A Practical Guide and Perspectives on Use of Experimental Pain Modalities With Children and Adolescents

Kathryn A. Birnie[1,2], Line Caes[2], Anna C. Wilson[3], Sara E. Williams[4], Christine T. Chambers[1,2,5]

[1]Department of Psychology and Neuroscience, Dalhousie University

[2]Centre for Pediatric Pain Research, IWK Health Centre

[3]Department of Pediatrics, Institute on Development and Disability, Oregon Health & Science University

[4]Department of Pediatrics, Medical College of Wisconsin

[5]Department of Pediatrics, Dalhousie University

Correspondence addressed to:

Kathryn A. Birnie

Centre for Pediatric Pain Research (West)

K8536 (8th floor, Children's site)

IWK Health Centre

5850/5980 University Avenue

Halifax, Nova Scotia, Canada B3K 6R8

Phone: 1-902-470-6906

Fax: 1-902-470-7118

E-mail: kbirnie@dal.ca

Summary

Use of experimental pain is vital for addressing research questions that would otherwise be impossible to examine in the real world. Experimental induction of pain in children is highly scrutinized given the potential for harm and lack of direct benefit to a vulnerable population. However, its use has critically advanced our understanding of the mechanisms, assessment, and treatment of pain in both healthy and chronically ill children. This review introduces various experimental pain modalities, including the cold pressor task, the water load symptom provocation test, thermal pain, pressure pain, and conditioned pain modulation, and discusses their application for use with children and adolescents. It addresses practical implementation and ethical issues, as well as the advantages and disadvantages offered by each task. The incredible potential for future research is discussed given the array of experimental pain modalities now available to pediatric researchers.

Keywords: experimental pain, children, adolescents, ethics, cold pressor task, water load symptom provocation test, thermal pain, pressure pain

A Practical Guide and Perspectives on Use of Experimental Pain Modalities With Children and Adolescents

Experimental infliction of pain has been used historically to study a variety of physical and psychological phenomenon, perhaps most famously and controversially as part of Stanley Milgram's investigations in the behavioral study of obedience [1]. While pain (delivered via electric shock) was not actually induced in his work, it revealed our susceptibility to the authority of researchers, and willingness to induce excruciating pain on others, within the context of experimental research. It should come as no surprise that the experimental induction of pain continues to receive considerable scrutiny, particularly when used with vulnerable populations such as children. Given the common nature of acute and chronic pain among children [2-4], it begs the question: pain is already so common, why do we need to inflict it?

The International Association for the Study of Pain cautions that children are particularly vulnerable to unfair exclusion from pain research [5], which would unjustly deny them its potential benefits [6]. However, a common concern about experimental pain is that pain is induced in children without the potential that the participating child will directly benefit [7,8]. Research lacking direct benefit, particularly among children, is only considered ethical when there are reasonable benefits to the population or group to which the participant belongs [8-10]. Indeed, experimental pain research with children and adolescents has critically advanced our ability to assess and treat pain across development in both healthy children and those with chronic conditions. Specifically, this work has improved understanding of the impact of biological and psychological variables [11,12], as well as the influence of parents [13-16], the role of coping strategies [17], and the effectiveness of various interventions in pediatric pain [18].

The major advantage, and real necessity, of experimental pain is that it allows researchers to answer questions that would not be feasible to investigate in the real world. This greater control over the environment and standardized pain stimulus allows more rigorous exploration of individual differences and/or environmental influences that impact the subjective pain experience. Although more naturally occurring pains (e.g., headache, muscle pain) are less easily induced, they are valuable and require further investigation of their usefulness and feasibility in pediatric research [19]. The most commonly used experimental pain modality with children is the cold pressor task, which has gained increasing popularity since its initial use in pediatric pain research in the 1980s [20]. Since then, other experimental pain modalities used with adults have been introduced and further modified for pediatric research, including the water load symptom provocation test, thermal pain, pressure pain, and conditioned pain modulation. The availability of different models of experimental pain is important given that they induce distinct dimensions of pain responding [21] with different genetic heritability [22] in adults, which may offer unique relevance given specific research questions. Furthermore, various experimental pain modalities, such as thermal and pressure pain, are included in larger batteries assessing sensation and pain threshold that correspond to various receptors, nerve fibers, and nervous system pathways (i.e., quantitative sensory testing; QST) [23].

This review introduces each of these pain modalities in turn and how they can be applied for use with children and adolescents, focusing on practical implementation and ethical issues, as well as comparing the advantages and disadvantages offered by each task (summarized in Tables 1 and 2). The expertise and opinion provided herein are from researchers who have been directly involved in the development, refinement, and/or use of these tasks in pediatric research. Other less common types of experimental pain used with children and adolescents that are not discussed include a modified submaximal effort tourniquet test [24] and an exercise task [13,25]. This review is timely for directing future pediatric experimental pain research given the broadening scope of acceptable available modalities.

Cold Pressor Task (CPT)

Pain is induced using the CPT by submersion of the hand in a bath of cold water, typically lasting no more than several minutes. Similar to the history of its use with adults, early application of the CPT with children focused on manipulation of blood pressure [26], later evolving to its current primary use for pain induction [20,27,28].

The CPT has been used with children aged 3 to 18 years [29], with unpublished reports of its use with children as young as one year [7]. Studies most frequently include healthy children and adolescents, with increasing use with clinical samples, such as children with chronic pain, anxiety, low mood, or premature birth [29,30]. Efforts have also been made to provide normative data for pain outcomes with healthy children [31] and those with chronic pain [20,32,33].

The CPT has been most commonly and effectively employed in pediatric studies examining the influence of psychosocial, cognitive, and parent/family factors on children's pain [13,34-37], with less frequent use for exploration of biological, physiological, and/or genetic factors [38,39]. The CPT is increasingly used as an initial testing ground for new psychological interventions for pain [18,40-43].

Advantages

Many advantages of the CPT arise from its widespread use, including recommendations to guide ethical and standardized use of the CPT with children and adolescents [29,30]. Practical advantages and appeal of the CPT include its portability, convenience, minimal training to use, standardization, few inherent risks, and the minimally threatening nature of cold-induced pain.

Furthermore, the CPT does not require expensive equipment, although high tech equipment is available and does offer some advantages, such as more sophisticated thermoregulation. The CPT is ideal for research questions needing pain to last at least several minutes (e.g., parent-child interactions).

Disadvantages

A primary disadvantage of the CPT is the significant methodological variability in use of the task and measurement of pain outcomes across research teams and studies, making it difficult to compare findings [29]. Another drawback of the CPT is its unclear relation to real world pain experiences. This is of note given that children's anxiety prior to the CPT is typically low [44] and the CPT seems more like familiar day-to-day experiences (e.g., hands under cold water) as compared to other painful experiences (e.g., needles, burns, etc.). The nature of the CPT makes it less valuable for the study of certain types of pain management (e.g., positioning, topical anesthetics).

Practical Use and Implementation

CPT apparatus can be built or purchased (e.g., Techne© www.techne.com). Apparatus vary widely in expense (~$200-6000USD), method of water cooling (ice vs. electric), water capacity, portability, water flow rate, and thermoregulation. Important practical considerations include access to water and ice, handling of spills, electrical needs, safety approval, equipment cleaning, and allotting adequate time for refilling, cooling, and stabilizing water temperature. Depending on research needs, it may also be relevant to consider portability of the CPT and noise level produced by certain types of cold pressor apparatus if interested in coding verbalizations during the task.

Practical procedural steps for using the CPT [29,30] and examples of CPT instructions are available (also see Appendix A) [31,45]. Studies with both adults and children reveal how methodological and/or procedural variability significantly influence pain outcomes, including water temperature [46,47], task instructions [48-50], slower cooling of the hand [51], and availability of temporal information [52].

Ethical Issues and Research Ethics Approval

Empirical evidence supports the ethical acceptability of the CPT from the perspective of pediatric researchers, and participating parents and children [7]. However, additional safeguards are recommended for younger children (i.e., under 7 years old), including further steps to ensure children's understanding of the task and very careful observation for verbal and nonverbal signs of dissent [45]. Furthermore, reported use of the cold pressor with children as young as one year [7] is highly questionable given their increased susceptibility to adult authority and more limited ability to communicate their dissent. Although researchers' experiences suggest that research ethics boards largely consider the CPT to be above minimal risk, we have previously argued that it should be considered minimal risk, or at most a minor increase above minimal risk, when used according to published guidelines [30]. This is because the child maintains control over the process and can remove their hand from the cold water at anytime, adverse events are extremely rare, parents and children report positive experiences, and the clear exclusion criteria identifying children with whom the task is contraindicated [7,30]. Of course, other aspects of research (e.g., use of deception) may appropriately alter the nature of overall risk posed. In our experience, research ethics boards unfamiliar with pediatric use of the CPT are more likely to consider it higher risk, and will likely lower their assessment of risk posed by the task over time. Researchers should minimize social desirability and/or influencing the child's responses to the CPT, but should consider observing the child while the complete the CPT for safety and to ensure study procedures are followed correctly (e.g., being out of eyesight or via video).

Relation to Real World Outcomes

Very little is known about how pain induced by the CPT is a model for clinical pain experiences among children and adolescents. Thus, it remains difficult to know how well findings from studies using the CPT generalize to real world pain experiences or to which clinical pain experiences findings are most relevant (i.e., acute or chronic). Furthermore, we are aware of only one study that uses outcomes from the CPT to predict behaviors outside of the lab. Higher pain ratings during the CPT predicted number of school absences over the next two years in a group of healthy 8-10 year olds [53]. The lack of research investigating relationships between the CPT and real world outcomes remains a clear limitation and a key area for future research.

Water Load Symptom Provocation Test (WL-SPT)

The Water Load Symptom Provocation Test (WL-SPT) is a test of visceral pain administered through ingestion of water until "complete fullness" [54]. The WL-SPT was developed as a laboratory analog of abdominal pain, a common chronic/recurrent pediatric pain problem, which was historically difficult to study experimentally. Research in adult populations utilized manometry, which involves insertion and inflation of a balloon in the upper and/or lower gastrointestinal tract [55]. This invasive medical procedure posed obvious disadvantages to a pediatric population. Therefore, early laboratory research on children with abdominal pain relied on other pain producing tasks, such as the cold pressor [20]. However, this approach posed another challenge because the task produced somatic, not visceral, pain sensations, which were less relevant to abdominal pain and therefore limited findings. To address these challenges, the WL-SPT was developed as a non-invasive, visceral pain producing procedure for use in an experimental setting.

A "water load" test was first developed for studies of gastric activity in adults [56] and was also described in healthy children [57]. These initial iterations were modified and tested in healthy children and abdominal pain patients (ages 8-16 years) as the WL-SPT [54]. The WL-SPT discriminated between groups; healthy children ingested more water than abdominal pain patients and had a lower GI symptom response. In addition, convergent validity was demonstrated with significant associations between abdominal pain patients' typical pain ratings and their laboratory responses. The WL-SPT is a valid laboratory analog of abdominal pain, producing clinically relevant symptoms.

Advantages

For researchers interested in studying visceral pain processes, the WL-SPT is arguably a more relevant way to experimentally induce pain compared to somatic pain producing tasks. In addition, the WL-SPT is affordable and easy to administer. Another major advantage is acceptability of the task to parents and children participating in this low-risk, minimally invasive procedure.

Disadvantages

Unlike other pain tasks where the pain stimulus is standardized between patients, due to the nature of this test to drink until "complete fullness," participants ingest different amounts of water. As a result, the pain stimulus is dependent on participant perception. This can be accounted for in statistical analyses by controlling for amount of water ingested. Finally, although the WL-SPT is a valid analog of abdominal pain that correlates with typical pain ratings, the overall scores are lower than usual pain episodes [54], which could affect generalizability of study outcomes.

Practical Use and Implementation

The basic elements required for the WL-SPT are simple; water and something from which to drink the water. To eliminate physical cues, it is recommended that participants drink water out of a device that prohibits them from holding or seeing the water. For the WL-SPT validation study [54], an opaque backpack was utilized for this purpose, which was hung on the wall next to the participant and contained a plastic water bladder with a tube and a mouthpiece attached, similar to common hydration systems used by cyclists or runners. Changing of the mouthpiece and thorough cleaning of the bag and tube between participants is required. Two liters of water were put into the bladder prior to the participant's arrival (the average amount ingested by pain patients was 608mL in the validation study). Participants should be introduced to the water drinking system so they are comfortable using it when the procedure begins; for the validation study, they simply had to hold the tube and drink from the mouthpiece.

After baseline assessment of symptoms, participants are instructed to begin drinking water until they feel "completely full" (see Appendix A), which can be illustrated through visual (e.g., a series of stomachs with varying degrees of liquid illustrating empty to full) and/or verbal rating scales (e.g., not at all, a little, somewhat, a lot, a whole lot full). Participants are allowed to drink for up to 15 minutes total, with short breaks allowed at the participant's discretion. The researcher should complete a "fullness" check using the visual/verbal scale every 5 minutes and upon completion of drinking; however, participants are instructed to stop drinking whenever they are full. Baseline symptom assessment is repeated immediately after the participant stops drinking. Researchers are advised to record the amount of time as well as the amount of water ingested for each participant.

Ethical Issues and Research Ethics Approval

Due to the non-invasive nature of the WL-SPT, ethical review boards should approve the task without difficulty. One potential concern could be for the exceptionally rare occurrence of water toxicity; this can be mediated by ensuring that there is an upper limit on how much water can be consumed (2L) and allow a specific time frame (15 minutes), conditions which make induction of water toxicity impossible. In the validation study [54], there was only one adverse event, in which a participant vomited during the task. The participant was debriefed and divulged that he was "racing" to drink the water; participants were subsequently instructed to drink at a steady pace, but not to rush during the test.

Relation to Real World Outcomes

The WL-SPT has been used in several studies of pediatric pain. One study looked at the diagnostic utility of the WL-SPT, finding that it produced good specificity, but poor sensitivity, in identifying children with a particular functional gastrointestinal diagnosis [58]. The WL-SPT has been used to observe parent-child interactions during a visceral pain episode, with several studies manipulating parents' interaction style and examining children's symptom response [16,59]. Other work has shown that functional disability and poor perceived coping efficacy significantly predicted WL-SPT symptom response [60]. Taken together, these studies suggest that a variety of individual or interactional pain factors can be studied through use of the WL-SPT. The WL-SPT may have future utility as an outcome of pain interventions or as a predictor of chronicity of pain problems.

Thermal Pain

Inducing thermal pain typically entails applying a thermode, capable of providing cold and warm sensations of different temperatures and durations, to a body part. This thermal pain stimulation has been used in healthy samples as well as clinical samples ranging in age from 6 to

18 years old [11,17,61,62]. Thermal (pain) stimulation has been used in various contexts, with quantitative sensory testing (QST) [63] being the most popular. Thermal stimulation within the context of QST is used to determine participants' cold and heat detection, as well as pain threshold. Heat pain threshold and tolerance level has also increasingly been used to determine the impact of biological and psychological factors on children's pain experience [11,17] or to investigate differences in pain experiences between clinical populations and healthy control samples [61]. Thermal heat pain is also used in pediatric samples to assess central sensitization by means of temporal summation or wind-up, in which a series of multiple, short stimuli of the same temperature are applied causing increasing pain sensations. [64].

Advantages

Thermal pain induction has several advantages, as the spatial extension, temperature and duration of the pain stimuli can be highly controlled. Specifically, rapid changes in stimulus temperature and duration are possible, which has been found ideal to assess stimulus-response functions [65] and allowing determining multiple thresholds in adults [66]. Moreover, the usage of thermal pain to deliver painful heat stimulation allows stimulation of almost every part of the body [65]. Although the forearm is the most commonly stimulated body part, studies have also reported using legs, forehead [67] and the abdomen [61]. Lastly, researchers can decide whether the child has control over the timing of pain stimulations, or whether they will be unpredictable.

Disadvantages

Although standardized guidelines exist for the use of thermal stimuli as part of temporal summation and QST protocols, few formal recommendations are available for its use outside of these contexts. In particular, there are no guidelines addressing the type of pain sensation (cold vs. hot, pain threshold or tolerance), the duration of the pain stimuli, how many times a pain sensation can be induced, and the required interstimulus interval when using thermal pain within as an experimental pain induction. Second, although the thermal sensors are typically equipped to provide stimuli with a long duration, due to the small contact area and temperature limitations becoming increasingly stricter with longer durations, participants quickly habituate to heat sensation of longer durations. Although this habituation is important for assessing perceptual sensitization, thermal pain might therefore be less suitable to induce widespread pain sensations of long durations.

Practical Use and Implementation

Although fairly expensive (~$30,000USD), the most frequently used equipment to deliver thermal stimulations has been the Medoc Neuro Sensory Analyzer, Model TSA or Pathway CHEPS/APS (Medoc Ltd. Advanced Medical Systems, Ramat, Yishai, Israel), equipped with Peltier contact thermodes of varies sizes (9cm^2 - 256cm^2). The entire thermode-stimulating surface is placed in contact with the skin testing side and secured by a Velcro strap [14,61,63]. The cooling unit needs to be filled with a water-alcohol mixture and be refilled each three months. Depending on the purpose of the thermal stimulation the specific instructions to participants, the heat/cold stimulations and number of trials can differ (see Appendix A for general task instructions). Specifically, pain threshold and tolerance levels are typically determined by starting stimulation at 32°C and increasing (for heat), or decreasing (for cold), the temperature at a rate of 1°C/s until the child indicates the stimulus feels painful (for threshold), or too painful to continue (for tolerance) [14,61,63,67,68]. Temporal summation, as an index of central sensitization, on the other hand is assessed by applying a series of 10 heat pain stimuli of the same temperature (e.g., 47°C) and asking the child to report on the pain intensity level after each stimulation [64]. Alternatively, perceptual sensitization can also be measured by applying heat stimulation at the temperature corresponding to the child's pain threshold for 30 seconds. Children are uninformed that the temperature remains unchanged and are asked at the end of the stimulation to readjust the temperature to their pain threshold level (i.e., so that it feels just painful again). A lowered temperature indicates perceptual sensitization, while an increased temperature indicates habituation [62,68]. The Medoc is typically introduced to the child by showing the equipment and in particular the thermode where the heat/cold sensation will be coming from. During the actual pain task, the Medoc equipment can be placed out of the child's sight by using a board to prevent the child from seeing the temperature and timing of the stimulation. Generally, research assistants attach and remove the thermode. The child is provided with an emergency button, giving them full control over stopping the pain stimulation when it becomes too painful to continue.

The UgoBasile 7360 Unit (UgoBasile Biological Research Apparatus) [11,17] is less expensive ($8,000USD) and assesses pain tolerance differently than the Medoc. Participants are instructed to place their forearm over a small spot on the metal block (e.g., between the wrist and elbow) and to keep their arm on the spot as long as they can. But they are free to remove their arm at anytime [17]. Pain tolerance is defined as the amount of time the child can tolerate the stimulus with an uninformed ceiling of 20 seconds.

Ethical Issues and Research Ethics Approval

Research should generally not encounter many difficulties in obtaining ethical approval for use of thermal pain sensations in healthy schoolchildren. Likewise, no adverse advents were noted in any studies using thermal pain induction. Caes and colleagues [14] reported that only one child stopped participation before the end of the pain task, due to the pain stimulus being too painful. This dropout is comparable to the dropout rate of other pain tasks.

Relation to Real World Outcomes

Thermal heat pain is often explained to children as comparable to placing their hand on a hot stove. In the study by Caes and colleagues [14], heat pain stimulation was chosen as it was thought to more closely resemble needle pain. Specifically, the use of heat pain allowed frequent, short, unpredictable stimulations with a sharp and piercing sensation within a short amount of time. However, to our knowledge no research evidence is available to support the sensory and affective qualities of the heat pain stimulation as comparable to needle pain.

Pressure Pain

A variety of pressure pain modalities have been used in research with children and adolescents. These tasks include application of pressure to various parts of the body, with the goal of obtaining information about pressure pain threshold or tolerance. Pressure tasks have largely been used previously with samples of healthy children [11,17,69,70], as well as children with growing pains [71], abdominal pain [72], joint and TMJ pain [73], headache [74], and in a small sample of children with mixed chronic pain problems [32]. Some investigators have used pressure applied to the fingertip, while others have utilized locations previously identified as fibromyalgia tender points. Most tasks use gradually increasing pressure application, while others utilize evoked pressure modalities [70].

Advantages

Advantages of pressure pain include the ability to assess a stimulus that may be of clinical relevance, particularly in the case of musculoskeletal pain or in cases where central sensitization may be relevant. Pressure application typically produces an achy somatic pain that is similar to muscle soreness, and thus may fairly closely approximate the kinds of pain sensations that children with musculoskeletal pain experience. The ability to capture precise recordings with computer-based equipment is also an advantage.

Disadvantages

Disadvantages include that researchers must choose from a huge number of possible stimuli that could be administered, with little research available to guide choices in pediatric samples. Additionally, multiple stimuli trials are often required or recommended to assess pressure pain responses accurately, which may put undue burden on child participants depending on the number of pain locations being assessed. For instance, standard programs in some computer systems require three pressure applications to a single location, and consider this the number of trials needed to calculate a mean score for an individual. While researchers can certainly deviate from these protocols, validation on testing using a reduced number of trials has not been conducted.

Practical Use and Implementation

Pressure pain tasks can be conducted with low-tech devices that investigators construct themselves (e.g., finger guillotine with weights added by hand), or with very high tech devices integrating electronic algometers that measure pressure with computerized data collection. Researchers must choose whether there are particular locations that they want to examine, or particular protocols they want to follow given their particular research question (e.g., applying pressure to specific fibromyalgia tender points) [75]. Equipment can be quite expensive, with hand-held digital algometers being under $1000USD, while full-computerized systems may be well over $10,000USD. Other considerations include paying careful attention to the physical set up of the area where testing occurs to ensure consistency, consideration of dominant vs. non-dominant side of the body, and the relatively high level of training needed to train research staff to be comfortable and consistent in their administration of the task.

Ethical Issues and Research Ethics Approval

Depending on the device and part of the body used, the participant may or may not be able to instantly withdraw the involved hand or other body part. This is in contrast to many heat and cold modalities or equipment that allow the participant to stop the stimuli by simply pulling away from it. Many computerized devices rely on the participant to push a hand-held button to signal pain threshold or tolerance, which then signals the device or task administrator to stop the application of pressure. Other variations require the participant to say, “Stop”. In general, there may be limited additional information gleaned from measures of pressure tolerance, whether those are tolerance times for a pre-set pressure, or a ceiling for the amount of pressure that can be tolerated. As these presumably confer a higher level of risk of tissue injury than pressure pain threshold measures, simple pain threshold measures might be preferable. See Appendix A for general task instructions. While these issues do need to be addressed with review boards, the information that can potentially be gained from administration of well-designed pain tasks is substantial.

Relation to Real World Outcomes

There is little information about how pressure pain responses relate to daily or clinical pain experiences in children, although a growing number of studies show differences in pressure pain responses in clinical pain vs. healthy samples. Pressure pain modalities are thought to have particular relevance to musculoskeletal pain problems, and have been used widely in research examining adults with fibromyalgia and temporomandibular joint disorder [76], as well as in adults with headaches [77]. However, there is little evidence that level of pain sensitivity or threshold is associated with pain frequency or intensity, with some studies showing no link between pressure pain and clinical pain features. Pressure pain stimuli result in large sex differences in adult samples, with females showing lower pain thresholds and tolerances [78], although this has not been observed in all samples of healthy children and adolescents [11].

Conditioned Pain Modulation (CPM)

Conditioned pain modulation (CPM; also know as diffuse noxious inhibitory control or DNIC) is assessed via dynamic psychophysical testing that requires multiple pain modalities. CPM refers to tests of pain responses administered in the absence and presence of a second pain stimuli, known as the conditioning stimuli. The degree of pain modulation is calculated by subtracting the pain response score in the presence of the conditioning stimuli from the score in the absence of the stimuli. These tasks are thought to reflect the body's endogenous pain modulation system [79]. CPM has been used widely in samples of adults with chronic pain, and deficiencies in CPM compared to healthy controls have been observed in adults with a range of painful conditions (e.g., headache, CRPS, etc.) [80,81,82]. Poor CPM, or lack of reduction in pain during the presence of the conditioning stimuli, appears to increase risk for the development of chronic pain in adults. Among children and adolescents, CPM tasks have been used with samples of healthy children [83], with children who were born prematurely [84], and with a sample of youth with mixed chronic pain conditions [39]. The work in this area to date has shown some differences in CPM among clinical samples.

Advantages

The main advantage to utilizing CPM tasks is the ability to measure a laboratory pain response, which likely reflects central descending inhibition, at least in adults [85]. This may be particularly relevant for work chronic pain conditions in which CPM is known to be impaired in adults [82], or when examining risk for the development of chronic pain. It is also possible that expectations and behaviors can be manipulated in order to examine the potential impact of key cognitive and social factors in pain modulation, which has begun to be demonstrated in adults [86].

Disadvantages

The primary disadvantage of CPM is the practical complexity of administering multiple pain modalities within the same task. If pressure or heat application is used, it is likely that expensive equipment is required. The timeline for the development of CPM in typically developing children is also not entirely clear, although one study to date shows that CPM is higher among healthy adolescents than children [83]. Careful consideration to age and development in study design is important and may require the addition of participants (e.g., studies of youth with chronic pain might benefit from the inclusion of age and gender matched controls).

Practical Use and Implementation

While it is possible to devise CPM tasks using any two pain stimuli, the cold pressor is often used as the conditioning stimuli with pressure or heat applied to the opposite forearm as the primary stimuli due to ease of simultaneous administration. Given that the perception of the painfulness of the conditioning stimuli affects CPM responses, such that the participant must experience the conditioning stimulus as sufficiently painful in order to elicit the conditioned pain modulation response [86], it is important that a conditioning stimulus be carefully chosen and administered. In the case of using the cold pressor for the conditioning stimulus, most protocols depend on the participant to rate the pain at an 8/10 on the 0-10 NRS (or equivalent) prior to administering the second primary pain stimuli. If something other than the CPT is chosen (e.g. heat via thermode), a pre-determined level of the painful stimulus can be used, but this requires administration of another painful stimulus prior to the CPM task to determine the level of heat that reaches moderate pain level for that participant. An additional note is that the initial response to the painful stimuli in the absence of the conditioning stimuli can provide information about pain responses (threshold and/or tolerance), so if this information is desired a separate task is not needed.

Ethical Issues and Research Ethics Approval.

As with any task in which painful stimuli are administered, the child should have control over stopping the stimuli at any time, and the number and intensity of painful stimuli should be kept as low as possible. Given this, CPM should be considered carefully as it requires administration of multiple painful stimuli, and requires the conditioned stimuli be sufficiently painful. However, gaining information about endogenous pain modulation is of direct relevance to a number of important research areas, thus these advantages may outweigh the risk.

Relation to Real World Outcomes

Very little information is available about the association between CPM and clinical pain outcomes in daily life of children and adolescents, although the literature with adults would indicate that the information gleaned from CPM tasks is highly relevant to chronic pain conditions. Higher heart-rate variability and higher age is associated with more efficient CPM (indicating better pain inhibition) [83], which likely reflects typical developmental maturity of the autonomic nervous system.

Discussion and Future Perspective

Despite their differences, a number of issues apply broadly across all experimental pain modalities. As with all pediatric research, informed consent and developmentally appropriate child assent should be obtained before participation [9,87]. Researchers should take reasonable steps to ascertain that each child understands the pain task and what is expected of him or her.

Understanding can be enhanced with standardized instructions given verbally, visually, or in writing, and by asking children to repeat the instructions. If multiple trials are employed, a brief reminder of instructions may be helpful. Child assent is continuous and researchers should clearly watch for signals of dissent throughout study procedures, particularly among younger children [88]. In some situations, task safeguards, such as upper limits for the intensity or length of painful stimuli, should also be in place in case the child does not understand or follow instructions. Reasonable upper limits could be inferred from previous research or by piloting participants. Researchers should also consider undergoing the experimental pain task themselves. Although parents and children show a willingness to engage in nonbeneficial experimental pain research [7], it is also relevant for researchers to consider differences between parents and children who choose to participate in research versus those who do not, including perceived importance or benefit of research to others and understanding of the study during consent [89].

As described, there are variable advantages and disadvantages offered by each experimental pain modality. For example, researchers should choose the CPT or the WL-SPT for instances requiring pain lasting at least several minutes, which may be particularly beneficial for examining interactions during pain experiences (e.g., with parents or with peers). Research suggests that the CPT is not particularly threatening to children [44], making the anticipatory anxiety minimal as compared with other experimental pain. Alternatively, the WL-SPT offers higher uncertainty over the onset and duration of the pain experience, which is more similar to recurrent real world pains. Use of pressure or thermal induced pain is particularly relevant for research requiring short and/or repeated pain stimuli. Although lacking empirical support, the experience of pressure and thermal stimuli seem more akin to a needle procedure or other acute pain experiences as compared to the CPT or WL-SPT [14]. Furthermore, small adjustments can be made quickly and easily to thermal and pressure pain, allowing for the individualization of stimuli and investigation of central sensitization via temporal summation/wind-up [64]. In addition to length of pain stimuli, researchers should consider how closely the pain stimuli they chose approximates real-life experiences of pain, particularly with clinical pain populations (e.g., pressure pain as similar to musculoskeletal pain, WL-SPT as similar to abdominal pain). While closely matched pain sensations may not always be needed, there are advantages to matching the lab task with the type of pain experienced by youth in daily life.

Given the increased challenges of conducting research with vulnerable populations, pediatric research often lags behind that with adults. In addition to continuing exploration of psychosocial influences, experimental pain has been increasingly used with adults to investigate biological, neurological, and genetic pain mechanisms [22,90-93] and race/ethnicity [94]. To date, research using the cold pressor task with children has assessed biomarkers of heart rate [12,39,84], blood pressure [32], and cortisol [95], as well as associations with race [96,97]. To our knowledge, of the other experimental pain modalities, biomarkers have only been examined in relation to conditioned pain modulation (i.e., heart rate variability) [83], and racial differences have not been investigated. These are trends that we expect will gain increasing focus in future pediatric research. Familiarity with and use of multiple experimental pain modalities within single studies will increase given their particular benefit for understanding pain modulation and central processing [39,53,84]. Use of experimental methods to examine early pain experiences and identify biopsychosocial risk factors in childhood will lead our understanding of how and for whom chronic pain develops later in life [98].

The limitations of our current use of experimental pain with children will also be critical for the field to address in the coming years. In particular, a distinct lack of evidence outlining the relation of experimentally induced pain to clinical pain or real world outcomes. As previously suggested, it is likely that these relationships will differ between experimental modalities [21]; however, research comparing the intensity, affect, and quality of pain induced by different modalities in the lab to pain in the real world is necessary and offers the potential to develop a model for integration of information from multiple pain assessments [11,17]. As this understanding grows and more recently introduced experimental pain modalities become familiar to pediatric researchers, they will be used more widely with clinical samples of children and adolescents to understand pain processes and examine treatment effects.

Although all described experimental pain modalities have been used with children, acceptability of the pain induction by parents and children has only been empirically investigated for the CPT [7]. Given the potential lack of direct benefit to participating children, reporting of the acceptability of other modalities is strongly encouraged. This information can be useful for research ethics boards in their assessment of risk posed by studies using experimental pain. Clearer guidelines are developing for pressure and thermal pain within the context of quantitative sensory testing with children [99]; however, the CPT offers the most established guidelines directing researchers' use of any single experimental pain modality [29,30]. Researchers using experimental pain with children are also encouraged to publish evidence and opinions on these issues to promote their use more broadly and ethically; furthermore, encouraging standardization of methods when beneficial to increase comparability of findings between research groups and across studies.

Despite these limitations, the introduction of different experimental pain modalities to pediatric research has and will continue to infinitely broaden the scope of research questions that can be addressed with children and adolescents. Already experimental pain research has evidenced its critical role in advancing our understanding and treatment of pain in children and adolescents, who would be unjustly denied these benefits without their inclusion in such research.

References

1. Milgram S. Behavioral study of obedience. *J Abnorm Soc Psychol*. 67(4), 371-378 (1963).

2. King S, Chambers CT, Huguet A *et al*. The epidemiology of chronic pain in children and adolescents revisited: A systematic review. *Pain*. 152(12), 2729-2738 (2011).

3. Stevens BJ, Abbott LK, Yamada J *et al*. Epidemiology and management of painful procedures in children in Canadian hospitals. *CMAJ*. 183(7), E403-10 (2011).

4. von Baeyer CL, Baskerville S, McGrath PJ. Everyday pain in three-to five-year-old children in day care. *Pain Res Manag*. 3(2), 111-116 (1998).

5. Charlton JE. *Core Curriculum for Professional Education in Pain*. IASP Press, Seattle, WA (2005).

6. Noel M, Birnie KA. Ethical challenges in pediatric pain research. *Pediatr Pain Lett*. 12, 1-5 (2010).

7. Birnie KA, Noel M, Chambers CT, von Baeyer CL, Fernandez CV. The cold pressor task: Is it an ethically acceptable pain research method in children? *J Pediatr Psychol*. 36(10), 1071-1081 (2011).

8. Fisher CB, Kornetsky SZ, Prentice ED. Determining risk in pediatric research with no prospect of direct benefit: Time for a national consensus on the interpretation of federal regulations. *Am J Bioeth*. 7(3), 5-10 (2007).

9. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council. *Tri-council policy statement: Ethical conduct for research involving humans* (2010).

10. World Medical Association. *Declaration of Helsinki: Ethical principles for medical research involving human subjects* (2008).

11. Myers CD, Tsao JC, Glover DA, Kim SC, Turk N, Zeltzer LK. Sex, gender, and age: Contributions to laboratory pain responding in children and adolescents. *J Pain*. 7(8), 556-564 (2006).

12. Dufton LM, Konik B, Colletti R *et al*. Effects of stress on pain threshold and tolerance in children with recurrent abdominal pain. *Pain.* 136(1-2), 38-43 (2008).

13. Caes L, Vervoort T, Eccleston C, Vandenhende M, Goubert L. Parental catastrophizing about child's pain and its relationship with activity restriction: The mediating role of parental distress. *Pain*. 152(1), 212-222 (2011).

14. Caes L, Vervoort T, Trost Z, Goubert L. Impact of parental catastrophizing and contextual threat on parents' emotional and behavioral responses to their child's pain. *Pain*. 153(3), 687-695 (2012).

15. Chambers CT, Craig KD, Bennett SM. The impact of maternal behavior on children's pain

experiences: An experimental analysis. *J Pediatr Psychol.* 27(3), 293-301 (2002).

16. Walker LS, Williams SE, Smith CA, Garber J, Van Slyke DA, Lipani TA. Parent attention versus distraction: Impact on symptom complaints by children with and without chronic functional abdominal pain. *Pain*. 122(1-2), 43-52 (2006).

17. Lu Q, Tsao JC, Myers CD, Kim SC, Zeltzer LK. Coping predictors of children's laboratory-induced pain tolerance, intensity, and unpleasantness. *J Pain*. 8(9), 708-717 (2007).

18. Dahlquist LM, Weiss KE, Law EF *et al*. Effects of videogame distraction and a virtual reality type head-mounted display helmet on cold pressor pain in young elementary school-aged children. *J Pediatr Psychol*. 35(6), 617-625 (2010).

19. Moore DJ, Keogh E, Crombez G, Eccleston C. Methods for studying naturally occurring human pain and their analogues. *Pain.* 154(2), 190-199 (2013).

20. Feuerstein M, Barr RG, Francoeur TE, Houle M, Rafman S. Potential biobehavioral mechanisms of recurrent abdominal pain in children. *Pain*. 13(3), 287-298 (1982).

21. Neziri AY, Curatolo M, Nüesch E *et al*. Factor analysis of responses to thermal, electrical, and mechanical painful stimuli supports the importance of multi-modal pain assessment. *Pain.* 152(5), 1146-1155 (2011).

22. Nielsen CS, Staud R, Price DD. Individual differences in pain sensitivity: Measurement, causation, and consequences. *J Pain*. 10(3), 231-237 (2009).

23. Blankenburg M, Boekens H, Hechler T *et al.* Reference values for quantitative sensory testing in children and adolescents: Developmental and gender differences of somatosensory perception. *Pain.* 149, 76-88 (2010).

24. Wollgarten-Hadamek I, Hohmeister J, Zohsel K, Flor H, Hermann C. Do school-aged children with burn injuries during infancy show stress-induced activation of pain inhibitory mechanisms? *Eur J Pain*. 15(4), 423.e1-10 (2011).

25. Reid GJ, McGrath PJ, Lang BA. Parent-child interactions among children with juvenile fibromyalgia, arthritis, and healthy controls. *Pain.* 113(1-2), 201-210 (2005).

26. Hines Jr EA. Reaction of the blood pressure of 400 school children to a standard stimulus. *JAMA*. 108(15), 1249-1250 (1937).

27. Zeltzer LK, Fanurik D, LeBaron S. The cold pressor pain paradigm in children: Feasibility of an intervention model (part II). *Pain.* 37(3), 305-313 (1989).

28. LeBaron S, Zeltzer L, Fanurik D. An investigation of cold pressor pain in children (part I). *Pain*. 37(2), 161-171 (1989).

*29. Birnie KA, Petter M, Boerner KE, Noel M, Chambers CT. Contemporary use of the cold pressor task in pediatric pain research: A systematic review of methods. *J Pain*. 13(9), 817-826 (2012). *Systematic review of methodological variability in cold pressor task use with pediatric samples and provides update to earlier guidelines.*

**30. von Baeyer CL, Piira T, Chambers CT, Trapanotto M, Zeltzer LK. Guidelines for the cold pressor task as an experimental pain stimulus for use with children. *J Pain.* 6(4), 218-227 (2005). *Guidelines directing standardized and ethical use of the cold pressor task with children.*

31. Trapanotto M, Pozziani G, Perissinotto E, Barbieri S, Zacchello F, Benini F. The cold pressor test for the pediatric population: Refinement of procedures, development of norms, and study of psychological variables. *J Pediatr Psychol*. 34(7), 749-759 (2009).

32. Tsao JC, Evans S, Seidman LC, Zeltzer LK. Experimental pain responses in children with chronic pain and in healthy children: How do they differ? *Pain Res Manag*. 17(2), 103-109 (2012).

33. Williams AE, Heitkemper M, Self MM, Czyzewski DI, Shulman RJ. Endogenous inhibition of somatic pain is impaired in girls with irritable bowel syndrome compared with healthy girls. *J Pain* (Epub 2013).

34. Moon EC, Chambers CT, McGrath PJ. "He says, she says": A comparison of fathers' and mothers' verbal behavior during child cold pressor pain. *J Pain.*12(11), 1174-1181 (2011).

35. Noel M, Chambers CT, McGrath PJ, Klein RM, Stewart SH. The influence of children's pain memories on subsequent pain experience. *Pain*. 153(8), 1563-1572 (2012).

36. Petter M, Chambers CT, MacLaren Chorney J. The effects of mindfulness-based attention on cold pressor pain in children. *Pain Res Manag*.18(1), 39-45 (2013).

37. Vervoort T, Trost Z, Van Ryckeghem DM. Children's selective attention to pain and avoidance behaviour: The role of child and parental catastrophizing about pain. *Pain* (Epub 2013).

38. Schmitz AK, Vierhaus M, Lohaus A. Pain tolerance in children and adolescents: Sex differences and psychosocial influences on pain threshold and endurance. *Eur J Pain*. 17(1), 124-131 (2013).

39. Evans S, Seidman LC, Tsao JC, Lung KC, Zeltzer LK, Naliboff BD. Heart rate variability as a biomarker for autonomic nervous system response differences between children with chronic pain and healthy control children. *J Pain Res.* 6, 449-457 (2013).

40. Dahlquist LM, McKenna KD, Jones KK, Dillinger L, Weiss KE, Ackerman CS. Active and passive distraction using a head-mounted display helmet: Effects on cold pressor pain in children. *Health Psychol*. 26(6), 794-801 (2007).

41. Dahlquist LM, Weiss KE, Clendaniel LD, Law EF, Ackerman CS, McKenna KD. Effects of videogame distraction using a virtual reality type head-mounted display helmet on cold pressor pain in children. *J Pediatr Psychol*. 34(5), 574-584 (2009).

42. Wohlheiter KA, Dahlquist LM. Interactive versus passive distraction for acute pain management in young children: The role of selective attention and development. *J Pediatr Psychol.* 38(2), 202-212 (2013).

43. Stuber M, Hilber SD, Mintzer LL, Castaneda M, Glover D, Zeltzer L. Laughter, humor and

pain perception in children: A pilot study. *Evid Based Complement Alternat Med*. 6(2), 271-276 (2009).

44. Tsao JC, Myers CD, Craske MG, Bursch B, Kim SC, Zeltzer LK. Role of anticipatory anxiety and anxiety sensitivity in children's and adolescents' laboratory pain responses. *J Pediatr Psychol*. 29(5), 379-388 (2004).

45. Weiss KE, Dahlquist LM, Wohlheiter K. The effects of interactive and passive distraction on cold pressor pain in preschool-aged children. *J Pediatr Psychol*. 36(7), 816-826 (2011).

46. Mitchell LA, MacDonald RA, Brodie EE. Temperature and the cold pressor test. *J Pain*. 5(4), 233-237 (2004).

47. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. *Pain*. 152(10), 2399-2404 (2011).

48. Hirsch MS, Liebert RM. The physical and psychological experience of pain: The effects of labeling and cold pressor temperature on three pain measures in college women. *Pain*. 77(1), 41-48 (1998).

49. Williams DA, Thorn BE. Can research methodology affect treatment outcome? A comparison of two cold pressor test paradigms. *Cognit Ther Res*. 10(5), 539-545 (1986).

50. Jackson T, Pope L, Nagasaka T, Fritch A, Iezzi T, Chen H. The impact of threatening information about pain on coping and pain tolerance. *Br J Health Psychol*. 10, 441-451 (2005).

51. Wolf S, Hardy JD. Studies on pain. Observations on pain due to local cooling and on factors involved in the "cold pressor" effect. *J Clin Invest*. 20(5), 521-533 (1941).

52. Coldwell SE, Kaakko T, Gärtner-Makihara AB *et al*. Temporal information reduces children's pain reports during a multiple-trial cold pressor procedure. *Behav Ther*. 33(1), 45-63 (2003).

53. Tsao JC, Glover DA, Bursch B, Ifekwunigwe M, Zeltzer LK. Laboratory pain reactivity and gender: Relationship to school nurse visits and school absences. *J Dev Behav Pediatr*. 23(4), 217-224 (2002).

**54. Walker LS, Williams SE, Smith CA *et al*. Validation of a symptom provocation test for laboratory studies of abdominal pain and discomfort in children and adolescents. *J Pediatr Psychol*. 31(7), 703-713 (2006). *Describes the development and use of the water load symptom provocation test with children.*

55. Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. *Gastroenterol*. 109(1), 40-52 (1995).

56. Koch KL, Bingaman S, Muth E, Ouyang A. Effects of physiological gastric distention on nausea, stomach fullness, satiety and gastric myoelectrical activity in patients with irritable bowel syndrome. *Gastroenterol*. 4, A763 (1997).

57. Sood MR, Schwankovsky LM, Rowhani A *et al*. Water load test in children. *J Pediatr Gastroenterol Nutr*. 35(2), 199-201 (2002).

58. Schurman JV, Friesen CA, Andre L *et al*. Diagnostic utility of the water load test in children with chronic abdominal pain. *J Pediatr Gastroenterol Nutr*. 44(1), 51-57 (2007).

59. Williams SE, Blount RL, Walker LS. Children's pain threat appraisal and catastrophizing moderate the impact of parent verbal behavior on children's symptom complaints. *J Pediatr Psychol*. 36(1), 55-63 (2011).

*60. Anderson JL, Acra S, Bruehl S, Walker LS. Relation between clinical symptoms and experimental visceral hypersensitivity in pediatric patients with functional abdominal pain. *J Pediatr Gastroenterol Nutr*. 47(3), 309-315 (2008). *Provides evidence for the relationship of pain responding during the water load symptom provocation test to clinical pain and real world outcomes.*

61. Zohsel K, Hohmeister J, Flor H, Hermann C. Somatic pain sensitivity in children with recurrent abdominal pain. *Am J Gastroenterol*. 103(6), 1517-1523 (2008).

62. Hermann C, Hohmeister J, Demirakça S, Zohsel K, Flor H. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. *Pain*. 125(3), 278-285 (2006).

63. Meier PM, Berde CB, DiCanzio J, Zurakowski D, Sethna NF. Quantitative assessment of cutaneous thermal and vibration sensation and thermal pain detection thresholds in healthy children and adolescents. *Muscle Nerve*. 24(10), 1339-1345 (2001).

64. Walker LS, Sherman AL, Bruehl S, Garber J, Smith CA. Functional abdominal pain patient subtypes in childhood predict functional gastrointestinal disorders with chronic pain and psychiatric comorbidities in adolescence and adulthood. *Pain*. 153(9), 1798-1806 (2012).

65. Ruscheweyh R, Stumpenhorst F, Knecht S, Marziniak M. Comparison of the cold pressor test and contact thermode-delivered cold stimuli for the assessment of cold pain sensitivity. *J Pain*. 11(8), 728-736 (2010).

66. Moloney NA, Hall TM, Doody CM. Reliability of thermal quantitative sensory testing: A systematic review. *J Rehabil Res Dev*. 49(2), 191-207 (2012).

67. Bar-Shalita T, Vatine JJ, Seltzer Z, Parush S. Psychophysical correlates in children with sensory modulation disorder (SMD). *Physiol Behav*. 98(5), 631-639 (2009).

68. Hohmeister J, Demirakça S, Zohsel K, Flor H, Hermann C. Responses to pain in school-aged children with experience in a neonatal intensive care unit: Cognitive aspects and maternal influences. *Eur J Pain.* 13(1), 94-101 (2009).

69. Goubert L, Vervoort T, Cano A, Crombez G. Catastrophizing about their children's pain is related to higher parent-child congruency in pain ratings: An experimental investigation. *Eur J Pain.* 13(2), 196-201 (2009).

70. Payne LA, Seidman LC, Lung KC, Zeltzer LK, Tsao JC. Relationship of neuroticism and laboratory pain in healthy children: Does anxiety sensitivity play a role? *Pain.* 154(1), 103-109

(2013).

71. Hashkes PJ, Friedland O, Jaber L, Cohen HA, Wolach B, Uziel Y. Decreased pain threshold in children with growing pains. *J Rheumatol*. 31(3), 610-613 (2004).

72. Duarte MA, Goulart EM, Penna FJ. Pressure pain threshold in children with recurrent abdominal pain. *J Pediatr Gastroenterol Nutr*. 31(3), 280-285 (2000).

73. Chaves TC, Nagamine HM, de Sousa LM, de Oliveira AS, Regalo SC, Grossi DB. Differences in pain perception in children reporting joint and orofacial muscle pain. *J Clin Pediatr Dent.* 37(3), 321-327 (2013).

74. Soee AB, Skov L, Kreiner S, Tornoe B, Thomsen LL. Pain sensitivity and pericranial tenderness in children with tension-type headache: A controlled study. *J Pain Res*. 6, 425-434 (2013).

75. Wolfe F, Smythe HA, Yunus MB *et al*. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum*. 33(2), 160-172 (1990).

76. Smith MT, Wickwire EM, Grace EG *et al*. Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder. *Sleep*. 32(6), 779-790 (2009).

77. Fernández-de-Las-Peñas C, Cuadrado ML, Arendt-Nielsen L, Ge HY, Pareja JA. Increased pericranial tenderness, decreased pressure pain threshold, and headache clinical parameters in chronic tension-type headache patients. *Clin J Pain*. 23(4), 346-352 (2007).

78. Riley JL, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: A meta-analysis. *Pain.* 74(2-3), 181-187 (1998).

79. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol*. 23(5), 611-615 (2010).

80. Cathcart S, Petkov J, Winefield AH, Lushington K, Rolan P. Central mechanisms of stress-induced headache. *Cephalalgia*. 30(3), 285-295 (2010).

81. Seifert F, Kiefer G, DeCol R, Schmelz M, Maihöfner C. Differential endogenous pain modulation in complex-regional pain syndrome. *Brain*. 132, 788-800 (2009).

82. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: A systematic review and meta-analysis. *J Pain*. 13, 936-944 (2012).

*83. Tsao JC, Seidman LC, Evans S, Lung KC, Zeltzer LK, Naliboff BD. Conditioned pain modulation in children and adolescents: Effects of sex and age. *J Pain.* 14(6), 558-567 (2013). *Provides example of conditioned pain modulation in children using pressure pain and a cold water conditioning stimulus.*

84. Goffaux P, Lafrenaye S, Morin M, Patural H, Demers G, Marchand S. Preterm births: Can neonatal pain alter the development of endogenous gating systems? *Eur J Pain*. 12(7), 945-951 (2008).

85. van Wijk G, Veldhuijzen DS. Perspective on diffuse noxious inhibitory controls as a model of endogenous pain modulation in clinical pain syndromes. *J Pain.* 11(5), 408-419 (2010).

86. Nir RR, Yarnitsky D, Honigman L, Granot M. Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation. *Pain*. 153(1), 170-176 (2012).

87. U.S. Department of Health and Human Services. *Protection of human subjects research 45 CFR 46.408* (2009).

88. Wendler DS. Assent in paediatric research: Theoretical and practical considerations. *J Med Ethics*. 32(4), 229-234 (2006).

89. Tait AR, Voepel-Lewis T, Malviya S. Participation of children in clinical research: Factors that influence a parent's decision to consent. *Anesthesiology.* 99, 819-825 (2003).

90. Chang PF, Arendt-Nielsen L, Chen AC. Dynamic changes and spatial correlation of EEG activities during cold pressor test in man. *Brain Res Bull*. 57(5), 667-675 (2002).

91. Diatchenko L, Nackley AG, Slade GD *et al*. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain.* 125(3), 216-224 (2006).

92. Mogil JS. Pain genetics: Past, present and future. *Trends Genet*. 28(6), 258-266 (2012).

93. Reimann F, Cox JJ, Belfer I *et al*. Pain perception is altered by a nucleotide polymorphism in SCN9A. *Proc Natl Acad Sci*. 107(11), 5148-5153 (2010).

94. Rahim-Williams B, Riley JL, Williams KK *et al.* A quantitative review of ethnic group differences in experimental pain response: Do biology, psychology, and culture matter? *Pain Med.* 13, 522-540 (2012).

95. Allen LB, Lu Q, Tsao JCI *et al.* Sex differences in the association between cortisol concentrations and laboratory pain responses in healthy children. *Gender Med*. 6, 193-207 (2009).

96. Evans S, Lu Q, Tsao JCI *et al.* The role of coping and race in healthy children's experimental pain responses. *J Pain Manag.* 1, 151-162 (2008).

97. Keenan K, Hipwell AE, Hinze AE *et al.* The association of pain and depression in preadolescent girls: Moderation by race and pubertal stage. *J Pediatr Psychol.* 34, 727-737 (2009).

*98. Wilson AC, Holley AL, Palermo TM. Applications of laboratory pain methodologies in research with children and adolescents: Emerging research trends. *Pain*. 154(8), 1166-1169 (2013). *A recent discussion of future directions for pediatric experimental pain research.*

**99. Blankenburg M, Boekens H, Hechler T *et al*. Reference values for quantitative sensory testing in children and adolescents: Developmental and gender differences of somatosensory perception. *Pain.* 149(1), 76-88 (2010). *Establishes feasibility and reference values for pressure*

and thermal pain stimuli with children and adolescents as part of quantitative sensory testing protocol.

Acknowledgments

Contact the following authors for more detailed information about use of the water load symptom provocation test (S.Williams: sewillia@mcw.edu), thermal pain (L.Caes: line.caes@iwk.nshealth.ca or A.Wilson: longann@ohsu.edu), pressure pain and conditioned pain modulation (A.Wilson: longann@ohsu.edu). All authors have used the cold pressor task with children/adolescents. Contact C.Chambers (christine.chambers@dal.ca) for information on building a cold pressor apparatus. Dr. Lynn Walker (Vanderbilt University) can also be contacted for more details regarding the water load symptom provocation test. A.Wilson's work on this manuscript was supported by NIH K23HD064705. K.A. Birnie and L. Caes are both trainee members of Pain in Child Health, a strategic research training initiative of the Canadian Institutes of Health Research. C.T. Chambers is supported by a Canada Research Chair. The authors have no conflicts of interest to disclose.

Summary Points

- Experimental induction of pain with children receives considerable scrutiny given the potential for harm and lack of direct benefit.
- Experimental pediatric pain research has critically advanced our assessment and treatment of pain across development in healthy and chronically ill children.
- Experimental pain offers greater control over the environment and standardization of pain stimulus that allows investigation of research not feasible in the real world.
- The cold pressor task is the longest and most widely used experimental pain with children; however, modalities used with adults (e.g., pressure and thermal pain, conditioned pain modulation) have rapidly growing applications in pediatric research.
- Evidence for the relation of experimental pain to clinical pain or real world outcomes in children is limited and a critical area for further research.
- Concurrent use of multiple experimental pain modalities with children is accelerating, which offers particular benefit for examining pain modulation and central processing.
- Experimental pain will be increasingly used with children and adolescents with chronic pain, and to examine biological, neurological, and genetic pain mechanisms.
- Greater use of experimental methods to examine early pain experiences and identify biopsychosocial risk factors in childhood will lead our understanding of how and for whom chronic pain develops later in life.

Table 1. Summary of use of experimental pain modalities with children and adolescents.

Pain Task	**Age Range**	**Samples**	**Estimated # of Published Studies**	**Task Advantages**	**Task Disadvantages**	**Pain Characterization**	**Possible Pain Outcomes**
Cold Pressor Task	3-18	Healthy and Clinical (pain and non-pain)	>60	- Established guidelines - Standardization - Convenience - Requires minimal training - Range of cost for equipment - Portability - Pain experience lasting up to several minutes	- Methodological variability across research teams - Unclear relation to real world outcomes - Less anxiety provoking/ threatening than clinical pain	- Under control of the child and lasts from few seconds up to maximum set by researcher (typically 3 or 4 minutes)	- Tolerance (seconds) - Threshold (seconds) - Intensity - Affect/ Unpleasantness - Behavioral (e.g., facial coding) - Physiological (e.g., heart rate, cortisol, respiratory rate, blood pressure)
Water Load Task	8-16	Healthy and Clinical (pain)	~7	- Only validated lab task that is a proxy of visceral pain - Established baselines for healthy and clinical samples - Requires minimal training - Low cost and convenient - Pain experience can last beyond task - Acceptable to	- Variability in amount of water consumed between subjects - Produces more discomfort than pain	- Visceral pain - Produces abdominal discomfort similar, but less painful, than usual abdominal pain episodes - Described as a "feeling of fullness" - Symptoms reported to begin during the task and can last	- Tolerance (amount of water consumed) - Intensity - Affect - Behavioral (e.g., children's verbal or facial pain complaints) - Physiological (e.g., heart rate variability, skin conductance)

				parents and children - Children control amount of water consumed		minutes to hours after completion	
Thermal Pain*	6-18	Healthy and Clinical (pain and non-pain)	~10 (outside QST field)	- Rapid changes in stimulus temperature, duration and location possible - All body parts - Easy to incorporate in a computer task - Child control over stimulus on- and offset can be manipulated	- No guidelines for use outside QST field - Less suited for long stimuli durations - No info on ethical acceptability - Expensive	- Can either be under control of the child or not - Lasts a few seconds	- Tolerance (Temperature) - Threshold (Temperature) - Intensity - Affect/ Unpleasantness - Temporal summation - Behavioral (e.g., facial coding) - Physiological (e.g., heart rate) - Warm/cold detection (Temperature)
Pressure Pain	6-18	Healthy and Clinical (pain)	~12	- Many locations and variations in terms of stimulus administration possible - Computerized programs guide administration and provide pre-designed programs and data	- No practical or ethical guidelines for use in clinical pediatric pain samples - Computerized versions expensive	- Typically gradually increasing discomfort - Duration variable - Sensation is of pressure, aching	- Threshold (kilopascals kPa) - Tolerance (kPa) - Intensity, bother, and/or unpleasantness ratings - Physiological (e.g., heart rate, EEG) - Behavioral
CPM	6-18	Healthy and Clinical	~3	- Relevance to pain disorders in which central	- Can be expensive depending on pain stimuli	- Multiple sources of pain/ discomfort	- Pain modulation (amount of reduction in pain threshold or

		(pain and non-pain)		sensitization is thought to play a role	equipment chosen	- Duration and sensations variable	tolerance) - Yields baseline/non-conditioned pain response measures if desired

*Information on thermal pain advantages, disadvantages, pain characterizations and pain outcomes are based on thermal pain studies using the Medoc equipment.

Table 2. Estimated cost, equipment, and practical needs for experimental pain modalities.

Experimental Pain Task	**Estimated Cost**	**Equipment Options**	**Practical Needs**
Cold Pressor Task	$200-4000USD	- Build own[a] - www.techne.com	- Access to water (and ice, if needed) - Hand towels - Handling spills - Electrical needs - Safety approval - Equipment cleaning - Time to refill/cool/stabilize water temperature
Water Load Task	$200-500USD	- www.camelbak.com	- Water reservoir - Backpack - Disposable mouth pieces - Cleaning kit - Water - Stop watch - Visual fullness scale
Thermal Pain	$8,000 - $30,000USD	- www.medoc-web.com - www.ugobasile.com	- Laptop to operate Medoc - Electrical needs - Safety approval - Water and alcohol solution to refill Medoc coolant every 3 months - Time to stabilize cooling unit of Medoc
Pressure Pain	$1,000 - $30,000USD	- www.medoc-web.com - Others	- Laptop to operate Medoc - Electrical needs - Training of research staff
CPM	Varies depending on pain stimuli chosen.	Varies depending on pain stimuli chosen.	- Set-up typically requires laptop, as well as other practical requirements for each pain stimuli

[a]Information on building your own CPT can be obtained by contacting C.Chambers.

Appendix 1. Examples of possible experimental pain task instructions

Cold Pressor Task
This is the part where you are going to put your hand in the water. Don't put your hand in now, but you can look at it. You need to lower your hand all the way down so that where your wrist bends (demonstrate wrist fold) *is in the water. Keep your hand open* (demonstrate). *Once you've put your hand in the water, we'd like you to leave it in for as long as you can, even if it is uncomfortable. If your hand gets too uncomfortable or hurts too much you can take it out of the water at any time.*

Water Load Symptom Provocation Test
Now it's time to begin drinking water. Here is the special tube and mouthpiece you get to drink the water out of. This piece on the end of the tube is what you'll use to drink the water out of. A lot of kids have to burp when they are drinking the water. So it's OK if you have to take a break and burp when you are drinking. OK? Do you have any questions about drinking the water? Now remember, we want to see how kids feel when their stomachs are really really full, so I want you to drink until you feel just like the picture we looked at earlier. We want you to drink water until you are completely full, just like you might feel when you eat a big Thanksgiving dinner. Please drink only to that point; don't push yourself to go beyond feeling completely full. I'm going to be filling out some forms while you are drinking. I'll check in with you from time to time. Just tell me when you feel like your stomach is totally full and you can't drink another drop.

Thermal Pain
Pain Threshold: *We will start the sensation with a stimulus that feels neither warm nor cold and the sensation will gradually become warmer/colder. As soon as the sensation starts to feel painful, you can press the button and the sensation will stop.*

Pain Tolerance: *We will start the sensation with a stimulus that feels neither warm nor cold and the sensation will gradually become warmer/colder. We will ask you to press the button when the sensation feels too painful to continue. The sensation will stop immediately when you press the button.*

Pressure Pain
General: *You can stop the task at any time if it becomes too painful or if you want to stop for any reason. Just say stop or push the button (on the patient response unit).*

Pain Threshold: *I'll be using this rubber tip to slowly apply pressure on your forearm. I will do this three times. Each time, I want you to push the button as soon as the pressure becomes painful. The button records the amount of pressure and also tells to us to stop pressing. Your job is to hold this and click the button just when the pressure becomes painful.*

Pain Tolerance: *I'll be using this rubber tip to slowly apply pressure on your forearm. Your job is to hold this (patient response unit) and click the button when can't tolerate the pressure anymore—just push it when you have had enough.*

Condition Pain Modulation
Instructions vary depending on which two experimental pain stimuli are used.