Research Report

Acupuncture needling sensation: The neural correlates of deqi using fMRI

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ABSTRACT

The needling sensation of deqi is considered by most acupuncturists to be an important component of acupuncture, yet neuroimaging research that investigates this needle sensation has been limited. In this study we have investigated the effect of deqi and acute pain needling sensations upon brain fMRI blood oxygen level-dependent (BOLD) signals. Seventeen right-handed participants who received acupuncture at the right LI-4 (Hegu) acupoint were imaged in a 3T MRI scanner. fMRI datasets were classified, on the basis of psychophysical participants’ reports of needling scores, into those that were associated with predominantly deqi sensations versus those with predominantly acute pain sensations. Brain areas showing changes in BOLD signal increases (activations) and decreases (deactivations) were identified. Differences were demonstrated in the pattern of activations and deactivations between groupings of scans associated with deqi versus pain sensations. For the deqi grouping, significant deactivations occurred, whereas significant activations did not. In contrast, the predominantly acute pain grouping was associated with a mixture of activations and deactivations. For the comparison between the predominantly deqi sensation grouping and the acute pain sensation grouping (deqi>pain contrast), only negative Z value voxels resulted (mainly from deactivations in the deqi grouping and activations in the pain grouping) in the limbic/sub-cortical structures and the cerebellum regions of interest. Our results show the importance of collecting and accounting for needle sensation data in neuroimaging studies of acupuncture.

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1. Introduction

Acupuncture needling sensation has been considered important to acupuncture practice since the early classical texts (Kong et al., 2007). A key term that relates to needle sensation is deqi, which is assumed by many acupuncturists to be associated with a therapeutic effect and for this reason is often sought during needling (MacPherson et al., 2001). To monitor needling sensations, Vincent et al. (1989) adapted the McGill Pain Questionnaire (Melzack, 1975), which was subse-
quently adapted by Park et al. (2002) to include both pain and deqi sensations. There have been a number of recent attempts to clarify more precisely the needle sensations associated with deqi. MacPherson and Asghar (2006) used expert opinion to delineate and weight the sensations of deqi from those that might be more properly associated with acute pain. Based on a hierarchical cluster analysis, a grouping of seven sensations was found to be associated with the category of deqi (“aching”, “dull”, “heav”, “numb”, “radiating”, “spreading” and “tingling”), and a grouping of nine sensations (“burning”, “hot”, “hurting”, “pinching”, “pricking”, “sharp”, “shocking”, “stinging” and “tender”) with the category of acute pain (MacPherson and Asghar, 2006). A number of other researchers have sought to establish a credible rating scale for needling sensations, including the Subjective Acupuncture Sensation Scale (Kong et al., 2005), the “deqi composite” (Hui et al., 2007), the Massachusetts General Hospital Acupuncture Sensation Scale (Kong et al., 2007), and the Southampton Needle Sensation Questionnaire (White et al., 2008).

There is considerable debate about whether specific acupuncture needling sensations, including deqi, are associated with therapeutic benefit (Kong et al., 2007). Despite the importance that practitioners have often placed on the deqi sensation (MacPherson et al., 2001), there has been limited research in this area. An early example was a mechanistic study that demonstrated correlations between acupuncture analgesia and sensations of “numbness”, “fullness” and sometimes “soreness”, sensations that are often associated with deqi (Chiang et al., 1973). This study also found that deqi might be an important component of acupuncture analgesia because both deqi and acupuncture analgesia could be blocked by intramuscular, but not subcutaneous, procaine injections at acupuncture points (Chiang et al., 1973). Their results were supported by a recent study that also found a similar relationship between acupuncture analgesia, numbness and soreness, but not for other sensations commonly associated with deqi (Kong et al., 2005). In a small clinical trial of acupuncture for osteoarthritis of the knee, the participants’ experience of deqi sensation was a predictor for improved outcome (Takeda and Wessel, 1994).

Our aim in the present investigation was to extend our previous fMRI analysis, which compared the impact of needling at two different depths (MacPherson et al., 2008), by grouping fMRI datasets into those in which participants experienced predominantly deqi sensations and those with predominantly acute pain sensations with needling at LI-4 (Hegu). In the current investigation, we determine if any significant differences result from the comparison between the predominately deqi sensation grouping and the acute pain sensation grouping (deqi>pain contrast) using fMRI.

2. Results

2.1. Impact of needling sensation (within-group analysis)

For the grouping of scans in which deqi sensations predominated (Table 1), we found no activations (increase in BOLD signal) above our selected Z threshold level of >4.3 (corrected cluster threshold P = 0.05), whether the needling was superficial (Table 2A) or deep (Table 2B). In contrast, for the grouping in which acute pain sensations predominated (Table 1), the peak activation voxels of the two most significant clusters were located to the cerebellum (anterior lobe) and insula with superficial needling (Table 2B), and in the cerebellum (anterior lobe) and anterior temporal lobe for deep needling (Table 2E).

In terms of deactivations (decrease in BOLD signal) associated with deqi and acute pain groupings, we report the patterns of responses using a threshold of Z<−4.3 (corrected cluster threshold P = 0.05) for both superficial and deep needling. For the predominately deqi grouping with superficial needling, the deactivations for the peak voxels of the two most significant clusters were located in the middle temporal gyrus and fusiform gyrus (Table 2G). For the scan grouping with predominately deqi sensations with deep needling, the peak voxels showing deactivations were located in the fusiform gyrus and the lingual gyrus (Table 2). For the scans with predominately acute pain sensations with superficial needling, the peak voxel deactivations were located in the fusiform gyrus and posterior temporal lobe (Table 2H). For the scans with predominately acute pain sensations with deep needling, the deactivations were located in the posterior temporal lobe (Table 2K).

2.2. Impact of needling sensation (between-group analysis)

For the deqi>pain contrast, with either superficial (Table 2C) or deep needling (Table 2F), there were no significant voxels with positive Z values. Significant negative Z values (Z<−2.3, corrected cluster significance threshold of P = 0.05) were found with the contrast deqi>pain (deactivations in the deqi grouping and activations in the pain grouping); the peak voxels were located in the limbic lobe (parahippocampal gyrus) with superficial needling (Table 2I) and in the cerebellum and thalamus with deep needling (Table 2J).

We used probabilistic masks of brain regions of interest in the limbic/sub-cortical structures (insula, hippocampus, amygdala, thalamus, and the posterior/anterior cingulate gyrus) and the cerebellum. Using these masks, a count was made of the number of significant voxels (Z<−2.3, corrected cluster significance threshold of P = 0.05) in each of the regions of interest for the contrast, deqi>pain. Voxels with significant negative Z values for deqi>pain (mainly from deactivations in the deqi grouping and activations in the pain grouping) were observed bilaterally in the insula, hippocampus, amygdala, thalamus and cerebellum regions of interest for both superficial and deep needling (Table 3 and Fig. 1). In the posterior cingulate gyrus, significant negative Z value voxels for deqi>pain (deactivations in the deqi grouping and activations in the pain grouping) resulted for both

| Table 1: Psychophysical scores for deqi and pain. |
|------------------|------------------|------------------|
| deqi score       | pain score       |
| Superficial needling | 3.0±0.2     | 2.8±0.2     |
| Deep needling    | 3.6±0.2     | 3.8±0.2     |
| Deep needling    | 3.6±0.2     | 3.8±0.2     |

Data are mean±SEM. For both superficial and deep needling, ten fMRI datasets were classed as deqi>pain and seven datasets were classed as pain>deqi.
depths of needling (Table 3 and Fig. 1). No significant voxels occurred in the anterior cingulate gyrus for deqi>pain despite using a probabilistic mask of ≥5% for this region of interest.

3. Discussion

Our primary finding demonstrated that the fMRI datasets associated with predominantly deqi and pain sensations resulted in different patterns of BOLD signal increases (activations) and decreases (deactivations). For the deqi grouping, significant deactivations were seen without activations. The scans grouped according to acute pain sensations were associated with a mixture of activations and deactivations. In the present investigation, we additionally considered the contrast of predominantly deqi>pain and found voxels with significant negative Z values (mainly from deactivations in the deqi grouping and activations in the pain grouping),

### Table 2 – Localizations of the deqi and pain groupings, and the deqi>pain contrast.

<table>
<thead>
<tr>
<th></th>
<th>Voxels with maximum effect</th>
<th>Cluster</th>
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<tr>
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<tr>
<td>Superficial needling</td>
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<tr>
<td>A. deqi grouping activations (n=10)</td>
<td>No activations</td>
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<td>B. pain grouping activations (n=7)</td>
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<tr>
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<td>R</td>
<td>10</td>
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<td>Insula (BA13)</td>
<td>L</td>
<td>−44</td>
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<tr>
<td>D. deqi&gt;pain contrast (unpaired t test, Z≥2.3)</td>
<td>No significant positive Z values</td>
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<td>Deep needling</td>
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<td>E. pain grouping activations (n=7)</td>
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<tr>
<td>Cerebellum (anterior lobe)</td>
<td>R</td>
<td>10</td>
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<tr>
<td>Anterior temporal lobe (sub-gyral)/parahippocampal gyrus</td>
<td>L</td>
<td>36</td>
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<td>F. deqi&gt;pain contrast (unpaired t test, Z≥2.3)</td>
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<tr>
<td>Superficial needling</td>
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<td>G. deqi grouping deactivations (n=10)</td>
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<td>Middle temporal gyrus</td>
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<td>Fusiform gyrus (BA20)</td>
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<td>Fusiform gyrus (BA19)</td>
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<td>Posterior temporal lobe (sub-gyral)/superior temporal gyrus</td>
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<td>−32</td>
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<td>I. deqi&gt;pain contrast (unpaired t test, Z&lt;−2.3)</td>
<td>Significant negative Z values</td>
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<td>Limbic lobe, parahippocampal gyrus (BA235)</td>
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<td>Limbic lobe, parahippocampal gyrus</td>
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<td>Deep needling</td>
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<td>Fusiform gyrus (BA18)</td>
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<td>Lingual gyrus</td>
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<td>K. pain grouping deactivations (n=7)</td>
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<tr>
<td>Posterior temporal lobe</td>
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<td>−42</td>
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<td>Posterior temporal lobe (sub-gyral)/fusiform gyrus</td>
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<td>Significant negative Z values</td>
<td></td>
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<td>Cerebellum (anterior lobe)</td>
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<tr>
<td>Thalamus</td>
<td>R</td>
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All Z value thresholding was >4.3 for activations, and <−4.3 for deactivations. The most significant clusters (highest P value, maximum of two clusters reported) with a corrected threshold of P=0.05 were presented along with the voxel having the peak Z value within each cluster. x, y, and z are MNI152 brain coordinates (mm). L, left; R, right. BA, Brodmann area.

a Voxel is part of a cluster which extends to the stated brain area.

b Values in parentheses are the Z values for the deqi grouping and the pain grouping, respectively.

c As only one large cluster was significant, the two voxels reported for this cluster are given in order of peak Z value.
without any voxels having significant positive $Z$ values. Taken together, our results emphasize the importance of needle sensation, which should be accounted for during neuroimaging studies of acupuncture. Furthermore, our classification of grouping scans according to the needle sensations of predominates $\textit{deqi}$ and $\textit{pain}$ sensations allows for finer stratification of neuroimaging results, which may lead to improved interpretation of fMRI data. Thus, if $\textit{deqi}$ and acute $\textit{pain}$ needle sensations are not considered, our results imply that it is possible to have a potential source of unaccounted variability.

Interestingly, in the limbic/sub-cortical structures and in the cerebellum, significant negative $Z$ values resulted for voxels with the contrast $\textit{deqi} > \textit{pain}$ (arising mainly from deactivations in the $\textit{deqi}$ grouping and activations in the $\textit{pain}$ grouping), without any voxels showing significant positive $Z$ values. This result is consistent with our primary finding that $\textit{deqi}$ and $\textit{pain}$ sensations have different impacts upon the BOLD response to acupuncture at LI-4. Since limbic/subcortical structures and the cerebellum are closely involved in the response to pain (Davis, 2000; Price, 2000; Wager et al., 2004), it is possible that BOLD signal decreases in these brain areas could mediate the putative analgesic effects of acupuncture needling especially when $\textit{deqi}$ is present. However, it is not possible to elucidate whether this is a physically or psychologically mediated mechanism of action. The involvement of the limbic/sub-cortical structures in acupuncture-induced BOLD signal decreases has been shown in several investigations. For instance, during acupuncture needling at ST-36 with $\textit{deqi}$, Hui and colleagues reported a predominance of signal decreases in various limbic/sub-cortical structures including the insula, hippocampus, amygdala, thalamus, posterior cingulate gyrus and cerebellum, whereas signal increases were uncommon (Hui et al., 2005). Similarly, the amygdala (acupoints LV2 and ST40) and hippocampus (acupoints LV2, LV3 and ST44) were shown to deactivate in participants who mostly experienced $\textit{deqi}$ without sharp pain (Fang et al., 2009). Wu and colleagues suggested that higher behavioral scores associated with $\textit{deqi}$ sensations during acupuncture at LI-4 and ST-36 were linked to the deactivation of multiple limbic system structures (Wu et al., 1999).

In the present study, no significant activations were reported for the $\textit{deqi}$ grouping alone, whereas other fMRI studies of acupuncture have reported at least some activations in, for example, the secondary somatosensory cortex (Fang et al., 2004, 2009; Hui et al., 2005). This difference could be explained by variations in the psychophysical methods used to classify fMRI datasets into $\textit{deqi}$ groupings, use of different acupoints, or it may have arisen from differences in the statistical methodology and level of thresholding used, which was relatively conservative in our study (cluster thresholding, $Z>4.3$).

Our observation that acute $\textit{pain}$ sensations are associated with activations is congruent with previous research showing activations at LI-4 in participants who experienced pain during acupuncture (Hui et al., 2000). For the acute $\textit{pain}$ grouping, we observed a combination of both activations and deactivations at LI-4. Combinations of BOLD signal increases and decreases have also been reported with needling at ST-36 in participants who were classified as having a mixture of $\textit{deqi}$ and $\textit{pain}$ (Hui et al., 2005). Some neuroimaging studies of acupuncture have reported signal activations rather than deactivations in the thalamus, insula, cingulate cortex and in the cerebellum (Biella et al., 2001; Fang et al., 2004, 2009; Hsieh et al., 2001; Yan et al., 2005; Yoo et al., 2004). Acupuncture at different acupoints, or inconsistent measurement of psychophysical ratings of acupuncture needle sensation in these studies, could explain the differences in the patterns of activations and deactivations seen across the various neuroimaging investigations of acupuncture.

### 3.1. Limitations of the present study

The BOLD signals identified in the current investigation resulted from analyzing a time series over a 16 min period, and identifying those voxels that reacted “on” and “off” in a manner that was synchronized with the periods of needle stimulation. Our two periods of 2-min stimulation of the needle, while modeled on a traditional approach to enhancing the therapeutic effect (Bovey, 2006), were of a longer duration than is commonly used in clinical contexts, and perhaps explain the acute $\textit{pain}$ sensation experienced by participants. It has also been argued that the subjective sensations of
acupuncture are influenced by the type of needling techniques (see Hui et al., 2005). As we used a needle rotation at 2 Hz, our results are primarily applicable to the simple “even method” technique (Deadman and Al-Khafaji, 1998).

The physiological effects of acupuncture can continue for many hours, as exemplified by endorphin release (Han, 2004), and clinical benefits have been observed up to 2 years after a course of treatment (Thomas et al., 2006). However, the putative longer-term impact of acupuncture on neural structures in the brain could not be evaluated with our current study design. Furthermore, our experimental paradigm did not reflect usual practice, in that it was conducted over a single session, with only a single needle inserted at one acupuncture point. Our use of healthy individuals may also limit the generalization of our results (Lewith et al., 2005).

3.2. Experimental and clinical implications

Given the value many acupuncturists attach to the elicitation of the deqi sensation during acupuncture (MacPherson et al., 2001), it is interesting that the present results show that a predominantly deqi sensation is associated with brain deactivations rather than activations. Whether or not such deqi-associated brain deactivations could constitute a possible mechanism which underlies the therapeutic effect of acupuncture is not ascertainable from our current results, although this may be a reasonable hypothesis to explore further.

Our results have potential implications for the design of experimental studies of acupuncture. For example, our evidence suggests that investigators should collect data on participants experiences of needle sensation, perhaps using one of the newly validated measures (Kong et al., 2005, 2007; MacPherson and Asghar, 2006; White et al., 2008). In addition, given that our findings indicate that needle sensation affects specific neural structures within the brain, researchers should aim to minimize the variability of needle sensation in order that it does not have the potential to act as a confounder when analyzing and interpreting the results. If an accepted standardized and validated behavioral questionnaire could be developed that effectively captured and rated the various acupuncture needling sensations (especially deqi and pain sensations) from study participants, this would allow for more
meaningful comparisons to be made across neuroimaging and other studies of acupuncture.

3.3. Conclusions

The acupuncture needle sensations of deqi and acute pain are associated with different patterns of activations and deactivations in the brain. We found that grouping of fMRI datasets into those associated with predominantly deqi sensations resulted in brain deactivations, but not activations. Scans grouped according to predominantly acute pain sensations were associated with a mixture of activations and deactivations. For the deqi>pain contrast, only significant negative Z value voxels occurred in the regions of interest in the limbic/sub-cortical structures and the cerebellum. Our results highlight the importance of quantifying and accounting for variations in needle sensations in neuroimaging studies of acupuncture.

4. Experimental procedures

We recruited 17 healthy right-handed adult participants who were naive to acupuncture; eight males (mean age 33 years, range 18 to 46) and nine females (mean age 39 years, range 20 to 54), with an overall average age of 36 years. The York Neuroimaging Centre’s Science and Ethics Committees approved the study.

4.1. Experimental paradigm

Manual acupuncture needling was performed at the acupuncture point Hegu (LI-4) on the right hand by an experienced acupuncturist (HM). Sterile, disposable and non-magnetic stainless steel needles (25 mm long and 0.28 mm diameter) manufactured by Hwato, China, were used. The insertion depth of the needle into the first dorsal interosseus muscle was randomized to be either superficial (1–2 mm), as commonly used in Japan (Birch and Felt 1999), or deep (8–12 mm), as commonly used in China (Deadman and Al-Khafaji, 1998).

Scans were conducted over two 16-min periods; one scan involved superficial needling and another separate scan involved deep needling. Participants were only informed that they would be receiving two types of acupuncture during their time in the scanner. For both superficial and deep needling the same block design with two active blocks separated by rest periods was utilized (Fig. 2), a block design used previously (MacPherson et al., 2008). For both superficial or deep insertion, two repeated 2-min periods of needle “stimulation” were used with an “even” method (Deadman and Al-Khafaji, 1998). This involved the needle being rotated clockwise and anti-clockwise continuously at approximately two cycles per second with an alternating 180° rotation.

4.2. Measuring needle sensation: deqi and acute pain

Immediately after each 16-min scan, participants were asked questions about their experience of all 25 individual needle sensations from the Park questionnaire (Park et al., 2002). Participants rated the intensity of each sensation on an ordinal scale: “none” (zero), “slight” (one), “moderate” (two) or “strong” (three). For each fMRI dataset and for each sensation we multiplied the participants sensation score (0 to 3) by the expert weighting (0 to 8) for the seven deqi sensations (aching, dull, heavy, numb, radiating, spreading and tingling) and nine acute pain sensations (burning, hot, hurting, pinching, pricking, sharp, shocking, stinging and tender) (MacPherson and Asghar, 2006). We then grouped scans (see Table 1) into those associated with predominantly deqi sensations (deqi scores greater than pain sensation scores) and those with predominantly acute pain sensations (pain scores greater than deqi scores).

4.3. Functional and anatomical MRI acquisition

Functional and structural scanning was performed with a 3T magnetic resonance imaging system (GE Signa HD Excite), with an eight channel head coil (GE Signa Excite 3.0T, High Resolution Brain Array, MRI Devices Corp., Gainesville FL) and axial images were acquired for the whole brain. For functional imaging, EPI (Echo Planar Imaging) images were acquired.

Fig. 2 – The fMRI block design showing manual LI-4 superficial (S) and deep (D) needling stimulation periods. For each participant two fMRI scans were performed, one with two consecutive superficial (S) needling stimulation periods and one with two consecutive deep (D) needling stimulation periods. The order (whether superficial needling only or deep only) of these two types of needling was randomized.
using a T2* weighted gradient echo sequence (TR 4 s, TE 30 ms, flip angle 90°, acquisition matrix 128×128, FOV 240 mm, in-plane resolution 2×2 mm, contiguous slice thickness 4.5 mm). The voxel size was 2 mm×2 mm×4.5 mm. High resolution T1-weighted structural images were acquired prior to the functional scans using an IR (Inversion Recovery)-prepared 3D-FSPGR (Fast Spoiled Gradient Echo) pulse sequence (TR 7.5 s, TE 3 ms, flip angle 20°, acquisition matrix 256×224 interpolated to 512×512, FOV 260 mm, in plane resolution 0.5×0.5 mm, slice thickness 2.6 mm with an overlap of 1.3 mm).

4.4. fMRI data analysis

FSL software (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) based on generalized linear modeling was used to analyze the fMRI data. The design matrix had a single explanatory variable which was “on” during the periods of stimulation and otherwise “off” (see Fig. 2). For each participant, a first level analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.63, part of FSL. Following pre-statistics processing (see MacPherson et al., 2008), a time series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001). Registration of EPI images to high resolution T1 images and then subsequently to the Montreal Neurological Institute standard brain (MNI152) was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001). All x, y, z (mm) coordinates reported are MNI152 brain coordinates.

The terms activation and deactivation are only used to refer to an increase (positive Z values) or decrease (negative Z values), respectively, in the BOLD response in the context of the deqi grouping alone or the pain grouping alone. Higher-level within-group analysis was performed using FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann et al., 2003; Woolrich et al., 2004). Z (Gaussianized T/F) statistic within-group images were thresholded using clusters pre-selected by Z>4.3 (significant activation) or Z<-4.3 (significant deactivation) and a corrected cluster significance threshold of P=0.05 (Worsley et al., 1992). Significant clusters were superimposed onto the MNI152 standard brain template.

Higher-level between-group contrasts were analyzed using two-sample unpaired t-tests. We compared scan groupings with predominantly deqi sensations versus scan groupings with predominantly acute pain sensations (deqi>pain contrast) to identify clusters with a pre-selected threshold of Z>2.3 or Z<-2.3, and corrected cluster significance threshold of P=0.05 (Worsley et al., 1992). Clusters of voxels showing significant positive (Z>2.3) or negative (Z<-2.3) Z values for the deqi>pain contrast, were superimposed onto the MNI152 standard brain template. Whenever Z values for the deqi>pain contrast are reported for voxels, the corresponding Z values for the deqi grouping alone and the pain grouping alone are also stated.

For the significant deqi>pain clusters, probabilistic brain area masks were utilized in a region of interest analysis. The left and right insula and cerebellum masks were selected from the MNI probabilistic structural atlas, the left and right hippocampus, amygdala, thalamus, and the posterior and anterior cingulate masks selected from the Harvard-Oxford sub-cortical and cortical probabilistic atlases (FSLview 3.0.2, FSL software 4.1.2). Since fMRI data of individual participants were transformed onto the MNI152 standard brain template, we opted to utilize relatively less conservative masks of brain structures; probabilistic threshold ≥25% for all masks except for the posterior and anterior cingulate gyri which was ≥50%. The selection of these relatively less conservative probabilistic masks in the regions of interest analysis allows for more inclusion of each structure and significant voxels despite the reduction in structure specificity. The number of voxels in each of the brain regions of interest was counted, and the voxel with the highest Z value located for each structure.

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