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Original article

The role of cognitive reappraisal in placebo analgesia: an fMRI study

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Abstract

Placebo analgesia (PA) depends crucially on the prefrontal cortex (PFC), which is assumed to be responsible for initiating the analgesic response. Surprisingly little research has focused on the psychological mechanisms mediated by the PFC and underlying PA. One increasingly accepted theory is that cognitive reappraisal—the reinterpretation of the meaning of adverse events—plays an important role, but no study has yet addressed the possible functional relationship with PA. We studied the influence of individual differences in reappraisal ability on PA and its prefrontal mediation. Participants completed a cognitive reappraisal ability task, which compared negative affect evoked by pictures in a reappraise versus a control condition. In a subsequent fMRI session, PA was induced using thermal noxious stimuli and an inert skin cream. We found a region in the left dorsolateral PFC, which showed a positive correlation between placebo-induced activation and (i) the reduction in participants' pain intensity ratings; and (ii) cognitive reappraisal ability scores. Moreover, this region showed increased placebo-induced functional connectivity with the periaqueductal grey, indicating its involvement in descending nociceptive control. These initial findings thus suggest that cognitive reappraisal mechanisms mediated by the dorsolateral PFC may play a role in initiating pain inhibition in PA.

Key words: cognitive reappraisal; dorsolateral prefrontal cortex; functional MRI; placebo analgesia; periaqueductal grey

Introduction

Our understanding of the neural basis of the placebo effect, in particular of placebo analgesia (PA), has increased substantially during the last decade. Several meta-analyses show consistent increases in activation associated with PA in prefrontal cortex (PFC) regions, the anterior cingulate cortex (ACC), and the periaqueductal grey (PAG) (Bingel *et al.*, 2006; Diekhof *et al.*, 2011; Wager *et al.*, 2011; Wager and Fields, 2013; Atlas and Wager, 2014). Activity in several of these regions correlated with decreases in reported pain (Wager and Fields, 2013). Prefrontal regions are assumed to be responsible for initiating the analgesic response (Wiech *et al.*, 2008; Amanzio *et al.*, 2013; Colloca *et al.*, 2013), whereas the involvement of the PAG points to possible activation of descending nociceptive control (Bingel *et al.*, 2006; Amanzio *et al.*, 2013; Wager and Fields, 2013). Further evidence for the role of the PFC comes from the reduction in PA when PFC function is disrupted by repetitive transcranial magnetic stimulation (Krummenacher *et al.*, 2010) or by Alzheimer's Disease (Benedetti *et al.*, 2006). Moreover, the structural integrity of white matter pathways from dorsolateral PFC (DLPFC) to the PAG is related to the individual placebo analgesic effect (Stein *et al.*, 2012).

Despite the importance of the PFC, surprisingly little research has focused on the psychological mechanisms mediated by this region and underlying PA. One difficulty is that there is

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considerable variability in activation of PFC sub-regions across studies and individuals, and these regions are involved in a range of other cognitive and affective processes (Kong *et al.*, 2006; Price *et al.*, 2008; Wiech *et al.*, 2008; Meissner *et al.*, 2011; Atlas and Wager, 2014). One hypothesis about the mechanism behind PA gaining increasing acceptance is that of emotion regulation, and in particular, cognitive reappraisal. Cognitive reappraisal is the reinterpretation of the meaning or affective content of adverse events (Gross, 2002). A placebo treatment may trigger cognitive reappraisal mechanisms, which then alter the physiological response and subjectively experienced negative affect associated with pain (Benedetti *et al.*, 2005; Wiech *et al.*, 2008; Tracey, 2010). Cognitive reappraisal has indeed been shown to be successful at moderating self-report and behavioural measures of pain (Hampton *et al.*, 2015).

Cognitive reappraisal and PA show a remarkable overlap in neural substrates, with increased activation in the PFC and ACC, and decreased activation in regions involved in affective processing (Benedetti *et al.*, 2005; Diekhof *et al.*, 2011; Amanzio *et al.*, 2013). Moreover, activity in regions associated with emotional appraisal (including DLPFC, ventrolateral PFC and orbitofrontal cortex), rather than cognitive control or pain processing, was the most predictive of individual differences in the placebo response (Wager *et al.*, 2011). In support of this, Lapate *et al.* (2012) have demonstrated that a common regulation ability impacts the experience of both emotion and pain, and placebo has been shown to modulate emotional perception of pictures and pain perception similarly (Petrovic *et al.*, 2005; Zhang and Luo, 2009).

Despite the strong indication for a role of cognitive reappraisal in producing PA, no study has yet investigated this possible functional relationship directly. Our aim was to investigate the influence of individual differences in reappraisal ability on PA and its prefrontal mediation. We expected to find placebo-related activation in prefrontal regions (especially the DLPFC) to 1) correlate with independent behavioural measures of cognitive reappraisal; and 2) to show increased functional connectivity with regions involved in descending pain modulation. This would provide a first indication for a possible role of cognitive reappraisal as one underlying mechanism of PA.

Methods

Participants

Thirty healthy volunteers (13 male, mean age: 25.7 ± 5.5 years) were recruited through advertisement at the University of Luxembourg. They gave informed consent according to the Declaration of Helsinki before participation and were paid remuneration for their effort and time. The study was approved by the Luxembourg national ethics committee (CNER), as well as by Luxembourg University's local ethics committee. Twenty-five participants were right-handed, two were ambidextrous and three were left-handed, as assessed with the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). All participants were in good health, had normal vision and were free of acute and chronic pain. They believed that they were taking part in a study about the effect of a known analgesic cream on brain responses to painful stimulation.

Experimental procedure

Participants were invited to two experimental sessions: first a laboratory session at the University of Luxembourg, and 1–2 weeks later an fMRI session at the ZithaKlinik hospital in Luxembourg. During the lab session we assessed cognitive reappraisal ability (CRA) of participants using a computer-based task, as well as self-report of CR using the Emotion Regulation Questionnaire (ERQ). In the fMRI session, we induced PA during functional brain imaging. For details please refer to the Supplementary Material.

CRA task

We used a well-established laboratory task to assess CRA (Ochsner *et al.*, 2004; Ray *et al.*, 2010; McRae *et al.*, 2012). This task compares negative affect evoked by pictures in a reappraise versus a control condition. The task started with detailed instructions for the reappraisal condition and a practice session. Participants were then presented with 30 negative and 15 neutral pictures (for 7 s each) selected from the IAPS picture dataset (Lang *et al.*, 2008). The task consisted of three conditions (with 15 trials per condition): watching neutral pictures, watching negative pictures and reappraising negative pictures. Conditions were presented in pseudo-random order. Each trial started with a cue word appearing on the computer screen (for 2 s), indicating the specific instruction for the upcoming trial. This was either the word 'look' (control and neutral condition) or the word 'decrease' (reappraisal condition). After each picture, participants rated their negative feelings on a visual analogue scale (VAS). These ratings were averaged for each condition, and a CRA score was calculated as the percent decrease in ratings in the reappraise compared to the watch negative condition. (For more details about the procedure and instructions, see Supplementary Material).

Questionnaires

We administered the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003) to assess self-report of habitual use of two emotion regulation strategies: cognitive reappraisal and expressive suppression (see Supplementary Material). Only the reappraisal sub-scores were used in the analyses. In addition, we measured anxiety and negative affect of participants both at the start of the lab session and at the start of the scanning session. To measure anxiety, participants filled out the state subscale of the State-Trait Anxiety Inventory (STAI; Spielberger, 1989). The trait subscale was also filled out once at the start of the lab session. To measure affect, participants filled out the Positive and Negative Affect Schedule (PANAS; Watson *et al.*, 1988).

PA procedure

PA was induced using a well-validated protocol (Wager *et al.*, 2004; Eippert *et al.*, 2009). Pain stimuli of 20 s each were administered to the lower forearms and every stimulus was rated according to its intensity and unpleasantness on a 100-point computerised VAS. First, participants underwent a calibration procedure to determine VAS pain intensity ratings of 40, 60 and 80%. Different skin patches were either treated with a 'real' analgesic cream or with a 'control' cream (in reality identical). In a manipulation phase, pain stimuli on the 'real' cream patch were surreptitiously lowered to 40%, while participants were told that all stimuli (6 on each patch) were at 80% of their tolerance level. This strengthened the suggestion and expectation of pain relief. The manipulation phase took place inside the MRI scanner, but without acquiring images. After this phase, structural brain images were acquired, followed by the test phase, during which functional brain images were made. In the test phase, participants received 15 stimuli in both the placebo and control condition (i.e. on both a 'real' and a 'control' cream patch), all at 60%. A behavioural placebo response score was obtained by calculating the percent reduction in intensity and

unpleasantness ratings in the placebo condition of the test phase as compared to the control condition. (For more details on the placebo protocol and pain stimulation procedure, see Supplementary Material).

fMRI analyses

Whole-brain functional images were collected during two runs; the placebo and the control condition. Since we were mainly interested in individual differences in placebo responses, we included all participants in the analyses (Enck *et al.*, 2008). Functional images were pre-processed and analysed using SPM8 (Wellcome Department of Imaging Neuroscience, London). (For details on the acquisition and pre-processing of fMRI images, see Supplementary Material).

For the analyses, the 20-s pain stimuli were divided into an early (first 10 s) and a late (last 10 s) period based on previous results regarding neural placebo effects (Wager *et al.*, 2004; Eippert *et al.*, 2009). First, we verified whether our pain stimuli elicited reliable pain-related activation in the brain, by collapsing the control and placebo conditions, and looking at the early and late pain periods together. We then looked for increases and decreases in activation in the placebo compared to control condition—i.e. the neural placebo effect—on a whole-brain level, during anticipation, early pain and late pain periods. Additionally, we explored which of these (de-)activated regions correlated with the reappraisal measures, by adding the CRA and ERQ scores as covariates.

Because of the putative role of the PFC in initiating PA (Wiech *et al.*, 2008; Amanzio *et al.*, 2013; Colloca *et al.*, 2013), we continued to refine our search to a ROI of the PFC, to investigate clusters where placebo-related increases correlated with reduced experienced pain and cognitive reappraisal measures.

Finally, to examine functional connectivity between the PFC and other brain regions, we used a generalised form of context-dependent psychophysiological interaction analysis (gPPI; McLaren *et al.*, 2012). This analysis identifies regions that show changes in functional connectivity as a function of task condition (placebo versus control). As seed region we used a cluster in the left DLPFC, as identified in the preceding analyses (this cluster showed a correlation between placebo-related activation during anticipation and CRA scores). (For more details on all fMRI analyses, please refer to the Supplementary Material).

Results

Behavioural placebo response

A summary of all behavioural data is presented in Table 1, including the mean pain intensity and unpleasantness VAS ratings from the test phase of the placebo protocol. Overall subjective pain report was significantly reduced in the placebo condition, as compared to the control condition, for intensity ratings ($F(1,29) = 28.19$, $P < 0.001$, Cohen's $d = 0.465$) as well as unpleasantness ratings ($F(1,29) = 28.00$, $P < 0.001$, Cohen's $d = 0.434$). The overall placebo-induced reduction was 12.8% for pain intensity and 16.4% for pain unpleasantness.

Cognitive reappraisal measures

Overall, participants were able to decrease their negative feelings in the reappraise ('decrease') condition of the CRA as compared to the control ('look') condition ($F(1,29) = 33.11$, $P < 0.001$, Cohen's $d = 0.495$). Negativity VAS ratings were reduced by 22.3%. ERQ reappraisal subscale scores ranged from 20 (indicating relatively low self-reported habitual use of reappraisal) to 37 (indicating very frequent habitual use of reappraisal) (Table 1).

Table 1. Summary of all behavioural data

Behavioural measure			M (SD)
Placebo paradigm	VAS Intensity ratings	Control	58.8 (15.8)
		Placebo	51.5 (15.9)
		Difference	12.8%
	VAS Unpleasantness ratings	Control	55.2 (20.1)
		Placebo	46.6 (19.4)
		Difference	16.4%
CRA task	VAS negativity ratings	Control	59.7 (22.8)
		Reappraisal	48.4 (25.0)
		Difference	22.3%
Questionnaires	Start of laboratory session	ERQ	29.7 (4.3)
		STAI trait	43.3 (9.2)
		STAI state	35.4 (8.0)
		PA	31.4 (5.3)
		NA	14.5 (4.8)
	Start of scanning session	STAI state	35.9 (6.0)
		PA	31.0 (5.5)
		NA	14.2 (3.4)

Note: CRA, cognitive reappraisal ability; ERQ, emotion regulation questionnaire; M, mean; PA, positive affect subscale of the Positive and Negative Affect Schedule; NA, negative affect subscale of the PANAS; SD, standard deviation; STAI, state-trait anxiety inventory; VAS, visual analogue scale.

Anxiety and negative affect

Mean scores on the STAI and PANAS can be found in Table 1. STAI scores were below cut-off for clinical anxiety and none of the scores differed significantly between sessions (STAI state: $F(1,29) = 0.12$, $P = 0.730$, Cohen's $d = 0.066$; Positive Affect (PA): $F(1,29) = 0.27$, $P = 0.607$, Cohen's $d = 0.076$; Negative Affect (NA): $F(1,29) = 0.11$, $P = 0.740$, Cohen's $d = 0.063$).

Correlations between behavioural data and questionnaires

Two-tailed Pearson correlation coefficients were calculated to search for correlations. There were no significant correlations between the CRA and the reappraisal subscale of the ERQ ($r = 0.166$, $P = 0.382$, bias-corrected and accelerated 95% confidence interval (BCa 95% CI) = [−0.188, 0.461]), or between the behavioural placebo response (reduction in pain intensity ratings) and the two reappraisal measures (CRA: $r = -0.142$, $P = 0.453$, BCa 95% CI = [−0.575, 0.345]; ERQ: $r = -0.200$, $P = 0.289$, BCa 95% CI = [−0.490, 0.191]). We also did not find significant correlations between the reappraisal measures or the behavioural placebo response and the anxiety or negative affect scores (all $P > 0.05$, all lower BCa 95% CI < 0, all upper BCa 95% CI > 0).

Neural pain response

First, we verified whether our pain stimuli elicited reliable pain-related activation in the brain, by collapsing the control and placebo conditions, and looking at the early and late pain periods together. This yielded a network of activations consistent with pain perception, including the bilateral insula, anterior cingulate cortex and right (contralateral) secondary somatosensory cortex (see Figure 1. Activations are also reported in Supplementary Table S1).

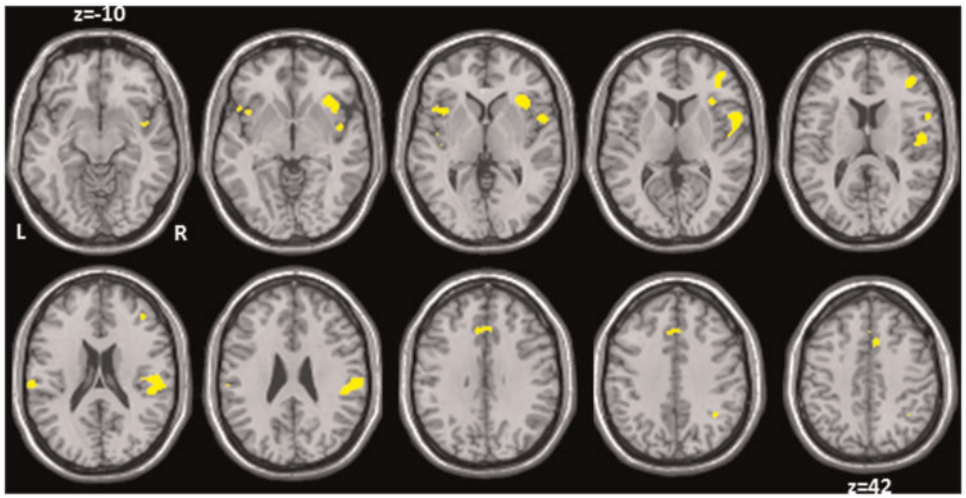

Fig. 1. Pain-related activation in our task. Control and placebo condition collapsed and early and late pain phase collapsed. Activations are reported in Supplementary Table S1 (L, left; R, right).

Table 2. Regions showing a reduction in activation during pain in the placebo condition as compared to the control condition

Region		BA	MNI coordinates			*k*	*T*	*Z*
			x	*y*	*z*			
Early pain								
SMA/precentral gyrus	R	6	14	−24	62	28	3.97	3.52
Late pain								
STG/Insula/IPL	R	13	44	−44	20	48	4.21	3.69
STG/insula/amygdala	R	38	36	2	−14	31	4.06	3.58
MCC/SMA	R	31	14	−28	46	27	4.03	3.56
ITG	R	37	46	−40	−16	9	3.90	3.47
PHG/lingual gyrus	L	19	−22	−46	−8	23	3.83	3.41

Note: BA, Brodman Area; MCC, midcingulate cortex; MNI, Montreal Neurological Institute; k, cluster size (voxels); L, left; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; PHG, parahippocampal gyrus; R, right; SMA, supplementary motor area; STG, superior temporal gyrus.

Table 3. Regions showing increased activation in the placebo condition as compared to the control condition

Region		BA	MNI coordinates			k	T	Z
			x	y	z			
Anticipation								
Cerebellum	L		2	−66	−48	205	4.90	4.15
Thalamus/brainstem	L		−12	−14	−2	31	4.53	3.91
MFG/SMA	L	6	−10	−12	60	53	4.26	3.72
Cerebellum	L		−22	−64	−42	20	4.05	3.58
Thalamus/VLN	R		14	−16	14	13	4.04	3.57
Precentral gyrus	L		−20	−24	66	6	3.69	3.31
MCC	L	31	−6	−28	46	6	3.59	3.24
Early pain								
PHG/hippocampus	R		22	−20	−18	22	3.94	3.50
PHG/brainstem	L		−18	−26	−22	23	3.84	3.42
FFG/PHG	L		−32	−2	−30	8	3.76	3.36
Cerebellum	R		20	−54	−44	14	3.72	3.34
Late pain								
—								

Note: BA, Brodman area; FFG, fusiform gyrus; MCC, midcingulate cortex; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; PHG, parahippocampal gyrus; k, cluster size (voxels); L, left; R, right; SMA, supplementary motor area; VLN, ventral lateral nucleus.

Whole-brain neural placebo effects

To investigate whether our participants showed a neural placebo response, we first compared activation in the placebo and control conditions on a whole-brain level. Placebo-induced reductions in activation during early pain were found in regions including the right supplementary motor area (SMA) and precentral gyrus, and during late pain in the right insula, right amygdala, anterior midcingulate cortex (MCC) and right inferior parietal lobule (Table 2).

Placebo-induced *increases* in activation were found in regions including the bilateral thalamus, MCC, left middle frontal gyrus, left SMA and left precentral gyrus (during anticipation) as well as in the left brainstem (during early pain, Table 3).

Correlations between whole-brain neural placebo effects and cognitive reappraisal

Regions which showed a positive correlation between the placebo-related reductions in activation and cognitive reappraisal measures, included the right SMA and right superior/middle frontal gyri (during early pain), as well as the left insula, left amygdala, bilateral thalamus, anterior MCC, left caudate and left putamen (during late pain, Table 4 and Figure S1 in the Supplementary Material).

Positive correlations between placebo-related increases and cognitive reappraisal measures were found in regions including the left insula, brainstem, bilateral middle frontal gyrus and ACC (during anticipation), as well as in the left superior frontal gyrus, MCC and right thalamus (during early pain, Table 5 and Figure S1 in the Supplementary Material).

To summarise, our participant group showed a consistent neural placebo effect, and moreover, this effect was related to individual differences in CRA.

Prefrontal mediation of the relationship between PA and cognitive reappraisal

The main aim of the study was to investigate whether there were any correlations between placebo-related increases and independent cognitive reappraisal measures, specifically in the

Table 4. Regions showing a positive correlation between cognitive reappraisal measures and placebo-related reductions in activation during pain

Region		BA	MNI coordinates			k	T	Z	CR measure
			x	y	z				
Early pain									
SFG/MFG/SMA	R	6	22	16	66	36	4.46	3.84	CRA
SFG	R	8	22	28	58	8	3.70	3.31	CRA
MTG	L		−50	−20	−14	8	3.69	3.30	CRA
Caudate	R		18	−20	22	8	3.67	3.29	CRA
—									ERQ
Late pain									
Putamen/globus pallidus	L		−18	−2	2	38	4.08	3.59	CRA
Caudate	L		−20	−6	24	12	3.85	3.42	CRA
Thalamus	R		12	−20	8	7	3.74	3.34	CRA
Thalamus	L		−8	−24	−2	10	3.71	3.32	CRA
Insula	L		−28	−18	24	9	3.65	3.27	ERQ
MCC	L		−12	4	32	14	4.17	3.65	ERQ
PHG/amygdala	L		−28	−2	−32	21	4.12	3.61	ERQ

Note: BA, Brodman area; CR, cognitive reappraisal; CRA, cognitive reappraisal ability test score; ERQ, emotion regulation questionnaire; L, left; MCC, midcingulate cortex; MNI, Montreal Neurological Institute; MFG, middle frontal gyrus; MTG, middle temporal gyrus; k, cluster size (voxels); PHG, parahippocampal gyrus; R, right; SMA, supplementary motor area; SFG, superior frontal gyrus. These activations are also shown in Figure S1 in the Supplementary Material.

Table 5. Regions showing a positive correlation between cognitive reappraisal measures and placebo-related increases

Region		BA	MNI coordinates			k	T	Z	CR measure
			x	y	z				
Anticipation									
IPL/supramarginal gyrus/Insula	L		−42	−50	22	196	5.23	4.33	CRA
Middle temporal pole	L	38/21	−50	14	−32	18	4.48	3.85	CRA
Brainstem	R		12	−24	−10	15	4.25	3.70	CRA
Middle frontal gyrus	L	10	−36	40	20	26	4.21	3.68	CRA
Middle frontal gyrus	R	9	36	20	32	18	3.96	3.50	CRA
Insula/IPL	L	13	−40	−30	20	10	3.89	3.45	CRA
Insula/IFO	L	13/44	−38	14	16	19	3.88	3.44	CRA
ACC	L	32	−14	36	18	5	3.73	3.33	CRA
Medial frontal gyrus	L	9/32	−20	36	22	5	3.52	3.18	CRA
—									ERQ
Early pain									
—									CRA
Putamen/pallidum	R		30	−10	−4	34	4.50	3.87	ERQ
SFG/paracentral lobule	L	6	−10	−18	74	25	4.08	3.59	ERQ
Thalamus	R		6	−22	4	5	3.90	3.46	ERQ
Medial SFG	L	10	−8	58	2	8	3.81	3.39	ERQ
Precuneus/MCC	R	31	12	−46	38	9	3.71	3.32	ERQ
Late pain									
—									CRA
Superior temporal gyrus	R		40	−48	8	14	4.37	3.78	ERQ

Note: ACC, anterior cingulate cortex; BA, Brodman Area; CR, cognitive reappraisal; CRA, cognitive reappraisal ability test score; ERQ, emotion regulation questionnaire; k, cluster size (voxels); L, left; IPL, inferior parietal lobule; IFO, inferior frontal operculum; MCC, midcingulate cortex; MNI, Montreal Neurological Institute; SFG, superior frontal gyrus; R, right. These activations are also shown in Figure S1 in the Supplementary Material.

PFC, given the putative role of the PFC in initiating the placebo response. We thus narrowed down our search to a region-of-interest of the PFC. First, we investigated which PFC regions showed placebo-induced increases in activation, correlating with the behavioural placebo response (i.e. reduction in pain intensity ratings). We found significant positive correlations in several bilateral DLPFC regions for the pain anticipation phase (Table 6; Figure 2A); participants with stronger activity in these regions during anticipation of pain in the placebo versus control condition, rated the stimuli as less intense. There were no significant negative correlations. For the early pain phase, activation of the bilateral DLPFC also correlated positively with the behavioural placebo response (Table 6; Figure 2B). Again, there were no significant negative correlations. For the late pain phase, we found no positive or negative correlations between PFC activation and the behavioural placebo response.

Next, we extracted parameter estimates from these DLPFC regions where activation correlated positively with the behavioural placebo response, based on ROIs defined as spheres with 5mm radius centred on the clusters' peak coordinates. We did this for

three contrasts of interest, namely placebo versus control during anticipation, early pain and late pain. We correlated these parameter estimates with our behavioural scores on the CRA laboratory task and with responses on the reappraisal subscale of the ERQ. We found significant positive correlations between the CRA scores and parameter estimates from the anticipation phase for two of these six clusters, one in the left and one in the right DLPFC (see Figure 2C). Participants with stronger activity in these regions during placebo-related anticipation of pain reduction also reported less negative affect when applying cognitive reappraisal during the lab task. The remaining clusters did not correlate with either cognitive reappraisal measure.

In a subsequent analysis, we added the CRA scores and ERQ reappraisal sub-scores as covariates to the placebo versus control contrasts, to examine the PFC directly for correlations between reappraisal measures and placebo-related activation during the different pain phases. For the anticipation phase, we found significant positive correlations with the CRA score in 3 clusters in bilateral DLPFC (Table 7; Figure 3A), and no negative correlations. There were no significant correlations with the ERQ. For the early pain phase, we found no correlations with the CRA, but a significant positive correlation in the left medial/orbitofrontal cortex with the ERQ reappraisal sub-score (Table 7; Figure 3B) (and no negative correlations). For the late pain phase, we found no positive or negative correlations between prefrontal activation and either cognitive reappraisal measure.

Between these two approaches to the analysis, there was a close convergence in the left DLPFC area, where the cluster identified using the first method (−34, 18, 30) overlapped with a cluster identified using the second method (−38, 14, 16). Both analyses found a positive correlation between placebo-related activation during anticipation and the CRA test score in this DLPFC region.

We then performed a mediation analysis, with the behavioural placebo response as dependent variable, the CRA score as independent variable, and the DLPFC activation (parameter estimates from the left DLPFC cluster emerging from both analyses above) as potential mediator. This revealed a small but significant mediation effect ($ab = 0.14$, 95% BCa CI [0.001, 0.403]). CRA thus partially predicted the subjective pain reduction in the placebo paradigm through the activation of the DLPFC.

Table 6. Prefrontal cortex regions showing a positive correlation between placebo-induced activation and behavioural PA

Region		BA	MNI coordinates			*k*	*T*	*Z*
			x	y	z			
Anticipation								
DLPFC	L	9	−38	42	34	11	3.90	3.45
DLPFC	L	9	−46	34	32		3.65	3.27
DLPFC	R	8	32	38	46	4	3.77	3.36
DLPFC	R	8	50	18	46	8	3.75	3.35
Early pain								
DLPFC	L	9	−34	18	30	24	4.50	3.87
DLPFC	R	6	40	−4	52	10	4.06	3.57

Note: These clusters are also shown in Figure 2A and B. BA, Brodman area; DLPFC, dorsolateral prefrontal cortex; MNI, Montreal Neurological Institute; *k*, cluster size (voxels); L, left; R, right).

Psychophysiological interaction

Finally, we investigated the task-related functional connectivity of the PFC with other brain regions, using a psychophysiological interaction (PPI) analysis (see methods and Supplementary Material). As seed region (see Figure 4A) we defined the left DLPFC cluster identified in the two correlation analyses above, showing a significant positive correlation between placebo-related activation during anticipation and the CRA score (−38, 14, 16). We entered the PPI contrast images for placebo versus control during anticipation from each participant into a group analysis, and found three regions that showed increased connectivity with the DLPFC as a function of task condition, namely the PAG, putamen and left middle frontal gyrus (Table 8, Figure 4A and B, and Supplementary Figure S2). These regions showed

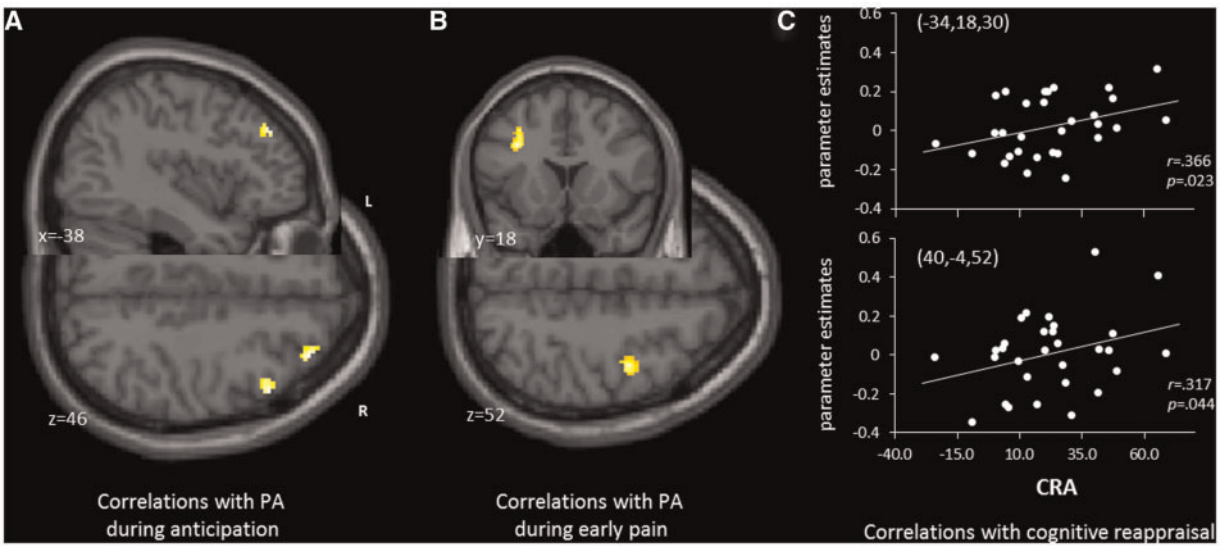

Fig. 2. Prefrontal cortex regions showing a positive correlation between placebo-induced activation and behavioural placebo analgesia. (A) Clusters showing a correlation during the anticipation phase. (PA = placebo analgesia, L and R indicate left and right for the transversal slice). (B) Clusters showing a correlation during the early pain phase. For illustrative purposes, activations in A and B are shown at p(unc) < 0.005 and images are masked to only show PFC activations. Shown clusters are reported (at p(unc) < 0.001) in Table 6. (C) Significant correlations between CRA scores and parameter estimates extracted from DLPFC clusters. (DLPFC = dorsolateral prefrontal cortex, CRA = cognitive reappraisal ability task scores).

Table 7. Prefrontal cortex regions showing a positive correlation between placebo-induced activation and cognitive reappraisal measures

Region		BA	MNI coordinates			k	T	Z	CR measure
			x	y	z				
Anticipation									
DLPFC	L	10	−36	40	20	26	4.21	3.68	CRA
DLPFC	R	9	36	20	32	14	3.96	3.50	CRA
DLPFC	L	46	−38	14	16	19	3.88	3.44	CRA
Early pain									
Medial/Orbito-frontal gyrus	L	10	−8	58	2	8	3.81	3.39	ERQ

Notes: Clusters also shown in Figure 3A and B. BA, Brodman Area; CRA, cognitive reappraisal ability test score; CR, cognitive reappraisal; DLPFC, dorsolateral prefrontal cortex; ERQ, emotion regulation questionnaire; MNI, Montreal Neurological Institute; k, cluster size (voxels); L, left; R, right.

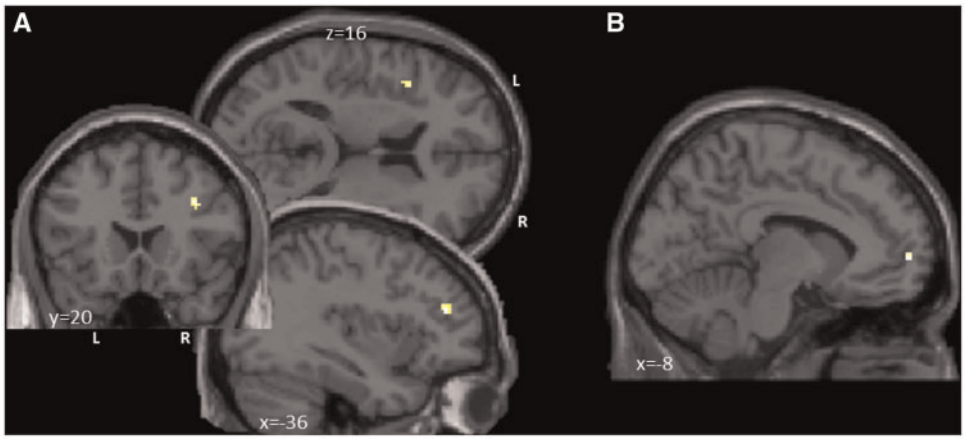

Fig. 3. Prefrontal cortex regions showing a positive correlation between placebo-induced activation and cognitive reappraisal measures. (A) Clusters showing a positive correlation during the anticipation phase with scores on the cognitive reappraisal ability laboratory task (CRA). (*L = left, R = right*). (B) Cluster showing a positive correlation during the early pain phase with scores on the emotion regulation questionnaire (ERQ). Images are masked to only show PFC activations, and activations are reported in Table 7.

increased functional connectivity with the DLPFC during the placebo condition, as compared to the control condition.

Discussion

Although the notion that cognitive reappraisal may play a role in PA has gained increasing acceptance, this is the first study to investigate this functional relationship directly. We demonstrated placebo-induced decreases in activation during pain in typical pain-processing structures, including the insula, amygdala, anterior MCC and sensorimotor cortex. These regions have consistently been found to be reduced following a placebo procedure (Wager *et al.*, 2011; Wager and Fields, 2013; Atlas and Wager, 2014). Importantly, this neural PA effect was related to individual differences in reappraisal measures: individuals with greater reappraisal success in the lab task (CRA) or more frequent self-reported use of cognitive reappraisal (ERQ) also showed smaller neural responses to noxious heat under placebo. This suggests that there is indeed a link between PA and cognitive reappraisal. When we then refined our search to the PFC, we identified a left DLPFC cluster, where placebo-induced increase in activation was modulated by individual differences in performance in the reappraisal lab task. The identification of this cluster was corroborated by two different analyses, both finding a significant positive correlation between placebo-related activation during anticipation of pain reduction and the CRA test scores. Participants with stronger activity in this cluster reported less negative affect when applying cognitive reappraisal in the lab task. Importantly, activity in this left DLPFC region also correlated positively with the behavioural placebo response, indicating its direct involvement in the down-regulation of pain. Furthermore, the region showed increased placebo-related functional connectivity to the PAG, an important structure of the descending pain control system (Basbaum and Fields, 1984). Finally, a mediation analysis showed that CRA partially predicted the subjective pain reduction, through the activation of the DLPFC. Our findings thus suggest that there may be a role for the left DLPFC in mediating PA and initiating pain inhibition through cognitive reappraisal mechanisms. Interestingly, cognitive reappraisal has been termed an 'antecedent-focused' regulatory strategy, which can be employed before the onset of an aversive event (Gross, 2002). We have confirmed previous demonstrations (e.g. Wager *et al.*, 2004) of prefrontal activation during *anticipation* of pain reduction. This reinforces the idea that it is the expectations one has before a painful event that trigger a cognitive frame in which the pain is reappraised.

Dorsolateral PFC in PA and cognitive reappraisal

The left DLPFC has been implicated consistently both in PA and in cognitive reappraisal studies, often within 10 mm from our cluster peak (see, for example, these meta-analyses on PA: Wager *et al.*, 2011; Atlas and Wager, 2014; and on cognitive reappraisal: Buhle *et al.*, 2014). Anticipatory activation in the same

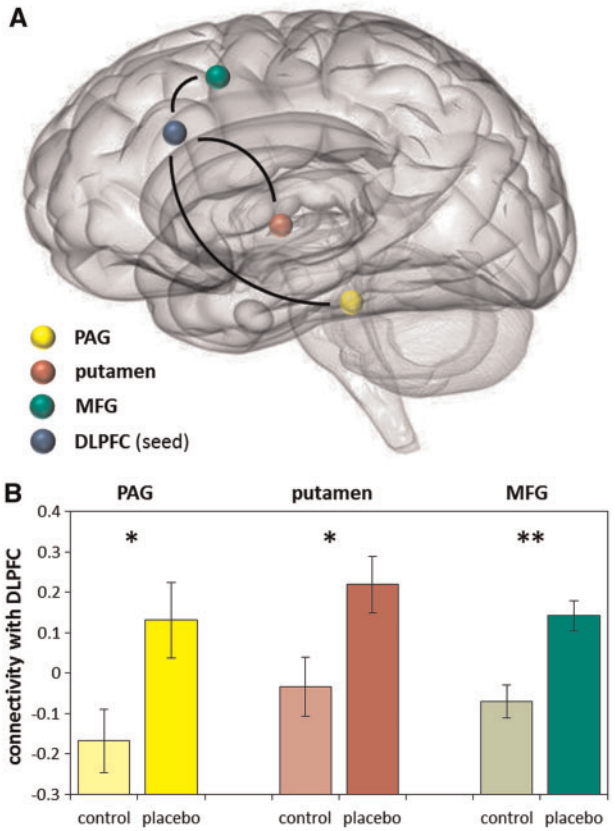

Fig. 4. Functional connectivity of the left dorsolateral prefrontal cortex. (A) The seed region (DLPFC) is indicated by the blue dot, whereas the areas showing increased placebo-related connectivity with the seed region are indicated by the green, red and yellow dots. These clusters are reported in Table 8 and also shown in Figure S2 in the Supplementary Material. (B) Connectivity of the PAG, putamen and MFG with the left DLPFC during anticipation in the control and placebo condition; mean eigenvariates from the PPI contrasts extracted for illustrative purposes from 5mm radius spheres around peak coordinates. (PAG = periaqueductal grey, MFG = middle frontal gyrus, DLPFC = dorsolateral prefrontal cortex, *$P < 0.05$, **$P < 0.001$).

Table 8. Regions showing increased task-dependent connectivity with the left dorsolateral prefrontal cortex

Region		BA	MNI coordinates			k	T	Z
			x	y	z			
Middle frontal gyrus	L	6	−30	8	42	34	3.79	3.39
Putamen	R		28	−14	−6	31	3.71	3.33
PAG	L		−2	−30	−26	21	3.18	2.92

Notes: Clusters are also shown in Figure 4A and Supplementary Figure S2. BA, Brodman area; MNI, Montreal Neurological Institute; k, cluster size (voxels); PAG, periaqueductal grey; L, left; R, right.

left DLPFC region, amongst others, predicted the magnitude of the placebo response across a large sample of studies (Wager *et al.*, 2011). The DLPFC has also been specifically associated with belief-related modulation of pain (Wiech *et al.*, 2008, 2014), perceived control over pain (Salomons *et al.*, 2004, 2007; Wiech *et al.*, 2006), supporting affective value, expectancy maintenance and regulation of emotion (Miller and Cohen, 2001; Kringelbach, 2005; Wager, 2005; Petrovic *et al.*, 2010), modulation of aversive stimuli (Wiech *et al.*, 2008), and emotional detachment from pain (Wiech and Tracey, 2009; Tracey, 2010). Notably, these are all functions consistent with cognitive reappraisal mechanisms. In support of the role of the DLPFC in PA, Krummenacher *et al.* (2010) have shown that repetitive transcranial magnetic stimulation of bilateral DLPFC completely blocked PA. Within the reappraisal literature, the DLPFC is considered an area responsible for reinterpretation (encoding contextual aspects of stimuli) and for constructing a 'new story' about the meaning of a stimulus (Ochsner and Gross, 2008).

Connectivity of DLPFC

The demonstration of increased connectivity between DLPFC and PAG in our study is in line with the idea that prefrontal mechanisms trigger pain control systems descending from the brainstem (Basbaum and Fields, 1984; Fields, 2004). The observation of increased functional connectivity between DLPFC and PAG is not entirely new. Wager *et al.* (2004) already demonstrated in a PA paradigm that bilateral DLPFC activation during anticipation of pain reduction correlated with placebo-increased anticipatory activation of the PAG. Subsequent studies have confirmed this coupling (Wager *et al.*, 2007; Eippert *et al.*, 2009; Wager *et al.*, 2011). Structural connections between the DLPFC and PAG have also been demonstrated (Mantyh, 1982; Linnman *et al.*, 2012), and have been shown to correlate with the placebo analgesic response (Stein *et al.*, 2012). Moreover, greater effective connectivity between the left DLPFC and PAG was predictive of the placebo response (Sevel *et al.*, 2015). Our study, however, is the first to link the DLPFC, and its connectivity with the PAG, to cognitive reappraisal as a possible underlying mechanism. The placebo-induced connectivity between DLPFC and putamen is also interesting given the role of the striatum in dopaminergic pain regulation (Hagelberg *et al.*, 2002, 2004). The ventral striatum has consistently been found activated in PA studies (e.g. Atlas and Wager, 2014), and is associated with reward processing (Scott *et al.*, 2007) and learning about affective value (Schoenbaum *et al.*, 2009; Liljeholm and O'Doherty, 2012). Alternatively, the putamen involvement could be related to the inhibition of motor responses to the pain stimuli during the placebo condition (Bingel *et al.*, 2004). Finally, the middle frontal gyrus cluster showing increased connectivity with the DLPFC is a region that has previously been associated with the cognitive reappraisal of high versus low intensity negative emotions (Silvers *et al.*, 2014), and may thus well play an important role in placebo-induced cognitive reappraisal.

Conclusion, limitations and perspectives

Our data point in the direction of a possible role of cognitive reappraisal, mediated by the DLPFC, as an underlying mechanism of PA. Placebo-induced activation of the left DLPFC (i) correlated positively with the reduction in subjectively experienced pain by participants; (ii) correlated positively with an independent behavioural measure of cognitive reappraisal and (iii) was functionally connected to the PAG, a key area of the descending pain control system. Our participant group also showed a clear neural PA effect (placebo-related reductions in pain-processing regions) which was related to individual differences in cognitive reappraisal. This suggests that the PAG network was indeed related to pain reduction in our group.

This relationship between PA and cognitive reappraisal is still rather indirect. An even stronger argument for a direct functional relationship would be to show an overlap in neural activation during PA and cognitive reappraisal within individuals,

or to show the direct influence of a reappraisal manipulation within a placebo paradigm. Another demonstration of a direct link would be a correlation between cognitive reappraisal test scores and the magnitude of behavioural PA. One possible explanation for why we failed to observe such a correlation could be that the percentage of reduction in pain intensity scores is too crude a measure to characterise the complex processes that underlie a placebo manipulation, and that the neural processes taking place may result in other behavioural modulations not captured by the pain intensity ratings. Another possibility is that our reappraisal lab task was not optimally designed to measure the type of reappraisal processes that may be involved in PA. The lab task was based on negative pictures whereas pain stimuli represent a completely different type of stimulus. We employed this reappraisal lab task because it is a well-established and validated task. Moreover, there is some evidence that reappraisal impacts the experience of negative pictures and pain similarly (Lapate *et al.*, 2012). However, the exact processes involved in PA and reappraisal of pictures may differ, and a cognitive reappraisal lab task targeting pain stimuli may have been more appropriate. These issues need to be addressed in future studies.

One limitation of this study is the use of mainly uncorrected statistical thresholds in the neuroimaging analyses. Since this study was explorative, we have taken a liberal statistical approach, allowing for Type I error rates to rise in the interest of keeping the Type II error rate low (Forstmeier *et al.*, 2016). However, results should be interpreted cautiously and should be corroborated using better control for false positives, possibly with a larger sample size and modified experimental and scanning protocols to yield more robust activations.

It would be interesting to further study the link between PA and cognitive reappraisal, by taking into account current knowledge about cognitive reappraisal and emotion regulation generally, and testing corresponding predictions for PA. For example, we know that self-regulatory resources are limited and self-regulation is cognitively demanding. When such self-regulatory resources are experimentally depleted, and if PA depends in part on these resources, will the placebo response be decreased correspondingly? Future studies could explore these possible venues to further our understanding of the mechanisms behind the placebo effect. Finally, a potential clinical implication of a relationship between cognitive reappraisal and PA is that clinicians may actively trigger or instil self-regulation techniques to maximise the benefit of patients from medication (Schneider and Kuhl, 2012).

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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