Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain

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DOI: https://doi.org/10.1523/JNEUROSCI.2568-06.2006

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-50400
Published Version

Originally published at:
DOI: https://doi.org/10.1523/JNEUROSCI.2568-06.2006
Behavioral/Systems/Cognitive

Anterolateral Prefrontal Cortex Mediates the Analgesic Effect of Expected and Perceived Control over Pain

Katja Wiech,* Raffael Kalisch,* Nikolaus Weiskopf, Burkhard Pleger, Klaas Enno Stephan, and Raymond J. Dolan
Wellcome Department of Imaging Neuroscience, Institute of Neurology, London WC1N 3BG, United Kingdom

Perceived control attenuates pain and pain-directed anxiety, possibly because it changes the emotional appraisal of pain. We examined whether brain areas associated with voluntary reappraisal of emotional experiences also mediate the analgesic effect of perceived control over pain. Using functional magnetic resonance imaging, we compared self-controlled noxious stimuli with physically identical stimuli that were externally controlled. Self-controlled stimulation was accompanied by less pain and anxiety and higher activation in dorsal anterior cingulate (dACC), right dorsolateral, and bilateral anterolateral prefrontal (alPFC) cortices. Activation in dACC and right alPFC was negatively correlated with pain intensity ratings. For externally controlled pain, activation in right alPFC was inversely correlated with the participants’ general belief to have control over their lives. Our results are consistent with a reappraisal view of control and suggest that the analgesic effect of perceived control relies on activation of right alPFC. Failure to activate right alPFC may explain the maladaptive effects of strong general control beliefs during uncontrollable pain.

Key words: pain; fMRI; prefrontal cortex; cognitive; emotion; analgesia

Introduction

Pain research has established that both acute and chronic pain are perceived as less intense when they are or appear to be controllable (Weisenberg et al., 1985; Scharff et al., 1995; Pellino and Ward, 1998). Accordingly, perceived control has been shown to attenuate brain responses to pain (Salomons et al., 2004; Mohr et al., 2005). It has been proposed that perceived control attenuates pain because it changes the “meaning” of pain, making it less threatening (Arntz and Schmidt, 1989). After this view, pain is appraised differently (is “reappraised”) when controllable.

Emotion regulation research has found ample evidence that a voluntary and consciously controlled form of reappraisal (reinterpretation) can attenuate aversive emotional reactions (Gross, 2002), including peripheral and neural reactivity to pain (Kalisch et al., 2005). This raises the possibility that, in humans, voluntary reappraisal efforts contribute to the analgesic effects of perceived control. On this basis, we asked whether a network of dorsal medial and lateral prefrontal areas implicated in voluntary reappraisal (Kalisch et al., 2005; Ochsner and Gross, 2005) mediates aspects of analgesia resulting from perceived control in normal human subjects.

To address this question, we used functional magnetic resonance imaging (fMRI) to measure brain responses to self-controlled and externally controlled painful stimulation (see Fig. 1). During self-controlled trials, participants were able to stop an ongoing train of painful electric stimuli when the pain became intolerable. During externally controlled trials, participants were told that the train of stimuli would either be stopped at some point by another person (external control by a “powerful other”) or by a computer that followed a random sequence (external control by “chance/fate”). The stimulation during the externally controlled trials was yoked to the self-controlled trials such that the participants received the same number and intensity of stimuli in both conditions (see Materials and Methods). At the end of each stimulation period, participants rated the perceived mean intensity of the stimulation during the previous trial. Ratings of the average anxiety perceived during painful stimulation in the three conditions were given at the end of the experiment. Subjects also provided a measure of their degree of belief in control over life as assessed by a questionnaire administered before the experiment.

We hypothesized that factual controllability in the self-controlled trials would attenuate the subjective intensity of pain and that this would be associated with activation in voluntary reappraisal-related brain areas. We specifically predicted activation in the contrast “self-controlled — externally controlled pain” in a right anterolateral prefrontal cortex (alPFC) area proposed recently by us (Kalisch et al., 2006b) as being crucial for reappraisal. We further predicted that activation in this area would be negatively correlated with subjective pain intensity. Finally, we explored whether and how the relationship between controllability and a control-related brain response would be moderated by the individual control belief.

Materials and Methods

Subjects. Twelve healthy female right-handed subjects, aged 20—29 years (mean ± SD, 24 ± 3.08 years) consented to take part in the study, which was approved by the Joint National Hospital for Neurology and Neuro-
Stimulation. Before the first session, individual current levels were determined and were adjusted between sessions if necessary (see below, Experimental protocol). The mean ± SD stimulation intensity was 2.61 ± 0.87 mA. The stimuli were applied to the back of the left hand using a commercial electric stimulation device (Constant Current Stimulator, model D57A; Digitimer, Hertfordshire, UK) delivering trains of 200 ms monopolar square waveform pulses via a silver chloride electrode (interstimulus interval, 500 ms). Because we aimed to apply the identical stimulation in all three conditions, the number of stimuli delivered per trial in the two external conditions (i.e., other-controlled and computer-controlled) were determined by the number of stimuli participants had chosen in the previous self-controlled trials. On average, participants stopped the stimulation after 37 ± 17.61 stimuli (mean ± SD; minimum of 13 and maximum of 99 stimuli).

In the first session, the two self-controlled trials had to precede the externally controlled trials to get a sample of chosen stimulation durations for the following externally controlled trials. In the following sessions, the number of stimuli per trial applied in the externally controlled conditions was taken from the self-controlled trials of the previous session. For instance, if the subject had stopped the stimulation after the 10th stimulus in the first trial and after the 13th stimulus in the second trial of the self-controlled trials of the third session. This procedure allowed for a fully randomized presentation of conditions, i.e., the two externally controlled conditions could be presented before as well as after the self-controlled trials. As a consequence, we can exclude order effects.

To control for motor responses that occurred in the self-controlled conditions, subjects also had to press a button at the end of the stimulus trains in the externally controlled conditions. They were cued by an enlargement of the fixation cross to press the button as quickly as possible. The large white cross appeared immediately after the stimulation had stopped.

**Trial-by-trial rating of subjective stimulation intensity.** At the end of each trial, subjects rated the average perceived mean intensity of the stimulation during the previous trial on a numerical rating scale ranging from 0 (not painful at all) to 100 (strongest imaginable pain) that was presented on the computer screen. The rating was given via a pointer that could be moved in both directions along the scale by holding either of two buttons pressed. Analgesic effects were inferred if average pain ratings in a given condition were significantly lower \( p = 0.05 \) than in a comparison condition. This operational definition of analgesia follows a general definition of analgesia as “a deadening or absence of the sense of pain without loss of consciousness” (Stedman, 1995).

**Rating of anxiety.** At the end of the experiment, participants gave a rating of how anxious they felt during each of the three conditions on a scale from 0 (not anxious at all) to 10 (extremely anxious).

**Control belief questionnaire.** To assess the general belief about who or what has an influence on one’s own life, participants were asked to fill in the “I, P, and C Scales” by Levenson (1981) before scanning. This questionnaire contains a scale (I scale) that measures the extent to which people believe that they have control over their own life. The I scale comprises an eight-item subscale with a seven-point Likert response format (0–6). A high score on the I scale indicates a strong control belief.

**Experimental protocol.** On arrival, subjects were provided with written task instructions and gave their informed consent. Subjects were then brought to the MR control room in which they were familiarized with the instructions displayed on the computer screen during the experiment and with the rating procedure. They were told that the second person who was supposed to control the stimulation in the other-controlled condition would be instructed at the same computer while they themselves were prepared for the scanning sessions inside the MR room.

Before the subjects were positioned in the MR scanner, the individual stimulation levels were determined within the scanner room. To find an individual level for electrical stimulation, trains of 100–200 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 70. Current levels that were rated as 70 were taken for stimulation during the experiment. To

<table>
<thead>
<tr>
<th>Self-controlled</th>
<th>Other-controlled</th>
<th>Computer-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>10</td>
<td>99</td>
</tr>
<tr>
<td>50</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>70</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>90</td>
<td>80</td>
<td>100</td>
</tr>
</tbody>
</table>

**Figure 1.** Design of the study. Participants were subjected to noxious electrical stimuli that were either controlled by themselves (self-controlled) or externally controlled. At the beginning of each trial, participants were informed, on the computer screen, about the focus of control over the upcoming pain stimulation (instruction). During the next 6 s, participants were awaiting the beginning of the stimulation (anticipation). In self-controlled trials, the ongoing painful stimulation was terminated by a button press of the participant. In the externally controlled condition, the number of stimuli applied was predetermined by the self-controlled trials (see Materials and Methods), and participants were instructed to press the button immediately after the stimulation had stopped. Subsequently, the mean subjective pain intensity was rated via the computer display (rating). Each trial was accomplished by a 12 s baseline period (baseline).
Table 1. Brain responses to self-controlled and externally controlled pain (main effect of pain; \( p < 0.001 \) uncorrected)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Laterality</th>
<th>Brodmann area</th>
<th>MNI coordinates</th>
<th>Cluster size (voxel)</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula/operculum/temporal lobe</td>
<td>R/L</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>871</td>
<td>4.98</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>L/R</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>456</td>
<td>4.88</td>
</tr>
<tr>
<td>Pallidum</td>
<td>L/R</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>18</td>
<td>4.75</td>
</tr>
<tr>
<td>SII</td>
<td>L/R</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>9</td>
<td>4.70</td>
</tr>
<tr>
<td>OFC</td>
<td>R/L</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>10</td>
<td>4.02</td>
</tr>
<tr>
<td>Inferior parietal lobe/SII</td>
<td>L/R</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>9</td>
<td>3.82</td>
</tr>
<tr>
<td>ACC</td>
<td>R/L</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>2</td>
<td>3.87</td>
</tr>
</tbody>
</table>

Table 2. Brain responses to externally controlled compared with self-controlled pain (\( p < 0.001 \) uncorrected)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Laterality</th>
<th>Brodmann area</th>
<th>MNI coordinates</th>
<th>Cluster size (voxel)</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFC</td>
<td>R/L</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>4</td>
<td>3.54</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>R/L</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>15</td>
<td>3.43</td>
</tr>
<tr>
<td>ACC</td>
<td>R/L</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>1</td>
<td>3.18</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R/L</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>2</td>
<td>3.52</td>
</tr>
<tr>
<td>MFPC</td>
<td>L/R</td>
<td></td>
<td>( x \quad y \quad z )</td>
<td>1</td>
<td>3.23</td>
</tr>
</tbody>
</table>

A standard coil was used that was packed with foam pads. Subjects had to wear MR-compatible pneumatic headphones to attenuate scanner noise. For display purposes, a high-resolution (\( 1 \times 1 \times 1 \text{ mm}^3 \) voxel size) T1-weighted structural MRI was acquired (three-dimensional modified driven equilibrium Fourier transformation; 176 partitions; matrix, 256 \times 256; field of view, 256 \times 224 mm; slab thickness, 176 mm) (Deichmann et al., 2004).

**Data analysis.** For the pain intensity and anxiety ratings, we first compared the two externally controlled conditions (i.e., other-controlled and computer-controlled) using Student’s t test. The analysis revealed that the difference between pain intensity ratings of both conditions did not reach significance. Because we were only interested in neural correlates of behaviorally relevant effects, other- and computer-controlled trials were pooled and considered as “externally controlled trials” in subsequent t test comparisons with self-controlled trials.

Neuroimaging data were analyzed using SPM2 (Welcome Department of Imaging of Neurosciences, London, UK) (Ashburner et al., 2004). The first five image volumes of each session were discarded to account for T1 relaxation effects. Then the data were realigned to the sixth volume to correct for head motion before statistical analysis. The EPIs were spatially normalized (Friston et al., 1995) to the template of the Montreal Neurological Institute (MNI) (Evans et al., 1993). The normalized EPIs were smoothed using an 8 mm full-width at half-maximum Gaussian kernel, temporally high-pass filtered (cutoff of 128 s), and corrected for temporal autocorrelations using first-order autoregressive modeling.

For each subject, contrast images were calculated for externally and self-controlled pain in which pain stimulation was compared with the 12 s baseline of each trial, resulting in two contrasts per subject. Furthermore, direct comparisons between self- and externally controlled pain (self > external; external > self) were calculated for each subject. In a separate analysis assessing the negative correlation between subjective pain intensity and brain activity, trial-by-trial intensity ratings were used as a parametric regressor of the categorical “pain — baseline” regressor (pooled across all conditions).

First level contrasts were taken to the second level for the group data analysis using one-sample t tests within a random effects model (Holmes and Friston, 1998). We also computed a second-level regression analysis to explore whether individual differences in brain responses to self-controlled compared with externally controlled pain covaried with individual differences in the general belief to have control over one’s own life as assessed by the I scale (Levenson, 1981). To further characterize this differential effect, correlations with self-control belief scores were calculated separately for self-controlled and externally controlled pain using the parameter estimates from the right anterolateral prefrontal peak voxel defined by the above correlation analysis with pain intensity ratings \([x, y, z] \text{ coordinates of } (36, 48, 15)\) (Kalisch et al., 2005). For the left
alPFC, a corresponding search volume was defined around the coordinates of (−42, 48, 18) (8 mm).

**Results**

**Behavioral effects of perceived control**

In the debriefing session after the experiment, all participants reported they had been convinced that the stimulation had been controlled by another person or by the computer, respectively, in the two externally controlled conditions. Pain intensity and anxiety ratings in the two externally controlled conditions were not significantly different ($t_{(11)} = -1.82, p = 0.10; t_{(11)} = 1.03, p = 0.32$, respectively), allowing us to pool the data from the two externally controlled conditions for a first analysis. As predicted, self-controlled pain (mean ± SD, 63.74 ± 9.97) was perceived as less intense than externally controlled pain (mean ± SD, 68.90 ± 11.03; $t_{(11)} = -3.06; p = 0.01$). Likewise, the subjects were less anxious when the stimulation was self-controlled (mean ± SD, 2.33 ± 2.31 vs 4.67 ± 2.42; $t_{(11)} = -4.08; p = 0.002$). Hence, perceived control had analgesic and anxiolytic effects, with the anxiolytic effects being relatively stronger than the analgesic effects.

**Neural effects of perceived control**

Across conditions, painful electrical stimulation led to bilateral activation in pain-related areas, including insula, secondary somatosensory cortex, anterior cingulate cortex (ACC), and OFC ($p < 0.001$ uncorrected) (Table 1).

The increased subjective pain intensity and anxiety in the pooled externally controlled conditions (other-controlled and computer-controlled) was paralleled by higher activation in bilateral OFC and right rostral ACC in the contrast “externally controlled pain” ($p < 0.001$ uncorrected) (Table 2). Masking with the main effect of pain at a conservative threshold of $p < 0.001$ (uncorrected) confirmed that the right lateral OFC peak was part of the pain network (Fig. 2). Interestingly, the peak of this activation is close to an area deactivated during relief from pain in a recent study from our group (Seymour et al., 2005).

The opposite comparison, testing for greater activation during self-controlled compared with externally controlled stimulation, revealed activations in right dorsal ACC (dACC), right dorsolateral prefrontal cortex (DLPFC), and bilateral alPFC ($p < 0.001$ uncorrected) (Table 3, Fig. 3), areas that have been observed during voluntary reappraisal (Ochsner and Gross, 2005). Importantly, the activation in right alPFC survived correction for multiple comparisons ($z = 3.66; p = 0.009$) in a predefined search volume, using coordinates from Kalisch et al. (2005) (see Materials and Methods). An activation peak in left alPFC also survived small volume correction in a corresponding left-sided search volume ($z = 3.63; p = 0.009$).

In a subsequent step, we addressed the question whether any of these areas showed significant differences in activity between the two externally controlled conditions (other-controlled and computer-controlled). To maximize statistical power in addressing this question, we used a hierarchical analysis in which we restricted the contrast “other-controlled versus computer-controlled pain” to those areas that showed a difference between the self-controlled and the externally controlled conditions (see results above). This was implemented by

![Figure 2. Brain responses to externally controlled compared with self-controlled pain (masked with main effect of pain). To identify pain-related brain regions that were less active when the painful stimulation was perceived as controllable, the contrast “externally controlled pain” ($p < 0.001$ uncorrected) was masked by the main effect of pain ($p < 0.001$ uncorrected). A significant reduction in pain-related activity under perceived control was observed in the right lateral OFC (peak voxel, coordinates of (24, 27, −15)).](image-url)
self-controlled > externally-controlled pain

In combination with the behavioral results, these findings suggest that activation in dorsal prefrontal regions is related to the analgesic effect of perceived control. To further test this, we performed a regression analysis on pain intensity ratings asking whether any of the prefrontal regions identified above was inversely related with pain intensity. Specifically, we used trial-by-trial pain ratings as a parametric modulator of the categorical pain regressor in a separate model. Across conditions, pain ratings were negatively correlated with activation in dACC and right aPFC ($p < 0.001$ uncorrected) (Table 4, Fig. 4a). The activation peak in dACC was located ventrally adjacent to the dACC activation observed for “self-controlled — externally controlled pain,” whereas the activation in right aPFC survived small volume correction in the same predefined search volume as used above ($z = 3.20$; $p = 0.042$). In contrast, left aPFC did not show a negative correlation with pain ratings. The correlation analyses thus corroborated the role of brains regions implicated previously in voluntary reappraisal, in particular the right aPFC, for control-induced analgesia.

Role of locus of control

Individual differences in coping behavior can partly be explained by trait-like differences in the tendency to perceive oneself as having control. According to Rotter (1966), individuals with an internal LOC tend to believe that environmental events are a consequence of their behavior, whereas those with an external LOC explain events with reference to luck or fate or consider them to be controlled by powerful others. Individuals with an internal LOC, and hence a strong belief to have control over life, usually have weaker stress responses than individuals with an external LOC, i.e., with a weak control belief (Kirkcaldy et al., 1999; Beekman et al., 2000; Bollini et al., 2004). However, in situations in which exertion of control is obviously not possible, individuals with an internal LOC show greater stress responses than individuals with an external LOC (Lundberg and Frankenhaeuser, 1978).

These findings once more highlight the importance of control perception as a mediator of coping and predict an interaction between control belief and controllability that could affect pain perception and related brain activity.

We therefore also investigated whether control-related brain activity was affected by the individual trait-like belief to have general control over one’s own life. In a group-level regression analysis, individual control belief scores were used as a regressor on whole-brain contrast maps from the contrast “self-controlled — externally controlled pain.” Across subjects, the

Taking the results from the “self — external” contrast as an inclusive mask for comparing the other- and computer-controlled conditions (note that these contrasts are statistically orthogonal). Despite the reduction in search volume and increase in power, we found no differences between the two externally controlled conditions in aPFC, DLPFC, or dACC. Because pain and anxiety ratings were also not different between the two externally controlled conditions (see above), this suggests that a common neural core mechanism mediates the effects of perceived control, regardless of the external locus of control (LOC).

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degree of general control belief was highly correlated with activation in right, but not left, aPFC \( [p < 0.001 \text{ uncorrected; coordinates of } (30, 48, 21); z = 4.62; \text{ cluster size, 65 voxels}] \) (Table 5, Fig. 4a,b). As in the analyses above, the right aPFC activation survived a hypothesis-driven small volume correction \( (z = 4.62; p < 0.001) \). Figure 4a illustrates the overlap between this activation cluster and the right aPFC area negatively correlated with pain intensity, as identified above.

Importantly, the correlation with the degree of general control belief was attributable to varying right aPFC activation in the externally controlled condition (Fig. 4c) but not in the self-controlled condition (Fig. 4d). That is, during self-controlled pain, participants engaged the right aPFC regardless of the strength of their general control belief (Fig. 4d). If, however, there was strong objective evidence against controllability (i.e., when the stimulation was externally controlled), activation in right aPFC decreased as a linear function of general control belief (Fig. 4c). In other words, in individuals with an internal locus of control, right aPFC was more strongly deactivated when pain was uncontrollable than in individuals with an external locus of control.

**Discussion**

The results of our study show that painful stimulation under conditions of perceived control activates areas that are involved in voluntary reappraisal (Ochsner and Gross, 2005) and, more generally, in high-level (i.e., conscious and effortful) reappraisal processes (Kalisch et al., 2006a) and that activation in these areas is negatively correlated to subjective pain intensity. Our results are therefore consistent with an important role of high-level reappraisal in mediating the analgesic effect of perceived control. At a neural level, they support a role for the right aPFC, an area that we proposed previously as critical for control-based reappraisal, this finding can be interpreted as additional evidence for an involvement of the right aPFC in this function. In line with our self report data, previous behavioral studies have shown that perceived control decreases the subjective pain intensity and increases pain tolerance (Staub et al., 1971; Maier and Watkins, 1998; Feldner and Hekmat, 2001) (but see Janssen et al., 2004; Salomons et al., 2004). As a possible mechanism, it has been suggested that perceived control exerts its effect on pain by interacting with anxiety. According to this hypothesis, anxiety-associated arousal amplifies nociceptive responses and perceived control alleviates pain by reducing anxiety (for a discussion, see Arntz and Schmidt, 1989). Our observation that lower pain intensity was paralleled by lower anxiety is in line with this idea. However, an extensive review of the literature on anxiety and pain suggests that the pain-alleviating effect of perceived control is not necessarily accompanied by a reduction in arousal or anxiety and that anxiety reduction does not necessarily reduce pain (Arntz and Schmidt, 1989). A dissociation between pain and anxiety is particularly obvious in fear-induced hypoalgesia (Bolles and Fanselow, 1980; Fanselow, 1986) in which the neces-
sity to produce a flight-or-fight response leads to a shutdown of nociception (for replication in humans, see Rhudy et al., 2004). In this context, it is worth mentioning that, in our study, the differential ratings for anxiety and pain ratings (i.e., “externally controlled − self-controlled”) showed a trend to be negatively correlated ($r = −0.56; p = 0.06$).

Alternatively, Miller (1979) proposed that perceived control can lead to a reduction of subjective pain because it allows individuals to rely on a stable, reliable source of coping (i.e., his or her own response) that can modify the aversive event or its impact. Therefore, future danger and discomfort can reliably be kept below an acceptable level. According to this perspective, perceived control triggers reappraisal processes that change the significance or meaning of the pain (Arntz and Schmidt, 1989). This change in motivational value may occur unconsciously (low-level) or also consciously (high-level) (Leventhal and Scherer, 1987; Robinson, 1998), such as when taking the explicit form of, for instance, “I can stop the pain whenever I want, so it doesn’t bother me that much.” An interesting implication of this theoretical viewpoint is that it predicts control-induced attenuations in affective–evaluative but not necessarily sensory–discriminative areas of the pain matrix.

Based on the assumption that controllable pain induces voluntary reappraisal, we predicted and found higher activity of dorsal medial and lateral prefrontal cortex, in particular right alPFC, during self-controlled compared with externally controlled pain (Fig. 3). (A separate line of research in rodents has established an important role of the ventral medial prefrontal cortex. For comments, see supplemental data (available at www.jneurosci.org as supplemental material).) A possible alternative explanation for the observed prefrontal activations, however, is that the self-controlled, but not the externally controlled, condition was not generally reduced (as might be expected if it reflected the cognitive task of exerting or preparing to exert control) but varied with the level of general control belief (Fig. 4).

In addition to prefrontal activations, cognitive modulation of pain by various methods can result in deactivation of pain processing areas (Petrovic et al., 2000; Bantick et al., 2002; Salomon et al., 2004; Wager et al., 2004; Wiech et al., 2005; Bingel et al., 2006). We found no evidence for a deactivation of lower pain processing areas or somatosensory cortex or for activation of descending antinoceptive systems such as periaqueductal gray or rostral ACC (Tracey et al., 2002; Wager et al., 2004). In contrast, we observed attenuation of pain-related lateral OFC activity in self-controlled compared with externally controlled pain (Table 2). This result is particularly interesting because OFC activation is not only observed during pain (Tracey et al., 2000; Wiech et al., 2005) but more generally during affective states (O’Doherty, 2004). Lateral foci in particular are typical for aversive affective states (O’Doherty et al., 2001), and pain-related lateral OFC activity correlates with fear of pain (Ochsner et al., 2006). This suggests that lateral OFC attenuation by control is involved in the emotional–motivational appraisal of pain rather than in encoding its sensory properties, a viewpoint in agreement with the general role of OFC in representing value information (Schoenbaum and Roesch, 2005). This observation (and the absence of effects in sensory–discriminative pain processing areas) further supports a reappraisal view of control in which control modifies the emotional meaning of a painful stimulus rather than its sensory properties. We note that a dissociation of primary versus higher-order processing areas has also been reported under hypnotic analgesia (Rainville et al., 1997) in which analgesia was induced by a specific type of hypnotis (Kiernan et al., 1995) that may share cognitive processes with reappraisal. It should be mentioned, however, that the absence of effects in sensory–discriminative pain processing areas may also be related to only moderate reductions in subjective pain compared with other studies (Bantick et al., 2002; Wager et al., 2004).

Table 5. Brain areas showing a correlation between the general belief in self-control and the differential effect (self > external) during painful stimulation ($p < 0.001$ uncorrected)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Laterality</th>
<th>Brodmann area</th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>Cluster size (voxel)</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>alPFC</td>
<td>R</td>
<td>46</td>
<td>36</td>
<td>48</td>
<td>21</td>
<td>65</td>
<td>4.62</td>
</tr>
<tr>
<td>Premotor cortex</td>
<td>R</td>
<td>46</td>
<td>33</td>
<td>57</td>
<td>15</td>
<td>4.34</td>
<td></td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>L</td>
<td>18</td>
<td>24</td>
<td>18</td>
<td>60</td>
<td>4</td>
<td>4.21</td>
</tr>
<tr>
<td>MI</td>
<td>R</td>
<td>37</td>
<td>42</td>
<td>72</td>
<td>9</td>
<td>1</td>
<td>3.15</td>
</tr>
<tr>
<td>SMA</td>
<td>R</td>
<td>4</td>
<td>27</td>
<td>21</td>
<td>63</td>
<td>5</td>
<td>3.33</td>
</tr>
<tr>
<td>Posterior parietal lobe</td>
<td>R</td>
<td>7</td>
<td>15</td>
<td>66</td>
<td>66</td>
<td>1</td>
<td>3.28</td>
</tr>
<tr>
<td>Posterior ACC</td>
<td>L</td>
<td>23</td>
<td>6</td>
<td>24</td>
<td>33</td>
<td>2</td>
<td>3.22</td>
</tr>
<tr>
<td>Thalamus</td>
<td>L</td>
<td>12</td>
<td>27</td>
<td>9</td>
<td>1</td>
<td>3.18</td>
<td></td>
</tr>
</tbody>
</table>

1. Left: L; right: R; DMpFC, dorsomedial prefrontal cortex; MI, primary motor cortex; SMA, supplementary motor area; $p < 0.001$ uncorrected at voxel level; voxel size, $1 \times 1 \times 1$ mm.
Bollini et al., (2004) but show greater stress responses than those when control is made impossible (Lundberg and Frankenhaeuser, 1978). This pattern may result from individuals with an internal LOC adopting powerful control-based reappraisal schema (“This problem doesn’t bother me, because I can solve it if I want”), which they use habitually to cope with challenging situations. Individuals with an external LOC may be able to use such reappraisal strategies in those few situations only in which strong objective evidence for controllability exists. They may therefore rely on alternative reappraisal schemata that acknowledge the influence of external factors, and this may result in greater stress responses. Those alternative reappraisals can be advantageous, however, in situations in which there is strong objective evidence against controllability and control-based reappraisals would lead to cognitive dissonance. In such situations, individuals with an internal LOC may experience problems exchanging established reappraisal schemes against alternative reappraisals, resulting in augmented stress responses. This view fits with our observation that, in the externally controlled condition, right dlPFC activation was reduced more strongly the higher the subjects’ general belief to have control over their lives. We propose that reduced right dlPFC activation could reflect a “breakdown” of a habitual reappraisal strategy. A caveat, however, is that we did not find a corresponding interaction between control belief and subjective pain intensity or anxiety in our data, possibly attributable to the small sample size (n = 12).

In conclusion, we described a neural basis for the analgesic effects of perceived control as well as a potential mechanism underlying the sometimes maladaptive effects of a strong internal control belief. This study therefore advances our knowledge about the neural mechanisms controlling pain and mediating successful coping. Successful recruitment of the right dlPFC is likely to be a key factor for success in cognitive therapeutic approaches enhancing the patient’s sense of self-efficacy and mastery (Bandura, 1977) but also in more recent acceptance-based treatments that stress the importance of not trying to control an uncontrollable situation (Hayes and Bissert, 1999; McCracken and Eccleston, 2005). Future studies may evaluate the use of right dlPFC activation as an objective biological marker for treatment response or as a target for therapeutic fMRI biofeedback (Weiskopf et al., 2003; deCharms et al., 2005).

References
Supplementary Figure 1:

(a) Pain intensity rating

(b) Anxiety rating

NRS (0-100)

- self
- other
- computer

NRS (0-10)

- self
- other
- computer
Supplementary Figure 2:

(a) ‘other’-controlled

(b) ‘computer’-controlled

Correlation Coefficient: r = -0.68, p < 0.05 for (a).
Correlation Coefficient: r = -0.67, p < 0.05 for (b).