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Painful effects of auditory startle, forehead cooling and psychological stress in
patients with fibromyalgia or rheumatoid arthritis

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Running title: stress-induced pain in rheumatoid disorders

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Abstract

Objective. The aim of this study was to determine whether the clinical pain associated with rheumatoid arthritis or fibromyalgia would increase during standard laboratory tasks and, if so, whether these increases were linked with individual differences in psychological distress.

Methods. Twenty-three patients with fibromyalgia and 16 patients with rheumatoid arthritis rated changes in clinical pain after an acoustic startle stimulus, during painful forehead cooling, and during stressful mental arithmetic. In addition, pain tolerance was assessed during a submaximal effort tourniquet test, and patients provided ratings of distress on a standard Depression, Anxiety and Stress Inventory.

Results. Pain at rest was associated with depression scores in patients with rheumatoid arthritis, and was associated with stress scores in the fibromyalgia group. However, pain tolerance was unrelated to individual differences in psychological distress in either group. In patients with fibromyalgia, clinical pain increased after the acoustic startle stimulus and painful forehead cooling, and increased during stressful mental arithmetic. Arthritic pain also increased during forehead cooling and mental arithmetic in association with indices of psychological distress.

Conclusions. These findings suggest that processes linked with individual differences in distress aggravate pain in rheumatoid arthritis, whereas some other mechanism (e.g., failure of stress-related pain modulation processes or an aberrant interaction between nociceptive afferent and sympathetic efferent fibres) triggers stress-induced pain in fibromyalgia.

Key words: fibromyalgia; rheumatoid arthritis; pain modulation; psychological stress; sympathetic nervous system; depression

Introduction

Fibromyalgia is characterized by chronic widespread pain, hyperalgesia and multiple somatic symptoms. The pathophysiology of fibromyalgia remains uncertain, but heightened excitability in central nociceptive circuits and impaired anti-nociceptive responses appear to be involved [1-6]. The pain of fibromyalgia increases during laboratory stress [7,8] and is exacerbated by negative mood [9], implying a link between disrupted pain modulation and stress-induced increases in pain.

Although subtle inflammatory changes may compromise central pain modulation in fibromyalgia [10], there is little evidence of systemic inflammation in peripheral tissues. In contrast, major inflammatory disturbances in the synovial joints lead to progressive destruction of cartilage and bone in rheumatoid arthritis [11]. Unlike fibromyalgia, effects of heterotopic noxious conditioning stimulation on sensitivity to pressure-pain are similar in arthritic patients and controls [12]. Furthermore, evidence of a link between psychological stress and arthritic pain is mixed. On one hand, elevations in daily stress were found to be associated with increases in arthritic pain [13]; in addition, joint and bodily pain were greater at baseline and increased more during stressful laboratory tasks (giving a five-minute speech followed by discussing a recent conflict with someone close to them) in rheumatoid arthritis patients with a history of recurrent depressive episodes than in others with one or no depressive episodes [14]. On the other hand, joint pain did not change during these procedures in patients who considered that they had some control over external events and *decreased* in patients with a low sense of control [15]. Although the mechanism of this analgesic response is uncertain, it is interesting to draw parallels with normal opioid-mediated increases in pain tolerance when stress is

perceived to be uncontrollable [16]. Thus, stressful laboratory tasks might augment pain only in association with depression in arthritic patients.

To investigate this in the present study, the nociceptive effects of various forms of laboratory stress and pain (stressful mental arithmetic, pain induced by cooling the forehead, and an acoustic startle stimulus) were compared between patients with fibromyalgia and rheumatoid arthritis, and were examined in relation to individual differences in depression, anxiety and stress. Experimental pain decreases in healthy participants during each of these procedures [17], presumably due to pain modulation mechanisms such as stress-induced analgesia, diffuse noxious inhibitory controls and distraction. To compare effects of distress on pain in fibromyalgia and rheumatoid arthritis, the mental arithmetic test had a forced failure rate of 75%. A similar task was found to evoke strong negative affect, together with endogenous opioid release and reductions in pain in the most discouraged participants [18]. In addition to inducing distress, noxious forehead cooling might alter clinical pain by effects on autonomic arousal and/or sensitized nociceptive pathways [17,19]. The acoustic startle stimulus was included because it evokes an abrupt but momentary increase in psychological and physiological arousal associated with fear, the primary trigger of stress-induced analgesia [20,21]. As anti-nociceptive mechanisms appear to be compromised in patients with fibromyalgia [1-3], and pain increases in these patients during laboratory stress and negative mood [7-9], it was hypothesized that pain would increase in the group as a whole during each of the procedures employed in the present study. However, as anti-nociceptive mechanisms appear to be largely intact in patients with rheumatoid arthritis [12], it was expected that pain would decrease except in depressed participants [14].

Method

Participants

The procedures were carried out on 21 women and two men aged between 19 and 66 years (mean \pm standard error 43.6 ± 2.9 years) with fibromyalgia, and on 10 women and 6 men aged between 28 and 65 years (mean age 42.7 ± 3.0 years) with rheumatoid arthritis. In each case, the diagnosis was made by a rheumatologist or a general medical practitioner, based on a medical history and physical examination supplemented where necessary by blood tests and joint imaging to confirm the diagnosis. All patients with fibromyalgia met the criteria of the American College of Rheumatology [22], and patients with rheumatoid arthritis met the 1987 revised classification criteria for this condition [23]. Fibromyalgia had persisted 6.5 ± 1.3 years and arthritis had persisted 9.0 ± 2.0 years. Patients were asked to refrain from taking non-prescribed medication on the day of testing but were advised to take prescribed medication. In particular, 15 fibromyalgia patients and 14 patients with rheumatoid arthritis took non-steroidal anti-inflammatory drugs and/or steroids (six arthritic patients) to control their pain. Additional medications included anti-rheumatic drugs such as methotrexate and/or hydroxychloroquine (eight arthritic patients and one with fibromyalgia) and antidepressants (two arthritic patients and eight with fibromyalgia). Nevertheless, pain persisted to some extent in each case during the procedures described below.

Participants were recruited from a rheumatology clinic and through advertisements in community newspapers, the Arthritis Foundation of Western Australia and Murdoch University. Each participant provided informed consent for the procedures, which were in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee.

Procedures

The procedures were presented in the same order for each participant with two minutes rest between each task. To minimize carry-over effects, the least demanding tasks were presented first. Participants initially filled out the short form of the Depression, Anxiety and Stress scale [24], a 21-item self-report questionnaire that assesses the frequency of depression, anxiety and stress symptoms in the past week. The scale has acceptable internal consistency and test-retest reliability, and is well-validated against external criteria [24]. Full scale scores were later referenced against scores in a normal adult population [25].

Ten seconds before a startle stimulus (1,000 Hz tone, 0.5 second duration, 100 dBA presented through headphones), participants recorded the intensity of their painful condition on a visual analogue scale where 0 corresponded to “no pain” and 10 to “pain as strong as it can get”. Immediately after the startle stimulus they rated pain again, and continued to rate pain at 10-second intervals for 60 seconds.

After resting for two minutes, a cylindrical metal bar (10 cm long, 1.3 cm diameter, 2°C) was placed lengthwise across the participant’s forehead and was rolled back and forth for 30 seconds. Participants rated the intensity of fibromyalgia or arthritic pain at 10-second intervals on the visual analogue scale, starting just before the bar was applied and continuing for 60 seconds after it was removed.

Two minutes later, participants were asked to rate pain intensity and then began to solve computer-generated additions and subtractions presented on a computer screen [18]. Participants were given up to 5 s to answer easy problems (e.g., $6 + 8 - 2$) and up to 11 s to answer hard problems (e.g., $116 + 138 - 12$) before the next was presented. The difficulty of problems was automatically adjusted to ensure a 75% failure rate. After each problem, feedback such as ‘CORRECT’ (green),

'INCORRECT' (red) or 'TOO SLOW' (purple) appeared on the computer screen, and either a pleasant 3-note jingle (correct response) or an aversive loud beep (too slow or incorrect response) sounded for 1 second. The program paused at 5-minute intervals throughout the 20-minute task for participants to rate the intensity of their painful condition on a visual analogue scale.

Finally, in a submaximal effort tourniquet test, a blood pressure cuff was attached to the upper part of the non-dominant arm. The arm was then raised for 60 seconds to drain venous blood and the cuff was inflated to 200 mm Hg. After the arm was returned to the horizontal level, participants flexed and extended the wrist every few seconds until they decided to stop (defined as pain tolerance).

Statistical approach

Initially, differences between groups in indices of psychological distress (depression, anxiety and stress) were investigated with Student's t-test. Next, the association between these indices and pain at rest, pain tolerance and the maximum increase in pain during each task was investigated within each group with Pearson's correlation coefficient. Differences in these correlations between groups were explored with Fisher's r-to-z transformation.

Changes in pain at rest were investigated in a Group (rheumatoid arthritis versus fibromyalgia) by Time repeated measures analyses of variance with planned contrasts between one task and the next. Effects on pain ratings of the startle stimulus, forehead cooling and stressful mental arithmetic were investigated in separate Group (rheumatoid arthritis versus fibromyalgia) by Time (the series of ratings) repeated measures analyses of variance with planned contrasts between pain ratings before the task and at each time point thereafter. As pain intensity ratings before each of the tasks were greater in participants with fibromyalgia than in those with rheumatoid

arthritis, differences between groups were also investigated in analyses of covariance with pain intensity before the task as the covariate. Pain reactivity in patients with rheumatoid arthritis was associated with indices of psychological distress during some of the laboratory tasks; therefore, changes in pain within each group at each point during each task were investigated in analyses of covariance with the psychological indices of distress as covariates. The aim of these analyses was to determine whether psychological distress accounted for increases in pain. Where appropriate, the Greenhouse-Geisser epsilon was used to correct for violations of the sphericity assumption in these analyses. Finally, differences in pain tolerance between the two groups were investigated with Student's t-test.

Data are reported as the mean \pm standard error, and the criterion of statistical significance was $p < 0.05$.

Results

When referenced against a normal adult population [24], depression, anxiety and stress scores were frequently elevated both in patients with fibromyalgia and rheumatoid arthritis (Table 1). However, mean scale scores did not differ significantly between groups (Table 1).

As shown in Table 2, pain at rest was associated with depression in patients with rheumatoid arthritis, whereas pain at rest was associated with stress in the fibromyalgia group. In addition, increases in pain during forehead cooling were associated with indices of psychological distress in patients with rheumatoid arthritis but not in patients with fibromyalgia. A weak association was also detected for arthritic patients during mental arithmetic. However, pain tolerance was unrelated to indices of psychological distress in either group.

Throughout resting periods, pain intensity ratings were greater in participants with fibromyalgia than in participants with rheumatoid arthritis [main effect for Group $F(1,37) = 8.37, p < 0.01$] (Figures 1-3). However, there was no evidence of carry-over effects from one task to the next [main effect for Time, $F(2,64) = 2.00$, not significant; contrasts between each task and the next not significant].

After the acoustic startle stimulus, pain ratings increased briefly in the fibromyalgia group but remained stable in patients with rheumatoid arthritis [Group x Time interaction (baseline to straight after the startle stimulus), $F(1,37) = 4.21, p < 0.05$] (Figure 1A). The pain-facilitatory effect of startle persisted in the fibromyalgia group after controlling for individual differences in psychological distress (Figure 1A), and remained greater in the fibromyalgia than arthritis group after controlling for differences in pain ratings at baseline [main effect for Group, $F(1,36) = 4.45, p < 0.05$] (Figure 1B).

The pain of fibromyalgia and arthritis increased slightly after 30 seconds of painful forehead cooling [$F(1,37) = 6.30, p < 0.05$] and for 10 seconds after the cold stimulus was removed [$F(1,37) = 5.47, p < 0.05$] (Figure 2A), independent of pain ratings at baseline (Figure 2B). Within the fibromyalgia group, pain ratings were significantly greater than baseline 40-80 seconds after the onset of forehead cooling after controlling for individual differences in psychological distress (Figure 2A). However, in a similar analysis for patients with rheumatoid arthritis, arthritic pain did not increase significantly during or after forehead cooling when individual differences in psychological distress were controlled.

Pain increased to a similar extent in both groups after 10 minutes of mental arithmetic [$F(1,37) = 6.56, p < 0.05$], and continued to increase after 15 minutes [$F(1,37) = 7.94, p < 0.01$] and 20 minutes of arithmetic [$F(1,37) = 12.06, p < 0.001$]

(Figure 3A and 3B). When individual differences in psychological distress were controlled, pain ratings within the fibromyalgia group were significantly greater than baseline after 15 minutes of arithmetic (Figure 3A). However, in a similar analysis for patients with rheumatoid arthritis, pain ratings did not differ significantly from baseline at any point during arithmetic.

The time taken to reach pain tolerance during the submaximal effort tourniquet test averaged 144 ± 19 seconds in the rheumatoid arthritis group and 114 ± 13 seconds in the fibromyalgia group. This difference was not significant either before or after adjusting for differences in psychological distress or pain ratings at baseline.

Discussion

The aim of this study was to determine whether the pain associated with rheumatoid arthritis or fibromyalgia would increase during standard laboratory tasks and, if so, whether these increases were linked with indices of psychological distress. In patients with fibromyalgia, pain increased after an acoustic startle stimulus and forehead cooling, and increased during stressful mental arithmetic. These increases were independent of individual differences in psychological distress. Pain also increased during forehead cooling and mental arithmetic in patients with rheumatoid arthritis in association with indices of psychological distress, but did not change after the startle stimulus. The potential implications of these findings for the pathogenesis of fibromyalgia and rheumatoid arthritis are discussed below.

Disruption of central pain modulation processes

In healthy controls, each of the tasks employed in the present study was found to suppress an experimental source of pain [17,18]. Thus, the present findings imply failure of stress-related pain modulation processes in fibromyalgia, and also in distressed patients with rheumatoid arthritis.

One of the key components of fibromyalgia appears to be disruption of broad inhibitory pain modulation processes which, in turn, may augment central sensitization [26]. Whether sensitization of nociceptive pathways accounts for the failure of startle, noxious forehead cooling and mental arithmetic stress to suppress the pain of fibromyalgia is uncertain; nevertheless, it is worth noting that ratings of clinical pain *increased* significantly after controlling for individual differences in psychological distress whereas experimental pain *decreased* significantly in healthy participants during these tasks [17].

Both peripheral and central sensitization could also be important in rheumatoid arthritis. However, there is little evidence that central inhibitory pain modulation processes are compromised [27].

Involvement of the sympathetic nervous system in stress-induced pain

Stress-induced pain might also involve an aberrant peripheral interaction between nociceptive afferent and sympathetic efferent fibres [19,28,29]. This mechanism may augment pain in fibromyalgia [30-32, but see 33].

Similarly, the sympathetic nervous system could play a role in rheumatoid arthritis [34,35], since sympathetic activity modulates the proliferation of immune cells, their migration to sites of inflammation, and cytokine production [36,37]. However, as it may take hours or days for inflammatory effects to be expressed, sympathetic-inflammatory influences on nociceptive activity may not have been captured within the timeframe of the present study.

Stress-induced pain and distress

Genetic-environmental interactions might increase vulnerability both to depression and chronic pain mediated, in part, by neurochemical disturbances in overlapping affective and pain modulation pathways [38]. Depressive symptoms and

other affective responses may also develop in reaction to suffering from pain, possibly aggravated by inflammatory mediators released during psychological stress and wound healing [39]. Depression is extremely common in fibromyalgia [38], and this was confirmed in the present study. Similarities in symptom profiles, pathophysiology and response to pharmacotherapy have led to consideration that they might represent two manifestations of a single underlying disorder [40]. Likewise, co-morbid depression in rheumatoid arthritis is associated with poor health outcomes [41]. This association probably is multifactorial, mediated in some instances by socio-economic factors related to education, income or employment, and in other instances by disease activity or ineffective stress or pain coping strategies.

Pain intensity at rest was greater in fibromyalgia than rheumatoid arthritis patients. However, neither distress ratings nor pain tolerance differed between groups, suggesting that differences in pain intensity did not simply reflect differences in negative affect. Within each group, pain at rest was associated with ratings of depression in rheumatoid arthritis patients and with ratings of stress in patients with fibromyalgia. In addition, arthritic pain during painful forehead cooling increased in line with indices of psychological distress, and an association between depression and stress-induced arthritic pain during mental arithmetic was similar to findings reported previously [14]. Thus, some aspect of distress might contribute to acute increases in stress-induced pain in rheumatoid arthritis.

Limitations and conclusions

The findings must be interpreted within the limitations of this study. These include the small sample size, the fact that participants were recruited from various sources as a convenience sample, possible effects of medication, and the absence of objective measures (e.g., of autonomic, muscular or neurophysiological activity) that

might have clarified nociceptive disturbances. Nevertheless, the findings suggest that processes linked with individual differences in distress aggravate pain in rheumatoid arthritis, whereas some other mechanism (e.g., failure of stress-related pain modulation processes or an aberrant interaction between nociceptive afferent and sympathetic efferent fibres) triggers stress-induced pain in fibromyalgia.

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Table 1

Depression, anxiety and stress in fibromyalgia and rheumatoid arthritis patients

	Mean \pm S.D.	Number of participants (%)		
		Normal Range	Mildly Elevated	Moderate-Severe
Depression				
Fibromyalgia	12.8 \pm 8.5	11 (48%)	2 (9%)	10 (43%)
Arthritis	10.8 \pm 9.3	8 (50%)	2 (12%)	6 (38%)
Anxiety				
Fibromyalgia	8.9 \pm 9.1	11 (48%)	4 (17%)	8 (35%)
Arthritis	6.1 \pm 7.5	11 (69%)	2 (12%)	3 (19%)
Stress				
Fibromyalgia	17.2 \pm 9.9	9 (39%)	4 (17%)	10 (44%)
Arthritis	15.3 \pm 9.0	6 (38%)	4 (25%)	6 (38%)

The normal range was defined as score below the 78th percentile when referenced against a normal adult population [24, Table 9]; a mildly elevated score corresponded with a score between the 78-87th percentiles, and a moderate-severe score above the 87th percentile.

Table 2
 Association between measures of pain and psychological distress in 23 patients with fibromyalgia and
 16 patients with rheumatoid arthritis

	Pearson's Correlation Coefficient					
	Depression		Anxiety		Stress	
	Fibromyalgia	Arthritis	Fibromyalgia	Arthritis	Fibromyalgia	Arthritis
Pain at rest	0.25	0.52*	0.24	0.43	0.43*	0.48
Pain tolerance	-0.20	-0.07	0.01	-0.20	-0.24	-0.07
<u>Maximum increase in pain</u>						
Startle	-0.11	0.35	-0.15	0.08	-0.14	0.33
Forehead cooling	-0.20	0.77*** #	-0.15	0.62** #	-0.21	0.59* #
Arithmetic	-0.07	0.55*	-0.14	0.46	-0.02	0.34

Pearson's correlation coefficient: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Differences between the two groups statistically significant (Fisher's r-to-z transformation, $p < 0.05$).

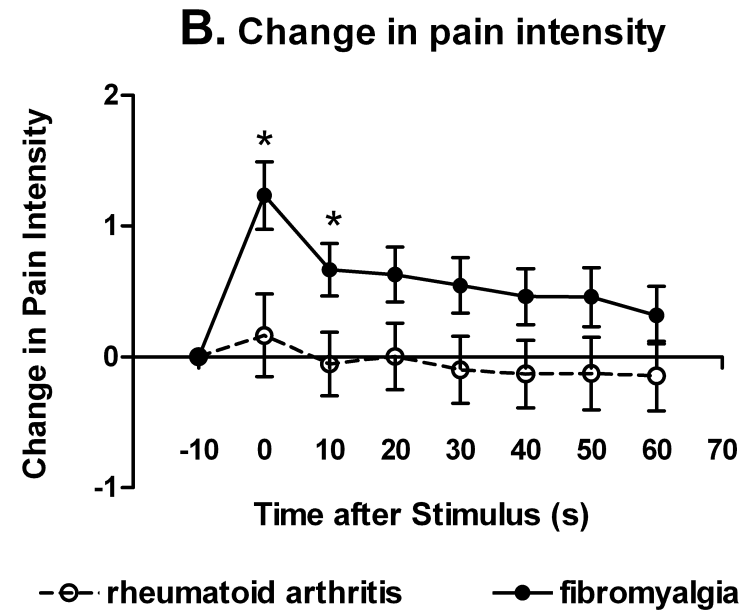
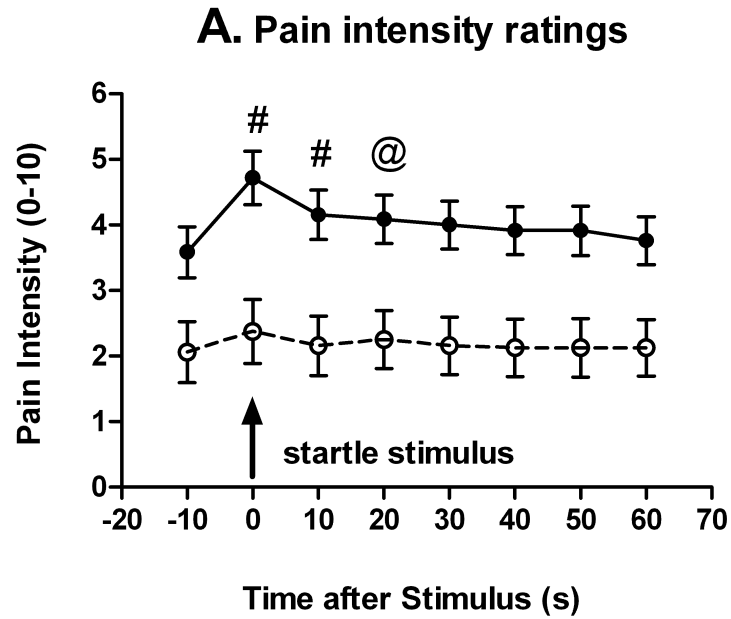
Figure legends

Figure 1. Change in pain (\pm S.E.) after an acoustic startle stimulus (a 1,000 Hz tone, 0.5 second duration, 100 dBA) in 16 patients with rheumatoid arthritis and 23 patients with fibromyalgia. (A) Pain increased in the fibromyalgia group (# $p < 0.05$ compared with baseline; @ $p < 0.05$ compared with baseline after controlling for individual differences in psychological distress) but did not change in patients with rheumatoid arthritis. (B) Increases in pain after the startle stimulus differed significantly between groups (* $p < 0.05$).

Figure 2. Change in pain (\pm S.E.) during and after forehead cooling in 16 patients with rheumatoid arthritis and 23 patients with fibromyalgia. (A) Pain increased in the fibromyalgia group after controlling for individual differences in psychological distress (@ $p < 0.05$ compared with baseline) and in the rheumatoid arthritis group before (# $p < 0.05$ compared with baseline) but not after controlling for individual differences in psychological distress. (B) Changes in pain intensity were similar in both groups after controlling for differences in pain at baseline.

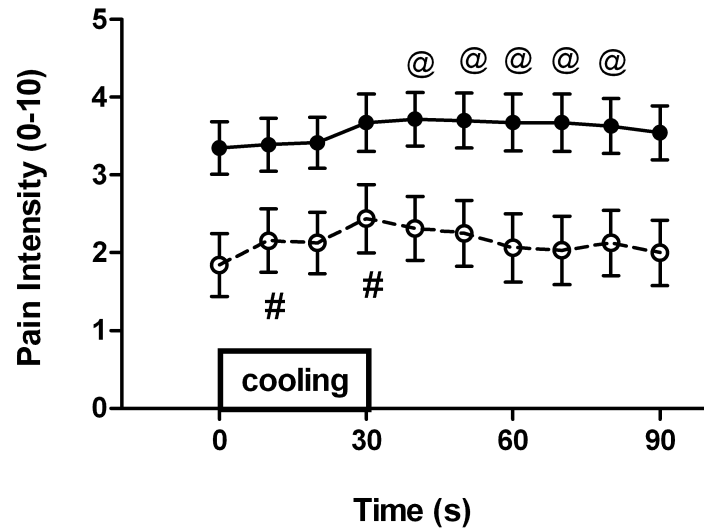
Figure 3. Change in pain (\pm S.E.) during mental arithmetic in 16 patients with rheumatoid arthritis and 23 patients with fibromyalgia. (A) Pain increased in the fibromyalgia group before (# $p < 0.05$ compared with baseline) and after controlling for individual differences in psychological distress (@ $p < 0.05$ compared with baseline), and in the rheumatoid arthritis group before (# $p < 0.05$ compared with baseline) but not after controlling for individual differences in psychological distress. (B) Changes in pain intensity were similar in both groups after controlling for differences in pain at baseline.

Response to the Startle Stimulus

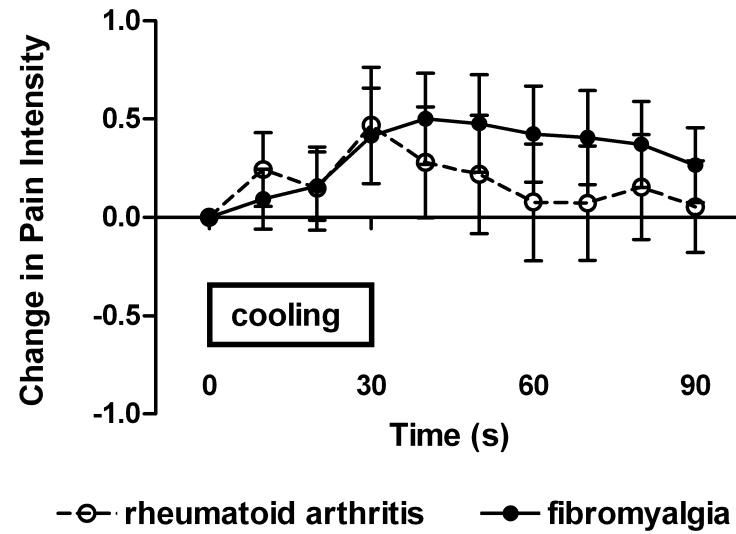


Response to Forehead Cooling

A. Pain intensity ratings



B. Change in pain intensity



Response to Arithmetic

