Acupuncture in Physiotherapy

www.aacp.org.uk

Acupuncture in Physiotherapy is printed twice a year for the membership of AACP. It aims to provide information for members that is correct at the time of going to press. Articles for inclusion should be submitted to the clinical editor at the address below or by email. All articles are reviewed by the clinical editor, and while every effort is made to ensure validity, views given by contributors are not necessarily those of the Association, which thus accepts no responsibility.

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The Association
The British association for the practice of Western research-based acupuncture in physiotherapy, AACP is a professional network affiliated with the Chartered Society of Physiotherapy. It is a member-led organization, and with around 6000 subscribers, the largest professional body for acupuncture in the UK. We represent our members with lawmakers, the public, the National Health Service and private health insurers. The organization facilitates and evaluates postgraduate education. The development of professional awareness and clinical skills in acupuncture are founded on research-based evidence and the audit of clinical outcomes.

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Peterborough PE1 5PP, UK

Tel: 01733 390007

Printed in the UK by Henry Ling Ltd
at the Dorset Press, Dorchester DT1 1HD

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Advanced Technologies

HANDY-CURE

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"I use the ***Handy Cure*** *in my chiropractic office for many different conditions. I have used more powerful lasers, more expensive lasers - but the* ***Handy Cure*** *does a fantastic job on my patient's conditions.*

It is easy to use... so easy that some of my patients have purchased ones for home use.

I have 350 doctors in my group and many have purchased the ***Handy Cure*** *to help even the most difficult patients. Powerful, easy to use and inexpensive is a winning combination."*

Dr. Craig S. Ross, CA, USA

"I gave the ***Handy Cure*** *device to one of the Rugby team players for the first couple of weeks to use on his Plantar Fasciitis. The report back was that it helped with the pain and has made things better".*

Richard W.,
Hollistic Massage Therapist, Reading, UK

I have owned my ***Handy Cure*** *Laser for more than six months. During this time I have successfully reduced my own pain in an arthritic joint and numerous other conditions on my patients. Some of these include carpal tunnel, low back pain and frozen shoulder.*

Rhonwen Warland
acupuncturist, July. 2016, NSW, Australia

"I have been using ***Handy Cure*** *devices for around six months.*

I was attracted to the device by the ease of use and by the price point. Before introducing it into my practice, I spent some time using it for self-treating and for treating family and friends. The feedback was consistently good. As a sports therapist, my preferred way of working is to use ***Handy Cure*** *once I have identified the probable cause of pain and determined that it cannot be readily, and comfortably, addressed by manual therapy."*

Amanda L.,
Sport Injuries Therapist, Cobham, UK

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Acupuncture in Physiotherapy

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Editorial

Welcome to the Spring 2018 edition of *Acupuncture in Physiotherapy*.

As you will notice as you read through this edition, we have begun to change the ratio of research to case studies in the composition of the journal, hoping to include more current and important research. To that effect we have included two interesting papers; Maeda *et al.* (pp. 25–43) and Harris *et al.* (pp. 11–24). We also have two extra summaries in the News section, by Rosemary Lillie, one on cupping and one discussing the future conflicts between opiods and acupuncture in the treatment of pain.

Maeda *et al.* (*Rewiring the Primary Somatosensory cortex in carpal tunnel syndrome)* have done some interesting work demonstrating that acupuncture needling is being carefully investigated with regard to the linkage between brain response to acupuncture and the subsequent analgesia, as measured by MRI. Taken together with another paper we are publishing, by Harris *et al.*, *Traditional Chinese Acupuncture and placebo (sham) acupuncture are differentiated by their effects on μ-opiod receptors (MORS),* it begins to appear that acupuncture processing in the brains of CTS patients differs from that in normal healthy controls. The new evidence suggests that chronic pain patients respond differently, and it may be that the acupuncture actually produces real changes in the receptors.

We have added copies of these papers to the news pages of the AACP website aacp.org.uk/news.

We would, of course, like our membership to supply us with many excellent research papers but, until that happy day, we are trawling the available papers. If you find something really interesting yourself, please let me know!

As always, we have a good selection of case studies:

- Michael Guest, Cervical Radiculopathy (pp. 77–83)
- Russ Walby, Lateral elbow pain (pp. 85–92)
- Michael Dunn, Cruciate ligament rupture (pp. 93–99)
- Kate Clark, Acute Achilles tendon rupture (pp. 101–109)

These are contributed mostly by our new members each issue and we are delighted to welcome them.

You may remember the AACP Survey last year; the results are in this journal (pp. 67–76) and show some interesting findings. It's particularly interesting to note that since we last carried out the survey in 2012, many things have remained consistent among practitioners; the choices of technique, location of acupoints, underlying theories and range of treatments remain as interventions clearly of use to physiotherapists, primarily for pain control but also, as the research improves, other conditions of clearer neurological background.

Please contact us if you have further questions.

We are also publishing the final masterclasses; the Extra Points and the Extra Meridians and hope to be able to collect them all together in one volume, sometime this year.

Together with the other reports and the book reviews (pp. 111–113) this is a tightly packed journal and we hope that you enjoy it.

Dr Val Hopwood, FCSP, FAACP
Clinical Editor, Acupuncture in Physiotherapy

Acupuncture in Physiotherapy, Volume 30, Number 1, Spring 2018, 7–8

Chairman's report

Welcome to the first edition of 2018 of the Acupuncture Association of Chartered Physiotherapists (AACP) journal, *Acupuncture in Physiotherapy*. There has been a lot of activity already this year, with much more yet to come. There are two conferences planned so far, with other regional events to follow. These are part of the AACP's continuing effort to reach members across the country and to improve access to the ever expanding knowledge base in research and approaches in clinical practice.

Our first conference of 2018 is the AACP's Annual Conference, to be held on 19 May in Reading. The conference will proudly host a number of internationally recognized and respected acupuncture practitioners, including Cheryl Mason who will be discussing acupuncture for pregnancy-related pelvic girdle pain and lower back pain, Chris Boynes who will be discussing the interaction and outcomes of acupuncture with deep oscillation treatment, John R. Cross who will be covering acupressure in the treatment of neurological conditions, and Dr Thomas Perreault from the US who will focus on needling for temporomandibular disorder. Bringing together a blend of research and clinical practice, the conference promises to be an enlightening day and a definite date for your diary.

Our second conference of the year will be held in October in Leeds, and more details will follow in due course. As ever, the conference events are designed to offer members an opportunity for learning, networking and continued professional development as well as catching up with some old friends and colleagues, and maybe making a few new ones too.

We will also be continuing the AACP's commitment to delivering continuing professional development (CPD) in Scotland through the study day on 3 November at the Queen Margaret University campus, situated east of Edinburgh city centre. The Scotland study day format differs from the conference events and delivers a full-day schedule of four 90-minute sections, designed to deliver practical clinically-applicable information. The scheduled speakers are Caroline McGuire, Lynn Pearce, Johnny Wilson and John Wood, who will be covering a variety of clinically-related topics including neurology, fascial connections, sport and pain.

2018 sees the departure of two members from the AACP board, George Chia and Christopher Hall, and so I take this opportunity on behalf of the AACP board, administration team and membership to thank them both for their significant contribution during their tenures on the board. Christopher has been a member of the board since 2015 and has brought his considerable knowledge to bear in all matters, particularly those of business and finance. George, who many members will be personally familiar with, has been a board member since 2012 but has a history with the AACP reaching much further back. George's contribution to acupuncture within physiotherapy stretches back some decades and he proudly retains AACP member number 17 status. He has taught more members than he probably cares to remember, longer ago than many of us care to remember. His influence has always been positive, thoughtful, and well measured. The contributions of both Christopher and George to the board will be missed.

I would like to welcome two new members to the AACP board. Firstly, Suzanne Nitta, an acupuncture clinical specialist and a physiotherapy manager with Ramsay Healthcare. Suzanne holds an MSc in Acupuncture and is also an AACP tutor and longstanding advanced member. Her experience both in the clinical setting and within private healthcare management will be a valuable contribution to the current board. The second new board member is Chris Collier MBE. Chris is a chartered accountant and ex-partner in accountancy firm Rawlinsons. His knowledge of finance in small to medium-sized businesses will be of great value to the

AACP and its development in the coming years. Suzanne and Chris will both have to be formally appointed by you, the members, at the Annual General Meeting on 19 May 2018 and so I would welcome you all to join us there.

As in previous issues, I would like to direct you to our website (www.aacp.org.uk) which features the AACP online shop. The online shop offers exclusive deals and a guaranteed price match promise against all like for like items, creating another valuable membership benefit.

I am also pleased to announce that Harmony Medical is a new collaborative partner of the AACP and is looking forward to supporting AACP courses and members. This is good news for members as the ever-supportive team at Harmony Medical offer a wide variety of supplies for all aspects of clinical acupuncture application and education at competitive prices.

As many of you will be aware, the AACP's Foundation in Western Acupuncture for Physiotherapists course is now also available with 30 Masters (M) level credits. In a limited offer these credits are now also available for those who have previously completed an AACP accredited foundation course within the last few years. Please feel free to contact Claire Buckingham (claire@aacp.uk.com), AACP training and education coordinator, who will be happy to discuss further details and eligibility with you. Claire can also advise you on how you can attend or organize a foundation course or a CPD event at your clinic or venue.

As always, the AACP administrative and management teams continue to toil behind the scenes to support members, and bring value and benefit to membership, offering the best experience possible for all involved. If, however, you feel there are issues the AACP needs to be addressing, or you have any ideas on how you would like to see the AACP develop or improve, then please feel free to get in touch with the office or me directly (chair@aacp.uk.com). As ever, I look forward to catching up with you at an AACP event somewhere soon.

Jonathan Hobbs
AACP Chairman

Chief Executive Officer's report

Stable and solid, but not complacent

A summary of AACP's state of affairs

After a period of re-organizing and developing the structure for the AACP as a Limited Company in the first decade of this century, the last few years could be typified for the Association as becoming more confident and professional.

We have achieved this through improvements in the organisational infrastructure and the addition of new disciplines like Clinical Advice and Marketing.

Developing this further in 2018, the Board agreed to extend the role of AACP marketing with a much more active account-targeted responsibility to suppliers (to create partnerships), hospitals (to generate central training arrangements) and private health insurers (to ensure ongoing recognition of AACP membership).

Against the backdrop of reported decreases in membership of similar organizations, AACP's membership income is stable and we see a continued significant interest in Foundation and CPD courses. As such the decision of NICE to remove acupuncture from Low Back Pain Guidelines so far has had no direct impact on our organization and this is not expected in 2018.

Furthermore we shall continue building on the increased AACP presence in press and social media, reaching out to millions of patients. For the latest, check this page on the AACP website www.aacp.org.uk/page/70/0917. Our patient approach maintains and builds awareness for acupuncture-physiotherapy in general for the benefit of our AACP members.

An AACP online shop was launched a few months ago as our most recent member benefit, which has proved very successful and will now be further developed in 2018 to give as many members as possible the benefit of great value-for-money products.

In terms of education provision the AACP will develop more CPD courses to refresh what you already know and Advanced Modules, to further your knowledge of acupuncture.

Laurels

Given the above, it would be easy to rest on them.

Our overarching aim however, to maximize the awareness of the advantages and the practice of acupuncture-physiotherapy for your benefit, will never be exhausted.

Therefore the Board and its committees intend to meet to discuss and develop strategic options for the AACP to build on its current strong and stable foundations.

Input

We would like to have your ideas to feed into our strategic discussions. Get in touch with me and let us know in which way you feel the AACP could further develop its strategy or activities to increase the awareness and use of acupuncture, for your benefit.

So, as always, do not hesitate to contact me directly via ceo@aacp.uk.com

Thank you.

Caspar van Dongen
Chief Executive Officer

Acupuncture in Physiotherapy, Volume 30, Number 1, Spring 2018, 11–23

RESEARCH STUDY

Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on μ-opioid receptors (MORs)

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Abstract

Controversy remains regarding the mechanisms of acupuncture analgesia. A prevailing theory, largely unproven in humans, is that it involves the activation of endogenous opioid antinociceptive systems and μ-opioid receptors (MORs). This is also a neurotransmitter system that mediates the effects of placebo-induced analgesia. This overlap in potential mechanisms may explain the lack of differentiation between traditional acupuncture and either non-traditional or sham acupuncture in multiple controlled clinical trials. We compared both short and long-term effects of traditional Chinese acupuncture (TA) versus sham acupuncture (SA) treatment on *in vivo* MOR binding availability in chronic pain patients diagnosed with fibromyalgia (FM). Patients were randomized to receive either TA or SA treatment over the course of 4 weeks. Positron emission tomography (PET) with [^{11}C]-carfentanil was performed once during the first treatment session and then repeated a month later following the eighth treatment. Acupuncture therapy evoked short-term increases in MOR binding potential, in multiple pain and sensory processing regions including the cingulate (dorsal and subgenual), insula, caudate, thalamus, and amygdala. Acupuncture therapy also evoked long-term increases in MOR binding potential in some of the same structures including the cingulate (dorsal and perigenual), caudate, and amygdala. These short- and long-term effects were absent in the sham group where small reductions were observed, an effect more consistent with previous placebo PET studies. Long-term increases in MOR BP following TA

were also associated with greater reductions in clinical pain. These findings suggest that divergent MOR processes may mediate clinically relevant analgesic effects for acupuncture and sham acupuncture.

Keywords: acupuncture, fibromyalgia, mu, opioid, pain, positron emission tomography

Introduction

Acupuncture as a component of East-Asian medical systems has been used to treat pain for over two millennia however the cellular and molecular constituents of this therapy remain largely unknown. Prevailing theories, arising largely from studies in animals, suggest that endogenous opioids and their associated receptors are involved in this treatment (He *et al.* 1985; Pert *et al.* 1981; Ho & Wen 1989; Pomeranz & Chiu 1976; Chen *et al.* 1996). Most studies have focused on the opioid neurotransmitters (Stux & Hammerschlag 2001), where enhanced release seems to accompany needle insertion, however less attention has been paid to the opioid receptors themselves (e.g. the μ, κ and δ opioid receptor classes) and their relationship with clinical response.

Recent controversy in the field of acupuncture research was generated when several large scale randomized controlled trials in chronic pain patients failed to show superiority of acupuncture over sham acupuncture methods (Brinkhaus *et al.* 2006; Linde *et al.* 2005; Melchart *et al.* 2005; Harris *et al.* 2005). This has lead opponents of acupuncture therapy to suggest that it is no more effective than a placebo intervention. Since placebo administration also induces activation of opioid receptors, specifically the μ-opioid receptor (MOR) class (Benedetti & Amanzio 1997; Zubieta *et al.* 2005; Amanzio & Benedetti 1999; Levine *et al.* 1978; Pomeranz & Chiu 1976), acupuncture may indeed operate in part via placebo mechanisms.

Neuroimaging methods allow for the ability to explore the central neurobiological mechanisms of both acupuncture and placebo interventions. Recent functional magnetic resonance imaging (fMRl) studies demonstrate deactivation of limbic structures including the amygdala, the hippocampus, and the perigenual cingulate via a mechanism that is distinct from pain and sham stimulation (Hui *et al.* 2000, 2005; Napadow *et al.* 2007). Thus while traditional acupuncture and sham acupuncture may have equivalent analgesic effects they may differ significantly in their underlying neurobiological response.

Here we directly explore the involvement of the endogenous opioid system during acupuncture treatment of chronic pain patients diagnosed with fibromyalgia (FM) (Wolfe *et al.* 1995). FM is a relatively common chronic pain condition thought to originate from augmented pain processing in the central nervous system (Gracely *et al.* 2002). We have previously demonstrated that FM patients have reduced central μ-opioid receptor (MOR) binding potential (BP; an *in vivo* measure of binding availability) using [^{11}C]-carfentanil (CFN) positron emission tomography (PET) with the μ-opioid selective radiotracer [^{11}C]carfentanil (Harris *et al.* 2007). In that study, patients with greater clinical pain displayed reduced MOR BP. Here we perform CFN PET on FM patients before and following acupuncture and sham treatment. We reasoned that dynamics in receptor binding could complement previous acupuncture research which has focused largely on the release of endogenous opioids. One study has examined acupuncture effects on central opioid receptor binding, however that study used a non-selective opioid receptor agonist and did not examine effects within a clinical population (Dougherty *et al.* 2008).

Based on animal data and *in vitro* measures of MOR binding (Gao *et al.* 1997), it was hypothesized that long-term acupuncture therapy may result in increased MOR BP, or receptor availability *in vivo*. Further, we reasoned that these effects would not be observed in the sham treatment group, thus differentiating

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"placebo" from active treatment conditions. Finally, since regional decreases in MOR BP have been associated with greater clinical pain in FM patients (Harris *et al.* 2007), increases in BP were expected to be associated with reduced clinical pain.

Materials and methods

Participants

As part of a study investigating the impact of acupuncture treatment in FM, 20 female patients (mean (SD) age: 44.3 (13.6) yrs) were examined with two CFN PET imaging sessions. Participants were randomized to receive either nine traditional acupuncture (TA; n = 10) or nine non-skin penetrating sham acupuncture (SA; n = 10) treatments. Demographics of the sample population are presented in Supplementary Table 1. No significant differences were detected between participants in the TA and SA groups for either age, race, duration of FM symptoms, or pre-treatment clinical pain scores. Participants gave written informed consent and all study protocols were approved by the University of Michigan Institutional Review Board and the Radioactive Drug Research Committee.

All participants: 1) met the American College of Rheumatology (1990) criteria (Wolfe *et al.* 1990) for the diagnosis of FM for at least 1 year; 2) had continued presence of pain more than 50% of days; 3) were willing to limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study; 4) were over 18 and under 75 years of age; 5) were female; 6) were right-handed; 7) had no alcohol intake 48 h prior to PET studies; and 8) were capable of giving written informed consent. Participants were excluded if they: 1) had previous experience with acupuncture; 2) had current use or a history of use of opioid or narcotic analgesics; 3) had a history of substance abuse; 4) had the presence of a known coagulation abnormality, thrombocytopenia, or bleeding diathesis that may preclude the safe use of acupuncture; 5) had the presence of concurrent autoimmune or inflammatory disease such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc. that causes pain; 6) had concurrent participation in other therapeutic trials; 7) were pregnant and nursing mothers; 8) had severe psychiatric illnesses (current schizophrenia, major depression with suicidal ideation, substance abuse within 2 years); 9) had current major depression; or 10) had contraindications to PET. Concomitant medications are listed in Supplementary Table 2.

Positron emission tomography (PET)

Image acquisition

Scans were acquired with a Siemens (Knoxville, TN) HR^{+} scanner in 3-D mode (reconstructed FWHM resolution ~5.5 mm in-plane and 5.0 mm axially), with septa retracted and scatter correction. Participants were positioned in the PET scanner gantry, and an intravenous (antecubital) line was placed in the right arm. A light forehead restraint was used to eliminate intrascan head movement. CFN was synthesized at high specific activity (> 2000 Ci/mmol), as previously described (Jewett 2001); 10–15 mCi (370–555 MBq) were administered during the scan. Fifty percent of the CFN dose was administered as a bolus, and the remaining 50% by continuous infusion for the remainder of the study. Twenty-eight frames of images were acquired over 90 min with an increasing duration (30 s up to 10 min). The total mass of carfentanil administered was maintained below 0.03 μg/kg, ensuring that the compound was administered in a tracer quantity (i.e. a subpharmacological dose). Receptor occupancy by this mass of carfentanil is estimated to be 0.2% to 0.6% depending on the brain region (Gross-Isseroff *et al.* 1990; Gabilondo *et al.* 1995). The methodology employed to quantify MOR sites (i.e. bolus-continuous infusion to more rapidly achieve full equilibrium conditions across kinetic compartments) has been shown not to be significantly susceptible to changes in blood flow, and therefore tracer transport, that could be caused by procedures such as acupuncture (Zubieta *et al.* 2003b; Joshi *et al.* 200 ^{811}C-carfentanil).

Fig. 1a displays the timeline for PET image acquisition, treatment procedures, and study outcomes. For the first and second PET image

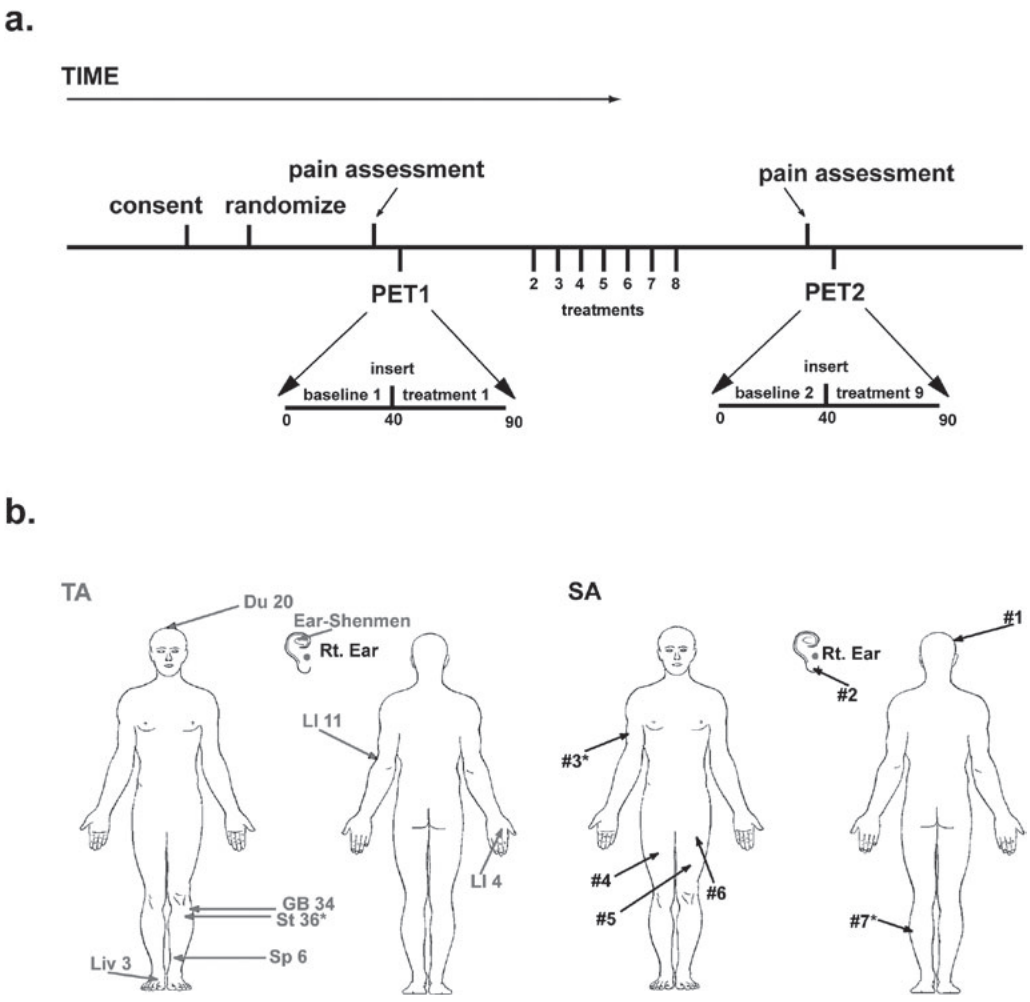

Figure 1. Study design.
a. Participant timeline from consent, through PET imaging sessions, and treatments. Following consent, all participants were randomized to either the traditional acupuncture (TA) or sham acupuncture (SA) treatment groups. Immediately before both PET imaging sessions (i.e. PET1 and PET2), participants completed the SF MPQ to assess clinical pain. During PET1, participants underwent a baseline scan (baseline1) and a treatment scan (treatment1) both of which were used to estimate short-term effects on MOR binding. Participants then received seven acupuncture or sham treatments outside of the scanner. This was followed by PET2, a second imaging session. The baseline scan during PET2 was used for comparison with the baseline scan in PET1 to estimate long-term changes in resting MOR binding.
b. TA (red) and SA (black) point locations. Similar body regions were used for both interventions.

session, PET1 and PET2 respectively, we used data from minutes 10 to 40 as our baseline measurement because the slope of the Logan plot (see below) for CFN becomes linear at approximately 7.5 min following CFN infusion (Zubieta *et al.* 2003b). This was followed by TA and SA procedures (see below) performed between minutes 40 to 45. Data from minutes 40 to 45 were omitted due to head motion during treatment procedures. After needle insertion and manipulation, scans from 45 to 90 min during PET1were used as the short-term treatment measurement (i.e. treatment1). During minutes 45 to 90, needles were retained in the TA group, whereas no needles were present in the SA group since SA did not involve skin penetration. For analysis of long-term changes in MOR binding, changes between PET1and PET2 baseline scans, baseline1 and baseline2 respectively, were examined.

Anatomical MRI scans were acquired in all subjects on a 3T scanner (Signa LX, General Electric, Milwaukee, WI). The acquisition sequence was axial SPGR Inverse Recovery-Prepared MR [echo time (TE) = 3.4 ms, repetition time (TR) = 10.5 ms, inversion time (TI) = 200 ms, flip angle = 25°, number of excitations (NEX) = 1, using 124 contiguous images, 1.5 mm-thickness].

Image processing

Images were reconstructed using iterative algorithms (brain mode; FORE/OSEM 4 iterations, 16 subsets; no smoothing) into a 128×128 pixel matrix in a 28.8 cm diameter field of view. Attenuation correction was performed through a 6 min transmission scan (^{68}Ge source) obtained prior to each PET study, also with iterative reconstruction of the blank/transmission data followed by segmentation of the attenuation image. Small head motions during emission scans were corrected by an automated computer algorithm for each subject before analysis, and the images were co-registered to each other with the same software (Minoshima *et al.* 1993). Time points were then decay-corrected during reconstruction of the PET data. Image data was then transformed on a voxel-by-voxel basis into two sets of parametric maps: (a) a tracer transport measure (K_1 ratio), and (b) a receptor-related measure (DVR). To avoid the need for arterial blood sampling, the tracer transport and binding measures were calculated using a modified Logan graphical analysis (Logan *et al.* 1996), using the occipital cortex (an area devoid of MORs) as the reference region. The slope of the Logan plot was used for the estimation of the distribution volume ratio (DVR), a measure equal to the $f_2(B_{max}/K_d) + 1$ for this receptor site and radiotracer. B_{max}/K_d (or DVR-1) is the receptor-related measure or binding potential (BP). The term f_2 refers to the concentration of free radiotracer in the extracellular fluid and is considered to represent a constant and very small value. K_1 and DVR images for each experimental period and MR images were co-registered to each other and to the International Consortium for Brain Mapping (ICBM) stereotactic atlas orientation. The accuracy of coregistration and non-linear warping algorithms was confirmed for each subject individually by comparing the transformed MRI and PET images to each other and the ICBM atlas template.

Group differences were mapped into stereotactic space using *t* maps of statistical significance with SPM99 (Wellcome Department of Cognitive Neurology, London, UK) and Matlabv6.5 (MathWorks, Natick MA) software, with a general linear model. No global normalization was applied to the data, and therefore the calculations presented are based on absolute B_{max}/K_d estimates. Only regions with specific MOR BP were included in the analyses (i.e. voxels with DVR values>1.1, or BP>0.1). To compensate for small residual anatomic variations across subjects and to improve signal to noise ratios, a three-dimensional Gaussian filter (FWHM 6 mm) was applied to each scan.

Image analysis

Short-term changes in MOR BP were detected using two sample *t*-tests between patients receiving TA and SA between experimental conditions in PET1 on a voxel-by-voxel basis using SPM99: (Comparison I = $[TA_{(treatment1 - baseline1)} > SA_{(treatment1 - baseline1)}]$ and Comparison II = $[SA_{(treatment1 - baseline1)} > TA_{(treatment1 - baseline1)}]$). Significant effects were detected for each comparison using two separate approaches: 1) an entire image-wide search that was unconstrained by regional predictions and 2) a regional approach that was based on *a priori* hypotheses. For the latter approach, *a priori* regions that had either been previously identified as involved in MOR mediated antinociception in humans (Zubieta *et al.* 2001, 2005) or PET trials using acupuncture (Biella *et al.* 2001) were determined using a standard brain atlas. These regions included: cingulate cortex, insula, nucleus accumbens, caudate, putamen, thalamus, hypothalamus, amygdala, and periaqueductal grey. When effects of treatment were observed in these regions we employed an uncorrected statistical threshold of $p<0.001$ with a minimum cluster size of 20 voxels. These typically had z-scores between 3.3 and 4.3 for this analysis. For brain regions not previously hypothesized, significant regions were identified with a threshold of $p<0.05$ after correction by multiple comparisons using family wise error approach (Friston *et al.* 1995a; Friston *et al.* 1995b). These typically had z-scores>4.3 for this analysis.

Long-term changes in MOR BP were also detected using two sample *t*-tests between patients receiving TA and SA between baseline scans in PET1 versus PET2 on a voxel-by-voxel basis using SPM99: (Comparison I =

[$TA_{(baseline2 - baseline1)} > SA_{(baseline2 - baseline1)}$] and Comparison II = [$SA_{(baseline2 - baseline1)} > TA_{(baseline2 - baseline1)}$]). Identical to the short-term changes, significant effects were detected for each comparison using two separate approaches: 1) an entire image-wide search that was unconstrained by regional predictions and 2) a regional approach that was based on *a priori* hypotheses. When effects of treatment were observed in *a priori* regions we employed an uncorrected statistical threshold of $p<0.001$ with a minimum cluster size of 20 voxels. These typically had z-scores between 3.1 and 4.5 for this analysis. For brain regions not previously hypothesized, significant regions were identified with a threshold of $p<0.05$ after correction by multiple comparisons using the family wise error approach (Friston *et al.* 1995a; Friston *et al.* 1995b). These typically had z-scores>4.5 for this analysis.

Positive and negative correlations between long-term changes in MOR BP (baseline2–baseline1) and changes in clinical pain (post–pre treatment) were performed using SPM99 again using a voxel-wise whole brain approach and an *a priori* region approach. Only regions showing significance after correction for multiple comparisons (i.e. $p<0.05$ corrected) are reported.

Numerical values for MOR binding were extracted from the image data by averaging the values of voxels contained in an area where significant effects were obtained in the voxel-by-voxel analyses, down to a threshold of $p = 0.01$. These values were then entered into SPSS version 14.0 (Chicago, IL) for plotting and assessment of possible outliers.

Treatment

We used an acupuncture treatment protocol previously utilized in a large clinical trial of acupuncture versus sham acupuncture in FM patients (Harris *et al.* 2005). This protocol was used because: 1) participants could not determine whether they were receiving real or sham acupuncture, and 2) this led to robust effects on chronic pain in both groups. Thus, this seemed an ideal protocol to isolate differences in mechanisms between acupuncture and sham acupuncture, in a group of chronic pain patients. During TA, nine acupuncture needles were inserted: Du 20, ear Shenmen, Large Intestine (LI) 4, LI 11, Spleen (SP) 6, Liver (LR) 3, Gall Bladder (GB) 34 and bilateral Stomach (ST) 36 (Fig. 1 b). All needles below the neck level were manually manipulated to elicit De Qi sensations. SA participants received a nonskin penetrating pricking sensation at nine non-acupuncture point locations using a previously validated sham procedure (Sherman *et al.* 2002). The sham locations were within similar body locations as the TA points however they were not on known acupuncture points or meridians. The length of time was similar for needle insertion and manipulation for TA and skin pricking for SA. All participants were blindfolded during each treatment to prevent patient knowledge of treatment assignment.

Clinical pain

Clinical pain was assessed immediately prior to PET1 and PET2 with the Short Form of the McGill Pain Questionnaire (SF MPQ) (Melzack 1987). The SF MPQ has two subscales that measure "sensory" and "affective" qualities of pain.

Assessment of masking

Following the first PET session, participants were asked to guess which treatment they thought they had been assigned to. The three choices were: 1) "Acupuncture", 2) "Sham Acupuncture", and 3) "Don't know". A Chi-squared test was used to determine whether there was a significant difference between groups (i.e. unmasking or un-blinding of the trial).

Results

Short-term differential changes in MOR BP during acupuncture and sham treatment

The design of this trial is depicted in Fig 1. Short-term differences in MOR BP between TA and SA treatments were examined with two separate comparisons: Comparison I= [$TA_{(treatment1 - baseline1)} > SA_{(treatment1 - baseline1)}$] and Comparison II=[$SA_{(treatment1 - baseline1)} > TA_{(treatment1 - baseline1)}$]. Fourteen regions were identified as having

Table 1. Regions displaying short-term increases in MOR binding following acupuncture.

Region	MNI coordinates			Voxels	*Z*	Acupuncture (TA) BP mean(s.e.m.)		Sham (SA) BP mean(s.e.m.)	
	x	*y*	*z*			Pre	Post	Pre	Post
Glbl V						0.62(0.03)	0.61(0.03)	0.58(0.03)	0.55(0.03)
dCC	−1	1	34	178	4.2	0.83(0.10)	0.95(0.09)	1.01(0.12)	0.87(0.08)
lsgACC	−11	20	−20	120	4.1	1.09(0.09)	1.18(0.11)	1.06(0.09)	0.90(0.09)
rsgACC	2	35	−20	399	3.9	1.42(0.07)	1.51(0.10)	1.39(0.12)	1.24(0.10)
lINS	−42	4	−20	540	3.6	0.91(0.06)	1.22(0.12)	0.92(0.07)	1.00(0.08)
lNAC	−12	12	−6	1004	7.2**	2.38(0.12)	2.81(0.23)	2.26(0.11)	2.22(0.11)
rCAU	14	16	2	212	3.9	2.12(0.10)	2.30(0.14)	1.87(0.10)	1.81(0.10)
lCAU	−9	7	6	140	4.1	1.02(0.13)	1.23(1.15)	0.98(0.09)	0.94(0.07)
dlTHA	11	−26	11	547	5.9**	1.41(0.14)	1.73(0.21)	1.36(0.09)	1.29(0.10)
vmTHA	2	−9	−5	91	4.9*	0.95(0.09)	1.29(0.18)	1.00(0.12)	1.03(0.11)
aTHA	−7	−4	10	203	4.4*	1.17(0.11)	1.46(0.14)	1.21(0.10)	1.21(0.08)
dmTHA	−5	−17	12	54	4.1	1.80(0.19)	2.08(0.21)	1.71(0.15)	1.75(0.13)
lAMY/tmpole	−26	11	−30	1556	7.1**	1.06(0.08)	1.39(0.14)	1.21(0.09)	1.10(0.08)
rAMY	18	−4	−25	34	3.3	0.79(0.07)	1.17(0.16)	0.88(0.11)	1.06(0.12)

**$p<0.001$ corrected;

*$p<0.05$ corrected; all other regions $p<0.001$ uncorrected.

Region definitions: (Glbl V) global value; (CC) cingulate cortex; (ACC) anterior cingulate cortex; (INS) insula; (NAC) nucleus accumbens; (CAU) caudate; (THA) thalamus; (AMY) amygdala; (tmpole) temporal pole; (l: left; r: right; a: anterior; d: dorsal; dl: dorsal lateral; dm: dorsal medial; sg: subgenual; vm: ventral medial).

differences in MOR BP between groups with Comparison I (Table 1 and Fig. 2). No regions were detected with Comparison II that met significance after correction for multiple comparisons (see Supplementary Fig. 1a glass brain results). Inspection of Table 1 and Fig. 2 indicates that treatment differences were attributable largely to increases in MOR BP following TA whereas SA evoked either a small decrease in MOR BP or resulted in no change. Two exceptions were the right amygdala and left insula which showed increases in BP for both groups, albeit larger increases for traditional acupuncture. Within the regions identified, the cingulate cortex, the nucleus accumbens, the thalamic nuclei, amygdala, and the temporal pole form part of an endogenous opioid circuit known to participate in the regulation of sensory and affective qualities of pain, as well as in emotional responses in humans (Zubieta *et al.* 2003a; Zubieta *et al.* 2001; Kennedy *et al.* 2006; Zubieta *et al.* 2003b).

To investigate whether the observed differences between TA and SA could be due to baseline differences between treatment groups, we compared baseline MOR BP values for the above 14 regions. None of the regions of interest (ROIs) showed significant baseline differences between groups in MOR BP (all $p>0.10$), confirming that the observed binding changes were due largely to effects during treatment.

Long-term differential changes in MOR BP following acupuncture and sham treatment

Long-term differences in MOR BP between TA and SA treatments were likewise examined with two separate comparisons: Comparison I=[$TA_{(baseline2-baseline1)}$>$SA_{(baseline2-baseline1)}$] and Comparison II= [$SA_{(baseline2-baseline1)}$> $TA_{(baseline2-baseline\ 1)}$]. Ten regions were identified as having differences in MOR BP between groups with Comparison I (Table 2 and Fig. 3). No regions were detected with Comparison II that met significance after correction for multiple comparisons (see Supplementary Fig. 1b for glass brain results). Inspection of Table 2 and Fig. 3 indicates that treatment differences were again largely attributable to increases in MOR BP following TA whereas SA evoked either small reductions in MOR BP or resulted in no change. Similar to the short-term effects, regions identified as showing increases in MOR BP included the amygdala, the cingulate cortex, the caudate, the putamen, and the temporal pole.

To investigate whether the observed differences following TA and SA could be due to baseline differences, between treatment groups,

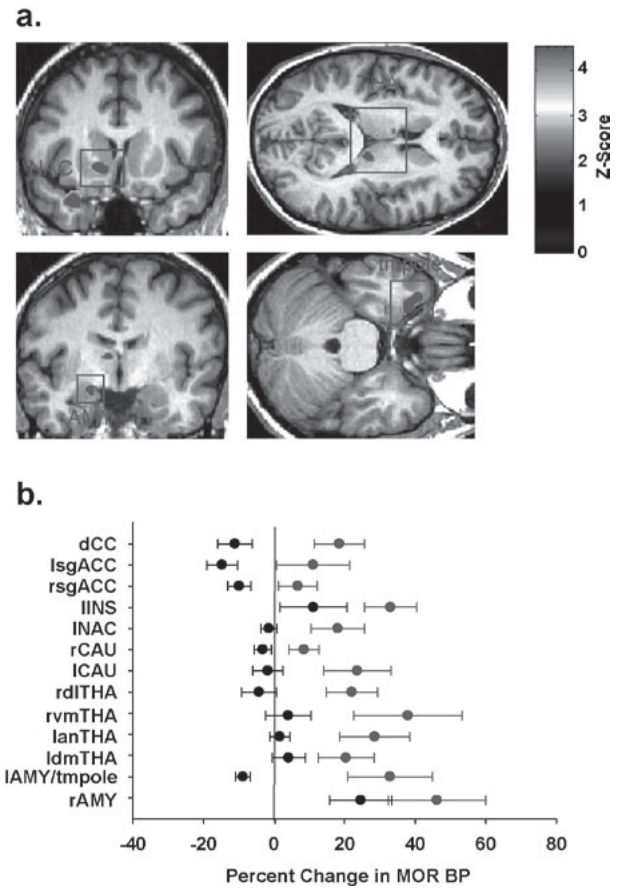

Figure 2. Differential short-term effects of acupuncture and sham acupuncture on MOR binding.
a. Regions of interest showing increased MOR BP following acupuncture as compared to sham treatment. Upper left: left nucleus accumbens (lNAC), upper right: three thalamic regions (THA), lower left and right: left amygdala (lAMY), and temporal pole (ltmpole) respectively.
b. Percent changes and S. E. M. in MOR BP (treatment1–baseline1) for all regions identified. Red circles (TA) and black circles (SA) represent group mean values with standard error bars. Overall acupuncture resulted in increases in MOR BP with sham treatment resulting largely in either no change or small decreases in BP.

we compared baseline MOR BP values for the above 10 regions. None of the ROIs showed significant baseline differences in MOR BP (all $p>0.15$) again supporting the conclusion that they were largely due to effects following long-term treatment.

Changes in clinical pain

Clinical pain intensity was assessed prior to both PET imaging sessions. Significant reductions in pain were observed for the entire cohort for the total score of the Short Form of the McGill Pain Questionnaire (SF MPQ Total; mean diff(SD) treatment – baseline; –3.45(7.39), $p<0.05$) and trended towards significance for the sensory and pain affect subscales (Sensory Score: –2.65 (5.98), $p = 0.06$; Affective Score: –0.80(2.26), $p = 0.13$). Both TA and SA resulted in clinically meaningful reductions in pain (SF MPQ Total Score mean diff(SD); TA: –4.00(6.72); SA: –2.90(8.33)), however there were no statistically significant differences in pain reduction between TA and SA ($p> 0.50$).

Changes in MOR binding are associated with changes in clinical pain

To investigate the analgesic relevance of the changes in MOR BP following TA, we correlated post–pre treatment changes in the SF MPQ Total score with the observed percent changes in MOR BP (i.e. baseline2 – baseline1) within participants that were treated with traditional acupuncture. Seven regions were identified as showing a negative correlation between changes in clinical pain and changes in MOR BP (Table 3 and Fig. 4). Among these regions the thalamus, the cingulate, and the insula are known to play significant roles in processing and modulating pain sensations. Other regions included the caudate, the putamen and the temporal pole. These regions have been identified in other studies as showing differential response to acupuncture and sham treatment (Napadow *et al.* 2005; Hui *et al.* 2000). No regions were identified in the TA group as showing significant positive correlations between changes in MOR BP and changes in pain (see Supplementary Fig. 1c for glass brain results). However the dorsolateral prefrontal cortex, which showed decreases in MOR BP in the SA group (see Fig. 3) had a significant positive correlation with pain reduction following sham treatment ($r = 0.69$; $p = 0.027$). Individuals with greater reductions in MOR BP within this region, had greater reductions in clinical pain.

Assessment of masking

To determine if the observed changes in MOR binding between groups could have resulted from participants knowing what treatment they received (i.e. unmasking of the trial), we asked

Table 2. Regions displaying long-term increases in MOR binding following acupuncture.

	MNI coordinates			Voxels	Z	Acupuncture (TA) BP mean(s.e.m.)		Sham (SA) BP mean(s.e.m.)	
Region	x	y	z			Pre	Post	Pre	Post
Glbl V						0.62(0.03)	0.65(0.03)	0.58(0.03)	0.59(0.04)
DLPFC	−30	29	26	351	3.3	0.63(0.04)	0.80(0.09)	0.79(0.11)	0.74(0.10)
ldCC	−3	−16	57	225	3.3	0.90(0.06)	1.02(0.05)	0.92(0.11)	0.82(0.07)
rdCC	10	−8	54	192	3.1	0.76(0.07)	0.94(0.08)	0.71(0.05)	0.67(0.06)
dACC	0	0	33	185	3.7	0.74(0.10)	0.89(0.09)	0.93(0.11)	0.81(0.08)
pgACC(1)	13	42	−1	628	3.3	0.92(0.08)	1.16(0.10)	0.87(0.06)	0.87(0.08)
pgACC(2)	14	44	12	114	3.2	0.91(0.09)	1.14(0.10)	0.81(0.08)	0.81(0.09)
PUT	20	12	−12	158	3.2	1.47(0.07)	1.66(0.07)	1.48(0.08)	1.45(0.08)
CAU	−8	15	4	23	3.2	1.11(0.15)	1.31(0.15)	1.05(0.12)	1.03(0.13)
AMY/tmpole	−30	11	−29	2417	4.8*	1.08(0.08)	1.24(0.09)	1.27(0.12)	1.09(0.07)
tmpole	−39	15	−28	1037	4.7*	1.27(0.06)	1.53(0.09)	1.27(0.09)	1.20(0.08)

*$p<0.05$ corrected; all other regions $p<0.001$ uncorrected.

Region definitions: (Glbl V) global value; (DLPFC) dorsal lateral prefrontal cortex; (CC) cingulate cortex; (ACC) anterior cingulate cortex; (CAU) caudate; (PUT) putamen; (AMY) amygdala; (tmpole) temporal pole; (l: left; r: right; d: dorsal; pg: perigenual).

all patients to guess what group they thought they were assigned to after the first PET imaging session. Participant guesses were consistent across the two groups. Four subjects in the TA group and three subjects in the SA group thought that they received traditional acupuncture. One participant in the SA group and two participants in the TA group thought that they received sham acupuncture, and four participants in the TA and six in the SA group did not know what treatment they received. These two distributions were not statistically different (Chi-Square value = 0.88; $p = 0.65$).

Discussion

We provide the first direct evidence of short- and long-term effects of acupuncture therapy on central MOR binding availability in chronic pain patients. Overall we find that traditional acupuncture therapy evokes an increase in MOR availability over both short and long periods. These changes were absent in sham treated patients where either no change was detected or decreases in MOR BP were observed. Reduction in central MOR BP during SA is consistent with increased endogenous opioid release during placebo administration (Zubieta *et al.* 2005; Scott *et al.* 2008). For both short- and long-term effects of TA, areas showing increases in BP included a number of brain regions classically implicated in the regulation of pain and stress in humans (Zubieta *et al.* 2001, 2003b), such as the amygdala, the dorsal and perigenual anterior cingulate, and the insular cortex. Other regions also shown to be involved in responses to pain and other salient stimuli and where TA induced significant effects on MOR BP included the nucleus accumbens, the caudate, and the putamen (Gear & Levine 1995; Scott *et al.* 2006). The nucleus accumbens and the dorsal cingulate are both regions that we identified previously as showing reduced binding in FM patients as compared to controls (Harris *et al.* 2007). Finally, a region of the temporal pole showed increases in binding following TA for both short and long time periods, and displayed a significant negative correlation with changes in clinical pain. This temporal pole region has previously been identified as showing responsiveness to negative mood (Kennedy *et al.* 2006; Zubieta *et al.* 2003b) as well as acupuncture treatment (Napadow *et al.* 2005; Hui *et al.* 2000).

Our findings of widespread increases in regional MOR binding availability are consistent with a previous trial of acupuncture in rodents showing that acupuncture induces an increase in the number of central MOR binding sites following treatment (Gao *et al.* 1997). For changes that arise following long-term therapy, this could involve increased transcription and translation of MORs and their subsequent insertion into the plasma membrane. Indeed acupuncture treatment has been shown to modulate the levels of transcription factors within the central nervous system (Lao *et al.* 2004). However this explanation does not address the relatively

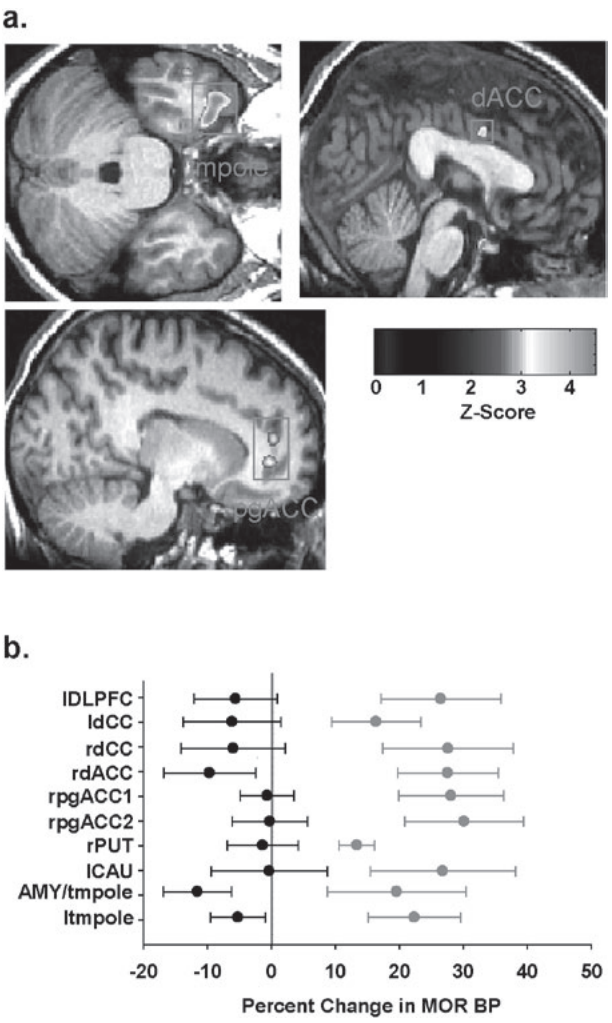

Figure 3. Differential long-term effects of acupuncture and sham acupuncture on MOR binding.
a. Regions of interest showing increased MOR BP following acupuncture as compared to sham treatment. Upper left: temporal pole (ltmpole), upper right: dorsal anterior cingulate cortex (dACC), lower left: two perigenual anterior cingulate regions (pgACC).
b. Percent changes and S. E. M. in MOR BP (baseline2 –baseline1) for all regions identified. Red circles (TA) and black circles (SA) represent group mean values with standard error bars. Overall acupuncture resulted in an increase in MOR BP whereas sham treatment resulted in either no change or a decrease in binding ability.

rapid increases in MOR BP that we observe (i.e. within 45 min) following needle insertion. One possible explanation originates from animal and tissue preparations where increases in the plasma membrane expression of all three classes of opioid receptors have been shown to occur in neurons following excitation. The sub-cellular localization of μ- (Browning *et al.* 2004), κ- (Shuster *et al.* 1999), and Δ- (Bao *et al.* 2003) opioid receptors all appear to

Table 3. Regions displaying negative correlation between MOR binding changes and changes in clinical pain following acupuncture.

	MNI coordinates			Voxels	*Z*	*r*
Region	*x*	*y*	*z*			
ldCC	−15	10	36	315	4.7	−0.50
raINS	36	24	−3	773	3.6	−0.78
lCAU	−7	10	2	686	6.8**	−0.70
rPUT-rCAU	19	7	−4	2096	6.0**	−0.76
lmTHA	−4	−12	11	1008	5.4*	−0.65
ltmpole	−29	15	−34	1310	6.3**	−0.71
rtmpole	26	11	−36	924	5.8**	−0.60

**$p<0.001$ corrected;
*$p<0.005$ corrected; all other regions $p<0.05$ corrected
Patients with greater increases in MOR BP displayed greater reductions in clinical pain.

be dynamically regulated by neural activity. Following neuronal excitation, all three classes of receptors have been shown to be trafficked to the plasma membrane within the time frame that we observe our short-term acupuncture effects (i.e. within 45 min). This type of regulation of glutamate receptors has been observed during long-term potentiation (LTP) and long-term depression (LTD) where neuronal activity modulates receptor expression at the plasma membrane (Malenka 2003). Interestingly a recent study by Xing *et al.* (2007) suggests that acupuncture can also induce LTD in the spinal cord in a rat model of chronic pain and this depression is abolished by the opioid receptor antagonist naloxone. LTD-type modulation of MORs and subsequent changes in synaptic strength could function as a mechanism for acupuncture analgesia given the lasting effects of acupuncture observed here and in other clinical trials (Brinkhaus *et al.* 2006; Linde *et al.* 2005; Melchart *et al.*; Witt *et al.* 2005).

Another intriguing result from the present study is that although MOR BP values were differentially altered by TA and SA, reduction in clinical pain was similar between groups. In a clinical trial, when an active treatment does not exhibit superior efficacy to a sham or placebo, the active treatment is assumed to be ineffective and only operating via a placebo effect. However this study suggests that this may be an erroneous conclusion. In this instance, our non-insertion sham procedure evoked a similar reduction in pain as our true acupuncture and

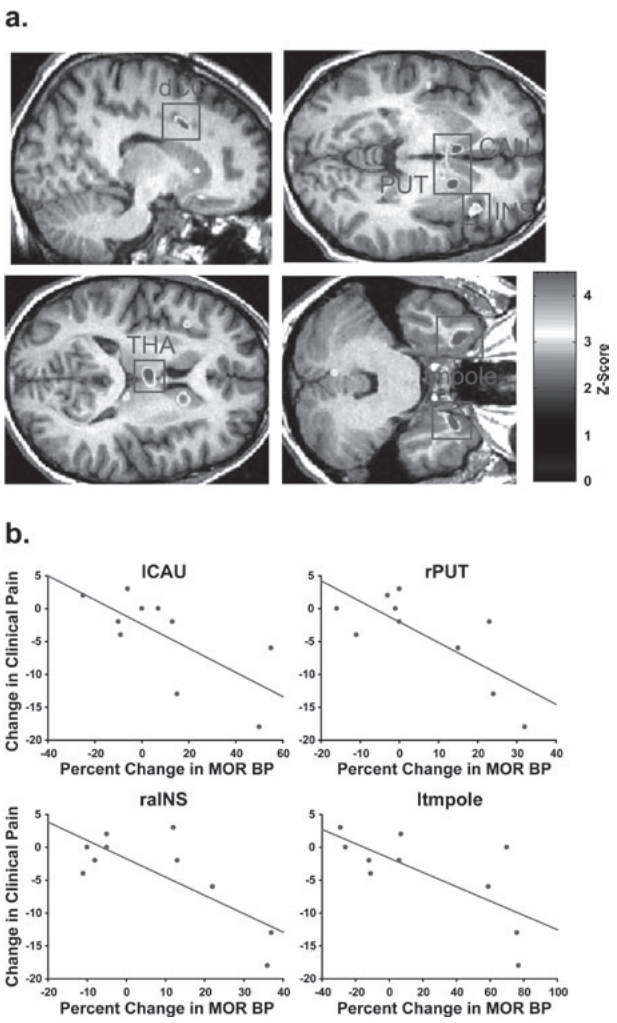

Figure 4. Long-term increases in MOR binding following acupuncture are associated with reductions in clinical pain.
a. Regions of interest showing negative correlations between changes in MOR BP (baseline2–baseline1) and changes in clinical pain (pain assessment2–pain assessment1) following acupuncture. Upper left: left dorsal cingulate cortex (ldCC), upper right: left caudate (lCAU), right putamen (rPUT), and right anterior insula (raIns), lower left: left medial thalamus (lmTHA), lower right: bilateral temporal pole (tmpole).
b. Scatter plots of percent changes in MOR BP (post-pre) and changes in clinical pain (post-pre) for four regions depicted in 4a.

we speculate that this occurred via a different mechanism. The analgesic effects of SA could have been due to regional reductions in MOR BP, consistent with activation of this class of receptors during placebo effects (Zubieta *et al.* 2005), whereas TA evoked an increase in receptor binding availability. This interpretation is entirely consistent with the observed positive correlation between decreases in MOR BP within the dorsolateral prefrontal cortex and decreased pain in the SA group. These reductions in MOR BP may also be operating in TA however these effects may be "masked" by the increases in receptor binding availability noted above.

Finally we explored the relationship between increases in MOR BP following acupuncture and subsequent changes in clinical pain. We found that many of the same regions showing increases in binding following acupuncture therapy were also associated with reductions in clinical pain. Since our previous study found reductions in MOR BP in FM patients (Harris *et al.* 2007), acupuncture may act to increase or "normalize" MOR binding ability in FM patients to levels that are more representative of pain free controls.

To determine if participants could tell the difference in treatments and un-blind the trial, we asked our participants to guess which treatment they thought they received following the first PET imaging session. We found that both groups had similar guesses for their treatment assignments suggesting our results were not likely to be explained by participant knowledge of treatment assignment.

In this work some participants were taking medications, however we monitored closely their usage (see Supplementary Table 2). Patients remained on stable doses of existing medications for the entire duration of the study. Therefore, medications are unlikely to represent a confounding factor in the analyses presented. Any medication confound would be operative in both pre- and post treatment scans as well as for TA and SA groups.

Our sham intervention was performed on non-acupuncture points and did not involve skin penetration. Therefore our differential effects of TA and SA may be due to point location and/or skin penetration. Future studies are needed to determine if the differential effects on MOR BP are due to either skin penetration or acupuncture point stimulation or a combination of both.

Overall our data strongly imply divergent opioid receptor mechanisms in acupuncture and sham acupuncture therapy. Although the fundamental mechanisms underlying these

processes await further investigation, central opioid receptors appear to be involved in both treatments, albeit with differing effects within the same brain structures. Greater insight into these effects may be obtained in animal models of chronic pain disorders.

Acknowledgments

This work was funded by Department of Army grants DAMD (17/002–0018 to D. J. C. and W81XWH-07–2-0050 to R. E. H.) and National Institutes of Health (M01-RR000 042 to R. E. H.; R01 AT 001 415 to J. K. Z., K01 AT01 111–01 to R. E. H., and K01-AT002 166 and P01-AT002 048 to V. N.).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.05.083.

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This article is reprinted from NeuroImage, 47 (3), Harris R. E., Zubieta J-K., Scott D. J., Napadow V., Gracely R. H., Clauw D. J., Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on μ-opioid receptors (MORs), 1077–1085, Copyright 2009, with kind permission from Elsevier.