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Ratings of experimental pain and pain-related negative affect predict clinical pain in patients with fibromyalgia syndrome

Roland Staud[a,*], Michael E. Robinson[b], Charles J. Vierck Jr.[c], Richard C. Cannon[c], Andre P. Mauderli[c], Donald D. Price[d]

[a]*Department of Medicine, McKnight Brain Institute, University of Florida College of Medicine, SW Archer Road, P.O. Box 100221, Gainesville, FL 32610-0221, USA*

[b]*Department of Clinical and Health Psychology, McKnight Brain Institute, University of Florida College of Medicine, SW Archer Road, P.O. Box 100221, Gainesville, FL 32610-0221, USA*

[c]*Department of Neuroscience, McKnight Brain Institute, University of Florida College of Medicine, SW Archer Road, P.O. Box 100221, Gainesville, FL 32610-0221, USA*

[d]*Department of Prosthodontics, McKnight Brain Institute, University of Florida College of Medicine, SW Archer Road, P.O. Box 100221, Gainesville, FL 32610-0221, USA*

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Abstract

Patients with fibromyalgia syndrome (FMS) report chronic pain related to abnormal sensitivity of muscles that is reflected by so-called tender points (TP). TP represent areas of abnormal mechanical pain thresholds that have only shown a minor correlation with clinical pain of FMS patients and seem to be better suited for predicting distress. Pain-related negative affect (PRNA), abnormal temporal summation of second pain (termed wind-up or WU), and abnormal WU decay are frequently present in FMS patients. WU and WU decay can provide measures of central sensitization, which may contribute to clinical FMS pain. We therefore investigated the role of WU, WU decay, TP count, and PRNA as predictors of clinical pain in FMS subjects.

Fifty-five FMS subjects rated their clinical pain at entry into the study using a visual analogue scale (VAS). After a TP evaluation, all subjects received two trials of thermal WU and WU decay testing. Hierarchical regression analysis demonstrated that the combination of PRNA ratings, TP count, and WU decay ratings predicted 49.7% of the variance of clinical pain in FMS. This model demonstrates independent relationships of biological and psychological factors to clinical pain and underscores the important role of abnormal peripheral and central pain mechanisms for FMS. Therefore, the combination of PRNA, TP count, and WU decay may provide an excellent measure for future clinical studies of FMS patients.

Keywords: Fibromyalgia; Muscle; Predictor; Chronic pain intensity; Temporal summation

1. Introduction

Widespread musculoskeletal pain is required for the diagnosis of fibromyalgia syndrome (FMS). The pain is most consistently described as dull and aching and appears to be related to deep tissue structures. Accordingly, FMS patients will present with widespread tenderness to mechanical stimulation of deep tissues (Simms et al., 1988; Arroyo and Cohen, 1993; Berglund et al., 2002). Tenderness in FMS is usually assessed by pressure algometry, the reliability of which has been reported previously (Jensen et al., 1986; Ohrbach and Gale, 1989a; Ohrbach and Gale, 1989b; Kosek et al., 1993). There is convincing evidence of generalized lower pressure pain thresholds in FMS patients compared to normal controls (NC) (Lautenschlager et al., 1988; Quimby et al., 1988; Tunks et al., 1988; Wolfe et al., 1990; Mikkelsson et al., 1992; Granges and Littlejohn, 1993; Kosek et al., 1995). The muscle tenderness of FMS patients is reflected by the allodynia of tender point (TP) which have been defined for 18 areas of the body by the American College of Rheumatology (ACR) (Wolfe et al., 1990). In contrast to NC, FMS patients report pain at TP sites when stimulated with pressures of ≤ 4 kg (Wolfe et al., 1990). TP counts of FMS patients have shown a disappointing lack of predictability for clinical pain in most studies

* Corresponding author. Tel.: +1-352-392-4681; fax: +1-352-392-8483.
E-mail address: staudr@ufl.edu (R. Staud).

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(Granges and Littlejohn, 1993; Wolfe, 1997; Jensen et al., 2000). They are, however, strongly associated with specific components of psychological distress (Wolfe, 1997; McBeth et al., 1999). Furthermore, TP appear to be a useful predictor of health care use, and disability in FMS (Croft et al., 1994a).

There is a strong association of clinical pain with negative mood (Keefe et al., 1986; Gaskin et al., 1992; Geisser et al., 1994; Robinson and Riley, 1998; Basbaum, 1999), and this relationship has been detected in many (Almay, 1987; Burckhardt et al., 1992; Wolfe, 1997; Wolfe et al., 1997) but not all FMS studies (Malt et al., 2002). Therefore, it appears that widespread mechanical tenderness predisposes FMS patients to psychological distress but not to pain.

Besides mechanical allodynia, other psychophysical abnormalities have been well characterized in FMS patients, including temporal summation of second pain or wind-up (WU) (Vierck et al., 2001; Staud et al., 2001; Price et al., 2002; Staud et al., 2003a). WU depends on input from unmyelinated (C) fiber afferents that can activate central *N*-methyl-D-aspartate (NMDA) receptor systems associated with enhancement of pain. WU and WU decay also likely rely on substance P neuromodulation in the dorsal horn (Kellstein et al., 1990; Price et al., 1994a; Budai and Larson, 1996). WU occurs only if the stimulation frequency of C-nociceptors is greater than once every 3 s (Mendell, 1966; Price, 1972; Price et al., 1977, 1978). This critical frequency appears to mimic the natural frequency of peripheral C-nociceptors that discharge at about once every 1–2 s at stimulus intensities likely to be minimally painful (Torebjork and Hallin, 1974). WU can be used to assess central pain processing and is relevant for chronic pain (Price et al., 1994a; Arendt-Nielsen and Petersen-Felix, 1995). Using repetitive thermal stimuli, FMS subjects not only show increased WU compared to NC (Staud et al., 2001; Price et al., 2002; Staud et al., 2003b), but also prolonged after-sensations (i.e. slower WU decay), both of which may reflect central sensitization (Dickenson and Sullivan, 1991; Price et al., 1994b; Li et al., 1999). In addition to stimulus frequency, WU depends on the subject's sensitivity to stimulus intensity (WU sensitivity) (Dickenson and Sullivan, 1991).

Because central sensitization may play a pivotal role for FMS clinical pain, we hypothesized that ratings of WU decay would be useful predictors for clinical pain of FMS subjects. We also wanted to evaluate the contribution of WU sensitivity, TP counts, and pain-related negative affect (PRNA) to the variance in clinical pain intensity of FMS subjects.

2. Materials and methods

The University of Florida Institutional Review Board approved all procedures described in this report. Informed consent was obtained from all subjects, and the study protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.1. Study subjects

Fibromyalgia subjects were recruited at the Health Science Center Outpatient Clinics and from FMS support groups. Prior to testing, all subjects underwent a clinical examination and were excluded from the study if they had abnormal clinical findings unrelated to FMS, including tenderness and pain from inflammatory joint disease, severe osteoarthritis, sciatica, and peripheral neuropathies. Continuation of analgesics, including non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen, were not allowed during the study. The subjects were asked to discontinue narcotic analgesics at least 2 weeks prior to study entry. Low dose muscle relaxants and amitriptyline (<15 mg/day) were permissible during the study for treatment of insomnia.

Fifty-eight subjects (48 females, 10 males) were enrolled in this study. All subjects were right handed, and all were Caucasian except for two African American and two Hispanic females. The average age ($\pm$SD) of the FMS subjects was 49.2 $\pm$ 8.1 years. During preliminary assessments three Caucasian female subjects had to be excluded from the study because they did not achieve the WU magnitude required for WU decay testing (Section 2.6.1). The demographics of the remaining 55 study subjects are listed in Table 1.

2.2. Ratings of clinical pain

Before the psychophysical testing session, the FMS subjects rated their current clinical pain using a mechanical visual analogue scale (M-VAS) (Price et al., 1983) ranging from 0 to 100. The scale was anchored on the left with 'no pain at all' and on the right with 'the most intense pain imaginable'.

2.3. Ratings of experimental pain

A numerical pain scale (NPS) with verbal anchors (Vierck et al., 1997) was utilized for rating the magnitude of late sensations produced by thermal stimulation. A printed copy of the ratings was constantly observable and consisted of integers in increments of 5, from 0 to 100. Ratings of 20 and 100 were defined as pain threshold and intolerable pain, respectively. Previous experience with the scale has shown that increments of 5 provide appropriate resolution for the discriminable levels of late sensation intensity from threshold to nearly intolerable levels (Vierck et al., 1997). Subjects were instructed to remove their hand from the apparatus at any time when sensory intensity reached a nearly intolerable level, so that intolerable sensory levels would never be produced.