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Psychological Factors Predict Local and Referred Experimental Muscle Pain: A Cluster Analysis in Healthy Adults

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Abstract

Background—Recent studies suggest an underlying three- or four-factor structure explains the conceptual overlap and distinctiveness of several negative emotionality and pain-related constructs. However, the validity of these latent factors for predicting pain has not been examined.

Methods—A cohort of 189 (99F; 90M) healthy volunteers completed eight self-report negative emotionality and pain-related measures (Eysenck Personality Questionnaire-Revised; Positive and Negative Affect Schedule; State-Trait Anxiety Inventory; Pain Catastrophizing Scale; Fear of Pain Questionnaire; Somatosensory Amplification Scale; Anxiety Sensitivity Index; Whiteley Index). Using principal axis factoring, three primary latent factors were extracted: General Distress; Catastrophic Thinking; and Pain-Related Fear. Using these factors, individuals clustered into three subgroups of high, moderate, and low negative emotionality responses. Experimental pain was induced via intramuscular acidic infusion into the anterior tibialis muscle, producing local (infusion site) and/or referred (anterior ankle) pain and hyperalgesia.

Results—Pain outcomes differed between clusters (multivariate analysis of variance and multinomial regression), with individuals in the highest negative emotionality cluster reporting the greatest local pain ($p = 0.05$), mechanical hyperalgesia (pressure pain thresholds; $p = 0.009$) and greater odds (2.21 OR) of experiencing referred pain compared to the lowest negative emotionality cluster.

Conclusion—Our results provide support for three latent psychological factors explaining the majority of the variance between several pain-related psychological measures, and that individuals in the high negative emotionality subgroup are at increased risk for (1) acute local muscle pain; (2) local hyperalgesia; and (3) referred pain using a standardized nociceptive input.

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1. Introduction

Individuals seek medical attention for musculoskeletal pain more than any other pain (Hasselstrom et al., 2002); making it a major health problem with considerable societal and individual costs (Mantyselka et al., 2002). Unfortunately, musculoskeletal pain is often poorly correlated to physical or pathologic findings (Turk, 1999). This discrepancy may be explained by a biopsychosocial model, where pain is the complex interplay between physical, psychological and social factors (Turk & Monarch, 2002; Turk & Okifuji, 2002). Research supports the role of psychological factors (i.e., negative emotionality and pain-related constructs) on the perception of pain in clinical (George et al., 2007b; Turk et al., 2004) and experimental pain (Bishop et al., 2011; George et al., 2006; George et al., 2008; Lee et al., 2010; Parr et al., 2012; Rhudy et al., 2011; Robinson et al., 2010; Trost et al., 2011).

Several measures are commonly used to investigate associations between psychological factors and pain (e.g., Pain Catastrophizing Scale, Fear of Pain Questionnaire, Trait Anxiety Inventory), and many of these scales are significantly correlated (Dixon et al., 2004; George et al., 2006; George et al., 2007a; Lee et al., 2010; Vancleef et al., 2006). Indeed, two recent studies found similar latent structures modeled the conceptual overlap and distinctiveness of these measures. The three underlying factors were described by Mounce (Mounce et al., 2010) and Vancleef (Vancleef et al., 2009), respectively, as: 1) General Distress or Negative Emotions; 2) Fear of Pain from Injury/Insult or Physical Health Concerns; and 3) Cognitive Intrusion of Pain or Pain-Specific Concerns. A 4th factor (Cognitive Performance Concerns) was reported by Vancleef and colleagues, but the authors confirmed both three- and four-factor structures provide consistent evidence for a reduced set of latent factors (Vancleef et al., 2011).

Although these studies examined the underlying structure of pain-related psychological constructs, neither study assessed how individuals are subgrouped based on these latent psychological factors, or whether the latent variables are predictive of pain. Further, no known studies examine these associations for acute peripherally (local) - versus centrally-mediated (referred) muscle pain sensitivity. Thus, the aims of this study were to: 1) examine whether a latent structure of pain-related psychological constructs would be observed; 2) determine if subgroups of individuals could be differentiated based on these latent psychological factors; and 3) analyze whether these subgroupings predicted experimentally-induced acute local and referred muscle pain. We hypothesized that: 1) we would find similar latent psychological factors as those observed by Mounce, Vancleef and colleagues; 2) small clusters of individuals (i.e., 2 to 5) would group together based on these latent baseline psychological factors; and 3) consistent with biopsychosocial theories, individuals with high negative emotionality, catastrophizing and/or pain-related fear would experience greater local and referred muscle pain sensitivity.

2. Methods

2.1 Participants

Healthy, pain-free volunteers (N = 189; 99F, 90M) were recruited from the local and University communities. Age range was from 18 to 54 years (see Table 1 for participant characteristics). Self-reported race and ethnicity was 92.1% Caucasian, 3.7% Asian, 3.7% Hispanic, and 0.5% Native American. Exclusion criteria included: significant current or past medical conditions (e.g., diabetes, asthma, and heart disease), pregnancy, current pain, history of chronic pain, prescription analgesics or medications (other than birth control or vitamins), previous loss of sensation or feeling in the arms or legs, or major left leg injury or surgery (e.g., ligament or muscle tear, fracture, etc.). All participants provided written,

informed consent prior to participation, as approved by the University of Iowa Biomedical Institutional Review Board, and were compensated for their time.

2.2 Psychological Measures

A total of eight validated psychological measures were assessed in this study. These constructs were chosen to represent several measures of negative affect/general distress, anxiety, anxiety sensitivity, catastrophizing, pain-related fear, and somatization/hypervigilance. These various pain-related variables are proposed to be related to the development of chronic pain (Leeuw et al., 2007; Vlaeyen & Linton, 2000) and several have been used in isolation or combination in other acute pain studies (Bishop et al., 2011; George et al., 2006; George et al., 2008; Lee et al., 2010; Rhudy et al., 2011; Robinson et al., 2010; Trost et al., 2011). There are additional psychological measures that are commonly used in clinical samples; however, we were interested in baseline psychological assessments, and thus eliminated instruments that assume or inquire about current clinical pain in most previous studies (i.e., Tampa Scale for Kinesiophobia or Fear-Avoidance Beliefs Questionnaire).

Neuroticism was assessed using the Eysenck Personality Questionnaire-Revised (EPQ-R), a commonly-used personality instrument (Eysenck & Eysenck, 1994). It consists of one hundred yes or no questions, twenty-four of which are used for the neuroticism subscale. Higher neuroticism scores indicate an anxious, worrisome, pessimistic, and overly emotional personality. The EPQ-R neuroticism scale has an internal consistency score of 0.86 and 1-month test-retest reliability of 0.89 (Eysenck & Eysenck, 1994).

Negative affect was assessed using the trait version of the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988). The instrument consists of twenty single mood descriptors, ten measuring negative affectivity. Participants rate each word (e.g., “guilty”, “distressed”) in terms of the extent to which they “generally feel this way, that is, on the average” (i.e., general instructions) on a 5-point scale ranging from “very slightly or not at all” to “extremely.” The PANAS is a valid and reliable measure, with an internal consistency of 0.87 and 8-week test-retest reliability of 0.68 for the negative affect scale (Watson et al., 1988).

Trait anxiety (TA) was assessed using the State-Trait Anxiety Inventory (Spielberger, 1983), a forty-item measure that differentiates between the temporary condition of “state” anxiety and the more general and long-standing quality of “trait” anxiety. The “trait” scale consists of twenty items that assess how respondents “generally” feel regarding each statement (e.g., “I feel at ease”) on a scale of 1 (almost never) to 4 (almost always). The Trait Anxiety Inventory has good validity and reliability, with a mean internal consistency score of 0.89 and mean test-retest reliability of 0.88 (Barnes et al., 2002).

The Fear of Pain Questionnaire (FPQ) (McNeil & Rainwater, 1998) is a thirty-item self-report measure of pain-related fear, with three subscales: minor pain, severe pain, and medical pain. Participants rate their anticipated fear of the pain associated with each event on a 5-point scale ranging from “not at all” to “extreme”. The FPQ is a valid and reliable measure, with an internal consistency of 0.92 and a 3-week test-retest reliability of 0.74 (McNeil & Rainwater, 1998).

The Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995) is a thirteen-item self-report measure of the extent to which individuals experience different catastrophic thoughts and feelings when in pain. Participants rate how frequently each statement reflects their general experience with pain (i.e., dispositional) on a 5-point scale ranging from “not at all” to “all of the time”. The PCS has three subscales: helplessness, rumination, and magnification. The

PCS is a valid and reliable measure, with an internal consistency of 0.87 and 6- and 10-week test-retest reliabilities of 0.75 and 0.70, respectively, among healthy adults (Sullivan et al., 1995).

The Anxiety Sensitivity Index (ASI) (Reiss et al., 1986) is a sixteen-item self-report measure of anxiety-related fear. Statements are rated on a 5-point scale ranging from “very little” to “very much”. Three subscales have been validated for the ASI: physical, cognitive, and social concerns (Zinbarg et al., 2001). The ASI is a reliable scale, with 2-week and 3-year test-retest reliabilities of 0.75 (Reiss et al., 1986) and 0.71 (Maller & Reiss, 1992), respectively, and an internal consistency score of 0.83 (Vujanovic et al., 2007).

The Somatosensory Amplification Scale (SSAS) (Barsky et al., 1990) is a ten-item self-report measure of sensitivity to a range of normal bodily sensations. Participants rate statements on a 5-point scale ranging from “not at all true” to “extremely true,” where higher scores indicate greater perceived bodily sensitivity. The SSAS demonstrates adequate validity and reliability, with an internal consistency of 0.82, test-retest reliability (~74 days) of 0.79 (Barsky et al., 1990), and good discriminant validity (Speckens et al., 1996). According to Speckens (Speckens et al., 1996) and Longley (Longley et al., 2005), the SSAS consists of a single factor loading primarily on a reduced set of 7 items (items 4 through 10). Thus, we only used this single seven-item ‘total score’ as the primary subscale for the SSAS in this study.

Health concerns were assessed using the Whiteley Index (WI), a fourteen-item self-report measure of hypochondriacal worries and beliefs (Pilowsky, 1967). Participants rate each statement on a 5-point scale, ranging from “not at all” to “extremely”. Although, multiple factor structures for the WI have been reported (Conradt et al., 2006; Hiller et al., 2002; Rief et al., 1998; Speckens et al., 1996), we used the 2-factor solution proposed by Longley et al. (Longley et al., 2005). This WI structure includes cognitive and affective subscales. The WI has an internal consistency of 0.80 and a test-retest reliability of 0.90 (Speckens et al., 1996).

2.3 Experimental Pain Model

A relatively new experimental muscle pain model, the intramuscular infusion of acidic phosphate buffer (pH 5.2), was used to induce the experimental muscle pain. This model has been previously described in both the extensor muscles of the forearm (Issberner et al., 1996) and the anterior tibialis of the shin (Frey Law et al., 2008). Intramuscular infusions provide a safe and reliable model of musculoskeletal pain, allowing control over the pain stimulus location, duration, and intensity (Graven-Nielsen, 2006), while producing a pain quality similar to clinical muscle pain (Graven-Nielsen et al., 1997; Svensson et al., 1997). Finally, experimental pain allows us to assess baseline psychological measures prior to experiencing pain, minimizing the potential confounds of pain-induced negativity and eliminating the inherent variability in underlying pathology among clinical populations.

The intramuscular infusion was performed largely as previously described (Frey Law et al., 2008). Briefly, muscle soreness was induced by infusing a sterile, acidic (pH 5.2) phosphate buffer solution at 40 ml/hr (Model A-99 syringe pump, Razel Scientific Instruments, USA) into the mid-belly portion of the anterior tibialis muscle for five minutes. In our previous characterization of this model, we infused the acidic buffer for fifteen minutes, but found that peak pain was achieved by three minutes and remained roughly constant thereafter (Frey Law et al., 2008); thus we reduced the total infusion time to five minutes for this study. This model produces rate-dependent pain (Issberner et al., 1996), but not volume-dependent pain as pain ratings do not change beyond the first few minutes of infusion.

despite the steady increase in total volume over time (Frey Law et al., 2008). This suggests the model is not sensitive to the muscle volume of each participant.

The acidic muscle infusion model typically produces light to moderate local muscle soreness at the injection site (anterior shin) and referred pain to the anterior ankle joint (in approximately 60% of individuals) (Frey Law et al., 2008). When the infusion is stopped, the pain decays rapidly over a period of 3-4 minutes (Frey Law et al., 2008). The intramuscular infusion of an acidic buffer is a safe and reliable method to induce nociceptor-specific acute muscle pain (Frey Law et al., 2008; Issberner et al., 1996). The anterior tibialis muscle was chosen due to its well-defined and distinct local and referred pain patterns (Frey Law et al., 2008; Graven-Nielsen et al., 1997). Referred pain is believed to be due to centrally-mediated pain processing (Graven-Nielsen, 2006). Thus, both peripheral and central pain sensitivity are incorporated in this model.

Participants completed this study in two visits. They were blinded to the pain infusion condition, as they received either a saline control or the acidic buffer infusion at each visit, separated by approximately ten days, in a blocked-random order. Only the acidic test condition pain results are considered here.

2.4 Pain Assessment

2.4.1. Pain Intensity—Participants were asked to verbally rate their pain intensities at the infusion site and the ankle/foot region (site of referred pain; Graven-Nielsen et al., 1997) every 30 seconds during the infusion and then every 60 seconds during the ‘recovery’ period. We used a 0-10 numeric pain rating scale, the Borg Category-Ratio 10 (CR10). This scale allows for fraction or decimal ratings and has demonstrated ratio properties for rating sensory perceptions (Borg, 1998). A written script, modified from (Borg 1998), was read to each participant to ensure consistent instructions for scale use. Highest pain intensity ratings at the infusion site (i.e., local pain intensity) and ankle/foot (i.e., referred pain intensity) regions were extracted as peak pain values. Pain incidence was operationally defined as the presence or absence of pain (peak pain ≥ 0.5) at each location (i.e., local and referred pain incidence).

2.4.2. Mechanical Hyperalgesia—Pressure pain thresholds (PPT) are a common and reliable (Chesterton et al., 2003; Rolke et al., 2005) means to measure mechanical sensitivity. We assessed PPTs at six locations on bilateral lower extremities as previously described (Frey Law et al., 2008) using a hand-held digital pressure algometer with a 1-cm² tip (Somedic AB, Farsta Sweden) at a rate of 30 kPa/s. The mean of four PPT repetitions were used for baseline and during-pain assessments. Only PPTs surrounding the infusion site (i.e., the average of ~4 centimeters above and below the infusion site on the anterior tibialis muscle) and the referred pain site (anterior ankle) were considered in this study. The remaining locations did not change, and served as within subject controls. Participants were instructed to press an indicator button when they first experienced pain, approximately a 1 (“light pain”) on the CR10 scale. The mean PPT scores were standardized by their respective baseline values (%PPT). Deep-tissue mechanical hyperalgesia (increased pain sensitivity) was indicated by lower PPTs (i.e., values less than 100%), whereas hypoalgesia (decreased pain sensitivity) was indicated by elevated PPTs (i.e., values greater than 100%).

2.4.3. Procedures—Participants completed two sessions, lasting approximately ninety minutes each. All of the psychological measures were completed in a pain-free state (baseline), prior to the intramuscular infusions (control or acidic). The order of the psychological measures was randomized to minimize testing order or fatigue effects, with

approximately half assessed prior to the control infusion and half prior to the test infusion (also randomized).

2.4.4. Analyses—Descriptive statistics (mean, standard deviation) were determined for each study variable, including separate means and standard deviations for males and females (SPSS v20). Independent samples t-tests were used to test for significant differences between the sexes in the psychological measures. Significance was set at $p = 0.05$ for all statistical analyses.

2.4.5. Factor Analysis—A total of 15 psychological subscales (or total scales if no validated subscales have been reported) from the 8 instruments (see above) were considered in the factor analyses. First, Pearson product-moment correlation coefficients were calculated among each of these fifteen psychological scales/subscales. Next, Principal Axis Factoring (PAF) with Oblimin rotation (SPSS v20 and verified using SAS v20) was used to examine the underlying or latent factor structure of the psychological measures. Factor eigenvalues, visual examination of the Scree plot (Cattell, 1966), and ease of factor interpretation were used to determine the most appropriate number of latent variables to extract. Latent variables were then calculated from the optimal factor structure using the regression option in SPSS for all subsequent analyses.

2.4.6. Cluster Analysis—Cluster analysis was used to subgroup the participants, using the factor scores from the previous analysis as indicators. Two-step clustering (SPSS v20), with Log-Likelihood distance measures and Schwarz's Bayesian Information Criterion (BIC) (Schwarz, 1978), was used to determine participant subgroups (automatically considering up to 15 clusters). Two-step clustering first assigns cases to 'preclusters', then uses hierarchical clustering algorithms to determine final group membership. The BIC provides a systematic approach for comparing the possible cluster models, without a priori assignment of cluster numbers (Fraley & Raftery, 1998), thus providing an unbiased estimate of optimal cluster number (Kayri, 2007). Secondary hierarchical cluster analyses using Ward's method with Pearson's Correlation Coefficients were also calculated to ensure consistent cluster membership with the two-step methodology. Cluster membership was then saved as a categorical variable (SPSS v20). Multivariate analysis of variance (ANOVA) was used to confirm differences in baseline psychological variables (both the latent psychological factors and the original psychological measures) between the final cluster subgroups.

2.4.7. Pain Responses between Cluster Subgroups—Multivariate ANOVA was used to compare pain intensity and hyperalgesia responses between the cluster subgroups, to test for pain patterns that correspond to the psychological subgroupings. If significant between-group differences for the continuous variables (local and referred peak pain intensity and local and referred mechanical hyperalgesia, % of baseline) were observed, Tukey's post-hoc tests were performed. For the dichotomous pain incidence variables, multinomial logistic regression was used to determine the odds of experiencing local and referred pain between cluster memberships, using the lowest negative emotionality cluster as the referent.

3. Results

3.1. Psychological Measures

Summary statistics for the demographic and psychological variables are provided in (Table 1). All psychological scale scores were normally distributed and within expected population-based norms. Females had significantly higher neuroticism, fear of pain (severe subscale

only) and somatosensory amplification scores than males. No other sex differences were observed.

3.2. Experimental Muscle Pain

Peak local pain intensity at the infusion site typically averaged 2.1 (SD = 1.5) across all participants (range: 0.0 to 8.0 out of 10). Incidence of local pain at the infusion site was 88.8% of the total sample. Mean local pain only in those experiencing pain was 2.4 (SD = 1.4). Referred peak pain intensity averaged 1.0 (SD = 1.2) at the anterior ankle/foot region across all participants, ranging from 0.0 to 7.0. Incidence of referred pain was 60.1% of the participants. Of those experiencing referred pain, the average peak intensity was 1.6 (SD = 1.2). No significant sex differences were observed in local or referred pain intensity ($p = 0.78$ and $p = 0.19$, respectively) or incidence ($p = 0.10$ and 0.38 , respectively) in this cohort.

3.3. Correlations among Psychological Measures and Factor Analysis

The psychological measures demonstrated numerous significant positive inter-correlations (table S1), with 83% (87 of 105) achieving significance at the $p = 0.05$ level. Of the 15 total psychological scales and subscales, 13 were correlated with at least 11 other measures; ASI physical, WI affective and the SSAS total were associated with every other psychological measure. These significant correlations support the use of factor analysis to explore their underlying structure.

Factor analysis most clearly supported a three-factor solution. The Scree plot demonstrated a “stress elbow” at three factors. However, based on previous literature (Mounce et al., 2010; Vancleef et al., 2011; Vancleef et al., 2009), both 3- and 4-factor solutions were considered. The 3-factor solution had unrotated eigenvalues of 1.5 through 5.0, was readily interpretable, explained 55.9% of the total variance, and all variables except SSAS total and ASI social concerns clearly loaded (i.e., > 0.3) on one or more factors. The four-factor solution only explained an additional 8% of the total variance, did not improve the factor loadings for the SSAS total or ASI social subscale (i.e., still < 0.3), resulted in greater dual-factor loadings, and provided no clear improvement over the simpler three-factor solution. Thus, we selected the three-factor solution as the most parsimonious and clearly defined model (see Table 2). Based on the primary loadings for each factor, we labeled them as: 1) General Distress; 2) Catastrophic Thinking; and 3) Pain-Related Fear, with corresponding rotated eigenvalues of 4.98, 1.50, and 1.90, respectively.

The General Distress factor was defined primarily by the three global measures of neuroticism and negative affect: the EPQ-R neuroticism (loading = 0.89), STAI trait anxiety (0.84), and PANAS negative affect scales (0.65). In addition, the cognitive subscales of the ASI (0.38) and WI (0.31) loaded with the General Distress factor, along with a modest contribution from SSAS (0.25). Catastrophic Thinking, the second factor, included the three PCS subscales (loadings ranged from 0.67 to 0.86), and also consisted of loadings (0.30) for the WI affective (0.46), WI cognitive (0.30) and ASI physical concerns (0.37) subscales. The third factor, Pain-Related Fear, consisted primarily of subscales from the FPQ (loadings ranged from 0.68 to 0.85), with secondary loadings from the SSAS (0.22) and the ASI physical subscale (0.25).

3.4. Cluster Analysis

Individual's best fit into three clusters using the three latent psychological variables (i.e., General Distress, Catastrophic Thinking, Pain-Related Fear, Figure 1). These three clusters produced the lowest Schwarz's BIC (321.5) and the largest ratio of distance measures (2.2) when considering 1 to 15 subgroupings. Multivariate ANOVAs confirmed that the three clusters were well differentiated by the cluster solution (Wilks' Lambda = 0.175, $F[6,368] =$

85.1, $p < 0.0001$). In addition, univariate ANOVAs confirmed that each baseline psychological variable was significantly differentiated between the clusters, but no cluster differences were observed for age or sex (Table 3).

The three clusters were differentiated based on all three latent variables. Cluster 1 was the smallest cluster ($n = 50$) and contained individuals scoring highest on all three latent psychological factors: high General Distress, Catastrophic Thinking and Pain-Related Fear. Follow-up univariate analyses demonstrated that scores on every psychological scale and/or subscale were highest for Cluster 1, except the FPQ minor and severe pain subscales (though they were very similar to Cluster 2; Figure 1, Table 3). Cluster 2 was the largest cluster ($n = 71$) and was characterized by low General Distress, moderate Catastrophic Thinking, and high Pain-Related Fear (Figure 1). This cluster contained individuals with low neuroticism, negative affect and trait anxiety scores, moderate scores on the PCS, ASI, and WI subscales, moderate SSAS total score, and high FPQ subscale scores (Table 3). Thus, these individuals were mixed on their negative emotionality scores (high fear but low general distress). Cluster 3 contained 68 people and generally consisted of individuals scoring lowest on all three latent psychological measures: low General Distress, Catastrophic Thinking and Pain-Related Fear. Similarly, the baseline psychological scales and subscales demonstrated this subgroup consistently scored the lowest on all the negative emotionality measures assessed (Table 3). Accordingly, we labeled the 3 clusters: high negative emotionality, high fear only, and low negative emotionality, based on their respective psychological characterizations.

3.5. Pain Responses between Clusters

Pain responses differed significantly between clusters of individuals, with the subgroupings based solely on their baseline psychological measures (Table 4, Figure 2). The high negative emotionality subgroup reported significantly higher local pain intensity compared to the low negative emotionality subgroups, but not compared to the high fear only subgroup. Local hyperalgesia was greater in the high negative emotionality cluster than the high fear only cluster, but no significant differences were observed between the low negative emotionality and the fear only clusters. Thus, the highest negative emotionality subgroup reported the greatest local pain and hyperalgesia relative to either the high fear only or low negative emotionality subgroups, depending on the assessment. The incidence of local pain did not significantly differ between the 3 clusters (p 's > 0.05) and the highest odds ratio observed (2.26 OR, 95% CI: 0.86 to 5.92, high versus low negative emotionality subgroups) was not significant ($p = 0.10$).

While there were no significant differences between the 3 subgroups for referred peak pain intensity or referred hyperalgesia (p 's > 0.05), referred pain incidence was 2.2 times more likely to occur in the high negative emotionality subgroup ($p = 0.046$, 95% CI: 1.01 to 4.84 OR) compared to the low negative emotionality subgroup, controlling for sex. The odds of experiencing referred pain were not significantly different, however between the high negative emotionality and the high fear only subgroups (OR = 1.88, $p = 0.11$, 95% CI: 0.87 to 4.09).

4. Discussion

Our study confirmed that three latent factors: General Distress, Pain-Related Fear, and Catastrophic Thinking, best explain the common variance observed in eight pain-related psychological measures. Individuals clustered into three subgroups based on these factors: (1) high negative emotionality: consistently high scores across all three latent psychological factors; (2) high fear only: high Pain-Related Fear, moderate Catastrophic Thinking, but low General Distress; and (3) low negative emotionality: low scores across all three latent factors. Based on these factors, individuals in the high negative emotionality subgroup

experienced the greatest local pain and hyperalgesia, and had greater odds of referred pain than the low negative emotionality subgroup. Individuals in the high fear subgroup were unique in showing the most heterogeneity between the latent factors. Our findings suggest the combination of, and possibly interaction between, high baseline general distress, catastrophic thinking and pain-related fear predict increased acute local and referred muscle pain.

These results are partially consistent with previous investigations that found fear of pain (George et al., 2006; George et al., 2007a; Parr et al., 2012), pain catastrophizing (Dixon et al., 2004; Sullivan et al., 2004; Thorn et al., 2004), or other pain-related measures (James and Hardardottir, 2002; Jones & Zachariae, 2004; Lee et al., 2010; Robinson et al., 2004) were predictive of other experimental pain modalities (e.g., cold pressor, delayed onset muscle soreness). However, ours is the first study to suggest a combination of elevated levels of all three latent characteristics may be most informative. This could provide some insight into the seemingly contradictory results between previous studies indicating either catastrophizing or fear of pain is the main predictor of musculoskeletal pain or disability (George et al., 2005; George et al., 2006; George et al., 2007a; George et al., 2008). It is possible that elevated levels of fear and catastrophizing (in combination with general distress) are most influential, rather than either in isolation. Indeed, individual differences may suggest that one or the other is more predictive of pain in certain individuals, but by clustering individuals into subgroups, we can better discern how consistently high negative emotionality scores may lead to increased muscle pain and hyperalgesia. Interestingly, our clusters of healthy individuals based on psychological factors were similar to those found in previous studies that identified subgroupings of patients diagnosed with musculoskeletal pain (Beneciuk et al., 2012; Boersma and Linton, 2005). They observed subgroupings of individuals characterized by: (1) high pain-related fear/avoidance and catastrophizing; (2) high fear only; and (3) low pain-related fear/avoidance and catastrophizing. Boersma and Linton (2005) also reported depressed mood influenced the subgroupings, but we did not examine depressed mood in our study.

This is the only study we are aware of that examined associations between psychological constructs and referred pain in a healthy sample. Referred pain is thought to be centrally mediated (Graven-Nielsen et al., 1997), suggesting these negative emotionality factors (General Distress, Catastrophic Thinking and Pain-Related Fear), may be acting through centrally-mediated pain processes and thereby influencing both peripheral and centrally-mediated pain perceptions. Moreover, these results are consistent with a recent study reporting significant associations between catastrophizing and temporal summation of pain (Robinson et al., 2010), theorized to be related to C-fiber mediated dorsal-horn central sensitization (Staud et al., 2007). Along these same lines, pain catastrophizing was related to temporal summation in a prior study involving patients with chronic low back pain (George et al., 2007b).

One biopsychosocial model of chronic pain, the fear-avoidance model (FAM), suggests pain catastrophizing leads to fear which, in turn, leads to disuse, depression, and disability, and continued or exacerbated pain (Vlaeyen & Linton, 2000). This is predominantly an indirect, negative feedback model, which suggests that the psychological factors indirectly influence pain through behavior (i.e., avoidance and disuse). We propose these associations between general distress, fear, and catastrophizing may also exhibit a feed-forward process or general vulnerability to higher pain as demonstrated by our results and other experimental pain studies reporting correlations between baseline psychological measures and pain (Dixon et al., 2004; George et al., 2006; George et al., 2007a; Lee et al., 2010; Robinson et al., 2004; Sullivan et al., 2004; Thorn et al., 2004; Trost et al., 2011). This does not preclude the likelihood that these psychological factors may also act concurrently to facilitate the

development and maintenance of chronic pain according to the traditional FAM, but rather suggests additional predictive aspects of these latent psychological factors. Future studies are needed to assess whether catastrophic thinking, pain-related fear, and/or general distress are important constructs to measure prior to (e.g., preoperatively) and/or immediately after the onset of acute muscle pain to identify individuals at risk for developing chronic pain. Indeed, evidence suggests acute pain intensity is a risk factor for the development of chronic pain (Hanley et al., 2007; Katz et al., 1996). Thus, vulnerability factors for elevated acute pain may be important to consider for the transition from acute to chronic musculoskeletal pain.

Our results confirm the results from two prior studies that also demonstrated a reduced factor structure explains the covariance between pain-related psychological measures in healthy adults (Mounce et al., 2010; Vancleef et al., 2009; Vancleef et al., 2011). Although there are discrepancies between these three studies, our results are consistent with a relatively robust, latent structure of pain-related negative emotionality constructs. First, the General Distress factor was observed in each study, confirming a single, underlying negative affect dimension. Second, our Catastrophic Thinking factor is largely consistent with the previously reported Cognitive Intrusion of Pain (Mounce et al., 2010) and Pain-Specific Concerns factors (Vancleef et al., 2009; Vancleef et al., 2011). Third, our Pain-Related Fear factor is consistent with the Fear of Pain from Injury/Insult (Mounce et al., 2010) and Physical Health Concerns factors (Vancleef et al., 2009; Vancleef et al., 2011). Although we assessed several health-related and anxiety measures (WI, ASI, SSAS, and TAI), we did not observe the distinct Physical Health Concerns factor reported by Vancleef (Vancleef et al., 2009), even when examining a four-factor solution for our results. Instead, we found these health-related anxiety measures loaded primarily on: General Distress (TAI and ASI cognitive); a combination of General Distress with Catastrophic Thinking (WI cognitive, WI affective); General Distress and Pain-Related Fear (SSAS), and/or Catastrophic Thinking and Pain-Related Fear (ASI physical).

The similarities observed between our factor structure and those reported previously persisted despite methodological differences, further supporting the existence of a robust latent structure. For example, of the 10 measures used by Mounce et al. (Mounce et al., 2010) and Vancleef et al. (Vancleef et al., 2009), and our eight measures, sixteen different instruments were examined between the three studies. Only three measures were common to all three investigations (TAI, ASI, PCS), with several additional measures common between two of the three studies. In addition, Vancleef and colleagues used a card-sorting task with individual items from the various pain-related measures. Individual survey items were omitted from the task if they required reverse scoring; consequently, not all items were included from several of the surveys. Despite these inconsistencies between investigations, results were generally similar, providing evidence for a stable, latent structure of pain-related constructs, with General Distress, Catastrophic Thinking, and Pain-Related Fear forming three distinct factors in healthy adults.

In a previous study involving cold pressor pain (Lee et al., 2010); we observed a slightly different factor structure of psychological measures. Specifically, all of the lower-order pain-related scales (PCS, FPQ, ASI, WI, and SSAS) loaded on a single Pain- or Body Sensitivity factor rather than distinct Catastrophizing and Fear factors. The higher-order Negative Affect and Positive Affect scales loaded on two separate factors. Our prior inclusion of both positive and negative affect psychological constructs, in combination with a smaller cohort ($n = 72$), likely explains this discrepancy. The existence of a hierarchical structure, where these pain-related constructs can be further factored, is certainly possible and would be consistent with both our current and previous findings (Lee et al., 2010).

Overall, these collective results suggest a reduced number of pain-related psychological measures may be considered in future studies.

There are several limitations to the current study worth consideration. First, results from this young and healthy sample may not generalize to clinical or older populations. Second, the intramuscular infusion task represents only one model of acute experimental muscle pain. Pain responses can vary across pain modalities (Hastie et al., 2005; Neziri et al., 2011); thus, it is unknown whether these results will generalize to other models of deep-tissue experimental pain (e.g., visceral) or cutaneous pain (e.g. surgical incisions). Third, the measures consisted of subjective, self-report (pain and psychological) assessments; consequently, observed associations may result from similar response biases. Finally, these are self-report instruments and thus are only a measure of the latent constructs we examined (Kiline, 2000). Despite these limitations, this study represents a unique approach to investigating the influence of negative emotionality factors on muscle pain in healthy adults.

In summary, our study revealed that a 3-factor structure (General Distress, Pain-Related Fear, and Catastrophic Thinking) explain much of the common variance observed across several pain-related measures. Further, these latent factors are predictive of acute musculoskeletal pain, with components of both local and referred pain and hyperalgesia. While more studies are needed to determine the optimal number of scales for experimental and clinical assessments, these findings suggest a minimum of three be used to account for these three latent factor domains. This information may be an important step toward optimizing our ability to provide individualized multidisciplinary therapeutic interventions for patients at risk for musculoskeletal pain. Specifically, consistently high ratings of general distress, catastrophic thinking and pain-related fear may suggest a greater vulnerability for developing acute muscle pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's already known about this topic?

- Recent studies reported an underlying three-to-four factor structure explains the conceptual overlap and distinctiveness of negative emotionality and pain-related constructs.
- These constructs are correlated with experimental pain in numerous previous studies.

What does this study add?

- this study shows that individuals cluster fall into three distinct subgroups of three latent psychological factors, and individuals in the high negative emotionality subgroup are at higher risk for local muscle pain and hyperalgesia, and referred pain.

Figure 1. Characteristic profiles for the three subgroups (High Negative Emotionality – solid line; High Fear Only, dashed line; Low Negative Emotionality – dash-dot line) of individuals as determined by cluster analysis of the three latent factors. Mean responses (standardized z-score of 0) are shown by the solid gray reference line.

Figure 2.

Standardized experimental pain measures (transformed to z-scores) are shown for the three clusters of individuals (High Negative Emotionality – solid line; High Fear Only, dashed line; Low Negative Emotionality – dash-dot line). Mean responses (standardized z-score of 0) are shown by the solid gray reference line.

Table 1

Participant characteristics (mean, SD), by sex.

	All (N = 189)	Females (n = 99)	Males (n = 90)
Age (yrs)	26.5 (8.0)	26.5 (8.1)	26.6 (8.0)
Neuroticism (0-24) *	9.1 (5.2)	10.3 (5.3)	7.8 (4.7)
Negative Affect (10-50)	15.1 (3.7)	15.3 (3.7)	14.9 (3.7)
Trait Anxiety (20-80)	33.6 (7.6)	33.9 (7.8)	33.3 (7.4)
Pain Catastrophizing (PCS; 0-52)	11.4 (7.4)	11.2 (7.2)	11.7 (7.7)
PCS helplessness (0-24)	3.7 (3.1)	3.5 (2.9)	3.9 (3.3)
PCS rumination (0-16)	4.9 (3.4)	4.9 (3.4)	4.9 (3.5)
PCS magnification (0-12)	2.9 (2.0)	2.8 (1.9)	2.9 (2.0)
Fear of Pain (FPQ; 30-150)	71.6 (16.8)	73.2 (16.3)	69.8 (17.2)
FPQ minor pain (10-50)	17.0 (5.2)	17.2 (5.5)	16.8 (4.9)
FPQ severe pain * (10-50)	32.9 (8.4)	34.0 (7.7)	31.6 (8.9)
FPQ medical pain (10-50)	21.7 (6.2)	22.0 (6.1)	21.5 (6.3)
Anxiety Sensitivity Index (ASI; 0-64)	13.1 (6.3)	13.4 (6.0)	12.6 (6.7)
ASI physical (0-32)	5.8 (4.3)	6.4 (4.1)	5.3 (4.5)
ASI cognitive (0-16)	1.3 (1.6)	1.3 (1.6)	1.3 (1.5)
ASI social (0-16)	5.9 (2.1)	5.7 (2.1)	6.1 (2.1)
Whiteley Index (WI; 11-55)	15.5 (4.3)	15.3 (4.7)	15.6 (3.9)
WI cognitive	7.4 (2.1)	7.4 (2.4)	7.4 (1.9)
WI affective	7.8 (2.6)	7.7 (2.7)	8.0 (2.4)
Somatosensory Amplification (7-35) *	16.1 (4.0)	17.1 (3.9)	15.1 (3.8)

* Significant difference between males and females, uncorrected ($p < 0.05$).

Table 2

Psychological measure factor loadings using Principal Axis Factoring with Oblimin rotation.

Scale	Factor 1 General Distress	Factor 2 [†] Catastrophic Thinking	Factor 3 Pain-Related Fear
Neuroticism	.89	-.04	-.03
Trait Anxiety	.84	-.06	-.01
Negative Affect	.65	-.05	.02
ASI cognitive	.38	.22	.01
WI cognitive	.31	.30	-.003
SSAS	.25	.16	.22
FPQ medical	-.003	-.04	.85
FPQ minor	.01	-.13	.78
FPQ severe	-.08	.19	.68
PCS rumination	-.01	.86	-.07
PCS helplessness	.04	.81	-.01
PCS magnification	-.13	.67	.04
WI affective	.32	.46	.02
ASI physical	.16	.37	.25
ASI social	.11	.20	.05

Note: Factor loadings 0.30 are shown in bold.

[†] Indicates factor loading coefficients are reversed keyed. ASI- Anxiety Sensitivity Index; WI- Whiteley Index; SSAS- Somatosensory Amplification Scale FPQ- Fear of Pain Questionnaire; PCS- Pain Catastrophizing Scale.

Table 3

Sample characteristics for each cluster.

	High Negative Emotionality n = 50	High Fear Only n = 71	Low Negative Emotionality n = 68	F _{2,188}	p-value
Age (yrs)	26.3 (7.5)	25.8 (7.7)	27.5 (8.7)	0.9	0.42
Sex (% female)	54.0	56.3	47.1	0.6	0.53
Neuroticism (0-24)	14.6 (4.3) ^a	7.1 (3.4) ^b	7.1 (4.5) ^b	63.3	<0.0001
Negative Affect (10-50)	18.6 (3.8) ^a	13.8 (2.8) ^b	14.0 (2.7) ^b	42.3	<0.0001
Trait Anxiety (20-80)	41.2 (6.8) ^a	31.3 (5.4) ^b	30.6 (6.3) ^b	52.0	<0.0001
Pain Catastrophizing (PCS; 0-52)	17.6 (7.8) ^a	11.5 (6.5) ^b	6.9 (4.2) ^c	42.7	<0.0001
PCS helplessness (0-24)	6.3 (3.5) ^a	3.5 (2.6) ^b	1.9 (1.7) ^c	41.9	<0.0001
PCS rumination (0-16)	7.5 (3.6) ^a	4.8 (3.1) ^b	3.0 (2.2) ^c	32.1	<0.0001
PCS magnification (0-12)	3.8 (1.9) ^a	3.1 (2.0) ^a	2.0 (1.6) ^b	15.0	<0.0001
Fear of Pain (FPQ; 30-150)	81.3 (13.1) ^a	81.0 (9.8) ^a	54.7 (10.5) ^b	126.6	<0.0001
FPQ minor pain (10-50)	19.1 (5.6) ^a	19.1 (4.7) ^a	13.2 (2.8) ^b	39.2	<0.0001
FPQ severe pain (10-50)	37.1 (5.4) ^a	37.3 (4.8) ^a	25.2 (7.5) ^b	86.1	<0.0001
FPQ medical pain (10-50)	25.1 (5.8) ^a	24.6 (4.5) ^a	16.2 (3.8) ^b	74.0	<0.0001
Anxiety Sensitivity Index (ASI; 0-64)	18.2 (6.6) ^a	12.6 (5.0) ^b	9.7 (4.7) ^c	36.7	<0.0001
ASI physical (0-32)	8.9 (5.0) ^a	5.8 (3.7) ^b	3.6 (2.7) ^c	28.7	<0.0001
ASI cognitive (0-16)	2.7 (1.8) ^a	0.8 (1.2) ^b	0.8 (1.1) ^b	38.9	<0.0001
ASI social (0-16)	6.6 (1.8) ^a	6.0 (2.0) ^{ab}	5.3 (2.3) ^b	5.5	0.005
Whiteley Index (WI; 11-55)	19.2 (5.5) ^a	14.5 (2.5) ^b	13.7 (3.0) ^b	36.2	<0.0001
WI cognitive	8.9 (3.3) ^a	6.9 (1.0) ^b	6.8 (1.3) ^b	20.4	<0.0001
WI affective	10.1 (2.9) ^a	7.3 (1.8) ^b	6.7 (1.8) ^b	40.8	<0.0001
Somatosensory Amplification (7-35)	18.4 (3.9) ^a	16.4 (3.6) ^b	14.2 (3.5) ^c	19.5	<0.0001

Note: Values are the mean (SD). Multivariate analysis of variance conformed that each latent psychological variable was differentiated by the cluster solution (Wilks' $F(6,368) = 85.1, p < 0.0001$); Univariate analyses of variance results for baseline sample characteristics are provided here. Within rows, means with different superscripts differ significantly from each other.

Table 4

Pain responses between cluster subgroups.

Measure	High Negative Emotionality n = 50	High Fear Only n = 71	Low Negative Emotionality n = 68	F2, 187	p-value
Local peak pain intensity (0-10)	2.4 (1.5) ^a	2.2 (1.4) ^{a, b}	1.8 (1.5) ^b	3.0	0.05
Referred peak pain intensity (0-10)	1.2 (1.2)	1.0 (1.3)	0.9 (1.2)	1.2	0.32
Local pain incidence (%)	94.0	91.5	82.1	#	0.10
Referred pain incidence (%)	72.0 ^a	57.7 ^{a, b}	53.7 ^b	#	0.05
Local hyperalgesia (%) ⁺	82.6 (18.0) ^a	91.9 (17.0) ^b	89.6 (14.6) ^{a, b}	4.8	0.009
Referred hyperalgesia (%) ⁺	95.7 (18.9)	97.4 (16.5)	95.8 (14.4)	0.2	0.79

Note: Values are the mean (SD). Significant between-group differences, using Tukey's post-hoc tests, indicated by superscripts:

- ^aWithin rows, means with different superscripts differ significantly from each other.
- ^bWithin rows, means with different superscripts differ significantly from each other.
- ^cWithin rows, means with different superscripts differ significantly from each other.
- ⁺Hyperalgesia is reported as % of baseline pressure pain threshold (PPT), where values less than 100% indicate greater pressure pain sensitivity or hyperalgesia.
- [#]See text for multinomial logistic regression results for dichotomous variables.