Strategy-dependent Dissociation of the Neural Correlates Involved in Pain Modulation

Jane M. Lawrence, Ph.D.,* Fumiko Hoeft, M.D., Ph.D.,† Kristen E. Sheau, M.Sc.,‡
Sean C. Mackey, M.D., Ph.D.§

ABSTRACT

Background: Cognitive strategies are a set of psychologic behaviors used to modulate one's perception or interpretation of a sensation or situation. Although the effectiveness of each cognitive strategy seems to differ between individuals, they are commonly used clinically to help patients with chronic pain cope with their condition. The neural basis of commonly used cognitive strategies is not well understood. Understanding the neural correlates that underlie these strategies will enhance understanding of the analgesic network of the brain and the cognitive modulation of pain.

Methods: The current study examines patterns of brain activation during two common cognitive strategies, external focus of attention and reappraisal, in patients with chronic pain using functional magnetic resonance imaging.

Results: Behavioral results revealed interindividual variability in the effectiveness of one strategy *versus* another in the patients. Functional magnetic resonance imaging revealed distinct patterns of activity when the two strategies were used. During external focus of attention, activity was observed mainly in cortical

What We Already Know about This Topic

- Although psychologic treatments for chronic pain benefit many patients, the underlying brain systems involved with different psychologic treatments are unclear

What This Article Tells Us That Is New

- Using functional magnetic resonance imaging in seven subjects with chronic pain, two different behavioral strategies – external focus of attention and reappraisal – were variably effective in reducing pain and resulted in different patterns of brain activity, with only the postcentral gyrus being activated by both strategies

areas including the postcentral gyrus, inferior parietal lobule, middle occipital gyrus, and precentral gyrus. The use of reappraisal evoked activity in the thalamus and amygdala in addition to cortical regions. Only one area, the postcentral gyrus, was observed to be active during both strategies.

Conclusions: The results of this study suggest that different cognitive behavioral strategies recruit different brain regions to perform the same task: pain modulation.

I T is well known that cognition influences pain perception.[1] Cognitive strategies use this concept and are used for day-to-day pain management by patients with chronic pain.[2–4] They reduce pain by addressing psychologic influences[5] through techniques such as diversion of attention, reappraisal, imagery, and control. It is unclear whether any single specific method is more effective than the others because some reports have found no difference in effectiveness[6] whereas others have found a difference.[5] However, these studies have been based on meta-analyses. On an individual basis, patients with chronic pain often find a particular strategy more effective depending on their personal coping strategies.[7] Behaviorally, these cognitive strategies are distinct. For example, reappraisal addresses negatively skewed interpretations of the chronic pain condition, whereas focus of attention relies on the ability to draw away from chronic pain. It would therefore be logical to anticipate that distinct brain regions would be recruited. There remains a need for more experimentally-based research to elucidate the neural mechanisms of pain modulation by specific cognitive strategies or coping styles.

The influence of cognition on pain-related neural activity and pain perception has been well studied but much remains poorly understood. Focused attention has been found to re-

sult in prefrontal, anterior cingulate, posterior parietal, and thalamic activity.[8] Distraction has been associated with a shift in insular activity from an anterior to a posterior location.[9] The evaluation of aspects of pain, such as control, has also been of significant interest. Wiech *et al.* attributed activity in the dorsal anterior cingulate, dorsolateral, and anterolateral prefrontal cortices to the emotional reappraisal when participants controlled the delivery of a painful stimulus compared with when delivery was externally controlled.[10] Fewer studies have investigated the brain regions that are recruited during the use of cognitive strategies to modulate pain. One study has used positron emission tomography to identify changes in brain activity during evoked visceral pain in patients with irritable bowel syndrome, before and after 10 weekly cognitive therapy sessions.[11] They identified reductions in limbic activity in the amygdala, parahippocampal gyrus, and subgenual part of the perigenual anterior cingulate cortex.

Previously, we used real-time neurofeedback of functional magnetic resonance imaging (fMRI) blood oxygenation level dependent signal and showed it to be effective in the volitional modulation of pain perception in both healthy individuals and those with chronic pain.[12] These individuals were using a variety of cognitive strategies to modulate brain activity and the perception of pain. That study motivated our current study to identify the neural correlates of the effects of different cognitive strategies on pain modulation. The current study uses fMRI in a small group of patients with chronic pain to investigate the neural correlates of pain modulation by two commonly used cognitive strategies: diversion of attention, and reappraisal. We hypothesized that these strategies would elicit distinct patterns of brain activity with some overlap in somatosensory areas directly linked to the perception of pain. More specifically, we hypothesized that the use of diversion of attention would result in modulation of brain regions of activity typically associated with attention such as the dorsolateral prefrontal and parietal cortex. During the use of reappraisal, we anticipated that areas associated with emotion would be modulated to recruit lateral prefrontal and limbic cortex including the amygdala.

Materials and Methods

Participants

Patients with chronic pain were selected from the Stanford University Pain Management Service (5 male, 2 female, mean age 34.6 yr, range 20–49 yr, mean duration of pain 4.9 yr, range 1–8 yr). This study was reviewed and approved by the Stanford University human subjects panel (Stanford, California). Before enrollment all subjects provided written informed consent and were paid for their time. Before and after the scan, participants completed several behavioral questionnaires including the short-form McGill Pain Questionnaire with the Present Pain Intensity Index; a 1–5 pain rating scale.[13] Subject demographics including Present Pain Intensity Index scores are shown in table 1.

Cognitive Strategies

The cognitive strategies chosen were comparable to those used in our real-time fMRI neurofeedback study of pain modulation.[12] At least 1 week before the day of the scan, subjects were provided identical written instructions (identified in the quotations below) to increase and decrease their pain using five specific strategies and asked to practice mentally at home:

1. Attentional modulation – "Focus attention on your pain *VS.* Focus attention on nonpainful area."
2. Stimulus severity – "Turn up your pain sensation *VS.* Create internal anesthetic for your pain."
3. Control – "Make pain feel WORSE now *VS.* Make pain feel BETTER now."
4. Reappraisal – "Feel sensation as harming your body *VS.* Feel sensation as touching only."

Table 1. Demographic Information of the Seven Participants with Chronic Pain

Subject	1	2	3	4	5	6	7
Sex	Male	Female	Male	Male	Male	Female	Male
Age (yr)	45	49	48	20	35	21	24
Condition	Low back pain	Back pain	Post-surgical pain (appendectomy)	Shoulder tendinitis	Fibro-myalgia	Fibromyalgia; temporo-mandibular joint disorder	Phantom limb pain
Laterality of condition	Bilateral	Left	Right	Right	Bilateral	Bilateral	Left
Years of condition	7	6	1	6	6	5	4.2
SF-MPQ PPI index Before	2	2	2	2	2	2	1
SF-MPQ PPI index After	3	2	2	2	3	1	2

PPI = Present Pain Intensity; SF-MPQ = Short-form McGill Pain Questionnaire.

5. Imagery – "Imagine worst pain you have experienced *VS.* Imagine yourself in a scenario without pain."

In addition to the quoted text, the instructions patients received included brief descriptions of how to perform each strategy. The description for attentional modulation included "For this strategy, concentrate on the area of your body where you feel the most pain sensation. When focusing your attention to a nonpainful area, direct your attention to any part of your body which is not associated with pain. For example, you could focus your attention to an area opposite the painful area, on the other side of your body." Verbally, patients were told to focus their awareness on a small region, such as the tip of the finger or nose. The description for reappraisal included "For this strategy, feel your pain as hurting your body, as if it were some type of injury or burn. When feeling sensation as touching only, feel the sensation as a therapeutic or comforting touch."

To ensure participants understood the directions, participants came into the laboratory before the test for a practice session in which an experimenter would read the instructions aloud and ask the patient how they would perform each strategy.

Imaging

Scanning was performed in a 3.0 Tesla (General Electric, Signa LX Horizon Echospeed, Waukesha, WI) scanner. After collection of localizing and high-resolution anatomic images, T2*-sensitive gradient echo spiral-out pulse sequences were acquired (repetition time of 1,000 ms, echo time of 30 ms, 70° flip angle, 64 × 64 Matrix, 220-mm field of view, 16 slices, 7 mm thick) as part of a real-time fMRI neurofeedback study (see DeCharms *et al.*[12] for details on how real-time feedback was provided). Sixteen 7-mm-thick contiguous slices were positioned to achieve full brain coverage. During fMRI scans, subjects repeated 30-s blocks (30 time points) of rest followed by 60 s (60 time points) of instruction to increase their chronic pain and 60 s (60 time points) to decrease their chronic pain, resulting in a total scan time of 13 min (780 time points). Instructions were projected to subjects using a liquid crystal display projector and a screen mounted on the coil. In all subjects, the strategies were performed in the same order. After scanning, subjects were asked to rate their perception of change in chronic pain on a scale of zero (no change) to five (most change).

Statistical Analysis

We chose to compare and contrast the neural systems involved in diversion of attention (number 1 in the list of cognitive strategies) and reappraisal of sensation (number 4 in the list of cognitive strategies) as they are commonly used in clinical practice and are significant components of both cognitive behavioral therapy and mindfulness-based stress

reduction.[14] Furthermore, the behavior of these two seem the most contrasting whereas some elements of some of the other strategies listed seemed to overlap. For example, reinterpretation, similar to reappraisal, may have been used during either the stimulus severity or imagery strategies. Finally, attention and reappraisal form the basis for our future investigations into neural correlates of pain modulation using directed brain modulation *via* real-time fMRI neurofeedback.

Data were preprocessed and analyzed using SPM2 (Wellcome Department of Cognitive Neurology, London, United Kingdom). After image reconstruction, each subject's data were realigned to the reference functional volume. Sessions were normalized by using the mean functional volume resampled to 2 × 2 × 2 mm voxels in Montreal Neurologic Institute stereotaxic space (12 nonlinear iterations, 7 × 8 × 7 nonlinear basis functions, medium regularization, sinc interpolation). Spatial smoothing was done with a gaussian filter (8 mm, full-width, half-maximum). Each subject's data were high-pass filtered at 300 s and analyzed by using a fixed-effects model including all conditions. Data were analyzed using a general linear model contrasting Attention To *versus* Attention Away [Attention], and contrasting Reappraising as Pain *versus* Nonpainful Sensation [Reappraisal].

Group analysis was performed with a random-effects model by using the increase *versus* decrease contrast images (one per subject per contrast). A joint expected probability of $P = 0.01$ for height and $P = 0.01$ for extent (familywise error corrected) was used. This method controls type I error but is more sensitive to a range of signals by identifying high, sharp signals with a high-intensity threshold so that voxels above the threshold are considered significant, and in addition, identifies broad extensive signal changes by also considering spatial extent with a threshold of the minimum number of voxels that must appear in a cluster in order for the region to appear significant.[15]

Results were viewed in three dimensions by overlaying the statistical maps onto the MRIcro template image.[16]|| Talairach coordinates were calculated from Montreal Neurologic Institute space using the mni2tal function. Brain regions were identified using the Talairach Daemon (Research Imaging Center, University of Texas Health Science Center, San Antonio, Texas) and confirmed with the Talairach atlas.

Results

The average self-reported ability to modulate pain was similar between strategies (table 2) during the increase pain conditions (t(6) = 0.471, $P = 0.654$) or the decrease pain condition (t(6) = −0.420, $P = 0.689$). Individually, most subjects found no particular strategy better than another. However, it should be noted that the purpose of this study was not to assess the comparative efficacy of the strategies and was not powered to detect a difference. One subject (subject 6) reported having the same, moderate control of pain, regardless of strategy. One subject reported having little to no control over pain with both strategies (subject 1). Three sub-

Table 2. Patient Self-reports of Ability to Modulate Pain Using the Specific Cognitive Strategy on a Scale of 0–5

Subject	Attention		Reappraisal	
	Increase Pain	Decrease Pain	Increase Pain	Decrease Pain
1	1	0	0	1
2	3	3	3	2
3	2	2	3	3
4	3	3	5	2
5	5	4	2	4
6	3	3	3	3
7	2	1	1	2
Mean	2.71	2.29	2.43	2.43
SD	1.25	1.38	1.61	0.98

jects reported having little to moderate control with both strategies (subjects 2, 3, and 7). One subject reported have high control during attention (subject 5) and one had higher control during reappraisal (subject 4).

fMRI revealed a strategy-specific dissociation in brain regions involved in pain modulation by attention and reappraisal (fig. 1). Areas in which activity was significantly different in the contrast between the increase and decrease pain conditions are listed for the use of Attention in table 3 and Reappraisal in table 4. Attentional modulation of pain recruited cortical regions including primary and secondary sensory cortices, inferior and superior parietal lobules, and lateral prefrontal regions (table 3). On the other hand, pain modulation by reappraisal resulted in brain activation in subcortical regions in addition to cortical areas (table 4). Brain regions included primary and secondary sensory cortices, anterior and midcingulate gyrus, posterior insula, medial frontal gyrus, basal ganglia, hippocampus, prefrontal cortex (PFC), amygdala, and thalamus.

Only one region was active during both strategies, the somatosensory cortex.

Discussion

Cognitive therapies are frequently used by patients with chronic pain as tools for coping with their condition. Yet the neural mechanisms by which they modulate pain are poorly understood. The current study, to the best of our knowledge, is the first to contrast brain regions recruited during two commonly used strategies for pain modulation in chronic pain. We hypothesized that the utilization of two behaviorally distinct strategies would evoke differing patterns of neural activity; mainly, that the use of diversion attention would result in the recruitment of dorsolateral PFC and parietal cortex whereas reappraisal would result in activity in lateral PFC as well as limbic regions commonly associated with emotion such as the amygdala. Our results demonstrate preliminary evidence of strategy-dependent patterns of brain activity during the modulation of constant chronic pain. This suggests that different neural networks are involved in the modulation of pain when different cognitive processes are used.

Our study contributes to existing knowledge mainly conducted in healthy participants with acute, evoked pain. Kalisch et al. found strategy-dependent differences in the neural correlates of the modulation of pain-related anxiety related to an electrical shock delivered to the hand in healthy participants.[17] In their study, they identified left lateral PFC activity during self-distraction and right anterolateral PFC activity during reappraisal.[17] Distinct laterality was not observed in the current study, probably because of the heterogeneity of the chronic pain population we examined.

The perception of pain involves a complicated network of structures including the primary sensory cortex, thalamus, in-
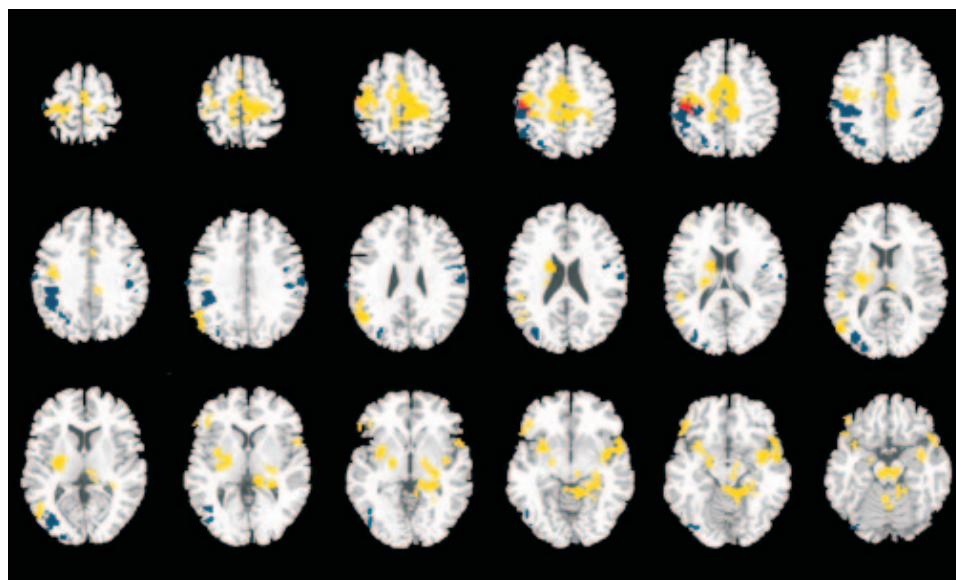

Fig. 1. Overlay maps during modulation of pain using attention (*blue*) and reappraisal (*yellow*). Areas recruited by both strategies (*red*) are shown.

Table 3. Talairach Coordinates of Peak T Statistic Voxels during Pain Modulation by Attention

Region	Brodmann Area	Side	x	y	z	T	Cluster Size
Inferior parietal lobule	40	Bilateral	48	−33	46	9.56	1,649
Postcentrall gyrus (SI)	1, 2, 3, 40		48	−33	48	6.73	1,649
Precentral gyrus	4, 6		−61	−3	24	4.46	386
Cuneus	18	Right	20	−86	19	4.46	608
Fusiform gyrus	19		36	−80	−11	3.55	608
Middle and inferior temporal gyrus	37		44	−62	1	3.77	608
Precuneus	7, 19		22	−60	44	5.77	1,649
Superior parietal lobule	7		24	−60	44	5.03	1,649
Supramarginal gyrus (SII)	40		44	−41	35	6.01	1,649
Inferior frontal gyrus	9, 44	Left	−46	−1	20	3.78	386

SI = Primary somatosensory cortex; SII = Secondary somatorsensory cortex.

sula, anterior cingulate cortex, and PFC. The frontal cortex, amygdala, periaqueductal gray matter, and rostral ventral medulla have been implicated in the descending modulation of pain by both emotion and attention.[1] We observed activity in a number of regions that have been implicated with descending systems of pain modulation. However, these were more widely

recruited during reappraisal. Only one region, the primary sensory cortex, appeared active during both cognitive strategies.

The use of reappraisal has been examined extensively in emotion research.[18–22] Reappraisal involves the reinterpretation of a sensation to assign a new context or perception. Within emotion literature, this may involve taking a sadden-

Table 4. Talairach Coordinates of Peak T Statistic Voxels during Pain Modulation by Reappraisal

Region	Brodmann Area	Side	x	y	z	T	Cluster Size
Cingulate gyrus	24, 31, 32	Bilateral	−8	2	42	10.01	4,609
Fusiform gyrus	20		48	−3	−25	8.47	1,957
Basal ganglia	Globus pallidus		22	−8	4	9.4	1,957
	Putamen		−30	−21	−2	8.31	4,712
Inferior parietal lobule	40		−30	−38	53	4.02	4,609
Inferior temporal gyrus	20		46	−3	−27	7.23	1,957
Insula	13		−42	−10	−1	4.89	4,712
Medial frontal gyrus	6, 32		14	−9	48	8.47	4,609
Middle and superior temporal gyrus	21		−53	0	−8	13.89	4,712
Paracentral lobule	4, 5, 6, 31		10	−13	47	10.29	4,609
Parahippocampal gyrus	28		−20	−33	−2	6.29	4,712
Postcentral gyrus (SI)	3, 5		48	−17	51	9.92	4,609
Precentral gyrus	4, 6		24	−24	66	10.59	4,609
Precuneus	7		8	−46	54	4.8	4,609
Superior frontal gyrus	6		4	10	53	4.23	4,609
Transverse temporal gyrus	41		46	−30	13	3.31	543
Thalamus	Pulvinar		−14	−33	3	8.49	4,712
Uncus	28		32	5	−22	4.04	1,957
Amygdala		Right	20	−8	−13	7.18	1,957
Angular gyrus	39		48	−70	37	3.81	543
Basal ganglia	Putamen		24	−7	6	8.03	1,957
	Caudate body		14	1	17	5.69	1,957
Inferior frontal gyrus	13, 45, 47		46	34	−12	6.85	1,957
Middle frontal gyrus	6, 10, 11, 47		38	−3	55	5.88	4,609
Supramarginal gyrus (SII)	40		53	−53	30	4.84	543
Thalamus	LPN		22	−19	16	4.08	1,957
	VAN		12	−7	13	4	1,957
	VLN		22	−15	12	4.21	1,957
	VPN		24	−21	8	3.15	1,957
Basal ganglia	Caudate tail	Left	−32	−35	5	4.89	4,712
Hippocampus			−26	−35	−3	8.47	4,712
Lingual gyrus	19		−14	−43	−3	3.39	4,712
Thalamus	MDN		−8	−21	12	4.13	4,712

LPN = lateral posterior nucleus; MDN = medial dorsal nucleus; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; VAN = ventral anterior nucleus; VLN = ventral lateral nucleus; VPN = ventral posterior nucleus.

ing stimulus and reinterpreting it as nonemotional. Studies of the suppression or reappraisal of sadness have found activity in the dorsolateral PFC and anterior cingulate cortex[23] and increases or decreases in the amygdala and posterior insula depending on the goal of reappraisal.[24] In the context of emotion modulation, McRae *et al.* compared reappraisal and distraction and found reduced amygdala activity and increased PFC activity during both strategies.[25] However, during reappraisal, activity was also observed in areas related to affective meaning such as the medial PFC, ventrolateral PFC, and inferior temporal regions whereas distraction also recruited areas linked with attention, such as the inferolateral PFC, lateral PFC, and superior parietal cortex.[25] They concluded that these distinctions in neural correlates underlie the behavioral differences in performing the strategies because reappraisal requires attending to the emotion first before it can be processed, and distraction requires ignoring affective meaning. Consistent with the study by McRae *et al.*,[25] during reappraisal we observed activity in the middle frontal gyrus, amygdala, parahippocampal area, precuneus, and middle and superior temporal regions. During diversion of attention, as in the study by McRae *et al.*, we report activity in the precentral gyrus and superior parietal lobule. We similarly believe that it is the distinct behaviors required to perform reappraisal and focus of attention that lead to unique patterns of activity during pain modulation. Compared with their study, we report several additional recruited areas in each condition. This is anticipated due to the context (pain modulation) and chronic pain patient group.

In the context of pain modulation, the neural correlates of reappraisal have been far less studied. Behavioral studies of evoked pain have identified changes in pain perception due to modulations in mood and emotion through smell,[26] pictures,[27,28] reading statements,[29] movies,[30] and romantic love.[31] We observed activity in the ventral lateral PFC, an area that has recently been proposed as an analgesic control center by Wiech *et al.*[10] They noted that during self-controlled delivery of a noxious stimulus, there was a strong (r = 0.94) inverse correlation of right ventral lateral PFC activity with perceived pain. In the current study, reappraisal of chronic pain resulted in midcingulate activity (Talairach coordinate −8, 2, 42). The anterior midcingulate has been associated with fear.[32] In the monkey, the midcingulate is known to receive input from the amygdala[33] and also have motor projections to the spinal cord.[34] The current study revealed activity in limbic areas including the amygdala and parahippocampal gyrus, as well as in regions of the brainstem. This supports the findings that the descending systems *via* the periaqueductal gray matter may depress mean discharge rates of spinal nociceptive dorsal horn neurons.[35–38] These mechanisms seem to contribute to the endogenous pain-controlling systems and suggest they are under cognitive control, but further exploration of these cortical control mechanisms is needed. The influence of attention on pain management has been more widely studied.[4,37] Previous im-

aging studies of healthy participants with an evoked painful stimulus have identified activity in the perigenual anterior cingulate cortex,[40] posterior thalamus,[40] and periaqueductal gray matter[40,41] during the diversion of attention. In the current study we observed activity mainly in cortical areas. The activity observed in sensory and prefrontal cortices was expected. However, it was also anticipated that activity would be observed in additional areas such as the anterior cingulate cortex. During our attention task we asked subjects to divert their attention to another area of their body that is not in pain. It may be difficult for some individuals, especially those with chronic pain, to focus their attention on a region of the body without a particular sensation.

To the best of our knowledge, the current study is the first neuroimaging study to contrast the modulation of chronic pain by specific cognitive strategies. Meta-analyses have reported the effectiveness of cognitive strategies for pain modulation based on behavioral reports.[5] However, only one neuroimaging study has investigated the changes in pain-related neural activity after cognitive behavioral therapy.[11] Positron emission tomography has been used to examine brain responses to bowel distention in patients with irritable bowel syndrome before and after a 10-week training period of cognitive therapy based on an empirically validated manual that included reappraisal.[42,43] After training, patients exhibited a reduction in limbic activity including in the amygdala. Previous studies have provided an important contribution in understanding the neural mechanisms of pain modulation due to cognitive therapy.[11] Further work is necessary to characterize the neural basis of the specific strategies used in the modulation of pain because this in turn will aid in improving methods in cognitive therapy. The current study demonstrates the recruitment of different brain regions during two strategies commonly used in cognitive therapy albeit, presented in a more simplified form outside of a formal training program. As in the study by Lackner *et al.*,[11] the current study identifies involvement of the amygdala during reappraisal.

Our study faces some challenges common to studying chronic pain. Primarily, chronic pain is a heterogeneous condition. As with most patient work, studies rely on the subjects "who walked through the door." These are often people who have not been able to find satisfactory relief from other pain interventions. As a result we have a subject group composed of several chronic pain conditions. Two patients suffered from fibromyalgia, a condition that can be characterized by widespread and fluctuating pain. A growing body of research has identified structural and functional differences in the neural networks of patients with chronic pain, including those with fibromyalgia.[44–47] As a result, it is possible that these patients may present with greater variance in pain ratings and neural signal changes. This preliminary work includes a small sample size. In the future, it would be worthwhile to focus study on a single chronic pain condition; however, variation will still exist in terms of severity and

location of pain, and the patient's clinical care will also have to be considered.

In our methodology, the strategies and direction of pain modulation were given in the same order. This raises the issue of order effects. The rationale for presenting instructions this way was to simplify the methods so that patients clearly understood what strategy would be coming next. An alternative method would be to randomize the order of strategies and direction of control; however, we were more concerned about introduced additional confounders such as delays in implementing the strategies or more importantly, implementing the wrong strategy or direction of control. By making the method predictable to patients in this first imaging session for them, we aimed to ensure patients were performing the strategies to the best of their abilities. Future work with well-trained patients may explore randomizing the order of the strategies as well as direction of control.

In our previous real-time fMRI neurofeedback study, we did not focus on the influence of specific cognitive strategies on pain reduction and control of the fMRI signal. It has been suggested that the use of real-time feedback is more effective when a cognitive strategy is also used.[48] The findings of the current study of a strategy-dependent dissociation of functional brain networks during pain modulation have an important implication for real-time feedback of specific brain areas. The cognitive strategies used by the individual should also be considered when selecting a feedback region. The characterization of the neural networks involved with specific strategies will help guide selection of a region for feedback and therefore aid in improving the effectiveness of real-time fMRI feedback.

In conclusion, comparison of the neural correlates recruited during modulation of chronic pain by two different cognitive strategies resulted in unique patterns of activity with overlap observed only in the primary sensory cortex. This suggests that different analgesic networks are recruited in the modulation of pain by behaviorally distinct cognitive strategies. Future studies may expand this knowledge to investigate other cognitive strategies used commonly in cognitive behavioral therapy and mindfulness-based stress reduction and if there is a link between the patterns of neural activity and the effectiveness of pain reduction.

References

1. Fields HL: Pain modulation: Expectation, opioid analgesia and virtual pain. Prog Brain Res 2000; 122:245–53
2. Flor H, Fydrich T, Turk DC: Efficacy of multidisciplinary pain treatment centers: A meta-analytic review. Pain 1992; 49:221–30
3. Vranceanu AM, Safren S: Cognitive-behavioral therapy for hand and arm pain. J Hand Ther 2011; 24:124–30
4. Vázquez-Rivera S, González-Blanch C, Rodríguez-Moya L, Morón D, González-Vives S, Carrasco JL: Brief cognitive-behavioral therapy with fibromyalgia patients in routine care. Compr Psychiatry 2009; 50:517–25
5. Fernandez E, Turk DC: The utility of cognitive coping strategies for altering pain perception: A meta-analysis. Pain 1989; 38:123–35
6. Tan SY: Cognitive and cognitive-behavioral methods for pain control: A selective review. Pain 1982; 12:201–28
7. Forys KL, Dahlquist LM: The influence of preferred coping style and cognitive strategy on laboratory-induced pain. Health Psychol 2007; 26:22–9
8. Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, Mauguiere F, Michel D, Laurent B: Haemodynamic brain responses to acute pain in humans: Sensory and attentional networks. Brain 1999; 122(Pt 9):1765–80
9. Brooks JC, Nurmikko TJ, Bimson WE, Singh KD, Roberts N: fMRI of thermal pain: Effects of stimulus laterality and attention. Neuroimage 2002; 15:293–301
10. Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ: Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. J Neurosci 2006; 26:11501–9
11. Lackner JM, Lou Coad M, Mertz HR, Wack DS, Katz LA, Krasner SS, Firth R, Mahl TC, Lockwood AH: Cognitive therapy for irritable bowel syndrome is associated with reduced limbic activity, GI symptoms, and anxiety. Behav Res Ther 2006; 44:621–38
12. deCharms RC, Maeda F, Glover GH, Ludlow D, Pauly JM, Soneji D, Gabrieli JD, Mackey SC: Control over brain activation and pain learned by using real-time functional MRI. Proc Natl Acad Sci U S A 2005; 102:18626–31
13. Melzack R: The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1975; 1:277–99
14. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD: Meta-analysis of psychological interventions for chronic low back pain. Health Psychol 2007; 26:1–9
15. Poline JB, Worsley KJ, Evans AC, Friston KJ: Combining spatial extent and peak intensity to test for activations in functional imaging. Neuroimage 1997; 5:83–96
16. Rorden C, Brett M: Stereotaxic display of brain lesions. Behav Neurol 2000; 12:191–200
17. Kalisch R, Wiech K, Herrmann K, Dolan RJ: Neural correlates of self-distraction from anxiety and a process model of cognitive emotion regulation. J Cogn Neurosci 2006; 18:1266–76
18. Beauregard M, Levesque J, Bourgouin P: Neural correlates of conscious self-regulation of emotion. J Neurosci 2001; 21:RC165
19. Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S: Regulation of emotional responses elicited by threat-related stimuli. Hum Brain Mapp 2007; 28:409–23
20. Gross JJ, John OP: Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. J Pers Soc Psychol 2003; 85:348–62
21. Gross JJ: Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. J Pers Soc Psychol 1998; 74:224–37
22. Ochsner KN, Gross JJ: The cognitive control of emotion. Trends Cogn Sci 2005; 9:242–9
23. Lévesque J, Eugène F, Joanette Y, Paquette V, Mensour B, Beaudoin G, Leroux JM, Bourgouin P, Beauregard M: Neural circuitry underlying voluntary suppression of sadness. Biol Psychiatry 2003; 53:502–10
24. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD: Rethinking feelings: An FMRI study of the cognitive regulation of emotion. J Cogn Neurosci 2002; 14:1215–29
25. McRae K, Hughes B, Chopra S, Gabrieli JD, Gross JJ, Ochsner KN: The neural bases of distraction and reappraisal. J Cogn Neurosci 2010; 22:248–62

26. Villemure C, Slotnick BM, Bushnell MC: Effects of odors on pain perception: Deciphering the roles of emotion and attention. Pain 2003; 106:101–8

27. Meagher MW, Arnau RC, Rhudy JL: Pain and emotion: Effects of affective picture modulation. Psychosom Med 2001; 63: 79–90

28. de Wied M, Verbaten MN: Affective pictures processing, attention, and pain tolerance. Pain 2001; 90:163–72

29. Zelman DC, Howland EW, Nichols SN, Cleeland CS: The effects of induced mood on laboratory pain. Pain 1991; 46:105–11

30. Weisenberg M, Raz T, Hener T: The influence of film-induced mood on pain perception. Pain 1998; 76:365–75

31. Younger J, Aron A, Parke S, Chatterjee N, Mackey S: Viewing pictures of a romantic partner reduces experimental pain: Involvement of neural reward systems. PLoS One 2010; 5:e13309

32. Vogt BA: Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 2005; 6:533–44

33. Vogt BA, Pandya DN: Cingulate cortex of the rhesus monkey: II. Cortical afferents. J Comp Neurol 1987; 262:271–89

34. Dum RP, Strick PL: The origin of corticospinal projections from the premotor areas in the frontal lobe. J Neurosci 1991; 11:667–89

35. Gebhart GF, Sandkühler J, Thalhammer JG, Zimmermann M: Quantitative comparison of inhibition in spinal cord of nociceptive information by stimulation in periaqueductal gray or nucleus raphe magnus of the cat. J Neurophysiol 1983; 50:1433–45

36. Jones SL, Gebhart GF: Inhibition of spinal nociceptive transmission from the midbrain, pons and medulla in the rat: Activation of descending inhibition by morphine, glutamate and electrical stimulation. Brain Res 1988; 460:281–96

37. Pertovaara A, Kontinen VK, Kalso EA: Chronic spinal nerve ligation induces changes in response characteristics of nociceptive spinal dorsal horn neurons and in their descending regulation originating in the periaqueductal gray in the rat. Exp Neurol 1997; 147:428–36

38. Sandkühler J: The organization and function of endogenous antinociceptive systems. Prog Neurobiol 1996; 50:49–81

39. Elomaa MM, de C Williams AC, Kalso EA: Attention management as a treatment for chronic pain. Eur J Pain 2009; 13:1062–7

40. Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR: Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain–an fMRI analysis. Pain 2004; 109:399–408

41. Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM: Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 2002; 22: 2748–52

42. Blanchard EB: Chapter 18. The Albany Cognitive Therapy Treatment Manual, Irritable Bowel Syndrome: Psychosocial Assessment and Treatment. Edited by Anonymous. Washington, D.C., American Psychological Association, 2001, pp 247–76

43. Lackner JM: Chapter 20. Irritable bowel syndrome, The Health Psychology Handbook: Practical Issues for the Behavoral Medicine Specialist. Edited by Cohen LM, McChargue DE, Collins FLJ. Thousand Oaks, California, Sage Publications, 2003, pp 397–423

44. Burgmer M, Pogatzki-Zahn E, Gaubitz M, Stüber C, Wessoleck E, Heuft G, Pfleiderer B: Fibromyalgia unique temporal brain activation during experimental pain: A controlled fMRI Study. J Neural Transm 2010; 117:123–31

45. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL: Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003; 48:1420–9

46. Robinson ME, Craggs JG, Price DD, Perlstein WM, Staud R: Gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome. J Pain 2011; 12:436–43

47. Staud R: Abnormal pain modulation in patients with spatially distributed chronic pain: Fibromyalgia. Rheum Dis Clin North Am 2009; 35:263–74

48. Caria A, Veit R, Sitaram R, Lotze M, Weiskopf N, Grodd W, Birbaumer N: Regulation of anterior insular cortex activity using real-time fMRI. Neuroimage 2007; 35:1238–46