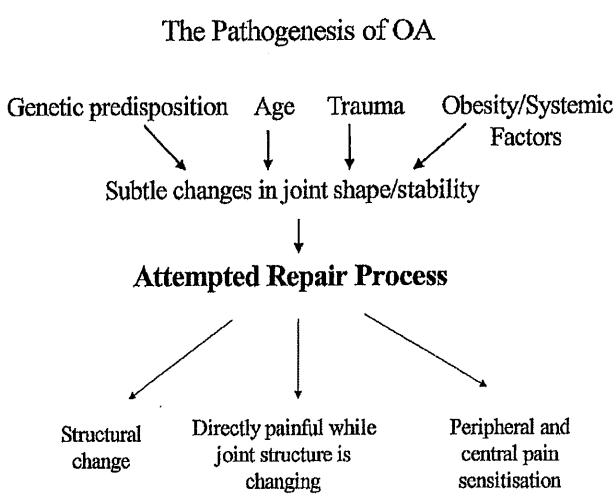

Figure 6. Likely pathways in the pathogenesis of both the structural changes and the symptoms of OA. Changes in joint shape and stability induce an attempt by the joint to repair damage. This is the "OA process." Pain is generated by direct nociceptive mechanisms when the process starts. In addition, in some people, peripheral and central pain sensitization occurs so that normal movements become painful. These are the people who develop chronic OA symptoms, which persist even if structural changes stabilize.

Lawrence, we still don't know why OA is sometimes painful[6]. Pain could arise from the synovium (inflammation), joint capsule (stretching), subchondral bone (raised intraosseous pressure), periosteum (elevation by osteophyte growth), or periarticular tissues (secondary to altered biomechanics of the joint). There are some data to support each of these hypotheses, but it is likely that in different individuals different types of tissue damage are important, perhaps, in part, explaining the heterogeneity of the clinical condition.

Recent data suggest that another important mechanism may be operating in patients with OA — sensitization of the nociceptive pathways, resulting in pain with normal movement of the joints[7]. If this is the case it may be that the OA process generates pain only initially, after which the joint/pain pathways are sensitized to pain in some patients, explaining the chronicity of the symptoms in some, but not all, of those with joint damage (Figure 6).

So, what are the important targets for t herapy? If we accept the primacy of some of the data summarized above, efforts to treat OA that focus on structural change alone are likely to be misplaced. The findings suggest we need to focus on other aspects as well, including:

- Biomechanical abnormalities that lead to joint damage
- Processes that initiate both joint damage and sensitization to pain
- Psychosocial factors that are determinants of symptom severity

In short, future management of OA should concentrate on the control of pain and on pain sensitization and disability in older people, without worrying about the type or severity of joint damage. That is not a new conclusion[8].

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PAIN-RELATED BELIEFS AND AFFECTIVE PAIN RESPONSES: IMPLICATIONS FOR ETHNIC DISPARITIES IN PREFERENCES FOR JOINT ARTHROPLASTY

Laurence A. Bradley, Georg Deutsch, Nancy L. McKendree-Smith, and Graciela S. Alarcón

In the 2002 Workshop[1] we described preliminary findings of our continuing work regarding central mechanisms involved in pain associated with knee OA. The major premise guiding our work is that our understanding of OA pain, and optimal management of this pain, requires that we attend to factors that influence the central processing of neurosensory input from affected joints and soft tissue as well as the factors that influence disease activity in the joint. We now describe recent findings concerning 2 factors relevant to the pain associated with knee OA: (a) pain-related beliefs and (b) ethnic variations in these beliefs, including expectations of the outcome of total knee arthroplasty (TKA). The latter discussion includes a description of a study we have recently initiated, involving methods for altering the negative pain-related beliefs that are associated with ethnic disparities in preferences for TKA.

Pain-Related Beliefs

Numerous investigations have shown that individual variations in pain-related beliefs are associated with differences in pain responses. This discussion focuses primarily on

recent findings concerning the relationships between catastrophizing and alterations in pain sensitivity and behavior.

Catastrophizing. This construct represents a tendency to focus upon and exaggerate the threat posed by painful stimuli and to negatively evaluate one's ability to cope with pain. The Pain Catastrophizing Scale (PCS)[2] is a particularly useful measure that assesses 3 dimensions of the construct: helplessness, magnification of negative consequences of pain, and rumination, or difficulty in distracting oneself from pain. Among patients with knee OA, relatively high levels of catastrophizing are associated with higher clinical pain ratings on the McGill Pain Questionnaire (MPQ)[3] and lower pain threshold and tolerance responses[4].

In the 2002 Workshop we reported preliminary findings of our study examining the relationship between catastrophizing and affective pain responses among patients with bilateral knee OA and age-matched healthy controls[1]. Participants completed the PCS and produced MPQ ratings of the sensory intensity and unpleasantness of phasic pressure stimulation of their knees under 2 conditions: (a) low intensity (1 kg) and (b) high intensity (4 kg above the subject's pain threshold level). Participants also underwent xenon^{133} single photon emission computed tomography imaging of regional brain cerebral blood flow during stimulation. Thus, we compared patients and controls with respect to PCS scores, MPQ ratings of the intensity and unpleasantness of pain, and neural correlates of their MPQ responses, while controlling for individual differences in pain sensitivity.

We found that patients with knee OA produced significantly higher scores on the PCS measure of catastrophizing than controls. In comparison with patients, controls also produced significantly higher MPQ pain unpleasantness ratings of the high intensity stimulation even though sensory intensity ratings in the 2 groups were similar (Table 1). In addition, after statistically controlling for differences between patients and controls on the PCS magnification and helplessness subscales, the between-group difference in pain unpleasantness ratings was substantially reduced. This analysis and similar tests of mediation indicate that the participants' PCS scores were highly associated with their MPQ pain unpleasantness ratings and contributed substantially to the difference between patients and controls with respect to MPQ ratings.

Table 1. Mean (± SEM) McGill Pain Questionnaire (MPQ) subscale scores in response to pressure stimulation of the right knee of patients with bilateral knee OA and healthy controls. These preliminary data were presented initially in Bradley LA, J Rheumatol 2004;31 Suppl 70:54-60.

MPA Subscale	OA Patients	Healthy Controls	p
Sensory	19.6 ± 1.4	17.0 ± 3.0	0.465
Affective	9.6 ± 2.1	1.8 ± 0.5	0.007

We recently reanalyzed the brain imaging data from this study, using an improved procedure for statistical parametric mapping, SPM 2 (MEDx; Sensor Systems, Sterling, VA, USA). Among both patients and control participants, we found that high intensity pressure stimulation of the knee evoked enhanced activation of the contralateral somatosensory cortex and contralateral thalamus (Figure 7) structures involved in processing the sensory and intensity dimensions of pain[5]. However, in comparison with controls, patients displayed significantly greater increases in activation of the contralateral anterior cingulate cortex and contralateral insular gyrus. The enhanced activation within the insular gyrus, which we did not observe in our initial analysis, is associated with anticipation of pain[6]. These brain imaging findings are consistent with the higher levels of catastrophizing and pain unpleasantness ratings produced by the patients and with recent evidence concerning the neural correlates of catastrophizing among patients with fibromyalgia[5].

Ethnic Group Differences in Measures of Pain Affect and Pain-Related Beliefs

Our initial report[1] included a comparison of the MPQ pain intensity and unpleasantness ratings of African American and Caucasian patients with knee OA. We found that the African American patients produced higher pain unpleasantness scores than their Caucasian counterparts. In addition, the African American patients tended to report higher scores on all 3 subscales of the PCS. These findings are consistent with reports that, among healthy college students and patients with chronic pain, African Americans produce higher scores than Caucasians on measures of pain affect, catastrophizing, and hypervigilance[7-9].

Implications for ethnic disparities in preferences for joint arthroplasty. We believe that examination of the literature concerning ethnic group differences in pain affect and pain-related beliefs may lead to better understanding of the factors that underlie the consistent finding that African Americans are significantly less likely than Caucasians to agree to undergo knee or hip arthroplasty[10]. Two recent studies[10,11] strongly suggest that this disparity is related to differences in patients' expectations of pain-related outcomes such as postsurgical pain, walking ability, length of hospital stay, and unintended consequences (e.g., persistent pain, death). On all of these variables, expectations of African Americans are significantly more negative than those of Caucasians.

Several recent editorials have recommended that investigators devote greater effort to understanding ethnic differences in language, culture, and other factors that may negatively affect the success of health-related communications between patients and health professionals[12]. Consistent with these recommendations, we recently initiated an investigation of the effects of message-framing in altering the expectations of patients about pain-related outcomes of TKA and

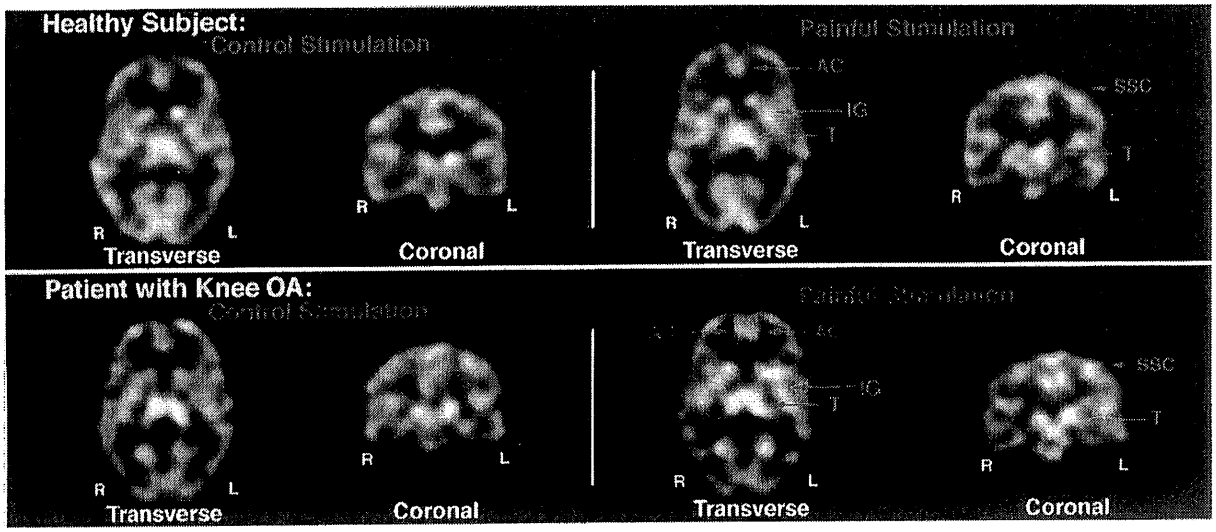

Figure 7. Xenon[133] SPECT brain imaging showing brain responses to low intensity pressure stimulus (Control Stimulation) and a painful stimulus (Painful Stimulation) of a healthy subject (top panel) and a patient with knee OA (bottom panel), both delivered to the right knee. The low intensity stimulus was set at 1 kg for both participants. The painful stimulus was set at 4 kg above the pain threshold level of the participant. For the healthy participant, in comparison with the low intensity stimulus, painful stimulation produced a small increase in activation of the left thalamic region (T) and left somatosensory cortex (SSC), a moderate increase in activation of the left insular gyrus (IG), and minimal activation of the anterior cingulate area (AC). In contrast, for the patient with OA, painful stimulation produced a modest increase in activation of the left thalamus (T) and moderate to large increases in activation of the left and right anterior cingulate cortices (AC), left somatosensory cortex (SSC), and left insular gyrus (IG). All findings of this preliminary analysis, with the exception of those concerning activation of the insular gyrus, were presented in Reference 1.

their willingness to undergo the procedure if recommended by their physician.

The message-framing intervention is based on prospect theory[13], which suggests that brief, structured education interventions regarding health-related decisions are most effective when (a) they are tailored to the individual's ethnic background and (b) their content is framed according to the individual's beliefs about the outcomes of these decisions[14]. Thus, we predict that individuals who enter the study with negative expectations about the outcomes of TKA will be more strongly influenced by loss-framed, compared to gain-framed, messages, i.e., messages that emphasize the losses that are likely to occur if the surgical procedure is refused. Conversely, we predict that patients with more positive initial expectations regarding the outcomes of TKA will be more strongly influenced by gain-framed messages that emphasize the likely benefits of the procedure.

This hypothesis has been supported in studies of message-framing involving health-related decisions, such as obtaining HIV testing[14] or a Pap test[15]. However, our investigation is the first to assess the effects of message-framing on the patient's expectations of outcomes and willingness to undergo a complex medical procedure, such as TKA, that involves surgery and a high level of compliance with post-surgical rehabilitation.

We are currently initiating the first of 3 preliminary investigations that will help determine the content of our education intervention for TKA. We will ask African Americans and Caucasians with persistent knee pain or knee OA to rate their willingness to undergo TKA, if it were recommended by their physician. We also will examine the outcome-related beliefs or expectations underlying their willingness to undergo TKA. We then will use this information to develop a video-based education intervention concerning TKA to be shown to an independent group of patients with knee OA after they have rated their willingness to undergo the procedure if recommended by their physician, and their outcome-related beliefs or expectations. The information content presented in the video will be consistent across participants, and the ethnic backgrounds of the actors in the video will be matched with those of the participants. However, the manner in which the information is framed (i.e., negative or positive) will be determined on a random basis. Following the video presentation, the patients will again rate their willingness to undergo TKA and their outcome-related beliefs and expectations. This procedure will allow us to evaluate the effects of gain-framed versus loss-framed education messages upon changes in willingness to undergo TKA among patients with relatively negative or positive outcome-related beliefs and expectations.

Conclusions

Our work and that of other investigators indicates that African Americans, compared to Caucasians, tend to report higher levels of catastrophizing and pain-related affect in both clinical and laboratory-based settings. We believe these

findings are highly relevant to the associations that have been observed between negative expectations of pain-related outcomes and the relatively low preferences for TKA among African Americans[10,11]. We also believe it is reasonable to use research concerning medical decision-making, such as tests of prospect theory, to develop interventions that may alter the patient's pain-related beliefs and thus help reduce ethnic disparities in preference for TKA or other health care interventions. However, as we begin to test our theory-based interventions, it will be imperative that we continue to perform both quantitative and qualitative studies of patients from diverse backgrounds so as to better understand their needs, beliefs, and experiences with health care[12]. This understanding will be essential to the development of optimal psychosocial or educational interventions to reduce ethnic disparities in health care preferences and evaluate the effects of these interventions.

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FINDING CLINICAL ENDPOINTS AND BIOSURROGATES IN PRECLINICAL KNEE OSTEOARTHRITIS

Paola De Pablo and Matthew H. Liang

To evaluate disease-modifying drugs for OA (DMOAD) among subjects who have no or minimal symptoms, but who are destined to develop OA or to attempt primary prevention in those with early signs of OA on radiographs and/or MRI, we will need to develop and validate surrogate outcome measures for preclinical disease[1].

Outcome variables currently used in clinical trials assessing DMOAD have focused on pain, function, patient global assessment, and structural changes[2]. Subjective measures are limited in their ability to detect change and are prone to floor and ceiling effects. In contrast, outcomes such as rate and extent of cartilage damage, change in joint space width (JSW) on radiographs, and cartilage volume on MRI have face validity, provide objective measurements, and are continuous variables. The incidence and extent of cartilage surface defects by arthroscopy or MRI also have face validity, permit objective measurement, and are continuous variables, but their significance with respect to disease progression in asymptomatic subjects or patients with early OA remains to be established.

Surrogate endpoints. Useful clinical endpoints are outcomes that measure meaningful clinical outcomes (i.e., need for total joint arthroplasty, or mortality) or how a patient feels or functions. Surrogate endpoints substitute for a true endpoint and are often not perceived or felt by the patient. Examples include measures of cartilage degradation, such as urinary C-telopeptide fragments of type II collagen (CTX-II), which has been associated with both prevalence and progression of radiographic OA and JSW. For a surrogate endpoint to be an effective substitute for the clinical outcome, effects of the intervention on the surrogate must reliably predict the overall effect on the clinical outcome[3]. Surrogate endpoints should be of proven reliability, validity, and sensitivity to change. Hence, if a surrogate outcome measure is to be used to evaluate a chondroprotective agent, it must predict cartilage loss.

How might surrogate endpoints for preclinical OA be identified? Let us speculate on one possible study: For this, we would assemble a group of subjects at very high risk of