

Topical review

Applications of laboratory pain methodologies in research with children and adolescents: Emerging research trends

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1. Introduction and background

Historically, laboratory pain research with children and adolescents has largely been conducted with healthy samples using the cold pressor task (CPT). Additional laboratory methodologies, commonly referred to as quantitative sensory testing (QST), include a variety of psychophysical tests assessing sensory perception (eg, pressure and heat tolerance) and sensory abnormalities. There is significant variation in QST protocols in terms of methodology (eg, number and type of measurement modalities) and data gleaned (eg, pain threshold vs central sensitization).

Generally speaking, QST laboratory assessment methodologies yield measures of pain tolerance, pain threshold, or self-report of pain intensity. Studies utilizing these methods have greatly expanded knowledge of individual and social factors contributing to acute pain responses, including parental behavior [8], child sex differences, coping, distraction, catastrophizing, and anxiety [26]. CPT guidelines and reviews of use in pediatric pain research are available [4,34]. Additionally, researchers have begun to identify reference values and validate other QST protocols in healthy children and adolescents [5,23,30].

Despite the plethora of laboratory research examining pain responses in healthy children, much less is known about pain responses in pediatric clinical samples. In adult populations, laboratory pain research has proven useful for characterizing the neurobiology of chronic pain disorders [15,27]. The underlying biological, psychological, and motoric domains that contribute to the pain experience [31] change and become more complex as children move through childhood into adolescence and adulthood. Because youth are at risk for pain to persist into adulthood [6], a more complete understanding of factors that influence the onset and development of alterations in pain processing systems is critical. This information can be used to both inform lifespan models of pain conditions and to help identify potential targets for preventative interventions.

This topical review aims to: (1) outline current knowledge of laboratory pain responses in clinical pediatric pain populations, (2) review emerging research methodologies, and (3) provide recommendations for future research that addresses gaps in the current literature.

2. Previous research with clinical pediatric pain populations

Published studies reporting on laboratory responses to pain in clinical pediatric pain populations have most frequently examined pain responses in children with abdominal pain and headache. Commonly used methodologies are similar to those used in healthy samples including pressure and thermal stimuli. Pressure methods have typically used a handheld algometer applied to various pressure points, or an impact/mechanical pressure device applied to a fingertip. Thermal stimulation methods generally use a small heat thermode device or immersion of a limb in cold water (CPT). As in healthy samples, the most common data obtained from these methodologies include pain threshold, tolerance, and intensity.

Although some laboratory research studies have demonstrated group differences between clinical and healthy samples, findings are equivocal. For example, youth with abdominal pain have demonstrated lower pressure or mechanical pain thresholds compared to healthy controls in some studies [1,12], as have youth with arthritis [20] and musculoskeletal pain [18]. However, other studies have found no differences between pain and healthy groups in CPT tolerance [13], pressure, or heat pain tolerance or intensity [33].

Further lack of consistency in findings is illustrated in studies utilizing multiple laboratory modalities. For example, in a study comparing youth with and without abdominal pain, no differences were found in heat or mechanical pain threshold at either the abdomen or a distal site. However, youth with chronic abdominal pain demonstrated lower sensitization to repetitive heat and mechanical stimulation [39]. In another study, youth with juvenile idiopathic arthritis demonstrated lower CPT pain tolerance than healthy youth, but this did not differ for CPT pain threshold, intensity, or discomfort [32].

3. Emerging methodologies and novel applications

3.1. Assessment of conditioned pain modulation

In conditioned pain modulation (CPM) methods, response to a painful test stimulus is evaluated in both the absence and presence of a second painful (conditioning) stimulus to test the efficiency of endogenous analgesia or the ability to modulate pain messages sent from peripheral nerves [37]. Deficiencies in CPM (ie, lack of pain inhibition in the presence of conditioning stimuli) have been

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identified in adults with chronic pain (ie, headache, fibromyalgia) compared to healthy controls [7]. Recent adult research has highlighted poor CPM as a risk factor for development of chronic postsurgical pain [21], and for development of temporomandibular joint disorders [11].

Current knowledge of CPM in children is very limited, both in terms of typical development of CPM and of potential CPM dysfunction. To date, published studies have included small samples of children born prematurely [17] and school-aged youth with burn injuries [36], with both these populations demonstrating poorer pain modulation compared to healthy controls.

3.2. Temporal summation

Temporal summation, or wind-up, describes the increased perception of pain after undergoing repetitive painful stimuli, and is thought to be associated with central nervous system reactivity. Recent research in clinical pediatric samples has found evidence of wind-up in children with complex regional pain syndrome (CRPS) [28], migraine [40], and abdominal pain [38]. Additionally, chronic pain during childhood predicts wind-up to heat pain in adult women [10].

3.3. Neurophysiological measures

Neurophysiological measures provide novel information about brain activation during pain states. Electroencephalogram responses in children with migraines have been demonstrated to have longer amplitude and shorter latency compared to healthy youth during a QST perceptual sensitization task [38], suggesting that youth with pain conditions may demonstrate an attentional bias to pain. Another study examining cortical responses in youth with abdominal pain demonstrated similar results [19].

Functional magnetic resonance imaging (fMRI) methodology has been used primarily in adults to gain information on how pain is processed in the brain and to examine pain modulation. In the only pediatric study to date, Lebel and colleagues [22] used fMRI to examine changes in brain activity in children with CRPS during pain and pain-free periods who underwent mechanical (brush) and thermal (cold) stimuli. fMRI results revealed cortical activation in areas consistent with adult neuroimaging that continued even during pain-free periods, suggesting that functional abnormalities in central nervous system circuitry may alter pain processing even after pain resolution for youth.

3.4. Condition-specific laboratory pain protocols

Studies also utilize methods that isolate the bodily area affected or that mimic pain associated with particular conditions. For example, Walker and colleagues [35] developed a procedure where children drink water quickly to induce abdominal discomfort. Findings demonstrated that children with chronic abdominal pain reported higher pain intensity during the task compared to healthy youth, suggesting alterations in visceral pain processing. Research examining pain thresholds have found effects for pain location such as affected vs unaffected limbs in CRPS [28], and inflamed vs noninflamed areas in children with juvenile idiopathic arthritis [20]. Differences were in the expected direction, with youth reporting lower pain thresholds in clinically relevant locations.

3.5. Assessment of psychological factors

To date, associations among laboratory pain responses and key psychological (eg, anxiety, pain catastrophizing) and social (eg,

parental presence) variables in clinical pain populations have been minimally investigated. In a few studies, more active coping was associated with lower heart rate and less anxiety in children with abdominal pain who underwent a CPT [13], and with less pain during a laboratory pressure task in children with sickle cell disease [16]. Other studies have noted differences in pain threshold on the basis of social factors such as maternal presence vs absence, with maternal presence associated with increased mechanical pain threshold in youth with migraine [40]. Audience effects and parental behaviors have been linked with laboratory pain responses in healthy children [4,8]. Thus, additional examination of social factors with clinical samples is warranted.

4. Summary and agenda for future research

This review highlights the importance of examining laboratory pain responses in clinical pediatric pain samples, and below we provide a summary of key gaps in knowledge that may serve as an agenda for guiding future research.

4.1. Longitudinal research to examine pain modulation and risk for chronic pain

Laboratory pain studies can be used to help understand differences in pain responses in the context of known risk factors (eg, physiological, psychological, and social/environmental factors) and other poor health outcomes over time. Although the adult literature suggests that CPM may predict the development of chronic pain, there are not yet any pediatric data on this topic. Future research might examine how wind-up develops with chronic pain in childhood and examine differences among clinical pain samples. Moreover, longitudinal data will be important to gather in pediatric clinical and at-risk samples because stability or change in laboratory pain responses may reflect changes in pain experiences or other functional outcomes. Larger samples and use of more comprehensive and validated laboratory pain methods will be required for this research.

4.2. Increased understanding of mechanisms that might explain differences (or lack thereof) between clinical and healthy samples

The presence of a given pain condition is not the only determinant of laboratory pain responses; other biological, psychological, and social determinants require investigation. Sex differences [40], selection factors, generalized effects of long-standing pain, differences in sensitivity to audience effects, choice of laboratory pain stimuli, and other potential mediators or moderators may account for some portion of the similarities and differences in pain responses observed between clinical and healthy samples.

4.3. Comprehensive assessment of risk factors for altered pain responses

Given the higher levels of psychological symptoms in youth with chronic pain compared to healthy samples and the importance of parental behavior, it will be important for laboratory pain methods to expand assessment of psychological factors, including audience factors, maternal/paternal presence, and parent behaviors in the laboratory setting. Measures of child pain-specific anxiety (catastrophizing and fear) are available, and future research can determine how anxiety affects laboratory pain responses in clinical samples. In the adult chronic pain literature, poor sleep and depression are associated with lower CPM efficiency [9,14]. Examining similar associations in children will help better characterize pain processing in youth.

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