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An fMRI study measuring analgesia enhanced by religion as a belief system

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Abstract

Although religious belief is often claimed to help with physical ailments including pain, it is unclear what psychological and neural mechanisms underlie the influence of religious belief on pain. By analogy to other top-down processes of pain modulation we hypothesized that religious belief helps believers reinterpret the emotional significance of pain, leading to emotional detachment from it. Recent findings on emotion regulation support a role for the right ventrolateral prefrontal cortex (VLPFC), a region also important for driving top-down pain inhibitory circuits. Using functional magnetic resonance imaging in practicing Catholics and avowed atheists and agnostics during painful stimulation, here we show the existence of a context-dependent form of analgesia that was triggered by the presentation of an image with a religious content but not by the presentation of a non-religious image. As confirmed by behavioral data, contemplation of the religious image enabled the religious group to detach themselves from the experience of pain. Critically, this context-dependent modulation of pain specifically engaged the right VLPFC, whereas group-specific preferential liking of one of the pictures was associated with activation in the ventral midbrain. We suggest that religious belief might provide a framework that allows individuals to engage known pain-regulatory brain processes.

Keywords: Pain; fMRI; Cognitive; Modulation; Prefrontal cortex; Analgesia; Religion

1. Introduction

Religious lore is full of stories of physical pain withstood and vanquished through the power of religious belief. Although such analgesic effects have not yet been demonstrated in a controlled experimental setting, it is not implausible that religious states and practices can have an influence on pain [24,25,30,31]. Indeed, over the past decade research has demonstrated a wide range of ways in which top-down processes can modulate the intensity of pain. These include diversion of attention [6,29,35] as well as more high-level cognitive processes such as placebo-induced analgesia [19,23,32], emotional detachment [14] or perceived control over pain [26,33]. In contrast to the attentional modulation of pain, these

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high-level processes induce a reduction in pain by generating expectations, selecting alternative interpretations or changing judgments about pain. Functional magnetic resonance imaging (fMRI) studies indicate that the key brain area implicated in such high-level pain-modulatory effect is the ventrolateral prefrontal cortex, predominantly in the right hemisphere (VLPFC; [14,19,23,26,32,33]. Although it is unclear what psychological and neural mechanisms might underlie analgesic effects that draw on religious belief, it is likely to involve such high-level processes of pain modulation given that reported strategies for religious coping include framing the painful event in terms that allow for its positive appraisal [4,22]. As of yet, however, there has been little study of how cultural and religious traditions and practices might draw on high-level forms of pain modulation to enable practitioners to deal with pain. We thus set out to investigate (a) whether religious belief could be shown to modulate pain in a controlled experimental setting, and (b) whether such modulation of pain by religious belief is mediated by the right VLPFC, reflecting high-level cognitive modulation of pain.

Using fMRI we investigated the perception and neural processing of pain in 12 practicing Catholics and 12 non-religious subjects. Both groups received repetitive noxious electrical stimulation while they were either presented with an image of the Virgin Mary ("religious condition") or a matched image without a religious connotation ("non-religious condition"; see Fig. 1 and Section 2). Participants were instructed to look at the presented image for 30 s prior to the onset and during the electrical stimulation. At the end of each stimulation period participants rated the perceived intensity of the stimulation.

2. Methods

2.1. Subjects

Twelve religious (8 female, mean age 24.58, range 19–33) and 12 atheist and agnostic (9 female, mean age 26.17, range 21–34) healthy subjects were included in the study. Subjects were recruited by advertisements in University Colleges and Roman Catholic churches in Oxford. All religious participants were of Roman Catholic denomination, attending mass at least weekly, praying everyday, and regularly performing other devotional actions (e.g., taking part in retreats, going to confession). The control groups were constituted by participants who reported to be neither religious nor spiritual. A questionnaire on religious beliefs was given to all participants to verify the fulfillment of these criteria [2]. All subjects had normal pain thresholds at the site of stimulus application, no history of neurological or psychiatric disease, no history of chronic pain, and were free to withdraw from the study at any time. The study was conducted in accord with the declaration of Helsinki and approved by the local research Ethics Committee. All participants gave written informed consent before participating in the study.

2.2. Experimental design and protocol

The study involved a 2 × 2 factorial design with the factors GROUP (religious vs. non-religious) and CONDITION (religious vs. non-religious; see Fig. 1). The experiment was divided into four sessions, each lasting about eight minutes. In both groups the two conditions (i.e., religious and non-religious context) were presented

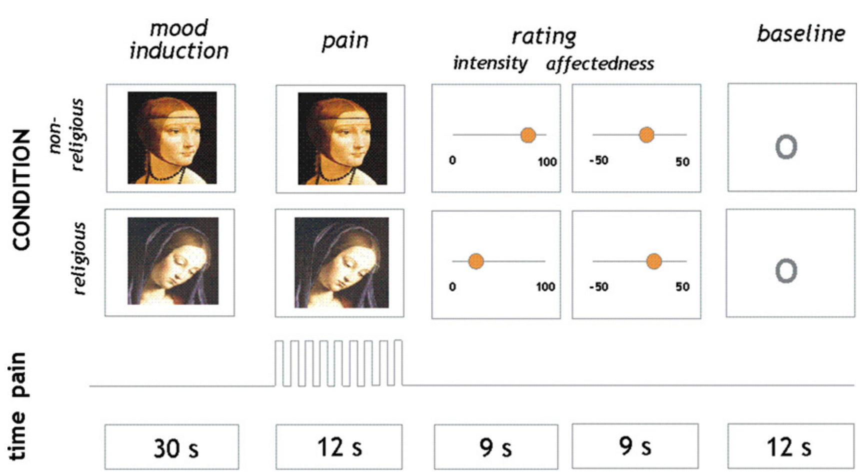

Fig. 1. Study design. We investigated the combination of two factors in a 2 × 2 factorial design (factor I (between-subject): GROUP religious vs. non-religious, factor II (within-subject): CONDITION religious vs. non-religious). In the "religious" condition participants were presented with an image of the Virgin Mary during the painful stimulation in order to induce a religious state. In the "non-religious" condition a comparable image without religious connotations was shown. Participants were instructed to focus on the image that was displayed 30 s before and during the application of the noxious stimulation. In each trial a series of 20 painful electric stimuli was applied to the back of the left hand. After the stimulation had stopped the participants rated the intensity of the electric stimuli (0–100) and to what an extent they had been affected by the image (−50 to +50) on a visual analogue scale. At the end of each block a circle appeared on the computer screen that signalled a baseline period of 12 s.

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six times (trials) and in random order throughout the session.

On arrival, participants were provided with written task instructions and gave their informed consent. They were told only that the purpose of the study was to investigate whether the perception and neural processing of pain vary when people look at pictures of different contents while receiving a noxious stimulation. Although some subjects may have guessed that the hypotheses tested concerned religious belief, it is unlikely that this had a significant biasing effect on our objective measures. Subjects were familiarized with the pictures shown during the experiment and with the rating procedure (see below). Subsequently, the individual stimulation level was determined and a test paradigm was run to acquaint the subjects with the overall structure of the experiment.

During each session a train of 20 electrical stimuli was applied to the back of the left hand in each trial. Thirty seconds before the electrical stimulation started subjects were either presented with a picture of the praying Virgin Mary ("Vergine Annunciate" by Sassoferrato) or an image without a religious connotation ("Lady with an Ermine" by Leonardo da Vinci). The pictures remained on the computer screen while the electrical stimulation was applied. Participants were instructed to fixate the face of the figure shown in order to avoid large eye movement related artefacts. To inform the participants about the upcoming electrical stimulation and avoid startling, the picture disappeared from the computer screen for 500 ms 5 s prior to the onset of the electrical stimulation. After the stimulation had stopped the participants had to rate the subjective intensity of the electrical stimulation and how they had been affected by the picture (see below). At the end of each trial subjects were instructed to fixate a white dot that was displayed in the center of the computer screen for 12 s (baseline).

2.3. Electrical stimulation

Monopolar square waveform pulses of 100 ms duration were delivered to the back of the left hand using a commercial electric stimulation device (Constant Current Stimulator, Model DS7A; Digitimer, Hertfordshire, UK). In the calibration procedure trains of ten 100 ms-stimuli of increasing intensities were applied. After each train the subject gave a verbal intensity rating between 0 and 100. The calibration procedure stopped when participants rated the intensity as 80. Current levels that were rated as 80 were taken for stimulation during the experiment. To account for sensitization or habituation processes current levels were readjusted prior to each session. Each trial consisted of a train of 20 stimuli (interstimulus interval: 500 ms).

2.4. Visual stimuli

Our aim was to use a stimulus to induce a religious state of mind that would affect indigenous neural systems of pain modulation. Since there was very little prior research to which we could appeal to in selecting an appropriate religious symbol or image to induce such a state, we decided to choose the visual stimuli based on two criteria. The religious image had to reliably evoke a religious mind set in believers and the non-religious picture had to be sufficiently similar to the religious one in order to minimize the influence of confounding factors. In the Christian tradition, the image of the Crucifixion, and perhaps to a lesser extent that of Jesus Christ, is often associated with a certain attitude to suffering that may introduce immensely complex confounding factors which would be impossible to control for. It also is virtually impossible to find a non-religious image that would be similar enough to a familiar image of the Crucifixion. Furthermore, it is likely that some believers would react in a negative way to an image of a non-religious person that repeatedly alternates with the image of Jesus Christ. For these reasons we decided instead to use the image of the Virgin Mary, a very popular image of Catholic devotion lacking immediate association with suffering. This image also permitted a reasonable neutral control image that is suitably similar in visual appearance. For the control condition we needed a picture that would be as similar as possible as a picture of the Virgin Mary without a religious nature. We assembled five portraits of the Virgin Mary which were rated by four Roman Catholics volunteers for their power to evoke religious feelings. After the most evocative portrait of the Virgin Mary was selected ("Vergine annunciate" by Sassoferrato), four additional judges of different denominations rated which of the secular portraits presented the greatest similarity with the religious one. The categories in which the two pictures were compared were the age, shape and posture of the figure, as well as the drawing style and colour scheme of the picture. Based on these ratings we chose the "Lady with an Ermine" by Leonardo da Vinci as the control picture. As shown in Fig. 1 the paintings were cropped to delete distracting features such as the ermine in the control picture and the hand of the Virgin Mary in the religious picture in order to make them as visually similar as possible. During the scanning session the pictures were displayed on a black screen over an area of 25×40 cm. In previous studies, such dimensions were found to be large enough to induce powerful emotional modulation, while allowing the subject to scan the pictures with minimal eye movement, thus minimizing artifacts. On completion of the scanning session all participants were asked which figures were shown in the two pictures. All participants stated that the religious picture was a portrait of the Virgin Mary. The figure of the Lady with Ermine was unknown to most participants. Furthermore, all participants had to rate how familiar the two pictures were to them using a visual analogue scale with the endpoints "not at all" to "very much". The ratings were transformed into a scale from 0 to 10. The comparison of the ratings for the two pictures revealed no significant difference (picture of the Virgin Mary: religious group, M = 5.80, SD = 3.77, non-religious group, M = 5.37, SD = 2.93; picture of the Lady with an Ermine: religious group, M = 5.57, SD = 3.88, non-religious group, M = 2.87, SD = 4.23; CONDITION: $F(1,22) = 1.70$, $p = 0.21$; GROUP: $F(1,22) = 2.03$, $p = 0.17$; interaction GROUP × CONDITION: $F(1,22) = 1.15$, $p = 0.30$), indicating that both pictures were equally familiar to the participants.

2.5. Ratings

At the end of each trial subjects rated the average perceived mean intensity of the stimulation during the previous trial on a visual analogue scale with the endpoints "0 = not painful at all" to "100 = very painful" that was presented on the computer screen. Furthermore, participants gave a rating to what an extent they had been positively or negatively affected by the image. In order to cover possible positive as well as negative affective responses to the pictures the affectedness scale ranged from a negative (−50) to a positive (+50) pole. Participants were given nine seconds for each of the ratings. Ratings were given via a pointer that could be moved in both directions along the scale by holding either of two buttons pressed. At the end of the scanning experiment subjects provided a rating to what an extent the images had been helpful in coping with the pain and how familiar the pictures were to them using visual analogue scales with the endpoint "not at all" to "very much". Ratings were transformed into scores between 0 and 10.

2.6. Image acquisition

MR scanning was performed on a 3T MRI system (Oxford Magnet Technology, Oxford, UK) with the use of a Nova Medical quadrature birdcage coil (Nova Medical, Wilmington, USA). For the functional measurement, 33 axial slices (slice thickness 3 mm, 1 mm gap) were acquired using a gradient echo echo-planar (EPI) $T2^*$-sensitive sequence (repetition time, 2.38 s; echo time, 30 ms; flip angle, 90°; matrix, 64 × 64; field of view, 192 × 192 mm^2). Subjects wore MR-compatible electrostatic headphones to attenuate the scanner noise. For display purposes, a high-resolution (1 × 1 × 1 mm^3 voxel size) T1-weighted structural MRI was acquired (three dimensional modified driven equilibrium Fourier transformation; matrix, 256 × 192; field of view, 256 × 192; slab thickness, 175 mm). These structural images were co-registered with the mean EPI from the functional acquisition, normalized into a standard space using the normalization parameters applied to the EPIs and subsequently averaged for overlay of statistical parametric maps.

2.7. Data analysis

For the ratings of subjective pain intensity, affectedness, coping with pain, and familiarity, repeated measurement ANOVAs with the within-subject factor CONDITION (religious vs. non-religious) and the between-subject factor GROUP (religious vs. non-religious) were performed. Comparisons between the two conditions were performed separately for each group using Student's paired *t*-tests. Since these were planned comparisons, no correction for multiple comparisons was applied. Correlations between the differential pain rating (i.e., pain during presentation of the religious minus the non-religious image) and the differential affectedness rating (i.e., affectedness by the religious minus the non-religious image) were calculated separately for both groups using Pearson's correlation coefficient.

For the neuroimaging data image preprocessing and statistical analysis were carried out using SPM2 (www.fil.ion.ucl.ac.uk/spm). The first five image volumes of each session were discarded to account for T1 relaxation effects. The remaining volumes were realigned to the sixth volume to correct for head motion before statistical analysis. The EPI images were spatially normalized [8] to the template of the Montréal Neurological Institute (MNI; [7]). The normalized EPI images were smoothed using an 8-mm FWHM (full-width at half maximum) Gaussian kernel, temporally high-pass filtered (cut-off 128 s) and corrected for temporal autocorrelations using first-order autoregressive modelling. The subsequent data analysis was limited to the 12 s time window when the electrical stimuli were applied. For each subject, contrast images were calculated across the two conditions (i.e., religious and non-religious). Furthermore, comparisons between pain in the religious and the non-religious context ($Pain_{religious\ condition} > Pain_{non\text{-}religious\ condition}$; $Pain_{non\text{-}religious\ condition} > Pain_{religious\ condition}$) were calculated for each subject. First level contrasts were taken to the second level for the group data analysis using one-sample *t*-tests within a random effects model [10] for within-group comparisons (i.e., pain-related activation across conditions) and two-sample *t*-tests for (i) group comparison of pain-related activation across conditions and (ii) for the interaction between CONDITION and GROUP factor (i.e., group differences for "$Pain_{religious\ condition}$" >

"$\text{Pain}_{\text{non-religious condition}}$"). For all comparisons a global threshold was set at $p < 0.001$ uncorrected.

To further explore the role of the right VLPFC and pons/midbrain found in the interaction analysis we tested whether these regions were specifically activated in the condition (i) that was preferred by the religious sample (i.e., the religious condition) and (ii) that was preferred by the non-religious sample (i.e., the non-religious condition). Since we were specifically interested in these two regions we adopted a small volume correction (SVC) approach for multiple comparisons. The search volume was defined by a 4-mm sphere centered around the peak voxels (see crosshair Fig. 3c and d). Differential activation in the peak voxels of the right VLPFC and pons/midbrain as determined in the interaction analysis (parameter estimates; $\text{Pain}_{\text{religious condition}} > \text{Pain}_{\text{non-religious condition}}$) was correlated (i) with differential pain ratings and (ii) with differential affectedness ratings using Pearson correlation coefficients.

3. Results

3.1. Ratings

The repeated measures ANOVA for pain ratings revealed significant effects for CONDITION ($F(1,22) = 5.43$, $p = 0.03$) and the interaction GROUP × CONDITION ($F(1,22) = 9.23$, $p = 0.006$). However, the factor GROUP did not reach statistical significance ($F(1,22) = 0.67$, $p = 0.42$), indicating that the religious sample was not less sensitive to pain *per se*. A group-specific paired *t*-test confirmed that they only perceived less pain when presented with the image of the Virgin Mary ($t(11) = 2.81$, $p = 0.02$; Fig. 2a). In contrast, the atheist control group rated the pain as equally intense in both conditions ($t(11) = -1.17$, $p = 0.27$).

Analysis of the affectedness ratings showed a significant effect for GROUP ($F(1,22) = 25.52$, $p < 0.001$; Fig. 2b), but no main effect CONDITION ($F(1,22) = 1.43$, $p = 0.24$). As shown in Fig. 2b, the significant interaction (GROUP × CONDITION: $F(1,22) = 9.24$, $p = 0.006$) was driven by the positive ratings the Catholic sample gave when presented with the religious imaging ($t(11) = -2.31$, $p = 0.04$). Interestingly, the atheist control sample also showed a differential effect, but with more positive ratings for the non-religious image ($t(11) = 2.33$, $p = 0.04$). Hence, although both groups showed a comparable difference in affectedness between images, only the religious group showed a modulation of pain by their preferred image.

Correlation analyses between differential pain and affectedness ratings performed separately for each group confirmed that only in the Catholic sample (positive) affectedness was significantly related to a reduction in pain ($r = -0.93$; $p < 0.001$), whereas in the atheist/agnostic control group the degree of affectedness had no significant effect on the pain rating ($r = 0.06$; $p = 0.85$).

On completion of the experiment, all participants gave a rating of how helpful the images had been in coping with the pain and how familiar the images had been to them. For the first measure, the analysis revealed significant main effects for both factors, CONDITION ($F(1,22) = 5.49$, $p = 0.03$) and GROUP ($F(1,22) = 11.13$, $p = 0.003$) as well as a significant interaction (GROUP × CONDITION; $F(1,22) = 8.00$, $p = 0.01$). Group-specific comparisons showed that the religious participants rated the image of the Virgin Mary as significantly more helpful in coping with pain (M = 5.75, SD = 0.76 vs. M = 1.37, SD = 0.69; $t(11) = 3.33$, $p = 0.007$). The non-religious sample found both images equally helpful (religious image: M = 2.29, SD = 0.75; non-religious image: M = 1.69, SD = 0.63; $t(11) = -0.39$, $p = 0.71$). Importantly, the analgesic effect could

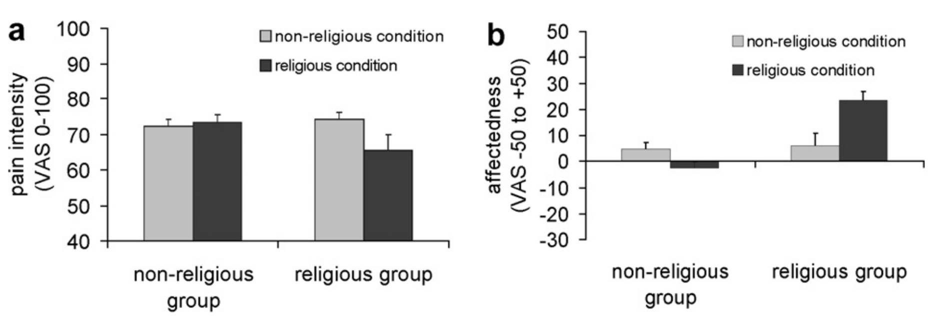

Fig. 2. Mean pain intensity and affectedness ratings for both groups during the "religious" and the "non-religious" state. The religious participants perceived the electrical stimulation as significantly less intense while they were looking at the image of the Virgin Mary compared to the secular image (a). Moreover, they were more positively affected by the religious image (b). In contrast, the non-religious participants were significantly more affected by the non-religious image (a), but did not report a difference in pain rating between conditions (b). Pain intensity ratings, interaction GROUP × CONDITION: $F(1,11) = 9.26$, $p = 0.006$; affectedness ratings, interaction GROUP × CONDITION: $F(1,11) = 9.24$, $p = 0.006$. Error bars show mean ± standard error.

not be attributed to differences in familiarity with the picture (see Section 2.4).

3.2. Neuroimaging data

In both groups, the electrical stimuli produced bilateral activation in brain regions which have shown increased activity in previous studies of pain (Table 1; [1]. The group comparison of pain-related brain responses across the two conditions did not reveal any significant results, thus confirming that compared to the non-religious group the Catholic sample was not generally less sensitive to pain. In order to identify brain areas specifically activated by the religious sample when presented with the religious image, we compared the differential activation (i.e., "$\text{Pain}_{\text{religious condition}}$" > "$\text{Pain}_{\text{non-religious condition}}$") between groups. This interaction analysis revealed significant activation in the right VLPFC (x, y, $z = 48, 30, 6$; $z = 3.29$; $p < 0.001$ uncorrected; x, y, and z coordinates in Montréal Neurological Institute (MNI) space; Fig. 3a, Table 2) and pons/ventral midbrain (x, y, $z = -6, -21, -27$; Z score $= 3.23$; Fig. 3b), consistent with our hypothesis that the right VLPFC plays a central role in pain modulation based on religious belief.

To rule out that the activation in right VLPFC and pons/midbrain found in this interaction analysis simply reflected preferential liking of one of the images in each group, we tested whether both groups activated these two brain regions in their preferred condition compared to the non-preferred condition using a small volume correction (SVC) approach. If the right VLPFC and pons/ventral midbrain correspond to preferential liking of one of the pictures (i.e., image of the Virgin Mary in the Catholic sample, "Lady with an Ermine" in the non-religious sample), we would expect these areas to manifest increased activation during the preferred condition compared to the non-preferred condition in *both* groups. Interestingly, the results show a dissociation between both brain regions: The right VLPFC cluster was specifically activated in the Catholic sample when presented with the image of the Virgin Mary ($z = 2.82$, $p = 0.045$), but not in the non-religious participants when presented with the non-religious image (Fig. 3c). This supports the assumption that the religious image triggered a group-specific process in the right VLPFC that was not induced when the non-religious participants looked at the non-religious image, despite both groups being similarly distracted or absorbed by their preferred image. In contrast, pons/midbrain activation was found in both groups (religious sample: $z = 2.83$, $p = 0.045$; non-religious group: $z = 2.53$, $p = 0.05$; Fig. 3d), probably reflecting the positive affectedness participants experienced when presented with their pre-

Table 1
Brain responses to pain across conditions ($p < 0.001$, uncorrected)

Brain region	Laterality	Brodman area	MNI coordinates			Cluster size (voxel)	*Z* score
			x	*y*	*z*		
Religious group							
SII/insula	R	48	51	−21	27	263	4.99
		48	48	−33	27		4.49
Insula	R	48	36	6	18	4	3.31
	R	48	39	−21	3	2	3.12
SII	L	48	−54	−33	24	17	3.43
Occipital lobe	R	17	18	−102	15	86	4.84
	R	17	48	−81	−9	3	3.39
Hippocampus/ amygdala/insula	R		24	−9	−9	87	3.88
Amygdala	L	34	−27	3	−12	1	3.13
	R	34	21	0	−15		3.47
	R	48	39	3	−6		3.23
Operculum	L	48	−54	−3	12	33	3.75
	R	48	57	0	9	33	3.59
MI	R	4	33	−30	75	24	3.72
SMA	R	6	9	−15	54	10	3.38
Cerebellum	L	37	−18	−45	−27	2	3.17
Temporal pole	R	38	33	9	−21	1	3.1
Non-religious group							
SII/insula	R	48	45	−24	21	110	5.24
Temporal lobe	L	42/48	−60	−24	21	19	3.7
SII	L	48	−48	−33	21		3.11
Temporal pole	R	38/48	57	6	0	15	3.45

Note: L, left; R, right; SII, secondary somatosensory cortex; MI, primary motor cortex; SMA, supplementary motor cortex; $p < 0.001$ uncorrected at voxel level; voxel size: $3 \times 3 \times 3$ mm.

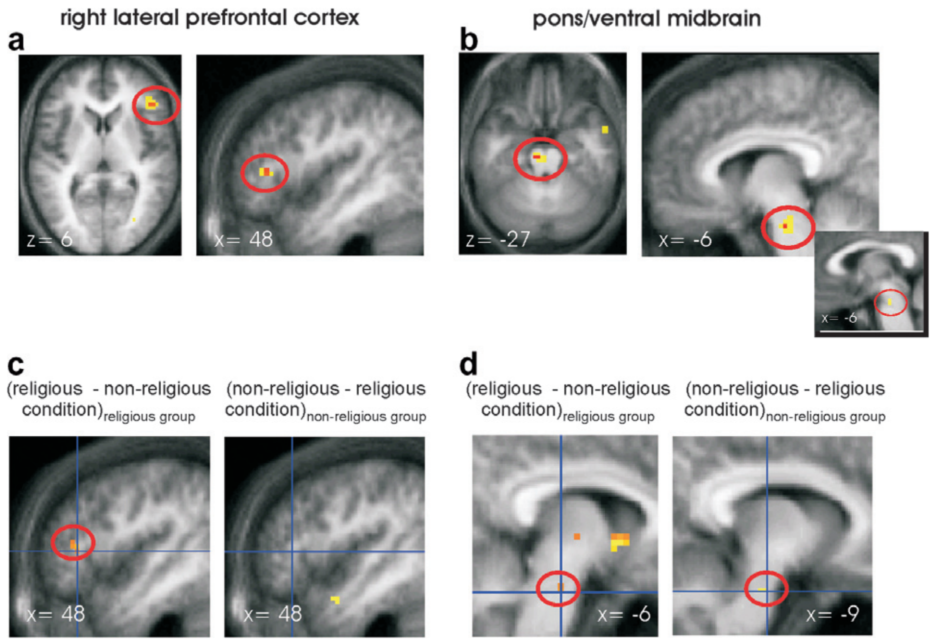

Fig. 3. Interaction analysis: [(Pain$_{religious\ condition}$ > Pain$_{non\text{-}religious\ condition}$)$_{religious\ group}$] − [(Pain$_{religious\ condition}$ > Pain$_{non\text{-}religious\ condition}$)$_{non\text{-}religious\ group}$]. (a) Compared to the non-religious group the Catholic sample showed an increased activation in the right VLPFC when presented with the religious image. Effects significant at $p < 0.001$ are shown in red, and effects significant at $p < 0.01$ are shown in yellow to illustrate the full extent of the activation (overlaid on the average structural image across all subjects). (b) Additional activation was observed in the brainstem. The activation peak at a threshold of $p < 0.001$ (uncorrected) is localized in the pons but also extends further up the brainstem into the midbrain as illustrated by an additional cluster maximum observed on a more liberal threshold (x, y, z: −3, −21, −21; $p < 0.01$, uncorrected; see inset). Activation in the right VLPFC (c) and pons/midbrain (d) specific for the condition preferred by the religious sample (i.e., religious minus non-religious condition) and the non-religious sample (i.e., non-religious minus religious condition). The activation in pons/midbrain survived small volume correction in both group-specific comparisons, whereas significant activation in the right VLPFC was only found in the religious group when they were presented with the image of the Virgin Mary.

ferred image. Correlation analyses between activation in the two interaction brain areas and (i) affectedness and (ii) perceived pain intensity confirm the different roles of right VLPFC and the pons/midbrain (Fig. 4). The latter showed a negative correlation with pain intensity ($p = 0.007$), but a stronger positive association with affectedness ($p = 0.001$), whereas activation in the right VLPFC was significantly negatively correlated with pain intensity ($p = 0.007$), but showed no significant association with affectedness ($p = 0.053$).

4. Discussion

In this study we demonstrate that religious believers are able to down-regulate the perceived intensity of a noxious stimulation when they are presented with a religious image. In the same group, presentation of a non-religious image had no effect on the perception of pain. Non-religious control subjects did not show a modulation of pain during presentation of either of the pictures.

Table 2
Interaction analysis

Brain region	Laterality	Brodman area	MNI coordinates			Cluster size (voxel)	Z score
			x	y	z		
[(Pain$_{religious\ condition}$ − Pain$_{non\text{-}religious\ condition}$)$_{religious\ group}$] − [(Pain$_{religious\ condition}$ − Pain$_{non\text{-}religious\ condition}$)$_{non\text{-}religious\ group}$]							
VLPFC	R	45	48	30	6	3	3.29
Pons/midbrain	L	–	−6	−21	−27	2	3.23
[(Pain$_{non\text{-}religious\ condition}$ − Pain$_{religious\ condition}$)$_{religious\ group}$] − [(Pain$_{non\text{-}religious\ condition}$ − Pain$_{religious\ condition}$)$_{non\text{-}religious\ group}$]							
SMA	R/L	6	0	−15	75	4	3.65
	R	6	18	−12	75	1	3.37
Occipital lobe	R	19	51	−75	9	8	3.64
MI	L	4	−15	−24	78	5	3.43

Note: L, left; R, right; VLPFC, ventrolateral prefrontal cortex; SMA, supplementary motor area; MI, primary motor cortex; $p < 0.001$ uncorrected at voxel level; voxel size: 3 × 3 × 3 mm.

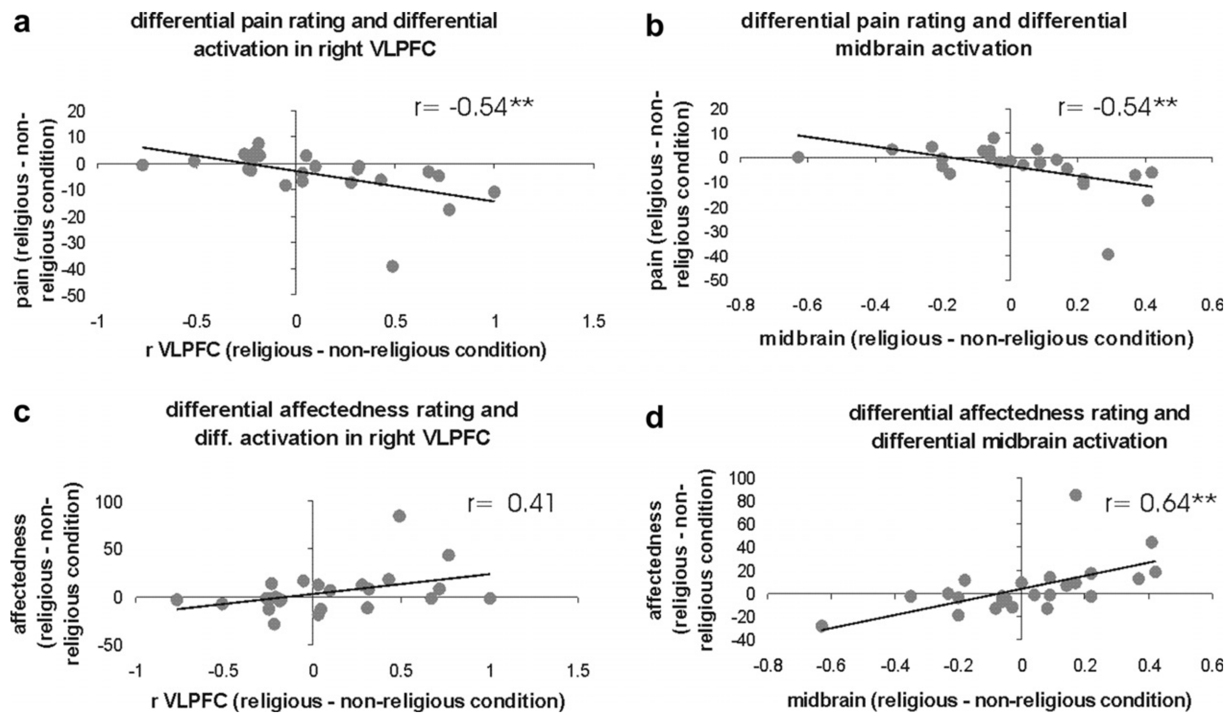

Fig. 4. Correlation between differential behavioral measures ($\text{Pain}_{\text{religious condition}} > \text{Pain}_{\text{non-religious condition}}$) and differential activation in the right VLPFC and pons/midbrain ($\text{Pain}_{\text{religious condition}}$ minus $\text{Pain}_{\text{non-religious condition}}$). Correlations between activation in the right VLPFC and pain intensity ratings (a), activation in the pons/midbrain and pain intensity ratings (b), activation in the right VLPFC and affectedness ratings (c), and activation in the pons/midbrain and affectedness ratings across participants (d).

How did presentation of a religious image lead to a reduction of pain in the Catholic sample? The presentation of "pleasant pictures" during the application of noxious stimuli has previously been shown to increase the pain threshold [5] and to help individuals to tolerate pain longer [20]. It might be argued that the images simply distracted the participants from the noxious stimulation and that this distraction effect was stronger the more absorbing the image was for the individual (i.e., for the religious sample an image of the Virgin Mary would draw more attentional resources than a non-religious image). It has also been proposed that pleasant pictures activate an appetitive system (associated with approach behavior) and that responses which are incompatible with this activated positive system are inhibited [16,17]. According to this second, motivational priming hypothesis, looking at an image of the Virgin Mary might have primed this positive state in the Catholic sample and thereby attenuated the perceptual and neural response to pain. A third possible explanation is that the Catholic sample could have used the religious image to reappraise the negative experience of pain. Reappraisal is a process of reinterpreting the meaning of a stimulus leading to a change in one's emotional response to it [9]. Such strategies of reappraisal have been shown to be effective in attenuating negative emotions induced by aversive pictures [12] and anticipation of pain [11,13].

We decided against the inclusion of a further task whose performance would have served as an indicator for degree of absorption in the image because it is likely to have hindered the attainment of a religious contemplative state. Our experimental design therefore does not include a direct measure of the degree of attentional absorption in each image. Instead, we included post-scan interviews to gain indirect insight into the strategies subjects may have employed. However, although at this stage it cannot be ruled out that distraction or motivational priming alone explains the analgesic effect observed here, we believe that our data provide significant evidence for the involvement of a reappraisal process for the following reasons. Under the motivational priming hypothesis, and, on the plausible assumption of a tie between degree of preferential liking and attentional absorption, under the distraction hypothesis as well, preferential liking of either of the images should have produced a corresponding reduction of pain in both groups. Hence preferential likings in both groups accompanied by differences in pain experience between conditions in one group but not in the other would tend to undermine those hypotheses as sufficient explanations. It is the latter conjunction that we find: In the Catholic sample more positive affectedness ratings for the image of the Virgin Mary were accompanied by an analgesic effect in the same condition. However, the non-religious sample also had a significant preference for one of the images (i.e., the non-religious "Lady with an Ermine"), yet their pain ratings did not significantly differ between the two conditions (Fig. 2). Therefore, our findings favour the hypothesis that a reappraisal process was involved in the analgesic effect, although it should be noted that measures of preferential liking are only a partial measure of possible differential activation of picture-specific cognitive or affective processes.

On the neuronal level, activation in the right VLPFC seems to reflect this context-specific analgesic effect observed in the religious group: An increase in activation in this cluster was only observed in the preferred condition of the Catholic sample (i.e., religious > non-religious image) which was accompanied by a decrease in subjective pain intensity, but not in the condition that was preferred by the non-religious group (i.e., non-religious > religious image). Previous studies have consistently shown the involvement of the right VLPFC in cognitive down-modulation of pain [14,19,23,32,33], suggesting that contemplating an image of the Virgin Mary helped the religious sample to engage well-known neural mechanisms of pain modulation. Activation in this region also has recently been discussed as a hallmark of reappraisal in emotion regulation [15,18,27]. Post-scan reports suggest that the Catholic sample used a strategy known as self-focused reappraisal or detachment: Participants reported being in a calm meditative state accompanied by thoughts and feelings with religious content when presented with the religious image (e.g., "I felt calmed down and peaceful", "I felt being taken care of", "I felt compassion and support", "I felt safe"). In contrast, both groups described their largely positive experience of the non-religious image using aesthetic terms (e.g., religious group: "I liked the picture and found it interesting", "The picture was purely aesthetic", "I liked the features of her face"; non-religious group: "Her mouth looked smug", "She looked serene, chilled out", "She looked attractive").

The second interaction cluster located in the pons/ventral midbrain also showed a negative correlation with perceived pain intensity across participants (Fig. 4). Although brainstem activation has previously been shown in pain modulation [28,29], it should be noted that these activations were usually located superior to our cluster (i.e., in the periaquectual gray or ventral tegmental area). As shown in Fig. 3, the peak voxel of our brainstem activation is located in the pons, but the extended cluster borders the midbrain. Furthermore, this cluster in pons/midbrain was not specifically activated when the religious stimuli were accompanied by an analgesic effect, but rather showed increased activity in both groups during their preferred condition (Fig. 3), and was more closely related to affectedness than to the perceived intensity of pain (Fig. 4). These findings suggest that the pons/midbrain cluster reflects an affective process that was associated with reappraisal or accompanied it rather than reappraisal itself. In line with this hypothesis, activation in this part of the brainstem has recently been discussed to reflect the subjective value of a stimulus [21].

In conclusion, our findings suggest that, in certain contexts, at least some religious believers can modulate their experience of pain and that such analgesic effects might be based on cognitive reappraisal of the negative emotional impact of pain via activity in the right VLPFC. However, further investigation is needed to better understand the neural mechanisms underlying this form of pain modulation. First, given that the VLPFC is also involved in other cognitive processes such as retrieval from long-term memory and working memory maintenance [3], future research is needed to identify the relative contribution of different VLPFC functions to the analgesic effect observed here. Second, it is still unclear how exactly an increased VLPFC activation is linked to a decrease in perceived pain intensity. Although it is often assumed that this down-modulatory effect is mediated via an attenuation of activation in pain-related brain areas, it is also possible that the prefrontal influence occurs subsequently to nociceptive processing in classical pain regions. In this context, it also needs to be investigated whether the pain-modulatory effect is initiated by the VLPFC or whether the VLPFC is ultimately driven by the dorsolateral prefrontal cortex, the brain region most commonly discussed as a "source" of pain modulation (e.g., [32]; see also [34]). Third, the interplay between value and reappraisal-related processes as observed in this study needs to be further clarified. Most importantly, future research is needed to investigate whether religious belief played a distinctive role in the observed analgesic effects or whether similar effects can be induced using stimuli which lack religious connotations but have had similar cultural and nurturing influences on the target group. We believe our results could have wider implications regarding how major cultural influences such as religious belief might change the developing brain and its subsequent capacity for dealing with life's challenges.

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