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Acupuncture Produces Central Activations in Pain Regions

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Acupuncture is largely used for pain control in several pathological conditions. Its effects on the central nervous system are not well defined. We investigated the effect of the application of acupuncture to 13 normal subjects (males, 21–32 years). $H_2{}^{15}O$ bolus PET scans were read before the application of the needles (Rest, R) and after 25 min of needle insertion. Data were acquired by scanning in 3-D mode. The acupuncture application, true acupuncture (TA), was alternated to a placebo needle application (PA) in two different sequences (seven and six subjects, respectively), either R,PA,R, TA or R,TA,R,PA, a period of 15 min being left after every first TA or PA to allow for the recovery of basal conditions. Here we show that classic acupuncture activates the left Anterior Cingulus, the Insulae bilaterally, the Cerebellum bilaterally, the left Superior Frontal Gyrus, and the right Medial and Inferior Frontal Gyri. Most of the activated areas are shared with areas activated in acute and chronic pain states as described in the literature. Thus acupuncture appears to act by activating areas also involved in pain. This indicates that acupuncture could relief pain by unbalancing the equilibrium of distributed pain-related central networks. © 2001 Academic Press

Key Words: **acupuncture; positron emission tomography; anterior cingulus; insulae; cerebellum; superior frontal gyrus; medial frontal gyrus; inferior frontal gyrus; pain; human.**

INTRODUCTION

Acupuncture has been recently accepted by the National Institutes for Health (NIH) of the United States as a technique of peripheral sensory stimulation (PSS), in the therapy of painful syndromes (Han, 1997). In the literature it is hypothesized that acupuncture elicits analgesic effects with mechanisms comparable to those induced by nerve low frequency stimulations, the needle representing the activating source for structures like receptors and nerve fibers (LeBars *et al.*, 1989; MacDonald, 1989). It has been proposed another possible mechanism of action that associates the effects of acupuncture to long-term depression (LTD) of the excitatory synapses (Sandkühler, 1996). LTD is a widely described event in several areas of the central nervous system of experimental animals (Artola and Singer, 1993), where prolonged and low frequency stimulations are adequate to induce long lasting synaptic depression and/or depotentiation.

Furthermore, studies on acupuncture activated central structures have shown that, both in man and in experimental animals, the ponto-bulbar descending sensory modulatory pathways are activated with endorphin release (He, 1987).

In our study, we have used PET imaging techniques in normal subjects to examine changes in brain activity associated with classic acupuncture applied as for pain treatment. We wanted to define which areas are affected by acupuncture in the absence of noxious stimuli or painful conditions. To this end, we examined regional cerebral blood flow (rCBF) changes (as an index of altered synaptic activity) induced by acupuncture. As a control rCBF changes induced by "placebo acupuncture" were compared.

MATERIALS AND METHODS

Subjects

Thirteen young male healthy subjects (age 21–32) were enrolled. All had refrained from alcohol or drug consumption in the previous 24 h. All volunteers signed a written informed consent form, approved together with the study protocol by the H. S. Raffaele Ethical Committee.

Experimental Procedure

The experimental design included three conditions: (1) Rest state (R); (2) Placebo (or False) acupuncture (PA); (3) True acupuncture (TA), in two sequences: R PA R TA and R TA R PA. The subjects were previously

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informed that the study was aimed to match two different acupuncture procedures. They were instructed to maintain immobility and closed eyes during the recording sessions. A panel prevented the recognition of the experimenters' maneuver. At the end of the first rest (R) PET scan, either the first or the second sequence was applied. For TA the points denominated Zusanli (36 St.) and Qi-ze (5 Lu.) were bilaterally needled about 1–2 cm deep. They corresponded, respectively, to the volar aspect of the proximal forearm 1 cm from the articulatory ply and to the proximal fifth of the tibial extensor, on the anterolateral aspect of the leg, respectively. Stainless steel needles (5 cm, 30 gauge) were slowly rotated producing the characteristic "Teh-Qi" effect (heaviness, tension and numbness) and then left for 25 min. When asked, the subjects recognised the painless presence of needles. For PA the needles were inserted superficially, 1 cm lateral to each TA point, in non-meridian-points, and immediately extracted. The subjects recognized a "continuous painless presence" of needles, without the characteristic "Teh-Qi" effect. All subjects were submitted to both TA and PA: 7 to the "TA then PA" and 6 to the "PA then TA" sequences. No subject throughout either experimental condition TA or PA declared pain sensation. In TA the heaviness, tension, and numbness sensation was reported. In PA only a presence of needles was reported. During TA or PA applications the subjects were asked to rest for 25 min. Then, a second PET scan was performed. At that time in TA the needles were removed. After further 15 min a R PET scan was performed, followed by either TA or PA according to the protocol, as described before. After 25 min of the second PA/TA phase the last PET scan was performed.

The subjects had to declare however the absence (or the possible presence) of pain during the acupuncture session. The perception of pain should have indicated the experiment termination.

PET Procedures

rCBF was measured by recording the distribution of radioactivity following the intravenous injection of ^{15}O-labeled water ($H_2{}^{15}O$) with the GE-Advance scanner (General Electric Medical System, Milwaukee, WI), which has an axial field of view of 15.2 cm, allowing sampling of the entire brain and cerebellum at once. Data were acquired by scanning in 3-D mode. A 7-mCi slow-bolus of $H_2{}^{15}O$ was injected as a tracer of blood flow and 90-s scans were acquired immediately after initial raise of head-counts (Friston *et al.,* 1995a). After attenuation correction (measured by a transmission scan), the data were reconstructed as 35 transaxial planes by 3-D filtered-back projection using a Hanning filter (cut-off 4 mm) in the transaxial plane, and a Ramp filter (cut-off 8.5 mm) in the axial direction. The quantified counts accumulated over 90-s scans were used as an index of rCBF (Silbersweig *et al.,* 1993). PET data were analyzed with the Statistical Parametric Mapping 1996 (Wellcome Department of Cognitive Neurology, London, UK) (Friston *et al.,* 1996). The original brain images were first realigned and then transformed into a standard stereotactic anatomical space (Friston *et al.,* 1995b). Stereotactically normalized images were smoothed with a Gaussian filter ($16 \times 16 \times 16$ mm). Statistical analyses were performed according to the SPM 1996 implementation of the general linear model (Friston *et al.,* 1995b). Global differences in CBF across conditions were compensated for by proportional scaling. Comparisons of rCBF distribution across condition were made with the t statistic. The resulting set of t values constituted a statistical parametric map (SPM{t}), which was transformed into Z score maps (SPM{Z}). We first identified the brain areas commonly activated by placebo and true acupuncture in the form of a conjunction of the simple main effects of these two conditions compared with their time-matched resting state scans ($P < 0.01$ with correction $P < 0.05$ for spatial extent). The conjunction analysis identifies activations of comparable statistical magnitude of independent linear contrasts (Price and Friston, 1997). Given the experimental sequence Rest PA Rest TA, the conjunction analysis identifies comparable rCBF changes of the following two contrasts: -1 1 0 0 and 0 0 -1 1.

We then compared the magnitudes of the above two activations as a conjunction of the comparison of a given condition against rest and against the other condition (e.g., conjunction of the contrasts TA minus R). By using two different baselines we ensured that activation patterns were not confounded by relative rCBF decreases in a given baseline. For these more subtle comparisons an uncorrected threshold of $P < 0.01$ was adopted.

A meta-analysis map of the areas activated in pain conditions (shared by acupuncture induced activations) was obtained by averaging the data from the recent literature (Talbot *et al.,* 1991; Coghill *et al.,* 1994; Derbyshire *et al.,* 1994; Craig *et al.,* 1996; Casey *et al.,* 1996; Vogt *et al.,* 1996; Adler *et al.,* 1997; Andersson *et al.,* 1997; Derbyshire *et al.,* 1997; Rainville *et al.,* 1997; Paulson *et al.,* 1998), based on their common anatomic localizations (Talairach and Tournoux, 1988).

Note on Acupuncture Technique

Two different techniques of acupuncture application are known. One, called Acupuncture Analgesia, is produced for the treatment of acute, experimental, or surgically induced pain by a continuous painful stimulation (needling) for about 50 min. It is rarely used on patients with chronic disease that require much longer-term pain relief. The other technique is the

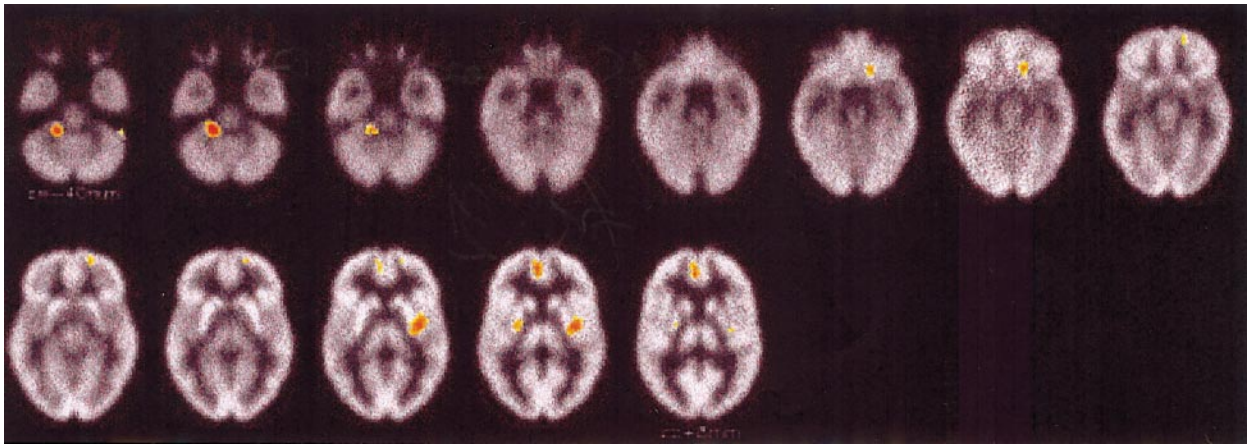

FIG. 1. Areas specifically activated with TA (classic acupuncture). The activation are inserted in an average stereotactically normalized PET image derived from the subjects who took part to the study. Slice thickness is 8 mm. The areas indicated are the residuals after subtraction of the results of placebo acupuncture (PA) and rest (R) from TA. Stereotactic coordinates and *Z* scores are reported in Table 1B. The conjunction of the contrasts was obtained by (1) TA - rest and (2) TA-PA.

Classical Acupuncture therapy. With this technique, a shorter (about 20–25 min) nonpainful needle application is delivered. We used this technique in order to avoid noxious stimuli possibly blurring the basic effects of acupuncture. As for the placebo acupuncture, after the insertion the needles were taken superfically and extracted. We chose this placebo technique since, as described by the report of the Shanghai College of Traditional Chinese Medicine (Shanghai College of Traditional Chinese Medicine, 1981), there are 747 acupoints in man and, therefore, as pointed out by MacDonald (1989), it would be very difficult to find a site which is not in the immediate vicinity of an acupoint or influencing it.

RESULTS

During the application of true acupuncture (TA) statistically increased rCBF in the left anterior Cingulate Cortex (ACC), the Insulae bilaterally, the Cerebellum bilaterally, and the right Superior and Medial Frontal Gyri (SFG and MFG respectively) was observed (Table 1a and Fig. 1). During PA statistically increased rCBF in the Raphè nuclei, the Hypothalamus and left Temporo-Parietal junction (Table 1b) were observed. PA and TA shared activations in Claustrum, Caudatus and Putamen, Medial and Inferior Frontal Gyri bilaterally and in lesser degree in the right anterior Insula were observed (Table 1c). An integrative meta-analysis

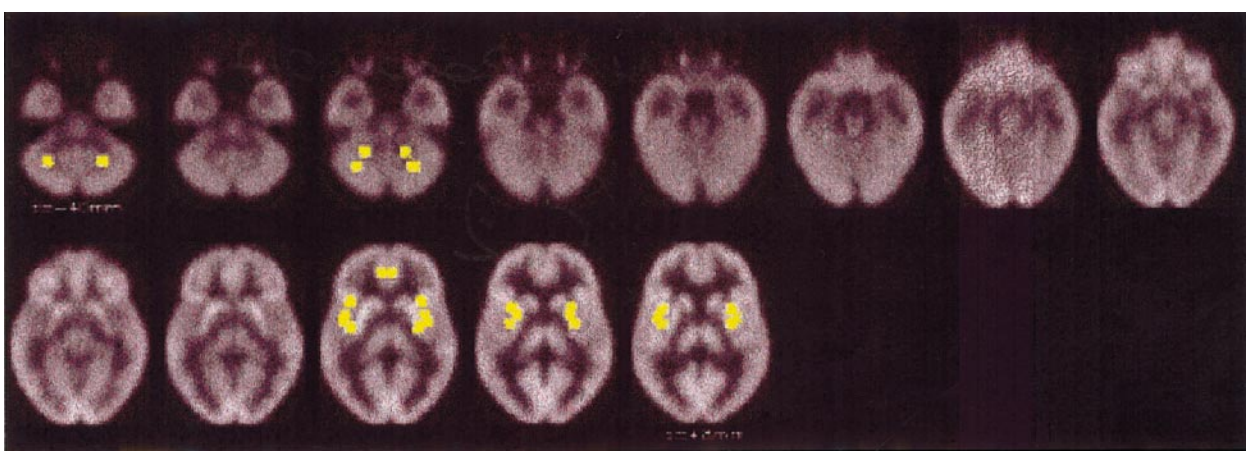

FIG. 2. Sites activated in pain experimental conditions shared with acupuncture are shown overlapped to a PET template averaged over subject images. Note that the marked sites are coincident with the area peaks and not representative of the area extension of the activations. In order to allow consistency with acupuncture data mediolateral coordinates were plotted to reflect bilaterally the responses. (Talbot *et al.,* 1991; Coghill *et al.,* 1994; Derbyshire *et al.,* 1994; Craig *et al.,* 1996; Casey *et al.,* 1996; Vogt *et al.,* 1996; Adler *et al.,* 1997; Andersson *et al.,* 1997; Derbyshire *et al.,* 1997; Rainville *et al.,* 1997; Paulson *et al.,* 1998).

TABLE 1A

Stereotactic Coordinates and *Z* Scores of Brain Areas Identified by the Conjunction of the Contrasts (1) TA - Rest and (2) TA-PA

Brain areas of activation specific for true acupuncture	Left hemisphere				Right hemisphere			
Brain region	*x*	*y*	*z*[a]	*Z* score	*x*	*y*	*z*[a]	*Z* score
Insula	−28	−8	4	3.98				
Cerebellum					32	−28	−52	3.81
Insula					36	−8	0	3.39
Cingulate cortex	−6	42	8	3.35				
Middle/inferior frontal gyrus					16	20	−16	3.10
Insula					34	−16	4	3.09
Cerebellum	−18	−36	−36	2.92				
Superior frontal gyrus					20	54	−4	2.88
Cerebellum					50	−42	−52	2.66
Middle/inferior frontal gyrus					10	30	−16	2.42

[a] *x, y, z* are the coordinates of the maximum signal of the activated areas.

of the sites activated by acute and chronic pain in PET studies shared with the areas activated by TA is shown in Fig. 2. This demonstrates a good match in the regions of the ACC, the Insulae, bilaterally, and the Cerebellum. The averaged map of the areas activated in pain conditions was obtained from the recent literature (Talbot *et al.*, 1991; Coghill *et al.*, 1994; Derbyshire *et al.*, 1994; Craig *et al.*, 1996; Casey *et al.*, 1996; Vogt *et al.*, 1996; Adler *et al.*, 1997; Andersson *et al.*, 1997; Derbyshire *et al.*, 1997; Rainville *et al.*, 1997; Paulson *et al.*, 1998) and based on their shared anatomic localizations (Talairach and Tournoux, 1988).

All the results shown in the tables have been ordered along decreasing *Z* score values.

DISCUSSION

We found that TA activates structures such as the ACC, the Insulae and the Cerebellum (Fig. 1) also activated by acute and chronic pain (Fig. 2), as demonstrated by several studies with imaging techniques (Talbot *et al.*, 1991; Jones *et al.*, 1991; Coghill *et al.*, 1994; Derbyshire *et al.*, 1994; Craig *et al.*, 1996; Casey *et al.*, 1996; Vogt *et al.*, 1996; Adler *et al.*, 1997; Andersson *et al.*, 1997; Derbyshire *et al.*, 1997; Rainville *et al.*, 1997; Paulson *et al.*, 1998; Casey, 1999). Recent studies on fMRI imaging of acupuncture effects during needle manipulation (Wu *et al.*, 1999; Hui *et al.*, 2000) have shown different activation-deactivation of several supraspinal areas. However, the immediate central effects of needle manipulation do not necessarily correspond to the true central effects of acupuncture, leaving unsolved the question of the areas involved in the therapeutic effects induced by acupuncture. For this reason, in our study, we measured TA and PA effects 25 min after the needle insertion.

As for the common areas activated by both TA and painful stimuli, ACC is thought to be involved in the

TABLE 1B

Stereotactic Coordinates and *Z* Scores of Brain Areas Identified by the Conjunction of the Contrasts (1) PA - Rest and (2) PA-TA

Sites of areas of activations specific for placebo acupuncture	Left hemisphere				Right hemisphere			
Brain region	*x*	*y*	*z*[a]	*Z* score	*x*	*y*	*z*[a]	*Z* score
Parietal supramarginal gyrus	−68	−36	24	3.78				
Hypothalamus	−2	−12	−12	3.40				
Hypothalamus	−12	0	−8	3.17				
Hypothalamus					4	0	−8	3.07
Hypothalamus/pons raphé nuclei					2	−28	−20	3.05
Parietal supramarginal gyrus	−60	−38	24	2.95				
Parietal/temporal junction	−56	−46	20	2.93				
Hypothalamus	−6	−6	−8	2.58				

[a] *x, y, z* are the coordinates of the maximum signal of the activated areas.

TABLE 1C

Stereotactic Coordinates and *Z* Scores of the Brain Areas Identified by the Conjunction Analysis of the Comparison (1) TA versus Its Time-Matched Rest and (2) FA versus its Time-Matched Rest

Sites of areas shared by placebo and true acupuncture	Left hemisphere				Right hemisphere			
Brain region	*x*	*y*	*z*[a]	*Z* score	*x*	*y*	*z*[a]	*Z* score
Anterior cingulate cortex	−14	40	4	4.81				
Inferior frontal gyrus/insula					36	24	4	4.56
Claustrum					34	12	4	4.12
Caudate					14	12	−4	4.06
Gyrus rectus					18	18	−8	3.98
Inferior frontal gyrus					24	24	−12	3.94
Caudate					8	6	−4	3.89
Insula					36	4	8	3.82
Inferior/middle frontal gyrus					32	40	8	3.72
Anterior cingulate cortex	−6	34	−8	3.69				
Medial frontal gyrus/cingulate cortex	−14	40	20	3.66				
Medial frontal gyrus					24	52	8	3.61
Claustrum					34	−4	8	3.43
Medial frontal gyrus	−42	46	24	3.36				
Longitudinal superior fascicle/insula	−28	32	12	3.24				
Cingulate cortex gyrus	−24	40	16	3.14				
Putamen					26	−10	4	3.24
Inferior frontal gyrus	−38	40	20	3.03				
Inferior frontal gyrus					30	6	24	2.88

[a] *x*, *y*, *z* are the coordinates of the maximum signal of the activated areas.

estimation and modulation of sensory and cognitive signals. Complementary affective or psychological responses were attributed to the rostral part of that area (Rainville *et al.*, 1997; Casey, 1999). ACC is moreover involved in a number of pain responses both in tonic persistent and acute pain (Derbyshire *et al.*, 1997; Casey, 1999), in pain anticipatory mechanisms (Hsieh *et al.*, 1999) and in pain-related multiple cognitive procedures (Rainville *et al.*, 1999). ACC is also referred to as part of the attentional systems that accompany the painful sensation (Davis *et al.*, 1997). Possible "antinociceptive" properties of ACC regions have been shown in the correlation between hypnosis, delta waves, and ACC sulcal activation (Rainville *et al.*, 1999). Electrophysiologically, pain related neurons have been recently shown in human ACC (Hutchinson *et al.*, 1999). The insular region has been described as a focal node for pain intensity coding circuits, also labelled as intensity coding matrix (Peyron *et al.*, 1999). Several other authors showed also a contralateral insular region discriminative activity in response to painful stimuli (Casey, 1999; Craig *et al.*, 2000) or that these insular activations were bilateral (Jones *et al.*, 1991; Svensson *et al.*, 1997).

As for the SFG, this region is involved in several networks associated with various superior cortical functions (Royet *et al.*, 1999).

Both the midline (vermis) and neocerebellar regions are activated by pain stimulations (Casey, 1999). A role of the cerebellum has been also proposed as providing the necessary circuitry for the sensory system to extract temporal information (Penhune *et al.*, 1998). In this context, acupuncture could enable a disruption of noxious information temporally encoded by the cerebellum.

There were no signs of either primary or secondary sensory cortex activations. Though the needle insertion would have been effective for sensory cortical activation, the residual sensory input, after the long delay between the needle insertion and the PET scan, was presumably not strong enough to be detected.

In summary, the wide data-base on areas concerned with nociceptive processing shows activations in regions also involved in acupuncture. When compared to a meta-analytic map of sites of pain associated areas, acupuncture activations present only minor mismatches (Fig. 2) (Talbot *et al.*, 1991; Coghill *et al.*, 1994; Derbyshire *et al.*, 1994; Craig *et al.*, 1996; Casey *et al.*, 1996; Vogt *et al.*, 1996; Adler *et al.*, 1997; Andersson *et al.*, 1997; Derbyshire *et al.*, 1997; Rainville *et al.*, 1997; Paulson *et al.*, 1998).

While we are aware that these data do not explain the physiological acupuncture mechanisms, two theoretical frameworks can allow a conjecture on its effects: they comprise the concept of the "neuromatrix" proposed by Melzack in studies on pain (Melzack, 1999) and that of "fault tolerance," originated by studies on neural networks (Stevenson *et al.*, 1990; Neti *et al.*, 1992). In the original neuromatrix hypothesis it is considered that the thalamocortical pathways and the lim-

bic circuits enable parallel signal processing. The output of the activated network, as in pain states, represents a neurosignature, an integral image of the brain response to the overall peripheral conditions. Moreover, in the case of chronic pain, synaptic plasticity and learning can establish permanent synaptic changes, stabilizing the neuromatrix. The neuromatrix hypothesis introduces to models in neural networks. A special feature of neural networks is the resistance to inputs disturbing their current functions. This feature is labelled as fault tolerance (Neti *et al.,* 1992).

Can acupuncture be considered an interference that violates the tolerance of the neuromatrix in the state of pain? If so, acupuncture could be thought as a conflicting message in the pain neuromatrix, unbalancing it and thus modifying the perception of pain. This event should not necessarily lead to decreases in activation but to diverse estimates of the inputs by the cortex. A possible hypothesis is that acupuncture activates (as it does) a subset of the network activated in painful states. In addition, pain and acupuncture could present different modes of neuronal activation. A different "activation mode" could accordingly achieve diverse perceptual states.

As for the areas activated by PA, the temporo-parietal activation can be associated to the recent data by Apkarian (1999), showing gradual, time-related, anteroposterior transition of information in the parietal cortex involved in the distinction of pain perception from stimulus categorizing. As for the raphé nuclei and the hypothalamus a further hypothesis can be given. The raphé nuclei are an essential component of the descending pathways for the control of nociceptive inputs (Mason, 1999). Antidromic identification of hypothalamic neurons from lumbar nociceptive neurons has been described (Dado *et al.,* 1994) and regions responding to noxious stimuli and modulated by opioid iontophoretic administration have been identified (Dafny *et al.,* 1995). Activations of these areas in our experiments can be attributed to placebo effects due to experimental manipulation.

TA did not activate these areas. A hypothesis can be made that during TA, some control, arising from the activated cortical network, could mask activations of these areas. As a final comment, in this context, we remark that the subjects were unaware of the TA or PA application and that the perception of "Teh-Qi" effect during TA, absent in PA, was the only overt difference.

Common activations by TA and PA include Claustrum, Caudatus and Putamen, Medial and Inferior Frontal Gyri bilaterally, and in lesser degree the right anterior Insula. These areas are involved in movement programming and integrative tasks that are coherent to both TA and PA experimental conditions.

Finally, no pain associated memory seems a likely bias for the results. The onset and duration of pain associated memories critically depend upon LTP-like (Long-Term Potentiation) event and the type and intensity of conditioning stimuli (Sandkühler, 2000). Thus, the acupuncture low intensity and fast pricking stimulus could not induce a pain memory in our experimental conditions. The subjects had also been instructed to certify the presence or absence of pain throughout the entire experimental session. Any pain sign would have implied the rejection of the session and the discontinuation of the experiment.

Additionally, following the R PET scans, the subjects were instructed after the needle true/false insertion to wait still for 20–25 min before the next PET scan. Other expectancy effects, if any, was suppressed by the subtraction method used in the analyses.

Hence, both a quantitative and a modal explanation for the central effects of acupuncture seem conceivable. Several neurotransmission systems and events are probably at the basis of these effects. Further studies are thus warranted to deepen our knowledge on the analgesic properties of acupuncture.

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