Individual Differences in the Effects of Perceived Controllability on Pain Perception: Critical Role of the Prefrontal Cortex

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Abstract

■ The degree to which perceived controllability alters the way a stressor is experienced varies greatly among individuals. We used functional magnetic resonance imaging to examine the neural activation associated with individual differences in the impact of perceived controllability on self-reported pain perception. Subjects with greater activation in response to uncontrollable (UC) rather than controllable (C) pain in the pregenual anterior cingulate cortex (pACC), periaqueductal gray (PAG), and posterior insula/SII reported higher levels of pain during the UC versus C conditions. Conversely, subjects with greater activation in the ventral lateral prefrontal cortex (VLPFC) in anticipation of pain in the UC versus C conditions reported less pain in response to UC versus C pain. Activation in the VLPFC was significantly correlated with the acceptance and denial subscales of the COPE inventory [Carver, C. S., Scheier, M. F., & Weintraub, J. K. Assessing coping strategies: A theoretically based approach. *Journal of Personality and Social Psychology, 56,* 267–283, 1989], supporting the interpretation that this anticipatory activation was associated with an attempt to cope with the emotional impact of uncontrollable pain. A regression model containing the two prefrontal clusters (VLPFC and pACC) predicted 64% of the variance in pain rating difference, with activation in the two additional regions (PAG and insula/SII) predicting almost no additional variance. In addition to supporting the conclusion that the impact of perceived controllability on pain perception varies highly between individuals, these findings suggest that these effects are primarily top-down, driven by processes in regions of the prefrontal cortex previously associated with cognitive modulation of pain and emotion regulation. ■

INTRODUCTION

Perception of control over stressors is a critical determinant of an individual's physical and psychological well-being. A variety of adverse psychological consequences have been associated with exposure to uncontrollable stressors, including mood alterations and deficits in learning and motivation (Mineka & Henderson, 1985). Furthermore, perceived controllability has been found to predict several critical outcome variables in persons suffering from chronic illnesses, including reduced disability and enhanced emotional well-being (Keefe, Abernethy, & Campbell, 2005; Thompson, Armstrong, & Thomas, 1998).

Evidence suggests that the degree to which a physical stressor is perceived to be controllable may also affect the way that it is experienced. Animals exposed to uncontrollable pain stimuli have consistently demonstrated altered pain responses and the neural mechanisms by which these effects occur have been well delineated (Maier & Watkins, 2005). Results have been less consistent in human studies of the effects of perceived controllability, particularly in terms of self-reported pain perception (Arntz & Schmidt, 1989), and considerably less is known about the mechanisms through which these effects occur.

In a recent report (Salomons, Johnstone, Backonja, & Davidson, 2004), we used functional magnetic resonance imaging (fMRI) to demonstrate that perceived control over experimentally induced pain attenuates activation of neural regions such as the anterior cingulate and insular cortices that are routinely activated in pain studies (Peyron, Laurent, & Garcia-Larrea, 2000). Despite large activation differences, however, there was no difference between the conditions in terms of subjective ratings of pain, leading to questions as to how these activation differences may relate to the subjective experience of pain. A potential explanation for the lack of a clear effect on self-reported pain perception (as well as inconsistent findings in the human literature) is that there are individual differences in the way that perceived controllability affects subjective experience that may not be reflected in group mean scores. The present report

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investigates this hypothesis by examining individual differences in the degree to which perceived controllability alters pain perception.

The possibility that these effects vary greatly between individuals is consistent with the conclusion reached in early reviews (Thompson, 1981; Averill, 1973) that the degree to which perceived controllability alters pain perception is dependent on the meaning of controllability for the individual and the effectiveness of various options available for controlling it. The effects observed in the present study were particularly dependent on cognitive evaluation, as the subjects were presented with identical thermal stimuli in two conditions: one in which they were told an instrumental response could alter the pain stimulus, and one in which they were told the same response would make no difference. Because any effects of this manipulation would be dependent on the individual's cognitive evaluations, we made the following predictions:

The degree to which subjects reported subjective differences between the conditions would be associated with activation differences in regions such as the pregenual anterior cingulate cortex (pACC) and periaqueductal gray (PAG), which have been linked with cognitive modulation of pain in previous imaging studies (Bingel, Lorenz, Schoell, Weiller, & Buchel 2006; Bantick et al., 2002; Petrovic & Ingvar, 2002; Tracey et al., 2002).

The degree to which perceived controllability modulates pain perception would be driven by top-down (i.e., prefrontal) processes.

When instrumental control was explicitly removed (i.e., the ''uncontrollable condition''), the anticipatory period would afford the opportunity to cope emotionally with the impending pain stimulus. We would therefore expect activation during the anticipatory period in regions associated with regulation of negative emotion (Urry et al., 2006; Kalisch et al., 2005; Ochsner et al., 2004) to be associated with modulation of self-reported pain perception.

In keeping with this latter hypothesis, we were interested in whether coping style (an individual's tendency to adopt a particular coping strategy in the presence of a stressor) would predict neural activation and self-reported pain perception in response to perceived controllability. Previous evidence indicates that individual differences in coping style are associated with perceived control over chronic pain states (Toomey, Mann, Abashian, & Thompson-Pope, 1991) as well as differential clinical outcomes (Jensen, Turner, & Romano, 2001; Schmitz, Saile, & Nilges, 1996), suggesting that coping style may predict the response to an uncontrollable stressor (such as chronic pain) in a clinically meaningful way. It has been suggested that in instances (such as the present experiment) where behavioral control over a stressor is removed, coping strategies aimed at dealing with the emotions provoked by the stimulus (as opposed to strategies aimed at removal of the stressor itself) would be particularly effective (Carver, Scheier, & Weintraub, 1989).

In summary, the present investigation examines individual differences in how perceived controllability alters pain perception. Specifically, we hypothesized that individual differences in modulation of pain perception by perceived controllability would be associated with activation differences in regions previously implicated in cognitive modulation of pain and emotion regulation. We also predicted that these effects would be the result of top-down processes and largely driven by activation in the prefrontal cortex. Finally, we were interested in whether these differences in neural activation and self-reported pain perception were associated with individual differences in coping style.

METHODS

Subjects

Sixteen right-handed subjects (5 women) 19–35 (mean, 22) years old were recruited. Subjects were excluded if they were pregnant, claustrophobic, or had a present psychiatric or chronic pain disorder or significant history of such disorders. They were excluded for medical conditions that could affect pain sensitivity or regular use of drugs such as opioids or nonsteroidal anti-inflammatory drugs that could alter pain perception.

Study Task

The experiment consisted of two sessions. In the first session, subjects determined the intensity of the nociceptive stimulus used for their testing (see below) and were given standardized instructions explaining the task. A scanner-compatible joystick was placed in the hand opposite to the side being stimulated. To familiarize subjects with the study task and the imaging environment, the task was rehearsed in a mock scanner. In the second session, subjects were scanned while performing the same task.

We manipulated controllability by providing cues prior to the onset of painful thermal heat, which signaled whether the subject would be able to control the heat with a joystick response. Subjects were instructed that in the controllable condition (C) they could reduce the hot stimulus to a nonpainful duration (2 instead of 5 sec). In order to do so, they were told they had to meet two criteria. First, they had to respond in the correct direction, which was indicated by an arrow in the cue (see Figure 1). Arrows were presented in quasi-random order within each condition, so that subjects had to respond twice in each of four directions in each

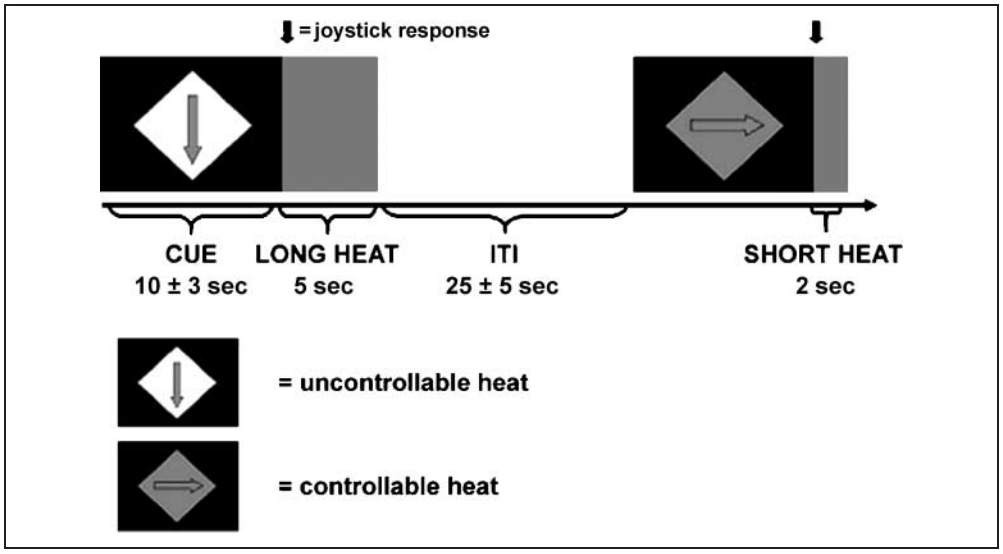

Figure 1. Study Task. Cues were presented in which the color of the diamond indicated whether a subject could control the length of the heat or not. In the controllable condition subjects were instructed that if they moved the joystick in the direction of the arrow and their response was faster than a threshold (based on their previous response times) they would receive the short, rather than long heat. Subjects were asked to respond on all trials, whether they had control or not. Pictured above are one controllable and one uncontrollable trial. Each subject received eight trials of each condition. Colors were counterbalanced between subjects, and the direction of the arrow varied randomly within condition. ITI = intertrial interval.

condition. The second criterion was that their response time had to be less than a ''response threshold'' that was based on their response time on previous trials. They were encouraged to try to beat this response threshold on every trial. In the uncontrollable condition (UC), subjects were asked to respond as they had in the C condition, but were instructed that their response would have no effect on the length of the heat.

Subjects received eight presentations of each condition, in quasi-random order (i.e., two presentations of each condition within each of four runs). To further control for order effects, the order in which the conditions were presented was randomized within each run. To control for effects due to uncertainty, subjects were told that the proportion of short and long stimuli in the UC condition would be based in an ongoing fashion on their performance in the C condition, so that the probability of getting a long, painful stimulus on a given trial was the same in both conditions. In reality, the subjects only had the illusion of control in the C condition, as the order and ratio of short to long stimuli was preset in both conditions. This ensured that all subjects would receive the same number of long, painful stimuli (four in each condition). In order to maintain the illusion of control, when subjects were supposed to receive a short stimulus on a control trial but responded unusually slowly or incorrectly, the short stimulus was traded for the next long stimulus. Conversely, if they were supposed to receive a long stimulus and they responded unusually quickly, the long stimulus was traded for the next short stimulus. To compensate for the fact that near the end of the trial there was no more flexibility to ''trade-off'' stimuli, subjects were instructed that they might find it more difficult to succeed toward the end of the trial due to a changing threshold that took their previous responses into account.

Cues were 10 ± 3 sec in duration. Cue offset was coincident with onset of the thermal stimulus. Subjects were asked to respond at stimulus onset. The duration of the intertrial interval (the time from stimulus offset to cue onset) was pseudorandomized with a mean of 25 ± 5 sec. Pseudorandomization of the cue and ITI duration was used to prevent subjects from predicting stimulus onset based on temporal cues, and for minimizing collinearity between the events in analysis.

Ten seconds after the offset of thermal stimuli (during the intertrial interval), subject were asked to rate their pain on an 11-point visual analog scale in which 0 was *no pain* and 10 was *the worst pain imaginable*. Following completion of the study task, subjects were interviewed to determine whether they understood the meaning of the various cues. To determine whether they believed they had control in the controllable condition, they were asked to respond to the statement, ''The color of the diamond accurately indicated whether I had control over the length of the heat,'' on a 5-point scale where 1 represented *strongly disagree* and 5 represented *strongly agree*.

In order to examine how individual differences in coping style are associated with differential response to uncontrollable and controllable pain, subjects were asked to complete the COPE inventory (Carver et al., 1989), a multidimensional coping questionnaire that assesses coping strategies in response to stressful events.

Nociceptive Stimulus

A thermal stimulator (TSA-II, Medoc Advanced Medical Systems; Haifa, Israel) was used to generate the painful heat. A 30 × 30-mm MRI-compatible Peltier device was attached to one of the subject's forearms. The side of stimulation was chosen at random and counterbalanced across subjects (eight subjects stimulated on the left, eight on the right).

Prior to performing the study task, a level of nociceptive stimulation was chosen based on the subject's own pain ratings. Stimulation began at 32°C and increased by 0.7°C/sec. Subjects were asked to stop the stimulation by pressing a button when their pain reached an 8 on an 11-point numeric rating scale, with 0 representing *no pain* and 10 representing *the worst pain imaginable*. This was repeated 10 times, with a 30-sec break between each presentation. The mean temperature from the final five trials was used as the painfully hot stimulus. The maximum temperature used in the experiment was not allowed to exceed 49°C and subjects were excluded if their ''hot, painful'' stimulus was less than 46°C.

fMRI Image Acquisition

Images were acquired on a General Electric (Fairfield, CT) Signa 3.0-T high-speed imaging device with a quadrature head coil. Functional images consisted of 30 × 4-mm sagittal echo-planar imaging (EPI) slices covering the whole brain (1-mm interslice gap; 64 × 64 in-plane resolution, 240 mm FOV; TR = 2000 msec; TE = 30 msec; flip angle = 90°; 240 image volumes per run). Four EPI images with identical acquisition parameters, but with TEs of 30, 31, 33, and 36 msec, respectively were also acquired, to be used in calculating magnetic field maps for use in image distortion correction. Immediately preceding acquisition of functional images, a whole-brain high-resolution T1-weighted anatomical scan (3-D T1-weighted inversion recovery fast gradient-echo; 256 × 256 in-plane resolution, 240 mm FOV; 124 × 1.1-mm axial slices) was acquired. Functional images were collected in four 8-min runs.

Analysis of fMRI Data

Analysis was carried out using fMRI Expert Analysis Tool (FEAT) Version 5.00 (Beckmann, Jenkinson, & Smith, 2003), part of FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Data preprocessing consisted of slice time correction, motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), and image distortion correction (using in-house software). Data were smoothed with a 5-mm full width at half maximum Gaussian blur. A separate regressor for each experimental condition and the rating screen was derived by convolving a stimulus-based binary boxcar function with an ideal hemodynamic response. The time series data for each voxel were then modeled as the linear sum of all regressors. Contrasts between conditions were calculated from the model parameter estimates. The resulting contrast maps were registered to standardized (MNI) space with FLIRT before mixed-effects modeling of group data (subject as a random factor and condition as a fixed factor) using FMRIB's Local Analysis of Mixed Effects (FLAME). Z (Gaussianized T/F) statistic images were thresholded at a voxelwise $p < .01$, with a cluster-based correction for multiple comparisons using Gaussian random field theory (Forman et al., 1995; Friston, Worsley, Frakowiak, Mazziotta, & Evans, 1994; Worsley, Evans, Marrett, & Neelin, 1992).

The present analysis examines clusters in which there was significantly more activation in the uncontrollable than the controllable condition (UC − C). We examined these differences both in response to pain (i.e., the response to the four 5-sec thermal stimuli in each condition) and in anticipation of pain (i.e., the response to the eight 10 ± 3-sec visual stimuli preceding the pain in each condition). In order to improve spatial specificity, the voxelwise threshold was increased from $p < .01$ ($z = 2.3$) to $p < .005$ ($z = 3.09$). In some cases, it was also necessary to further limit these clusters based on anatomical considerations. In particular, the SII/posterior insula cluster was restricted to parietal operculum and adjacent regions of insula (cf. Eickhoff, Schleicher, Zilles, & Amunts, 2006). The mean value of the standardized parameter estimates for all voxels within a selected cluster was extracted from the contrast map. In Figures 2 and 3, the activations from the original comparison maps (UC − C) that survived the more stringent voxelwise threshold are shown in yellow, with the clusters from which the values were extracted outlined in blue.

Analysis of the extracted imaging data and self-report measures was conducted in SPSS 11.5 (Chicago, IL).

RESULTS

Behavioral

All subjects reported being aware of the meaning of the cues signaling controllable and uncontrollable pain and most reported a strong belief that they had control over the controllable stimulus but not the uncontrollable stimulus. These results have been reported in greater detail elsewhere (Salomons et al., 2004). There was no significant overall difference between pain ratings in the two conditions: $M = 7.19$, $SD = 0.99$, for uncontrollable pain; $M = 7.20$, $SD = 1.00$ for controllable pain; $t(1,15) = -0.086$, $p < .9$. The present analysis therefore is concerned with examining individual differences in pain rating difference and the neural areas associated with these individual differences.

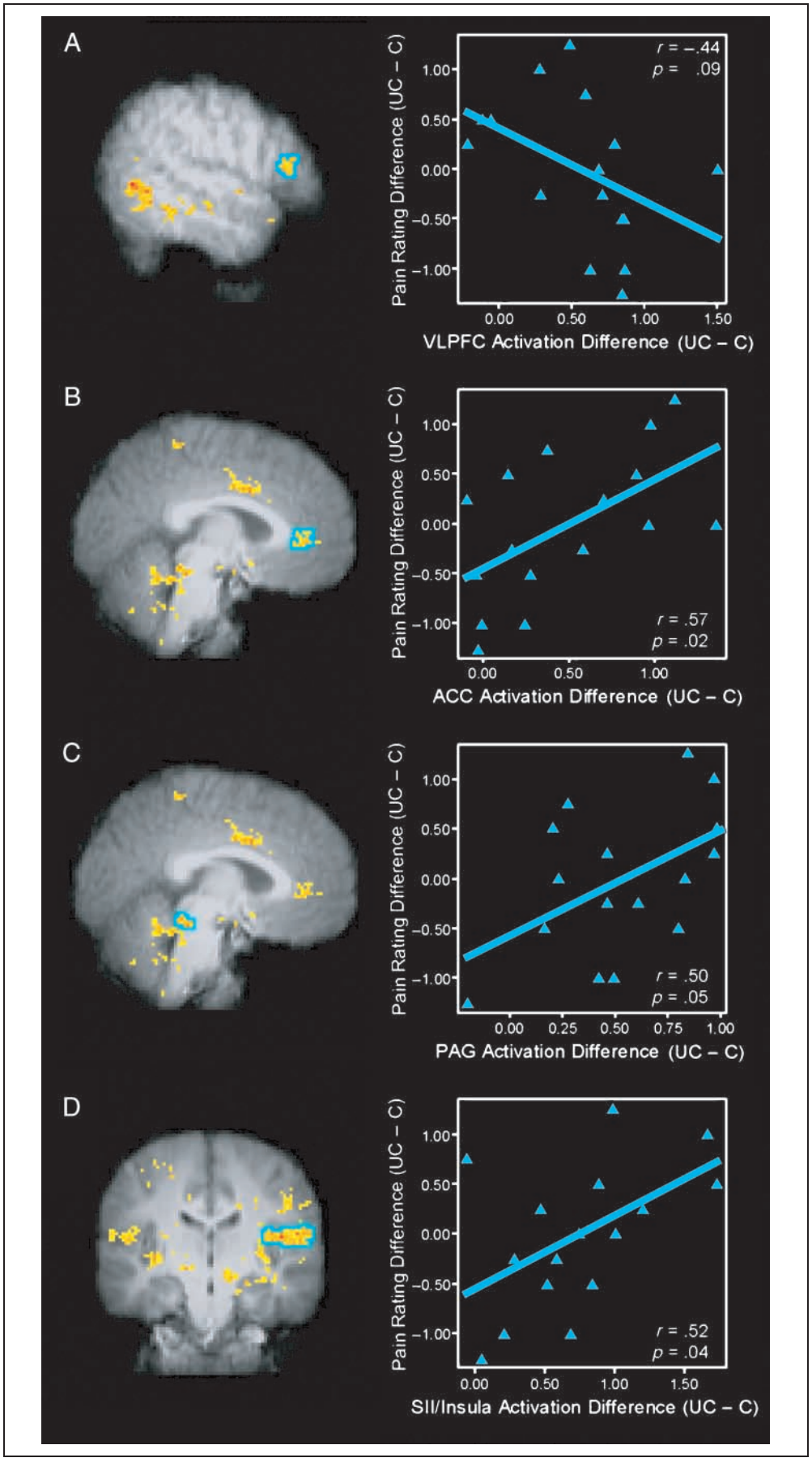

Figure 2. Correlations between pain rating difference (UC − C) and mean parameter estimates from the (UC − C) contrast for clusters in the (A) ventral lateral prefrontal cortex (VLPFC) (anticipatory response), (B) pregenual anterior cingulate cortex (pACC) (pain response), (C) periaqueductal gray (PAG) (pain response), and (D) posterior insula/SII (pain response). All four clusters were significant in the main contrast (UC − C) ($z = 2.3, p = .01$, corrected for whole-brain comparisons), VLPFC during anticipation, and pACC, PAG, and insula/SII during pain. Activations shown in the figure survived a higher threshold ($z = 3.09, p = .005$), with the regions extracted outlined in blue.

fMRI Results

Activation Difference in the Response to the Thermal Stimulus (Pain Response)

Group Differences. In a direct comparison of activations in response to uncontrollable and controllable pain we found significantly greater activation in response to uncontrollable pain (UC − C) in several regions of the pain-processing network, including the anterior cingulate, insula, secondary somatosensory and prefrontal cortices as well as subcortical regions such as the hippocampus, amygdala, and cerebellum (see Salomons et al., 2004, for details).

Zero-order Correlations with Self-reported Pain Perception. The goal of the present analysis was to find candidate regions that were associated with pain rating difference by examining zero-order correlations and then enter these regions into regression models to assess their relationship and relative importance in predicting pain rating difference. In order to examine regions associated with individual differences in response to perceived controllability over pain, we extracted mean parameter estimates for the UC − C contrast from clusters in the pACC (maximally activated voxel: 2, 38, −2; $z = 4.12$), posterior insula/SII (44, −20, 14; $z = 5.60$), and PAG (2, −38, −16; $z = 4.79$) for each subject. All three regions were significantly correlated with pain rating difference scores (UC − C), such that subjects who rated uncontrollable stimulation as more painful than controllable pain had a greater activation difference (UC − C) in these regions. The correlations between pain rating difference and activation difference in pACC, insula/SII, and PAG were 0.57 ($p < .02$), 0.52 ($p < .04$), and 0.50 ($p < .05$), respectively (see Figure 2B–D). As indicated in Table 1, these variables were highly correlated with each other.

To examine whether the effects observed in the right insula/SII were lateralized, we performed paired t tests with a cluster on the left side, which was extracted using the same threshold and anatomical guidelines as the cluster on the right. Although the mean activation on the right was slightly higher (mean z score = 0.74 on the right and 0.61 on the left), this difference was not significant, $t(15) = 1.52$, $p = .15$, suggesting that these are not lateralized effects. Furthermore, although the correlation between activation difference (UC − C) in the left insula was not significantly correlated with pain rating difference ($r = .28$, $p = .29$), this correlation was not significantly different from the correlation between right insula activation difference and pain rating difference ($z = 1.55$; $p = .12$; cf. Glass & Stanley, 1970, for correlation comparison technique). Thus, although there was a trend toward greater activation difference on the right and this activation difference was more highly correlated with pain rating difference, given that neither of these trends were statistically significant, no conclusions about laterality should be drawn from these findings.

Table 1. Correlations between Mean Parameter Estimates for Voxels in the Pregenual Cingulate (pACC), Posterior Insula/SII and Periaqueductal Gray (PAG) during the Pain Response and Ventral Lateral Prefrontal Cortex (VLPFC) during the Anticipatory Response

	pACC (Pain)	*Insula/SII (Pain)*	*PAG (Pain)*	*VLPFC (Anticipation)*
pACC (pain)	1	.57, $p = .02$	.47, $p = .06$	.19, $p = .48$
Insula/SII (pain)		1	.69, $p < .01$	−.23, $p = .39$
PAG (pain)			1	−.28, $p = .3$

These four regions were found to be associated with pain rating differences (UC − C) between the conditions.

Activation Difference (UC − C) in the Response to the Cue (Anticipatory Response)

Group Differences (UC − C). In addition to activation differences between uncontrollable and controllable pain, there was a significant activation difference (UC − C) in several regions during the anticipation period (the 10 ± 3 sec. while the cue was displayed). This included several regions of prefrontal, parietal, and visual cortices (see Table 2), which have been associated with the regulation and expression of emotion as well as attention. As the focus of the present report is to identify candidate regions associated with self-reported differences in pain and then assess their relative importance, however, only activations in regions that were correlated with the pain rating difference were pursued.

Zero-order Correlations with Self-reported Pain Perception. Of the regions activated during the anticipatory period, the left ventral lateral prefrontal cortex (VLPFC; inferior frontal gyrus: −60, 24, 8; $z = 4.21$) was the most strongly correlated with pain rating difference. Individuals who exhibited greater activation of this region of the VLPFC showed a marginally significant tendency ($r = -.44$, $p < .09$; see Figure 2A) to rate uncontrollable stimulation as less painful (relative to controllable stimulation). This region was therefore considered for the regression analysis. None of the other regions were even marginally significantly correlated with pain rating difference and as such, were not considered further.

Regression Models Predicting Pain Rating Difference (UC − C) from Candidate Clusters during the Anticipatory and Pain Responses

In keeping with our strategy of entering candidate regions into regression models to assess their relationship

Table 2. Regions with a Significant Activation Difference (UC − C) between Anticipation of Uncontrollable and Controllable Pain

Region	*X, Y, Z*	*Peak Activation*
Precentral gyrus (BA 6)	−54, −2, 42	3.47
Medial frontal gyrus (BA 9/10)	14, 44, 18	3.96
Medial frontal gyrus (BA 9/10)	0, 60, 26	3.75
Medial frontal gyrus (BA 10)	2, 64, −2	4.61
Medial frontal/anterior cingulate gyrus (BA 9/32)	−4, 42, 24	4.04
Posterior cingulate gyrus (BA 23)	−2, −12, 32	3.71
Middle frontal gyrus (BA 8)	−38, 22, 50	5.06
Inferior/middle frontal gyrus (BA 9/46)	−48, 18, 30	3.70
Inferior/middle frontal gyrus (BA 10/46)	−46, 48, 6	4.27
Inferior frontal gyrus (BA 45)	−60, 24, 8	4.21
Inferior frontal gyrus (BA 46)	−50, 40, 10	3.97
Inferior frontal gyrus (BA 47)	−50, 26, −14	4.60
Inferior frontal gyrus (BA 47)	−54, 30, 0	3.81
Lingual gyrus (BA 17/18)	−4, −84, 2	3.51
Cuneus (BA 18)	−14, −96, 4	4.49
Middle occipital gyrus (BA 18)	−12, −96, 12	4.29
Middle temporal gyrus (BA 21/37)	−58, −62, 2	5.71
Inferior parietal lobule (BA 40)	−38, −54, 52	5.06
Cerebellum	26, −80, −40	3.45
	−16, −82, −30	4.06
	−32, −80, −24	4.63

Coordinates are given in MNI space. Peak activations are the *Z* statistic for the maximally activated voxel in the cluster.

in predicting pain rating difference and our hypothesis that the effects of perceived controllability on pain perception would be driven by activation in the PFC, we entered the VLPFC (during anticipation) and pregenual ACC (during pain) as regressors, with pain rating difference (UC − C) as the dependent measure. This model was highly predictive of pain rating difference (UC − C), $r = .8$; $F(3,12) = 11.6$, $p < .01$, with both pACC and VLPFC significant predictors within the model ($t = 4.03$, $p < .01$ for pACC; $t = -3.36$, $p < .01$ for VLPFC). The model explained 64% of the variance in pain rating difference ($r^2 = .64$; see Table 3), more variance than the combination of both variables on their own (squared zero-order correlation with pain rating difference = 0.32 for pACC and 0.19 for VLPFC, combined $r^2 = .51$). Furthermore, partial correlations between pain rating difference and both pACC and VLPFC (0.75 and −0.68, respectively) within this model were higher than the zero-order correlation between these regions and pain rating difference (see Figure 3A–B). These regression results indicate that the two variables uniquely and nonredundantly predicted variance in pain ratings, a relationship obscured (or ''suppressed''; see Cohen, Cohen, West, & Aiken, 2003, definition) when simply looking at zero-order correlations between the individual variables and pain rating difference. Neither of the indicators of suppressive effects (partial correlations > zero-order correlations; the model having greater explanatory power than the sum of the predictive power of the regressors), were observed in models in which VLPFC was included along with either PAG or posterior insula/SII, indicating that this relationship was unique to the two prefrontal areas.

The explanatory power of the model including both prefrontal variables led to questions regarding whether the two other structures (PAG and SII/insula) contribute uniquely to modulation of pain perception. To determine this, we entered the variables hierarchically into a general linear model. Due to the high intercorrelation between the PAG and SII/insula variables ($r = .69$), a composite variable of the two ''sensory'' variables (i.e., the mean of the standardized activation differences of PAG and SII/insula) was created and entered first and was a significant predictor of pain rating difference ($r = .56$, $p = .03$). When the two prefrontal variables were entered on the next step, however, this ''sensory'' variable explained less than 1% of the variance in the model ($t = 0.07$, $p = .94$; partial correlation 0.02), whereas pACC and VLPFC were both significant predictors ($t = 2.85$, $p = .02$ and $t = -2.81$, $p = .02$, respectively) and explained large portions of the variance (0.24 and 0.24, respectively). To assess the individual predictive power of PAG and SII/insula, we added activation difference (UC − C) in all four regions simultaneously as predictors. In this model, the pACC and VLPFC remained significant predictors of pain rating difference ($t = 2.73$, $p = .02$; $t = -2.68$, $p = .02$, respectively) and uniquely predicted large portions of variance (r^2 change .24 and .23, respectively). PAG and SII/insula were not significant predictors within this model ($t = 0.17$, $p = .87$; $t = -0.08$, $p = .94$, respectively) and explained almost no additional variance (r^2 change <.01 for both). It should be noted that these regression models used a Type III sum of squares that evaluates each variable after removing overlapping variance, meaning that these effects are not simply due to shared predictive variance between the pACC, PAG, and insula/SII being assigned to the highest individual predictor (pACC). Statistics for selected models are presented in Table 3.

Table 3. Selected Regression Models Using Various Configurations of the Four Variables (Activation Difference in the Various Regions) to Predict Pain Rating Difference (UC − C)

Model	Model R^2 (Sig.)	pACC			VLPFC			SII/Insula			PAG		
		Partial Correlation	Unique Variance (R^2)	Sig.	Partial Correlation	Unique Variance (R^2)	Sig.	Partial Correlation	Unique Variance (R^2)	Sig.	Partial Correlation	Unique Variance (R^2)	Sig.
pACC PAG SII	.41 (*ns*)	.38	.1	.18	–	–	–	.13	.01	.65	.20	.02	.50
VLPFC PAG SII	.40 (*ns*)	–	–	–	−.36	.09	.21	.27	.05	.34	.19	.02	.53
pACC VLPFC	.64 (<.01)	.75	.45[a]	<.01	−.68	.31[a]	<.01	–	–	–	–	–	–
pACC VLPFC PAG	.64 (<.01)	.67	.29	<.01	−.64	.25	.01	–	–	–	.04	<.01	.88
pACC VLPFC SII	.64 (<.01)	.65	.26	.01	−.65	.26	.01	<.01	<.01	.99	–	–	–
pACC VLPFC PAG SII	.64 (.02)	.64	.24	.02	−.63	.23	.02	−.03	<.01	.94	.05	<.01	.87

The first column presents the significance and total R^2 for the model. The next four columns present the partial correlation, the percentage of variance uniquely contributed, and the significance (Sig.) of each individual region included as a regressor in the model. *ns* = not significant.

[a]Cf. Cohen et al. (2003) for discussion of why unique variance adds up to more than total variance when suppressive effects are observed.

Coping Style Data

Scores on subscales of the COPE were used to assess the degree to which individual differences in coping style were associated with response to perceived controllability over pain. In particular, we were interested in assessing whether emotion focused coping strategies (strategies aimed at coping with the emotional response to a stressor), which have been hypothesized to be adaptive responses to uncontrollable stressors could predict patterns of response to perceived controllability (Carver et al., 1989; Folkman & Lazarus, 1980).

Two emotion-focused strategies, denial (sample item, ''I pretend that it hasn't really happened'') and acceptance (sample item, ''I learn to live with it'') were associated with activation in the anticipatory period. Activation difference (UC − C) in the VLPFC cluster discussed above was positively correlated with scores on the acceptance subscale ($r = .53$, $p = .03$) and negatively correlated with scores on the denial subscale ($r = -.61$, $p = .01$). These correlations were similar or larger when the effects of pACC were partialled out (partial correlation between VLPFC activation difference and denial, $r = -.61$, $p = .02$; acceptance, $r = .61$, $p = .02$). Scores on these coping subscales were also associated with activation during anticipation in several regions not related to pain rating difference, including parietal (Brodmann's area [BA] 40: $r = .54$, $p = .03$ for acceptance; $r = -.75$, $p < .01$ for denial) and prefrontal (BA 8: $r = .539$, $p = .03$ for acceptance; $r = -.61$, $p = .01$ for denial) (BA 9: $r = .56$, $p = .02$ for acceptance; $r = -.63$, $p = .01$ for denial) cortices. Acceptance and denial were not significantly correlated with activation difference (UC − C) in pACC, PAG, or SII/insula during pain, or with pain rating difference.

DISCUSSION

In attempting to characterize individual differences in the way that perceived controllability modulates self-reported pain perception, the present report examined neural activation both in anticipation of thermal pain and in response to the thermal stimulus itself. We found that when uncontrollable pain is experienced as more aversive than controllable pain, there is a corresponding activation difference (UC − C) in response to the thermal stimulus in the pACC, posterior insular and secondary somatosensory cortices, and a midbrain region including the ventral portion of the PAG. Conversely, activation difference (UC − C) in ventral lateral PFC in anticipation of pain was negatively correlated with pain rating difference, such that persons having greater relative activation in this region in anticipation of uncontrollable pain were likely to rate uncontrollable thermal stimuli as less painful (relative to controllable).

Of particular interest is the finding that a model in which the two prefrontal regions (VLPFC during antici-

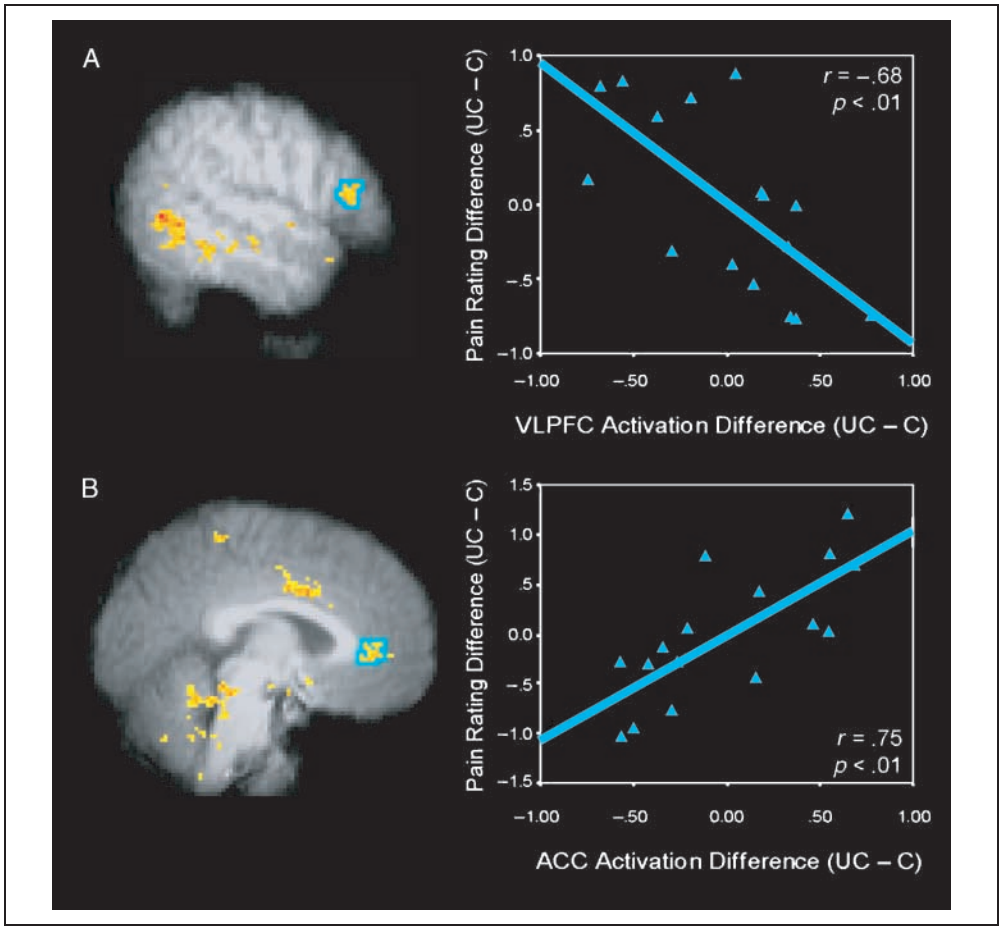

Figure 3. Partial Correlation Plots. Correlation between activation difference (UC − C) in the two prefrontal regions and pain rating difference (UC − C) when both are included in a regression model predicting pain rating difference. (A) Correlation of VLPFC (anticipatory response) and pain rating difference with effects of pACC (pain response) partialled out. (B) Correlation of pACC (pain response) and pain rating difference with effects of VLPFC (anticipatory response) partialled out.

pation and pACC during pain) were included was highly predictive of pain rating difference, above and beyond the additive predictive power of the two variables on their own. Although the correlation between activation in the two regions was relatively small (r = .19), the fact that accounting for both in the model increased their association with pain ratings (i.e., partial correlations > zero-order correlations) suggests that rather than representing redundant explanatory variance, this shared variance was suppressing the true relationship between activation in these regions and pain rating difference. Unlike the common case of suppression where one variable suppresses the relationship between two others simply by adding theoretically uninteresting (''noise'') variance, the present case may represent an example of two regions that are involved in opponent processes with regard to altered pain perception. This is consistent with the assertion of Cohen et al. (2003) that suppression is a plausible model for counteractive biological processes.

In light of the power of these two prefrontal regions in predicting self-reported pain perception differences, a critical question is what role structures such as the PAG and SII/Insula play in the processing of these effects. The region of SII/posterior insula associated with pain ratings in this study is usually associated with the sensory/discriminative component of pain (including determination of intensity, location and lateralization of the nociceptive stimulus) (Tracey, 2005) rather than cognitive or affective dimensions of pain. Unlike this region, the PAG has been associated with cognitive modulation of pain in previous studies (Bingel et al., 2006; Tracey et al., 2002) and plays a pivotal role in instantiating the effects of uncontrollable stress in animals (Maier & Watkins, 2005). Nevertheless, it is unlikely that critical cognitive operations necessary for these effects occur in the brainstem (Maier & Watkins, 1998). Recent animal data (Amat et al., 2005) have supported the hypothesis that the prefrontal cortex plays an executive role in processing the effects of controllability, assessing the relationship between a stressor and various options for controlling it and recruiting lower structures according to situational demands. This would suggest that although processes occurring in structures such as the PAG and SII/insula may be involved in modulating pain perception in response to perceived controllability, the involvement of these regions is dependent on processes that occur in the PFC. Consistent with this hypothesis, we found that whereas both PAG and SII/insula were associated with pain rating difference, they contributed almost no unique predictive variance once the effects of the two prefrontal

regions were removed, suggesting that the process by which perceived controllability modulates self-reported pain perception is dependent on the ''top-down'' influence of PFC structures such as the ACC and VLPFC.

The involvement of these particular prefrontal regions in modulation of pain perception by perceived controllability is consistent with previous research on cognitive modulation of pain, as well as emotion regulation. pACC has been consistently linked with modulation of pain in response to cognitive manipulations including placebo analgesia (Bingel et al., 2006; Petrovic, Kalso, Petersson, & Ingvar, 2002) and distraction (Valet et al., 2004; Bantick et al., 2002). This region is connected to structures such as the PAG (Bingel et al., 2006; Bush, Luu, & Posner, 2000), which are involved in a descending pain modulation circuit with both pain facilitatory and inhibitory cells at the level of the medulla (Fields & Basbaum, 1999), suggesting that it may play a critical role in linking cognitive evaluation and initiation of pain regulation routines in lower structures.

Although regions of VLPFC have been implicated in cognitive modulation of pain (Bantick et al., 2002; see Petrovic & Ingvar, 2002, for a review), it should be noted that the cluster examined here is dorsal to the activations noted in most previous studies and may share more in common functionally with nearby regions of inferior frontal gyrus activated in studies where subjects were asked to reduce their emotional response to an impending or ongoing negative stimulus (Urry et al., 2006; Ochsner et al., 2004), suggesting that this activation may be associated with attempts to regulate the negative emotions associated with an uncontrollable stressor. This is consistent with the negative correlation between activation in this region and pain ratings.

An adaptive strategy for coping with stress when behavioral options for altering the stressor have been removed is to employ cognitive strategies aimed at reducing the emotional impact of the stressor (Carver et al., 1989). We found activation in the VLPFC during the anticipatory period to be associated with what Carver et al. (1989) referred to as ''emotion-focused'' coping strategies. Individuals who scored high on the ''acceptance'' subscale (sample item: ''I learn to live with it'') and low on the ''denial'' subscale (sample item: ''I refuse to believe that it has happened'') of the COPE (indicating a tendency to accept and cope with a stressor rather than deny its presence) were likely to have a higher activation in this region in anticipation of uncontrollable (relative to controllable) pain. Higher activation in this region in anticipation of uncontrollable pain was also associated with lower ratings of uncontrollable (relative to controllable) pain. These findings are consistent with the interpretation that activation in this region of VLPFC may be associated with an attempt to regulate the emotional response to an impending uncontrollable pain stimulus. Given the lack of a significant correlation between scores on the acceptance and denial subscales and pain rating difference, however, it should not be concluded that these specific strategies directly accounted for the regulatory effects observed in this study.

These data support the interpretation that the effects of perceived controllability on pain perception vary among individuals and provide evidence for the neural mechanism of these individual differences. They support the conclusion that these effects are largely top-down (i.e., driven by executive processes in the prefrontal cortex, rather than lower regions associated with the properties of the stimulus). These data also provide some preliminary evidence that stable, dispositional differences in coping style may predict differences in the neural response to perceived controllability. The sample size used in this study demands that conclusions about coping style be made with caution, particularly given the complex relationship between dispositional coping tendencies and situational factors (Carver et al., 1989; Folkman & Lazarus, 1980). Nevertheless, previous research (Jensen et al., 2001; Schmitz et al., 1996) indicates that coping style is a predictor of clinical outcomes in response to chronic pain, suggesting that further exploration may provide important clues as to the behavioural strategies and neural responses associated with successful attempts to cope with seemingly uncontrollable conditions like chronic pain.

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