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Topical review

Quantitative assessment of experimental pain perception: multiple domains of clinical relevance

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1. Introduction

Inter-individual variation in pain perception is substantial (Gracely, 1999); threshold and tolerance in response to a variety of painful stimuli are approximately normally distributed in the general population. These individual differences are evaluated by administering standardized noxious stimuli and quantifying pain responses under controlled laboratory conditions. However, there is little consensus on whether findings from quantitative sensory testing (QST), or psychophysical studies of pain, are relevant to the clinical experience of pain (Gracely, 1999). Indeed, pain induced by laboratory-administered noxious stimuli can differ substantially from naturally-occurring pain along such dimensions as controllability, duration of stimulation, and range of stimulus intensities, such that the ascribed meaning of noxious stimulation is rarely comparable across laboratory and naturalistic settings (Edwards et al., 2004). Recently, however, studies demonstrating alterations in pain perception among many clinical populations have highlighted the potential value of experimental pain assessment, or QST (terms which we will use interchangeably), in understanding chronic pain. Moreover, scrutiny of this literature reveals multiple domains in which the clinical relevance of experimental pain assessment has been repeatedly demonstrated.

2. Group differences in pain perception

Perhaps the most frequent application of experimental pain assessment has been to identify group differences in pain perception. For example, sex differences in laboratory pain responses are widely recognized (Fillingim, 2000; Riley et al., 1998), and considerable evidence also suggests ethnic (Green et al., 2003) and age-associated differences in pain perception (Gibson and Helme, 2001). Interestingly, the direction of these group differences in experimental pain responses generally parallels group differences in reported clinical pain. For example, women report greater acute and chronic pain than men, and women also exhibit greater sensitivity to experimental noxious stimuli (i.e. lower pain tolerance, higher pain ratings). We suspect these findings are related, in that individual differences in pain sensitivity may place people (and groups) at reduced or elevated risk for the development of acute and chronic pain.

2.1. Differentiating clinical populations from controls

In addition to group differences within healthy populations, QST has been used to evaluate differences in pain perception between certain clinical populations and healthy controls (Lautenbacher and Fillingim, 2004). Such research has important implications regarding the pathophysiology of pain disorders and may ultimately be used to generate a system of mechanism-based diagnosis, which

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would inform treatment decisions (Woolf and Max, 2001). Indeed, a generalized enhancement of sensitivity to painful stimuli, which may suggest involvement of central mechanisms, is well-documented in fibromyalgia (FM) (Staud, 2004), temporomandibular disorders (TMD) (Sarlani and Greenspan, 2003), pelvic pain syndromes (Granot et al., 2002), and headache disorders (Bendtsen, 2000). Thus, generalized hyperalgesia may serve as a marker for certain pain syndromes, though it is unclear whether this hypersensitivity precedes or is consequent to the onset of chronic pain.

2.2. Sub-grouping pain patients

Diagnostic validity is an important issue in the classification of chronic pain, and many have argued that the current taxonomy is inadequate (Woolf and Max, 2001). QST, already used in the diagnosis of disorders such as FM, could potentially enhance diagnostic specificity in some chronic pain disorders by providing mechanistic information regarding abnormalities in pain processing. Indeed, QST has already become a valuable tool in diagnosing peripheral nerve disorders (Chong and Cros, 2004), especially early small-fiber neuropathies not assessed by standard nerve conduction studies (Cruccu et al., 2004). Additional applications include the classification of sensory abnormalities in central pain states associated with conditions such as Multiple Sclerosis or stroke (Boivie, 2003), though it is important to emphasize that QST abnormalities are not entirely specific to neuropathic pain (Cruccu et al., 2004).

Recent studies have examined QST findings within many chronic pain disorders. For example, Pappagallo et al. (2000) detected increased thresholds to heat and cold pain in the affected area of thoracic but not trigeminal post-herpetic neuralgia (PHN) patients, suggesting the potential for the differentiation of PHN syndromes based on distinct pathophysiological mechanisms. Relatedly, complex regional pain syndrome (CRPS) patients were sub-grouped according to the spatial extent of sensory deficits, with those patients who showed more widespread deficits also exhibiting greater mechanical hyperalgesia in the affected limb (Rommel et al., 2001). Kleinbohl et al. (1999) found that responses to phasic and tonic heat pain not only distinguished chronic pain patients from healthy controls but also discriminated among types of chronic pain (e.g. headache, back pain) with good sensitivity and specificity. Finally, QST and psychosocial measures were used to distinguish three subgroups of FM patients, in whom, it was hypothesized, different pain-maintaining mechanisms were operative (e.g. central sensitization vs. psychological distress) (Giesecke et al., 2003). Collectively, these studies hint that QST could be useful in creating an updated pain classification system which might: be based on pathophysiological mechanisms, cross anatomical boundaries, have prognostic value, and prove useful in selecting treatments on the basis of identified pain mechanisms.

3. Cross-sectional associations between QST responses and clinical pain

3.1. Healthy adults

Several studies have examined associations between QST responses and reports of daily pain symptoms among healthy adults. For example, healthy young women reporting high numbers of recent pain episodes showed significantly lower heat pain thresholds and tolerances than women with less frequent clinical pain (Fillingim et al., 1999). Another investigation revealed that heat pain tolerance was negatively associated with the number of pain sites reported over the past month, and ratings of suprathreshold thermal stimuli were positively correlated with the severity of recent pain symptoms (Edwards and Fillingim, 1999). More recently, diffuse noxious inhibitory controls (DNIC) were assessed in a sample of healthy adults by quantifying the effects of cold pain on concurrent heat pain (Edwards et al., 2003a). The DNIC index was significantly related to numerous SF-36 subscales, such that greater DNIC, reflecting more potent endogenous pain inhibition, was associated with less pain and better physical functioning. Taken together, these findings suggest that QST responses are associated with self-reported pain and pain-related symptoms in generally healthy samples.

3.2. Pain patients

Positive associations between pain sensitivity and clinical pain intensity have also been reported within groups of pain patients (Lautenbacher and Fillingim, 2004). For example, lower pressure pain thresholds were associated with higher back pain intensity and greater deterioration of physical functioning among patients with chronic low back pain (Clauw et al., 1999). Similarly, lower heat pain thresholds predicted more frequent angina episodes during exercise in coronary artery disease patients (Sheps et al., 1999). We previously reported that ischemic pain tolerance was correlated with greater clinical pain severity in a heterogeneous group of chronic pain patients (Edwards et al., 2001), and among TMD patients (Fillingim et al., 1996). Interestingly, this latter study analyzed only TMD patients representing the upper and lower quartiles of pain tolerance, suggesting that comparing extreme groups may facilitate detection of such relationships.

4. Prospective studies of acute surgical pain

Potentially more important than cross-sectional associations are findings that QST can predict future risk for developing pain. Several recent studies have examined pre-operative experimental pain responses as predictors of post-operative pain. Among individuals undergoing limb

amputation, pre-amputation pressure pain thresholds were significantly inversely correlated with post-amputation stump pain and phantom pain (Nikolajsen et al., 2000). In addition, preoperative thermal QST responses predicted postoperative pain scores at rest and during activity in women undergoing cesarean section, explaining up to 54% of the variance in post-surgical pain (Granot et al., 2003). Importantly, while suprathreshold pain ratings were highly positively correlated with postoperative pain, thermal pain thresholds did not show such strong associations. Other investigations have produced comparable results. Following anterior cruciate ligament repair, preoperative ratings of an intense noxious thermal stimulus were strongly correlated with joint pain ratings for several weeks post-surgery (Werner et al., 2004). Again, pain thresholds were not significantly correlated with post-surgical pain. Finally, preoperative cold pain tolerance predicted postoperative pain after laparoscopic cholecystectomy, even after controlling for neuroticism (Bisgaard et al., 2001). Taken together, these findings identify suprathreshold experimental pain responses as important predictors of acute pain intensity following surgical procedures; additional long-term prospective studies will be necessary to evaluate QST as a predictor of chronic pain following surgery.

5. QST and pain treatment outcomes

5.1. Predicting treatment outcomes

Given that experimental pain responses are sensitive predictors of outcomes following pain-producing interventions (i.e. surgery), it is natural to study their influence on outcomes of pain-relieving treatments. Two recent studies have directly addressed this issue. First, we evaluated associations between pre-treatment ischemic pain tolerance and outcomes of multidisciplinary treatment for chronic pain. Women with higher pre-treatment pain tolerance showed greater pain reduction, less pain-related interference, and more increases in activity level than women with lower pain tolerance (Edwards et al., 2003b). Interestingly, pain tolerance was not associated with positive treatment outcomes among men. In a study of vulvar vestibulitis, pre-treatment ratings of suprathreshold thermal pain predicted treatment outcomes (Granot et al., 2004). Women with lower thermal pain ratings more often chose surgery as a treatment and, across treatments, showed greater reductions in pelvic pain than women with higher heat pain ratings. Thus, two intervention studies have reported that greater pre-treatment sensitivity to pain predicts worse post-treatment outcomes of multidisciplinary treatment, at least among women.

5.2. Changes in QST responses as a correlate of changes in clinical pain

QST can also be used as an outcome measure to document treatment-related changes in somatosensory function. Recently, Kosek and colleagues reported thermal hyperalgesia, mechanical hyperalgesia, and deficient pain inhibition in osteoarthritis patients at baseline, but showed that these conditions normalize following successful pain-relieving surgery (Kosek and Ordeberg, 2000a,b). Other researchers have also addressed this issue by studying QST responses separately in treatment responders and non-responders. In a trial of pharmacologic treatment for FM pain, patients who showed a 50% or greater reduction in clinical pain intensity also showed increases in pressure pain threshold and tolerance, while non-responders showed no changes in pain sensitivity (Sorensen et al., 1997). Similarly, in a study of amitriptyline treatment for irritable bowel syndrome, gastrointestinal (GI) pain was reduced and visceral pain sensitivity (i.e. the pain threshold to rectal distention) was increased (Poitras et al., 2002); in this study, changes in pain sensitivity closely paralleled changes in clinical pain ($r = -0.71$). Collectively, treatment-related normalization of pain perception is observed only when clinical pain is reduced, suggesting that the QST measure may be a sensitive index of treatment outcome.

6. Factors influencing associations between clinical and experimental pain

First, we have reported that experimental pain responses are most highly related to clinical pain among women (Edwards et al., 2003b; Fillingim et al., 1999). We are as yet uncertain why this should be the case, though we have theorized that administration of experimental noxious stimuli is more likely to activate endogenous cognitive-affective pain-modulatory processes (which in turn also influence the experience of clinical pain) in women. Second, the characteristics of the noxious stimuli used during QST may be important in shaping relationships between experimental and clinical pain responses. Overall, suprathreshold pain responses are more clinically relevant than responses to threshold-level noxious stimuli. This may not be surprising, given that most naturally-occurring noxious stimuli are also likely to be well above threshold in magnitude. Third, statistical considerations may be important; associations between clinical pain and experimental pain responses may be most apparent when studying extreme groups (e.g. the most and least pain-sensitive patients) (Fillingim et al., 1996).

7. Summary

It has become increasingly clear that the same factors shaping responses to experimental pain stimuli also

contribute to the experience of clinical pain. For example, single nucleotide polymorphisms of specific genes regulating opioidergic responses are related to experimental pain responses (Zubieta et al., 2003); dysfunction in such opioidergic systems has also been implicated in the etiopathogenesis of numerous chronic pain conditions. In neuroimaging studies of experimental pain stimuli using both between-subjects and within-subjects designs, numerous brain regions such as primary somatosensory cortex exhibit increasing activation as subjective ratings of pain increase (Coghill et al., 2003), confirming that inter-individual differences in QST responses are accompanied by differences in CNS pain processing. Collectively, the findings reviewed here suggest that experimental pain responses relate to clinical pain report in a variety of samples (i.e. greater pain sensitivity is associated with greater clinical pain), that such responses predict the risk of acute procedural pain, that these responses also correlate with treatment outcome, and that QST might be useful in formulating mechanism-based diagnostic categories for pain disorders. However, despite the tremendous potential for utilizing QST in clinical settings, it has not yet become a standard component of clinical pain evaluation. For example, future studies may determine whether QST can be used to determine analgesic dosing, and whether this application of QST improves outcomes. Despite practical barriers to performing experimental pain evaluation in clinical settings, it is anticipated that QST will become an increasingly common pain assessment tool, advancing the understanding and management of a wide variety of painful disorders.

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