic shoulder pain (GRASP) – a pragmatic, controlled, patient-blinded, multi-centre trial in an outpatient care environment. *Pain* 2010;151(1):146–54.
- [6] Zhang H, Sun J, Wang C, Yu C, Wang W, Zhang M, et al. Randomised controlled trial of contralateral manual acupuncture for the relief of chronic shoulder pain. *Acupunct Med* 2016;34(3):164–70.
- [7] Kong J, Gollub R, Huang T, Polich G, Napadow V, Hui K, et al. Acupuncture de qi, from qualitative history to quantitative measurement. *J Altern Complement Med* 2007;13(10):1059–70.
- [8] Lund I, Näslund J, Lundeberg T. Minimal acupuncture is not a valid placebo control in randomised controlled trials of acupuncture: a physiologist's perspective. *Chin Med* 2009;4(1–1).
- [9] Carlsson C. Acupuncture mechanisms for clinically relevant long-term effects—reconsideration and a hypothesis. *Acupunct Med* 2002;20(2–3):82–99.
- [10] Kenjil K, White A. Physiological basis of therapeutic effects of sham acupuncture in recent clinical trials. *J Acupunct Moxib* 2010;6(1):92–7.
- [11] Vickers AJ, Cronin AM, Maschino AC, Lewith G, MacPherson H, Foster NE, et al. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med* 2012;172(19):1444–53.
- [12] Bekking R, van Bysse R. Segmental acupuncture. In: Filshie J, White A, editors. *Medical Acupuncture: A Western Scientific Approach*. Edinburgh: Churchill Livingstone; 1998. p. 105–35.
- [13] Le Bars D, Willer JC. Pain modulation triggered by high-intensity stimulation: implication for acupuncture analgesia? *Int Congress Series* 2002;1238:11–29.
- [14] Zaslowski CJ, Cobbin D, Lidums E, Petocz P. The impact of site specificity and needle manipulation on changes to pain pressure threshold following manual acupuncture: a controlled study. *Complement Ther Med* 2003;11(1):11–21.
- [15] Zheng Z, Feng SJQ, Da Costa C, Li CG, Lu D, Xue CCL. Acupuncture analgesia for temporal summation of experimental pain: a randomised controlled study. *Eur J Pain* 2010;14:725–31.
- [16] Zheng Z, Wang K, Yao D, Xue CC, Arendt-Nielsen L. Adaptability to pain is associated with potency of local pain inhibition, but not conditioned pain modulation: a healthy human study. *Pain* 2014;155(5):968–76.
- [17] Ware JE, Kosinski M, Bjorner JB, Turner-Bowker D, Gandek B, Maruish ME. SF-36v2 Health Survey: Administration Guide for Clinical Trial Investigators. QualityMetric, Incorporated; 2008.
- [18] Spielberger CD, Gorsuch RL, Lushene PR, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory*. 1st ed. California: Consulting Psychologists Press; 1983.
- [19] Ellingson LD, Colbert LH, Cook DB. Physical activity is related to pain sensitivity in healthy women. *Med Sci Sports Exerc* 2012;44(7):1401–6.
- [20] Robinson, M.E., E.A. Wise, C. Gagnon, R.B. Fillingim, and D.D. Price, Influences of gender role and anxiety on sex differences in temporal summation of pain. *J Pain*. 5:2: 77–82.
- [21] Tiede W, Magerl W, Baumgartner U, Durrer B, Ehler U, Treede RD. Sleep restriction attenuates amplitudes and attentional modulation of pain-related evoked potentials, but augments pain ratings in healthy volunteers. *Pain* 2010;148(1):36–42.
- [22] Zheng Z, Guo RJ, Helme RD, Muir A, Da Costa C, Xue CC. The effect of electroacupuncture on opioid-like medication consumption by chronic pain patients: a pilot randomized controlled clinical trial. *Eur J Pain* 2008;12(5):671–6.

- [23] Kothari DJ, Davis MC, Yeung EW, Tennen HA. Positive affect and pain: mediators of the within-day relation linking sleep quality to activity interference in fibromyalgia. *Pain* 2015; 156(3):540–6.
- [24] Laursen BS, Bajaj P, Olesen AS, Delmar C, Arendt-Nielsen L. Health related quality of life and quantitative pain measurement in females with chronic non-malignant pain. *Eur J Pain* 2005;9(3):267–75.
- [25] Neumann L, Lerner E, Glazer Y, Bolotin A, Shefer A, Buskila D. A cross-sectional study of the relationship between body mass index and clinical characteristics, tenderness measures, quality of life, and physical functioning in fibromyalgia patients. *Clin Rheumatol* 2008;27(12):1543–7.
- [26] Sawynok J. Caffeine and pain. *Pain* 2011;152(4):726–9.
- [27] Linde K, Witt CM, Streng A, Weidenhammer W, Wagenpfeil S, Brinkhaus B, et al. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain* 2007;128(3):264–71.
- [28] Witt C, Martins F, Willich S, Schützler L. Can I help you? Physicians' expectations as predictor for treatment outcome. *Eur J Pain* 2012;16(10):1455–66.
- [29] Irnich D, Behrens N, Gleditsch JM, Stör W, Schreiber MA, Schöps P, et al. Immediate effects of dry needling and acupuncture at distant points in chronic neck pain: Results of a randomized, double-blind, sham-controlled crossover trial. *Pain* 2002;99(1–2):83–9.
- [30] Brooks D, Davis AM, Naglie G. The feasibility of six-minute and two-minute walk tests in in-patient geriatric rehabilitation. *Can J Aging/La Revue canadienne du vieillissement* 2007; 26(02):159–62.
- [31] Stening K, Eriksson O, Wahren L, Berg G, Hammar M, Blomqvist A. Pain sensations to the cold pressor test in normally menstruating women: comparison with men and relation to menstrual phase and serum sex steroid levels. *Am J Physiol Regul Integr Comp Physiol* 2007;293(4):R1711–6.
- [32] Schliessbach J, van der Klift E, Siegenthaler A, Arendt-Nielsen L, Curatolo M, Streitberger K. Does acupuncture needling induce analgesic effects comparable to diffuse noxious inhibitory controls? *Evid Based Complement Alternat Med* 2012;2012:785613.
- [33] Benham A, Johnson MI. Effect of bidirectional rotation of an acupuncture needle at LI10 on acupuncture sensation and experimentally-induced contact heat pain in healthy human volunteers. *Acupunct Med* 2014;32(3):267.
- [34] Brinkhaus B, Witt CM, Jena S, Linde K, Streng A, Wagenpfeil S, et al. Acupuncture in patients with chronic low back pain: a randomized controlled trial. *Arch Intern Med* 2006;166(4): 450–7.
- [35] Linde K, Streng A, Jurgens S, Hoppe A, Brinkhaus B, Witt C, et al. Acupuncture for patients with migraine: a randomized controlled trial. *JAMA* 2005;293(17):2118–25.
- [36] Scharf HP, Mansmann U, Streitberger K, Witte S, Kramer J, Maier C, et al. Acupuncture and knee osteoarthritis: a three-armed randomized trial. *Ann Intern Med* 2006;145(1): 12–20.
- [37] Zheng Z, Bai LH, Li CG, Xue CCL. The Differential Effect of Electroacupuncture on Peripheral and Central Sensitisation in Humans. 2010.
- [38] Correa JB, Costa LO, de Oliveira NT, Sluka KA, Liebano RE. Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case-control study. *Exp Brain Res* 2015;233(8):2391–9.
- [39] Staud R, Weyl EE, Riley 3rd JL, Fillingim RB. Slow temporal summation of pain for assessment of central pain sensitivity and clinical pain of fibromyalgia patients. *PLoS One* 2014;9(2), e89086.
- [40] Deare JC, Zheng Z, Xue CC, Liu JP, Shang J, Scott SW, et al. Acupuncture for treating fibromyalgia. *Cochrane Database Syst Rev* 2013;5:CD007070.
- [41] Mann Fa. *Reinventing Acupuncture: A New Concept of Ancient Medicine*. 2nd ed. , Oxford: Butterworth-Heinemann; 2000.
- [42] Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. *Pain* 2008;136(1–2): 21–9.
- [43] Tobbackx Y, Meeus M, Wauters L, De Vilder P, Roose J, Verhaeghe T, et al. Does acupuncture activate endogenous analgesia in chronic whiplash-associated disorders? A randomized crossover trial. *Eur J Pain* 2013;17(2):279–89.
- [44] Devoize L, Chalaye P, Lafrenaye S, Marchand S, Dallel R. Relationship between adaptation and cardiovascular response to tonic cold and heat pain adaptability to tonic pain and cardiovascular responses. *Eur J Pain* 2015.
- [45] Wong Lit Wan D, Arendt-Nielsen L, Wang K, Xue CCL, Wang Y, Zheng Z. Dissociation between pain adaptability and conditioned pain modulation in individuals with chronic musculoskeletal pain. In: 16th World Congress on Pain, IASP; 2016. Yokohama, Japan.