Comparing Cutaneous Sensory Reactivity between Children with and without Global Developmental Delay

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Dedication

This thesis is dedicated to my husband Richard Barney and to our children Alyssa, Donavan, and Beckett. Thank you for believing in me and for standing by my side each and every step of the way. You made the good days great and the toughest days worthwhile.

Abstract

Our scientific understanding of pain among individuals with developmental delays and disabilities with associated intellectual, motor, and/or communicative impairments is limited because of the difficulty in reliably and validly assessing a complex experience when verbal self-report is compromised. One approach is to rely on non-verbal pain behaviors. There has been no work comparing non-verbal pain behavior of very young children with global developmental delays with age and gender matched typically developing children. This study used a calibrated tactile sensory test to provide a mechanisms-based approach to indirectly compare the functionality of the somatosensory pathways in children with and without global developmental delay (GDD). A case control design was used to test the reactivity of 20 children with GDD (60% male; M age = 4.91 years, SD=1.13) and 20 typically developing children (60% male; M age = 3.49 years, SD=1.08). Sensory reactivity was indexed by vocal, facial, and body activity during the sensory test.

This sample of children with GDD exhibited significantly greater duration of overall reactivity during the sensory test ($p<.01$) and specifically exhibited greater vocal ($p<.01$) and body ($p<.05$) reactivity compared to controls. For children with GDD, severity of self-injurious behavior significantly correlated with vocal ($r=.58$, $p=.01$) and body ($r=.56$, $p<.05$) reactivity during the pin prick trial. Children with GDD who were more reactive to the sensory test had significantly reduced epidermal nerve fiber densities ($p<.05$).

This study was the first to measure the behavioral response of children with GDD to a calibrated sensory test and in comparison to a typically developing control group. The results of the study provide information about the physiology and nociceptive pathways of children with GDD. Despite limitations in verbal self-report, children with GDD exhibited non-verbal pain behaviors to signal their reactivity to a calibrated sensory test.

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Chapter I

Pain can be a challenging problem for individuals with intellectual and developmental disabilities (IDD). First, like other vulnerable populations with reduced verbal and/or cognitive skills (e.g., preverbal typically developing children and infants, adults with dementia, and persons who are intubated or unconscious) accurate and reliable self-report of pain can be challenging or, for some, impossible (if completely nonverbal) to obtain and therefore individuals with IDD are at risk for having undocumented and undertreated pain (Herr et al., 2006). Second, individuals with IDD may be at greater risk for having undiagnosed pain due to a set of beliefs held by some that individuals with IDD are insensitive or indifferent to pain (Symons et al., 2008). Therefore, attempts to communicate pain (verbally or non-verbally) may be disregarded. Third, individuals with IDD are more likely to have disability-related medical conditions and procedures that would reasonably be suspected to cause pain and discomfort (e.g., constipation, scoliosis, surgery, physical therapy, etc.; Breau, Camfield, McGrath & Finley, 2003; Minihan, 1986). Finally, there is emerging evidence that at least some individuals with IDD may be more (rather than less) sensitive to pain than their typically developing peers (Defrin, Pick, Peretz, & Carmeli, 2004).

Despite the evidence that individuals with IDD are at risk for undiagnosed and undertreated pain, there has been relatively little attention given to the study of pain in this population (Breau et al., 2003; Minihan, 1986). In fact, in the 5 year epoch between 2005 and 2009 less than 30 papers about pain in children with IDD were published, in

stark contrast to a total of 100,000 published papers specific to “pain” and “human” research (Belew et al., 2013). The lack of scientific attention further exacerbates the clinical problem of pain because new resources and approaches are not being identified.

The lack of scientific study of pain in individuals with IDD may be, in part, due to longstanding cultural and personal beliefs that people with IDD are insensitive or indifferent to pain (Couston, 1954; Sobsey, 2006). Sobsey (2006) suggested this pain insensitivity/indifference perspective has likely persisted due to early intelligence testing methods that historically equated higher IQ with higher tactile sensory and noxious (i.e., pain) reactivity. Conversely this approach equated lower IQ with decreased tactile sensitivity. From this perspective, it followed that the pain thresholds of individuals with IDD are elevated (Sobsey, 2006). This view would suggest that individuals with IDD who experience identical noxious stimuli would have reduced pain sensation in relation to comparable peers without a disability. The problem with this view; however, is that studies are rarely designed to explicitly assess pain thresholds in individuals with IDD. As a consequence, there is little empirical evidence concerning noxious thresholds and sensory function related to pain in individuals with IDD (Belew et al., 2013; Sobsey, 2006).

As long as the insensitive/indifferent or ‘elevated thresholds’ perspective persists there is a danger that individuals with IDD are experiencing pain that is undocumented and undertreated. The ‘elevated thresholds’ perspective is especially problematic when individuals with IDD experience multiple impairments (i.e., intellectual, motor, communicative) making the communication of the severity, location, and cause of the

pain challenging (Breau et al., 2003; Symons, Shinde, & Gilles, 2008). Signs of pain may be ambiguous or even paradoxical (e.g., laughter) and can be easily missed, especially if caregivers and healthcare professionals hold the belief that individuals with IDD do not experience pain (Oberlander & Symons, 2006). With the exception of rare syndromes and conditions in which there is documented pain insensitivity/indifference (Nagasako, Oaklander & Dworkin, 2003), there is no reason to assume that all individuals with IDD would have such globally affected nociceptive physiological systems to warrant the assumption of elevated pain thresholds (Belew et al., 2013).

Despite frequent claims of altered or heightened pain threshold in individuals with IDD, only two studies have examined the pain thresholds of individuals with IDD. In the two studies (combined N= 39) the degree of IDD was mild or mild to moderate for all participants. Defrin et al. (2004) tested heat pain thresholds, using a method that controlled for reaction time, and found that adults with IDD were more (not less) sensitive to heat pain compared to a control group. Priano et al., (2009) tested pain thresholds and found that adults with Prader-Willi syndrome had higher thresholds for the detection of warm sensation and heat pain and lower thresholds for cool sensation and cold pain; however, this study did not control for reaction time. These results suggest that individuals with IDD may have altered thresholds and that at least some individuals with IDD are more (not less) sensitive to pain compared to their peers.

An alternative approach to pain threshold-specific studies are represented by studies in which calibrated sensory testing was used to determine if individuals with IDD respond to noxious stimuli and express signs consistent with pain that are directly

observable (Hennequin, Morin & Feine, 2000; Stengel, Oldham & Ehrenberg, 1955; Symons et al., 2010). These so-called 'stimulus-response' studies fall short of being considered pain threshold studies because they did not use stimuli with graded intensities to determine at what point the sensory stimulus becomes painful. Given the paucity of threshold studies, stimulus-response studies provide useful information regarding pain reactivity and expression that may be used to inform future research.

Of the three stimulus-response studies, two studies included participants in childhood through older adulthood (Hennequin et al., 2000; Stengel et al., 1955) and one included only adults (Symons et al., 2010). The researchers used different arrays of stimuli including cold (Hennequin et al.; Stengel et al.), pin prick and deep pressure (Stengel et al.; Symons et al.), light touch, warm, cool, and a sham stimulus trial (Symons et al.). All studies found that individuals with IDD were sensitive and reactive to the stimuli. One study that included a control group noted that individuals with IDD were comparatively slower to react (Hennequin et al.). While these studies were not testing pain thresholds, they do provide initial evidence that individuals with IDD react to noxious stimuli and display recognizable signs (i.e., facial reactions) consistent with pain expression.

Current Study

Quantitative sensory testing (QST) provides a mechanisms-based approach to indirectly examine the functionality of the nociceptive pathways (Cruz-Almeida & Fillingim, 2013). There have been few true QST studies in IDD relevant populations.

Pain threshold and stimulus-response studies provide initial evidence that individuals with IDD have functional (and possibly lower) thresholds for pain and respond to sub-threshold stimuli in a typical or even hypersensitive manner (Defrin et al., 2004; Symons et al., 2010). Objectively clarifying that individuals with IDD or at risk for IDD are sensitive and reactive to tactile and noxious stimuli could help to inform clinicians, educators, and caregivers that pain may be present in this developmentally vulnerable population.

Previous studies were not specific to children, either including all ages or only adults with IDD. The one previous 'stimulus-response' study that included a control group only tested latency of pain detection to a non-calibrated cold stimulus (Hennequin et al., 2000). The proposed study will characterize the responsiveness (i.e., reactivity) of young children with global developmental delay (GDD) who have failed to meet their developmental milestones and who, by definition, are at risk for IDD. Children with GDD have not attained adequate skills in two or more of the following areas: gross motor function, vision and fine motor, speech, hearing and language, or social skills. In Minnesota, a child up to age seven who is experiencing a measurable delay in development according to diagnostic instruments and procedures fits the Developmental Delay (DD) disability category.

The innovative features of the study that extend the current scientific literature include 1) testing somatosensory reactivity in a sample specific to young children with global developmental delay; 2) using a typically developing control group with comparable age and gender distribution to document differences in reactivity to

calibrated stimuli; 3) expanding the array of sensory stimuli to include the following calibrated stimuli for light touch, pin prick, cool touch, pressure, repeated Von Frey (as a partial test of central sensitization), and heat.

The primary research questions addressed in this study will be:

1. Do children with GDD exhibit observable and quantifiable facial, vocal and body signs of reactivity during a standardized sensory test?
2. Are children with GDD more or less reactive during sensory testing dependent on the modality of the sensory stimuli applied?
3. Is there a relationship between sensory reactivity and severity of GDD?
4. Are children with GDD more or less reactive during the sensory test compared to children in the control group (as indexed by facial, vocal, or body activity)?

The secondary research questions addressed in the proposed study are:

5. Is there a relationship between sensory reactivity and gender in children with and without GDD?
6. For children with GDD, is there a relationship between proxy reported pain experience (pain intensity, frequency, duration, interference with functioning) in the previous 7 days and reactivity during the sensory test (as indexed by facial, vocal, and body activity)?
7. For children with GDD, is there a relationship between sensory reactivity and birth history (i.e., pre-term birth and/or admittance to the neonatal intensive care unit [NICU]).

8. Are children with GDD who have self-injurious behavior (SIB) more or less reactive during sensory testing compared to children with GDD who do not have SIB (as indexed by facial, vocal, or body activity)?
9. Is there a relationship between sensory reactivity and peripheral innervation for children with GDD?

Chapter II

This section will provide a review of the empirical evidence surrounding the issue of whether or not individuals with IDD experience pain in normative ways. Some research findings have led to conclusions that individuals with IDD have heightened pain thresholds resulting in little or no pain response (Beirsdorff, 1994), while other research clearly shows individuals with IDD do react to noxious (i.e. pain producing) stimuli in a typical or even hypersensitive manner (Defrin et al., 2004; Symons et al., 2010). The apparent disagreement in the literature has the potential to create confusion among researchers, healthcare/rehabilitation/educational professionals and caregivers. This confusion may well impede progress toward future research inquiry and better clinical and educational practice. If professionals and caregivers believe that individuals with IDD or at risk of IDD are insensitive or indifferent to pain then pain assessment and management will not be a priority. Given this population is at risk for associated painful health conditions, interventions, and procedures – compounded by limited or absent communication skills – the implications for quality of care and quality of life are profound. Thus, it is important to review the current state of the scientific knowledge on this issue.

Despite frequent claims of altered or heightened pain threshold in individuals with IDD, there is little scientific literature on the topic. This synthesis of the literature will provide an overview of pain threshold studies, stimulus-response studies, and proxy report studies.

Pain Threshold Studies

The pain threshold is considered the point at which the sensation changes for the individual from simply being able to detect the presence of the stimulus to recognizing pain caused by the stimulus. Pain threshold studies use either the method of limits (MLI) or the method of levels (MLE; Figure 1) to determine the pain threshold. When the method of limits (MLI) is used the stimulus is applied to the skin and the intensity of the stimulus is increased at a constant rate from baseline to the point at which the participant reports (e.g., speaks, presses a button) that the stimulus has become painful. When the participant reports pain the stimulus returns to baseline. This method includes a possible reaction time artifact because of the lag between pain recognition and pain report. When the method of levels (MLE) is used the stimulus increases in intensity to a predetermined level and then returns to baseline. This occurs multiple times, with the stimulus ascending to an increasingly intense level each time. After each successive exposure to the stimulus the individual is asked to report if the stimulus was painful. After a report of pain, the stimulus is adjusted up and down in smaller increments to determine the precise measure of the pain threshold.

This section provides a review of the only two research studies to have tested pain thresholds in individuals with IDD (Defrin et al., 2004; Priano et al., 2009). Defrin et al. measured the heat pain threshold of 25 individuals (13 male; mean age 37.7 years, range 22-56) with unspecified intellectual disabilities (N=14) and Down's syndrome (N=11). Individuals with IDD had either been diagnosed with mild or mild to moderate

intellectual disability and were considered by a psychiatrist to have the necessary ability to communicate their emotions and sensations verbally. All individuals with IDD had an IQ of 66 or greater. The control group consisted of 7 males and 7 females (mean age 36.4, range 24-54).

Prior to the study, all participants with IDD were trained in pain threshold testing to ensure that they could distinguish between the different stimulus intensities. Measurement of heat pain was conducted using a computerized thermal stimulator that reached a maximum temperature of 51 °C and would not cause skin damage. Sensory testing protocols included both the MLI (includes reaction time artifact) and the MLE (controls for reaction time).

For both the MLI and MLE testing participants started from a baseline of 35 °C and the heat increased by 2 °C/s for MLI and 3 °C for MLE. For the MLI, four successive 'ramps' of increasing heat were applied and the participants were instructed to press a switch when the temperature was perceived as painful. If individuals with IDD showed behavioral signs of pain and did not press the switch then the trial was stopped and the participant was asked if they felt pain. This method includes reaction time and the threshold may be artificially inflated because of a lag between when the participant feels pain and when they actually press the switch (motor response time). For the MLE the heat probe ascended to a predetermined temperature and then returned to baseline. After each successively warmer stimulus, the participant was asked if it was painful or not. After the first report of pain, the temperature was adjusted up and down in smaller increments to precisely measure threshold.

Based on the MLE, the heat pain threshold of individuals in the sample with IDD was significantly lower than the controls. With MLI (which is reaction time dependent) there were no significant differences between groups despite the fact that the individuals with IDD had slower reaction times which would have artificially elevated their threshold temperatures. These results suggest that the individuals with IDD in this sample had lower (not higher) heat pain thresholds, (i.e., they were more, not less, sensitive to a noxious stimulus).

Priano et al., (2009) studied sensory impairment and altered pain perception among a sample of individuals with Prader-Willi syndrome (PWS). Although PWS has a genetic basis, a high pain threshold is part of the criteria to support the diagnosis. This study aimed to better understand the sensory pathways to evaluate peripheral or central involvement in altered sensory perception. To accomplish this, 14 individuals with PWS (7 male) with a mean age of 29.4 and with IQ level greater than/equal to 69 were studied. Participants had scores on the mini-mental state examination (MMSE) greater than 20 with a mean of 23.7 (*SD*= 3.8) suggesting participants had mild intellectual disabilities. A control group consisted of 10 obese non-diabetic individuals and 10 age-matched individuals.

Multiple tests were conducted including biochemical analysis of insulin-sensitivity, motor and sensory nerve conduction velocity, sympathetic skin response, somatosensory evoked potentials as well as sensory/pain thresholds using QST. For QST, a computerized device was used to test vibratory sensation, warm and cool sensation and heat and cold pain to assess the functioning of small caliber A-delta/C fiber and large

caliber A-beta sensory fibers. Each QST test was performed bilaterally on the hand palmar index, little finger and the plantar site of hallux.

The method of limits (MLI) was used, such that stimulus intensity increased at a constant rate (0.3µm/s for hand sites and 0.8µm/s for foot sites) from baseline (32° C) and individuals were instructed to press a button when they experienced the first sensation of vibration, temperature (warm or cool) or pain (hot or cold). When the button was pressed the stimulus returned to baseline. Each sensory test was conducted six times at each body site and then averaged for a mean score. Results indicated that individuals with PWS had higher thresholds for the detection of warm sensation and heat pain and lower thresholds for cool sensation and cold pain. There was no difference for vibration sensation. The authors conclude that individuals with PWS have markedly altered heat (elevated) and cold (reduced) pain thresholds.

The research conducted by Defrin et al., (2004) provides evidence for the importance of the methods used for QST testing because the participants had a typical threshold when the MLI (includes reaction time) was used but had a lower threshold when the MLE (reaction time free) was used. The MLI used by Priano et al., (2009) did not account for reaction time; thus, the authors could not definitively rule out a reaction time artifact. Priano et al. did not report training the individuals in their study to understand the QST testing procedure; nor did they report evaluating the individuals' understanding of these procedures. Despite these limitations, the findings from Priano et al are important because they represent half of the published literature specific to

thresholds among individuals with IDD and include a novel observation about possible modality differences with respect to pain thresholds.

Stimulus-Response Studies

Alternative approaches are represented by studies in which calibrated sensory testing was used to determine if individuals with IDD respond to stimuli and express signs consistent with pain that are directly observable (Hennequin et al., 2000; Stengel et al., 1955; Symons et al., 2010). These studies fall short of being considered pain threshold studies because they did not use stimuli with graded intensities to determine at what point the sensory stimulus becomes painful. Given the paucity of threshold studies, 'stimulus-response' studies provide useful information regarding pain expression that may be used to inform future research.

Stengel et al. (1955) used a battery of testing which included hard and soft pin pricks (applied to the palm, tongue, foot, and cheeks), deep pressure (applied to the shin bone, brow ridge and the Achilles tendons), cold pressor test (applied to the right arm), nasal probing, and an induced histamine headache. For each type of testing the participant's response was scored from 0-4 for degree of movement withdrawal, degree of facial wincing, and the participant's subjective experience as to whether each test 'did not hurt', 'hurt a little', 'hurt moderately', or 'hurt a lot'. The authors concluded that the individuals with IDD were sensitive to painful stimuli and did not observe differences in latency from stimulus application and time to respond (presumably the individuals in the sample were free of known or obvious motor impairments).

Hennequin et al. (2000) used nociceptive thermal stimuli to test pain tolerance in a group of 26 participants with Down's syndrome and 75 typically developing control participants. Participants with Down's syndrome were included in the study as long as they were able to independently communicate their thoughts and emotions and did not have autistic tendencies or self-injurious behavior. Participants were directed to hold ice cubes wrapped in cling film to their temple and to their wrist for as long as they could withstand the cold sensation. Then participants were asked to localize a non-painful cold stimulus (a cotton ball soaked in ethyl-chloride spray) when it was applied to their hands, face, and mouth. The individuals with Down's syndrome had longer pain latency scores and were less precise in their ability to localize the cold stimulus. The authors concluded that individuals with Down's syndrome were, in fact, sensitive to pain but slower to react.

Symons et al., (2010) developed a research protocol to test sensory evoked pain expression in 44 adults (52% male; 29 with self-injurious behavior) with IDD. This study also examined the common assumption that individuals with IDD who self-injure are less sensitive to pain. For this study each individual was seated looking away from a medical screen. From behind the screen a clinician randomly applied five different calibrated stimuli (i.e., light touch, deep pressure, pin prick, warm, and cold) to the participants' back during timed intervals. The participants' faces were digitally recorded and facial expression was quantified using the Facial Action Coding System (FACS; 2002). To guard against observer bias, coders were blind to stimulus application (audibly signalled) and sham trials (no stimulus application) were randomized with active stimulus trials. There was significantly more facial action unit activity during active stimulus versus

sham trials for all stimulus modalities. Females were more expressive than males and individuals with self-injurious behavior were more expressive (i.e., more reactive) than those without. Stengel et al., (1955), Hennequin et al., (2000), and Symons et al., (2010) were not testing pain thresholds; however, these studies do provide initial evidence that individuals with IDD react to noxious stimulus and display recognizable signs (i.e., facial reactions) consistent with pain expression.

Proxy-Report Studies

Several other studies include information germane to the issue under review (evidence for altered pain thresholds among individuals with IDD). In several, heightened pain thresholds were indicated based on proxy report of a parent, caregiver, or healthcare professional (Biersdorff, 1994; Butler et al., 2002; Couston, 1954; Devarakonda, Lowthian & Raghavendra, 2009). Although it is informative to understand the perspectives of those who are closely associated with any one individual with IDD, this method of assessment (proxy report, recall, rating scale) cannot substitute for pain threshold measurement and is subject to observer bias and inaccurate memory recall. For example, the study by Biersdorff (1994) is a common reference used to support statements suggesting that individuals with IDD are insensitive to pain. This conclusion is not warranted by the research methods used or the results provided by the study, however. Caregivers of persons with IDD were asked to report, from memory, a painful incident and the person's reaction to it. Of the 123 participants, 31 were reported to have 'high pain thresholds'. Those who were said to have high pain thresholds did in fact react

to the pain; the caregivers simply noted that they had to be observant to find circumstances in which there were pain behaviors to describe. There were other factors that could have led to the caregiver response, such as difficulty with memory recall, altered or dampened pain expression, or a delayed motor response to pain. Taken on its own, none of the study evidence scientifically justifies the notion that the 31 individuals reported on had a heightened pain threshold. The study certainly does not validate any statement that individuals with IDD have a heightened pain threshold or are insensitive to pain (nor was it ever intended to – the study was important as being among the first to raise the issue of the problem of pain among individuals with IDD from a range of perspectives).

Case studies have also documented an apparent insensitivity to pain based on clinical experience with a single patient (Devarakonda et al., 2009; Fitzgibbon, Kingston, Needhan & Gaunt, 2009). Devarakonda et al. reported on a 13-year-old girl with Rett syndrome who had posterior spinal fusion with instrumentation who reportedly required little pain medication and appeared pain free during her hospital stay. Unfortunately the authors did not explore the possibility that the child lacked the ability to effectively communicate pain in that situation and/or in a way that the physician recognized. Similarly, Fitzgibbon et al. (2009) reported on a five-year-old girl with IDD whose parents reported to be heat pain insensitive and unreactive to recurrent mouth ulcers. Upon brief and unsystematic testing, the physician concluded that the child seemed to be sensitive to touch but did not react to deep pressure. While it is useful for clinicians to

share their experiences, case study assessment relies on unsystematic proxy report and cannot substitute for pain threshold measurement and is subject to clinician bias.

Two proxy-report studies support that children with IDD experience pain but report pain to be difficult to detect and measure in this population (Fanurik, Koh, Schmitz, Harrison & Conrad, 1999; Hunt, Mastroyannopoulou, Goldman & Seers, 2003). Not surprisingly, one study reported that children with mild IDD were more effective at communicating their pain compared to children with severe or profound IDD. Parents felt that detecting their child's pain often required careful analysis of facial features, body movements, and changes in mood and routine (Hunt et al., 2003). Parents felt their child's pain was underestimated and undertreated by healthcare professionals (Fanurik et al.). Given how difficult detection of pain seems to be for parents who know their child best, it seems warranted to be concerned regarding accurate detection of pain by others (e.g., healthcare professionals, educators, and group home staff).

Summary

The purpose of this section was to provide a review of the empirical evidence surrounding the issue of whether or not individuals with IDD experience pain in normative ways. The review is necessarily brief because there are so few studies in which pain thresholds or sensory reactivity are measured. Taken together, there does not appear to be any compelling scientific evidence supporting claims regarding elevated pain thresholds or pain insensitivity as a general condition for individuals with IDD. From this review, it is clear that more research in this area is warranted.

Chapter III. Methods

Participants and Settings

Developmental delay group. Following Institutional Review Board approval, 20 children aged 2 to 7 years of age (60% male; M age = 4.91 years, SD=1.13) with global developmental delay were recruited from Gillette Children's Specialty Healthcare (GCSH). Children were Caucasian (n=14), African American (n=3), Asian (n=1), and Hispanic/Latino (n=1). Participant characteristics (developmental diagnosis, special education services, birth history, and pain experience) are reported in Table 1. Sensory testing was performed at GCSH in a clinic room or in a family consultation room. Parents and sometimes siblings were present during the sensory test. The testing space was quiet with minimal distraction.

Control group. Twenty children aged 2-6 years (60% male; M age = 3.69 years, SD=1.08) at the University of Minnesota Child Development Center (UMCDC) were recruited into the control group. Children were Caucasian (n=18), African American (n=1), and Asian (n=1). Sensory testing was performed in the research room on site at UMCDC. Parents and other family members were permitted to be present but most often were not because the testing took place during regular daycare hours when parents were at work. Because parents were most often not present the research staff engaged in a brief activity with the child prior to the testing to help the child become comfortable in the new setting. The testing space was quiet with minimal distraction.

Sample size calculation. Sample size was calculated based on the means and SD reported by Symons et al. (2010) for a comparable sensory testing protocol. Alpha was set at .05 with .80 power; it was determined that a sample size of 19 would be sufficient to determine a significant effect.

Inclusion/Exclusion Criteria

GDD group. Participants were included in the GDD group if they were between 2 and 7 years of age and had been referred to Gillette Children's Specialty Healthcare, a tertiary center for diagnosis of a developmental disability, due to failure to meet developmental milestones. Participants were excluded from the study if they had serious accompanying acute health impairments considered to be painful (e.g., reflux or otitis as determined by subjects' physician record review and/or examination if necessary). Participants were excluded if they were deaf and/or blind because 1) it would be difficult for a deaf and/or blind child to understand the testing in the same way as children who have sight and hearing because they can see the stimuli and hear the brief explanation of the sensory test, and 2) children who are blind and/or deaf have not had the same social learning experiences influencing how they would react vocally or facially to painful events, and 3) the observational measurement tool (PADS) has not been validated for deaf and/or blind children.

Control group. Participants were included in the control group if they were between the ages of 2 and 7 years of age and had met their developmental milestones to

date, did not have an individualized educational plan, and were not suspected of having an intellectual or developmental delay or disability.

Sensory Testing

Protection of human subjects & informed consent. All procedures were performed following informed parental consent. University of Minnesota and Gillette Children's Specialty Healthcare Committee for the Protection of Human Subjects (i.e., IRB) approval was received for all procedures described.

Sensory mechanisms. A tactile sensory test was designed to indirectly test the functioning of the peripheral afferent nerve fibers. A fibers are large diameter fibers, are myelinated, and have high conduction velocities (Basbaum, Bautista, Scherrer, & Julius, 2009). A beta fibers rapidly conduct innocuous mechanical stimulation and were assessed using light touch and deep pressure. A delta fibers mediate acute, well-localized 'first' pain and were assessed using pin prick. C fibers are small diameter fibers, are unmyelinated, and have a slower conduction velocity (Basbaum et al.). C fibers conduct poorly localized 'second' or slow pain and were assessed using heat and possibly cool touch (Basbaum, et al.).

A repeated von Frey monofilament was applied to assess a combination of fiber functioning in the acquisition of temporal summation; an increased pain perception to a repetitive nociceptive stimulus (Coste, Voisin, Luccarini & Dallel, 2008; Eide, 2000). This was a partial test of temporal summation because a von Frey monofilament was used rather than a nociceptive stimulus (e.g., repeated pin prick). This test of temporal

summation was used as a proxy for central sensitization which is a physiological state of hyperexcitability in the central nervous system leading to amplified processing of nociceptive messages (Meeus & Nijs, 2007; Woolf, 1983).

Sensory testing materials. The sensory testing was conducted by touching six stimuli to the back of the child's left and then right calf while the child was in a seated position. A light touch was applied with a Von Frey monofilament (2.0 g) pressed against the skin until the filament bent. The filament was touched lightly to the skin five times in five seconds. A light pin prick was applied for < 1 second with a plastic US Neurological pin made for use during neurological exams. A cool touch was applied lightly to the participant's skin for five seconds using a Tip Therm cool thermal probe. The end of the cool probe is circular with a radius of ¾ inch. Because the tip maintains room temperature it is cooler than the participant's body temperature. Deep pressure was applied using an algometer (Wagner model FDX) with a rubber tip that has a 0.5 inch circular diameter. The pressure was applied for 5 seconds with a consistent pressure of 4.0 lbs. A Von Frey monofilament (60 g) was applied repeatedly to the skin at 1 Hz for 30 seconds. The monofilament was touched to the skin until it bent and then removed. A thermal heat probe was applied at a temperature of 50°C. The thermal probe was electronic with a metal circle approximately 3 mm in diameter that was applied to the skin. The tester gently held the participant's ankle for stability in applying the stimuli; however, the participant was able to withdraw from any of the stimuli at any time if they became uncomfortable.

For 12 children with GDD and 5 children in the control group, a sham trial was also included prior to the application of any other stimuli. For the sham trial a von Frey monofilament was altered to remove the filament but otherwise looked comparable to the light touch and repeated touch applications. The sham trial lasted 5 seconds and was comparable in every way to the other applications with the exception of the missing filament. The sham von Frey was moved toward the child's calf; however nothing came in contact with the child's skin.

Because this sample included pediatric participants and because of the cognitive and communicative impairments for the GDD group, stimulus trials were modified to be time limited and of short duration (≤ 5 sec.) and were only conducted once per site per participant. A previous study (Symons et al., 2010) using similar stimuli tested research staff who were asked to report subjectively if the stimuli could be felt and if it was painful. The staff reported that the stimuli could be 'felt' but that the stimuli were not painful with the exception of the pinprick which was reportedly 'mildly painful'. An exception to this is that the heat probe used in the Symons et al. study was 40˚C and the heat probe used in this study was set at 50˚C which is considered to be mildly painful. But, it should be noted that the diameter of the heated surface coming in contact with the skin was much smaller in the current study and 'heat pain' is often applied at 53˚C.

Sensory testing procedures. Each participant was tested individually. The tester brought the child into the room and spent a few minutes playing with the child to help the child become accustomed to the environment. Then the tester had the child sit on a chair so that their lower legs hung over the edge to provide access to the calf. The tester was

seated to the child's left side and the six stimuli were arranged behind the child's chair. The tester announced "my fuzzy friends are going to touch you right here (touching left calf) and here (touching right calf)" and then the testing began. Each stimulus was audibly signaled by the tester saying a number (one through six) associated with each stimulus when the stimulus was applied to the calf and then audibly signaled by the tester saying "off" when the stimulus was removed. The sham trial was signaled as zero when it was applied. The stimuli were always applied in the following order: 0) sham, 1) light touch, 2) pin prick, 3) cool, 4) pressure, 5) repeated von Frey, and 6) heat. Participants did not observe movies, use electronic devices or other distracting toys or equipment during the test but were given a stuffed toy to hold if they chose. Children were instructed to watch a visual timer during the sensory test to signal the duration of the test and to encourage the child to remain in the seat. During the testing the tester would say "you're doing a good job" and "you're almost done".

The sensory stimuli were adapted in order to minimize fearfulness of the stimuli. The von Frey monofilaments (light touch, repeated von Frey, and sham stimulus) were adapted by covering with stretchy rubber animals. The cool probe, heat probe, and algometer were covered by stuffed toys. The pins were not adapted because each was small, disposable and applied quickly and from behind so the child did not see the application.

Behavioral Measurement

Sensory reactivity. To capture facial expression, vocalizations and body movements during the sensory testing a camera was set up approximately 2.5 meters away and focused on the participant's whole body. Digital video was used and coded using Pro-Coder for Digital Video (PCDV; Tapp, 2003). PCDV is a software program designed to facilitate the collection of observational data from digital media files. This system provides a keyboard-driven coding platform that enables coders to scroll through designated time windows with playback options available. Behavioral events are coded as either present or absent throughout the observational period based on specific operational definitions for each code.

The operational definitions for facial, vocal and body pain behaviors were derived from the items on the Pain and Discomfort Scale (PADS). The PADS was developed by Bodfish, Harper, Deacon and Symons (2006) and was used by Phan and colleagues to measure pain expression in adults with IDD during a dental scaling procedure (Phan, Edwards & Robinson, 2005). The PADS was completed at several time points before and after the painful procedure and once during the scaling. The PADS scores were significantly higher during the painful procedure compared to all other observations. The PADS showed high inter-rater reliability.

The PADS was used in the current study to measure pre-specified behavioral codes in relation to the application of calibrated stimuli - the majority of which were likely non-noxious. It was uncertain whether the children experienced pain per se in relation to the application of the stimuli nor are the behaviors measured specific to pain. However, the behaviors coded were selected from a non-verbal pain behavior checklist

and are certainly pain relevant. Thus, for short hand throughout the remainder of the manuscript, the term ‘pain behavior’ will be used when describing vocal, facial, and body reactivity.

Vocal pain behaviors were defined as moaning, whining, whimpering, crying, screaming, or yelling. Facial pain behaviors were defined as a cringe or grimace, furrowed brow, change in eyes, mouth open, lips pucker tight, pout, or quiver, clenches teeth, grinds teeth, or thrusts tongue. Body pain behaviors were defined as protecting or favoring a specific part of the body, flinching, or being sensitive to touch. Each of these items was explicitly defined based on the PADS descriptions (Appendix A). For example ‘crying’ is further defined by the PADS as “louder vocalizations made with mouth open or closed, tears may or may not accompany the vocalization” and ‘furrowed brow’ is further defined by the PADS as “inner and/or central portion of the eyebrow lowers; may produce vertical wrinkles between eyebrows; or produces muscle bulge from middle of forehead above middle of eyebrow down to inner corner of the eyebrow”. In addition to the PADS vocal items, laughter was also coded as a vocal pain behavior because there is evidence that under some circumstances it may be considered a paradoxical expression in relation to experiencing pain or sensation (Collingnon & Giusiano, 2001). Further, any child vocalizing pain or discomfort using words or sentences was coded as a vocal pain behavior (see Appendix A).

Each video was coded in PCDV using four passes. On the first pass the research assistant coded the onset and offset of each sensory stimulus. On the second, third, and fourth pass the research assistant coded vocal, facial, and body pain behaviors,

respectively. The research assistants were trained to a minimum 90% criterion across all observational codes using practice videos and demonstrated an inter-observer agreement on practice videos exceeding 90% prior to coding the videos obtained for this study. Inter-observer agreement was calculated on > 25% of all sensory tests conducted for this study. Inter-observer agreement was calculated by PCDV for each type of pain behavior (vocal, facial, and body).

Severity of GDD. Severity of GDD was measured using the Child Developmental Inventory (CDI) total behavioral score and expressive and receptive language scores. The CDI includes 300 items that are completed by the parent or caregiver to measure the child's development in the following areas: social, self-help, gross motor, fine motor, expressive language, receptive language, letters and numbers. The CDI also includes questions related to the child's health, growth, development and behavior. The CDI developmental scales correlate closely with age (r = 0.84) and the results identified the 26 children who were enrolled in early childhood/special education within the normative sample (N = 568; Ireton & Glascoe, 1995). The CDI scales correlated with reading and academic achievement in kindergarten (Ireton & Glascoe). The CDI has also demonstrated strong significant correlations with the Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS; r = .87, p <.001) and the Bayley Scales of Infant Development, 2nd Edition (BSID-II; r = .86, p < .001) demonstrating that the CDI generates scores consistent with content and construct validity evidence specific to typical and delayed child development (Doig, Macais, Saylor, Craver & Ingram, 1999).

Pain parameters. At the time of the sensory test the primary caregiver of each child with GDD completed the Dalhousie Pain Interview (DPI; Breau et al, 2003) and the Brief Pain Inventory (BPI; Cleeland & Ryan, 1994). The DPI is presented in an interview/script format consisting of 10 close ended questions that provide a measure of episodic pain in the previous 7 days as well as a description of chronic pain that has been ongoing for six months or more. This measure has been adapted from the methodology used in previous research for obtaining pain information via proxy report when self-report is not possible or otherwise difficult to obtain (Breau et al., 2003). Specific items are anchored to whether there has been pain in the past week, its general description, possible cause, duration (cumulative hours, minutes, and seconds), frequency (number of episodes), and intensity (0-10; zero means "no pain at all" and ten means the "worst pain ever"). All pain episodes reported are categorized as accidental, gastrointestinal, musculoskeletal, neurological, stretching, positioning, equipment, orthopedic, spasm, other, or unknown pain.

The BPI was developed initially as a method of measuring cancer pain (Cleeland & Ryan, 1994); however, the tool has since been revised and validated for use with individuals with developmental disability and cerebral palsy (Tyler, Jensen, Engel & Schwartz, 2002). The BPI was designed to efficiently measure the extent to which pain interfered with twelve different aspects of daily living such as communication, mobility, school, daily activities, self-care, sleep, and mood in the previous week. Each of the 12 items are scored from 0-10, 0 meaning pain "did not interfere" with that item and 10 meaning pain "completely interfered" with that item. Each item score is the 0-10 score

assigned by the rater. There are no subscale scores. Each participant receives a total score based on the addition of the 0-10 scores for each of 12 items. Thus, individual total scores have the potential to range from 0 to 120. Pain interference scores on the BPI have shown significant correlations with pain intensity ratings and have shown excellent internal consistency (Tyler et al., 2002; Osborne, Raichle, Ehde & Kraft, 2006).

Peri- & post-natal short history. Gillette Children's Specialty Healthcare medical records were reviewed to determine 1) the child's gestational age at birth (in weeks), 2) the child's weight at birth, and 3) whether the child with GDD was admitted to the NICU and if yes, the length of that stay (reported in days).

Self-injurious behavior (SIB). A secondary research question was to determine if the presence of SIB was related to a difference in sensory reactivity. SIB was determined to be present versus absent in the GDD group based on parent report. This was obtained using the self-injurious behavior (SIB) subscale of the Repetitive Behavior Scale-Revised (RBS-R; Bodfish, Symons & Lewis, 1999). The SIB subscale asks parents to report for each modality of self-injury (e.g., hits self, bites self, pulls hair, rubs or scratches, picks skin, etc.) whether the behavior 'does not occur', or occurs and is a 'mild problem', 'moderate problem', or a 'severe problem'.

Epidermal nerve fiber (ENF) density. A secondary research question was to determine if there was a relationship between ENF density and sensory reactivity in the experimental group. Epidermal nerve fibers are free nerve endings widespread in the epidermal layers of human skin (Kennedy & Wendelschafer-Crabb, 1993). As part of a larger study a subgroup of the children with GDD in this study had ENF density counts

from epidermal skin biopsies. The primary outcome measure for analyses was ENF density (number of nerve fibers per millimeter of skin).

Reliability and Validity of Scales in Relation to the GDD Sample

Previous work. In the previous studies I have conducted with children and adolescents with IDD (i.e., cerebral palsy, Batten disease, and Rett syndrome) I have used the DPI, the BPI, and the PADS. In these studies the BPI has demonstrated excellent internal consistency with coefficient alphas between .96 and .97. The BPI correlated significantly with parent-reported pain intensity ratings on the DPI (r= .76, p< .05) in children with cerebral palsy. In a study involving girls and women with Rett syndrome, the BPI significantly correlated with pain expression on the NCCPC-R (NCCPC-R total score; r=.58, p<.05). In the same study, both the PADS (scored by trained coders during a pain examination procedure) and the NCCPC-R (completed by parent proxies) demonstrated that girls and women with Rett syndrome are most likely to show pain using facial expression (p<.01).

Current protocol. In the current study the BPI's coefficient alpha was .90. PADS inter-observer agreement (IOA) for 26% of the sample was as follows: For the GDD group, IOA = 98% for vocal signs of pain, 91% for facial signs of pain, and 88% for body signs of pain. For the typically developing control group, IOA = 99% for vocal signs of pain, 96% for facial signs of pain, and 91% for body signs of pain. Average implementation fidelity scores (i.e., % correct application for each stimulus) for the

application of sensory stimuli were 98% for the GDD group and 99% for the typically developing control group.

A Note on Hypotheses and Statistical Analysis Approach Used

Given many of the hypotheses tested in the study were exploratory, some data were analyzed without multiplicity adjustment (Bender & Lange, 2001). Exploratory studies, such as the current study, necessitate a flexible approach to design and statistical analyses such that simply controlling for multiple tests does not solve the problem of making valid statistical inferences using an exploratory data-driven approach (Bender & Lange). A common multiple comparison correction procedure – the Bonferroni adjustment - was designed to reduce Type I error rates (probability of rejecting the null hypothesis when it is in fact true) for decision making processes, but in doing so Type II error rates (probability of accepting the null hypothesis when the alternative is true) are inflated such that truly important differences between groups could be missed (Perneger, 1998; Rothman, 1990).

Therefore, although there are differences of opinions on the issue, when it applies to reporting exploratory findings this technique is less useful and can actually be detrimental to revealing important effects (Perneger; Savitz & Olshan, 1998). Rothman noted that not making adjustments for multiple tests is preferred when the data are not random numbers but are based on observations occurring in nature – this will lead to fewer errors in the interpretation of results (Rothman, 1990). In one sense, the multiple sensory tests were quasi-independent of one another to the degree that the different

stimulus modalities were engaging functionally related but independent aspects of sensory (touch, pain) and transduction physiology (A beta, delta, and C fibers). Thus, in some of the testing for the different research questions, multivariate approaches were used, but in other instances multiple comparisons were conducted without adjusting for multiple tests. For this reason, and because of the exploratory nature of the current study, the results are descriptive only and not for purposes of decision making. Significant findings will need to be further tested in confirmatory studies.

Primary research questions and their rationale

1. Do children with GDD exhibit observable and quantifiable facial, vocal and body reactivity during a standardized sensory test? I hypothesized that children with GDD would exhibit observable vocal, facial and body pain behaviors during the sensory test and that these behaviors would be quantifiable. One previous study (Symons et al., 2010) systematically coded facial pain behaviors during a similar sensory testing protocol in adults with IDD. In addition, Stengal et al., (1955) detected movement withdrawal and facial wincing during sensory testing; however, these behaviors were not scored using a validated measure with operational definitions. Despite the limitations of the Stengal et al. study, both studies detected observable pain behaviors during sensory testing protocols. Other studies have demonstrated that parents, clinicians, and researchers are able to detect and quantify pain behaviors during painful events such as venipuncture and dental scaling procedures for individuals with IDD (Nader, Oberlander, Chambers & Craig, 2004; Phan et al., 2005). Specifically, the PADS (used in this study)

as well as the NCCPC-R from which the PADS was derived, successfully quantified the same vocal, facial, and body pain behaviors operationalized in the current protocol during other studies (Phan et al., 2005; Breau, Finley, McGrath & Camfield, 2002; Breau et al., 2003). Other observational pain measures with similar items have also successfully quantified pain behaviors in children and adults with IDD in different circumstances (Burkitt, Breau, Salsman, Sarsfield-Turner & Mullan, 2009; Hunt et al., 2004; Lotan, Moe-Nilssen, Ljunggren & Strand, 2009; Malviya, Voepel-Lewis, Burke, Merkel & Tait, 2006). Based on this combined literature there is sufficient evidence to support the hypothesis that the vocal, facial, and body pain behaviors in children with GDD would be observable and quantifiable during the sensory test. Descriptive statistics (i.e., means, standard deviation, and range) were used to describe the duration of vocal, facial, and body signs exhibited by children with GDD during the sensory test. A one-way analysis of variance (ANOVA) was used to determine if children with GDD exhibited a significantly greater duration of one type of pain behavior compared to the others (vocal, facial, and body activity) during the sensory test.

2. Are children with GDD more or less reactive during sensory testing dependent on the modality of the sensory stimuli applied? It is unclear whether to expect children with GDD to exhibit differential reactivity that is modality specific. Priano et al. (2009) found that individuals with Prader-Willi syndrome had elevated pain thresholds (less reaction) for heat pain but lower thresholds (more reaction) for cold pain. On the other hand, Symons et al. (2010) found that adults with IDD did exhibit differential facial reactivity during a sensory test that included warm and cool touch (heat

and cold induced pain were not tested). Priano et al. tested pain thresholds whereas the Symons et al. study was a stimulus-response study similar to the current protocol. It may be more reasonable to expect that the intensities of the stimuli tested may not differ significantly enough to warrant differential reactivity. There is evidence indicating that children and adults with IDD differentiate between the presence versus absence of stimuli. Symons et al. found that adults with IDD did exhibit significantly greater facial pain behaviors during active compared to sham stimulus trials. Similarly, studies by Nader et al. (2004) and Phan et al., (2005) demonstrated that children with autism and adults with IDD exhibited significantly more pain, including vocal (Phan et al.), facial, and body (Nader et al.; Phan et al.) behaviors during painful medical procedures compared to before and after the procedure. These studies indicate that children and adults with IDD differentiated between the presences versus absence of stimuli; however it is unknown whether the stimuli in the current protocol differ in intensity such that children with GDD will exhibit different degrees of responsiveness. A multivariate analysis of variance (MANOVA) was used to test whether duration of reactivity and expression mode (vocal, facial, and body activity) varied by stimulus modality (e.g., light touch, heat, cool, etc.).

3. Is there a relationship between sensory reactivity and severity of GDD? It is not clear whether severity of GDD will be related to reactivity during the sensory test, as there is no previous work that has reported specifically on this topic. While history and conventional wisdom may contribute to the belief that greater impairment is equated with reduced sensitivity (Sobsey, 2006), there is reason to believe the opposite may be true

(Blankenburg et al., 2010; Koch & Fitzgerald, 2013). In typically developing children Blankenburg et al. found that chronologically younger children were more sensitive to painful stimuli compared to older children. There is a possibility that when developmental milestones are more severely delayed, nervous system development is also delayed; thus, children with more severe GDD may be more sensitive in a way that is similar to chronologically younger children. Koch and Fitzgerald (2013) discussed the development of the central nervous system (CNS) and reported that the development of intact nociceptive pathways may be altered by early noxious experiences. Children with more severe GDD are at risk to have experienced more noxious experiences during early development due to associated health conditions, medical procedures, and, for some, premature birth. However, it is not clear whether this may affect the child's reactivity to a sensory test. A one-way ANOVA was used to test reactivity during the sensory test as a function of GDD severity (severe GDD, less severe GDD, controls). Children who exceeded -2 standard deviations (30%) below age level on 1) the total development score, 2) the expressive language score, and 3) the language comprehension score met criteria for the severe GDD group.

4. Are children with GDD more or less reactive during the sensory test compared to children in the control group (as indexed by facial, vocal, or body activity)? I hypothesized that children with GDD will exhibit more facial, vocal, and/or body pain behaviors during one or more stimulus trials of the sensory test compared to children in the control group. This hypothesis was based on the work by Defrin et al. (2004) that demonstrated that using a reaction time free methodology the heat pain

thresholds of individuals with IDD were lower (meaning they were more sensitive) than controls. Priano et al., (2009) also found that individuals with Prader-willi syndrome had a lower threshold for cold detection and pain compared to controls; however, they were less sensitive to heat. In a study of pain reactivity during venipuncture, Nader et al., (2004) found that children with autism exhibited significantly greater facial activity and behavioral distress during the painful procedure compared to age and gender similar controls. Although the current protocol does not test pain thresholds or reactivity during venipuncture, these studies suggest that children with GDD may have lower thresholds for some types of stimuli. If that is the case then children with GDD may also be more reactive to sub-threshold pain experiences. A MANOVA was used to test whether duration of reactivity and expression mode (vocal, facial, and body pain behaviors) varied during the sensory test as a function of group membership (GDD, controls). A two-way ANOVA was used to test whether the duration of reactivity varied by group membership (GDD, controls) and stimulus modality (e.g., light touch, heat, etc.).

Secondary research questions and their rationale

5. Is there a relationship between sensory reactivity and gender in children with and without GDD? It is unclear whether to expect gender differences in sensory reactivity (i.e., vocal, facial, body pain behaviors) in children with and without GDD during sensory testing. From a physiological standpoint there is disagreement. Selim et al. (2010) found typical female adults to have greater ENF density and associated lower tactile (light touch), mechanical (pin prick), and innocuous cold thresholds compared to

males. However, McArther, Stocks, Hauer, Cornblath, and Griffin (1998) reported normative reference ranges for ENF density and found no physiological gender differences. From an observational standpoint, Symons et al. (2010) found adult females with IDD displayed more facial activity compared to males during sensory testing. On the other hand, multiple other studies have not reported gender differences during sensory testing (Defrin et al., 2004; Priano et al., 2009; Meier, Berde, DiCanzio, Zurakowski & Sethna, 2001; Rattaz et al., 2013; Walker et al., 2009). To determine if there were gender differences in sensory reactivity a two-way analysis of variance (ANOVA) was used to compare differences between males and females within each participant group (children with GDD and typically developing control group).

6. For children with GDD, is there a relationship between proxy reported pain experience (pain intensity, frequency, duration, interference with functioning, chronic pain) and reactivity during the sensory test? I hypothesized that children with GDD who have experienced greater acute pain (i.e., intensity, duration, frequency, interference with functioning) and chronic pain would exhibit more pain behaviors during the sensory test compared to children with little or no pain. This hypothesis was speculative as there is currently no scientific evidence to support the hypothesis in children with GDD. However, this relationship has been reported in other populations; for example, Hubscher et al. (2013) reported this relationship in typically developing adults with back pain. Hubsher's study found that adults with chronic lower back pain had lower cold pain thresholds compared to adults with acute back pain. Other studies have demonstrated that mechanical and thermal pain sensitivity predicts clinical pain

intensity in adults with chronic musculoskeletal pain syndromes and fibromyalgia (Berglund, Harju, Kosek, Lindblom, 2002; Staud, Weyl, Price, Robinson, 2012).

To determine if children with GDD were more or less reactive during the sensory test when they had experienced pain in the previous 7-day period, the GDD group was divided into 'prior pain' and 'no pain' groups. This distinction was based on total frequency, intensity and duration of pain scores on the DPI and an independent samples *t*-test was used to test for mean differences in total reactivity between groups. The 'prior pain' versus 'no pain' grouping was based on a previous study (Barney, Krach, Rivard, Belew & Symons, 2013) in which the 'prior pain group' was defined as children who had experienced at least one type of pain in the previous 7 days that was rated ≥4 out of 10 and lasted 5 minutes or longer. In order to determine if there was a relationship between functional pain interference and sensory reactivity, a Pearson's correlation was computed between BPI total scores and the total duration of pain-related behaviors exhibited during the sensory test.

To determine if children with GDD were more or less reactive during the sensory test when they had chronic pain, the GDD group was divided into 'chronic pain' and 'no chronic pain' groups. The 'chronic pain' group was defined as children who currently experienced a type of pain that may have fluctuated in intensity but that had persisted for six months or longer. An independent samples t-test was used to determine if there were mean differences in total reactivity between children with and without any endorsement of chronic pain. A MANOVA was used to determine if children with chronic pain

exhibited significantly greater vocal, facial, and body pain behaviors during the sensory test compared to children without chronic pain.

7. For children with GDD, is there a relationship between sensory reactivity and birth history (i.e., pre-term birth, birth weight, and/or admittance to the neonatal intensive care unit [NICU])? It is not clear whether children with GDD with an eventful birth history (i.e., prematurity, low birthweight, NICU stay) will exhibit more or less reactivity during the sensory test. Walker et al., (2008) conducted quantitative sensory testing in typically developing children (mean age at testing = 11 years) who had been born preterm (<26 weeks gestation) compared to children who were term-born. Premature birth was associated with modality-specific changes in sensory processing. Specifically, children born premature had decreased sensitivity to all thermal stimuli (i.e., warm, cool, heat, cold) but did not differ from controls in sensitivity to mechanical stimuli. Weiss and Wilson (2006) examined several factors including birth weight and gestational age as predictors of tactile vulnerability (excessive reactivity and low tolerance for the sensation of touch) in infants observed during routine nursing care. Although birth weight and gestational age were negatively associated with tactile vulnerability in the initial correlations, these two factors had less impact in the multiple regression model when postnatal medical events, prenatal drug exposure, and maternal tactile predisposition were included. Slater et al. (2010) demonstrated that infants born preterm and who spent more than 40 days in the NICU had greater evoked potential responses to a painful event (heel lance) compared to term-born infants. A review paper by Koch and Fitzgerald (2013) discussed how repeated noxious experiences early in life

(as is common in the NICU) may alter the typical development of the CNS to process pain signals and to learn to respond in a way that dampens those signals. This limited research suggests that children born pre-term and/or admitted to the NICU are at risk for changes in somatosensory processing; however, there is not enough evidence to predict how this may impact reactivity to the sensory test in the current protocol.

Pearson correlations were conducted between proportion of reactivity during the sensory test and 1) gestation (in weeks), 2) birth weight, and 3) duration of stay in the NICU.

8. Are children with GDD who have self-injurious behavior (SIB) more or less reactive during sensory testing compared to children with GDD who do not have SIB (as indexed by facial, vocal, or body activity)? I hypothesized that children with GDD who were reported to exhibit SIB would be more reactive to the sensory test compared to children with GDD who were not reported to exhibit SIB. This hypothesis was based on the work of Symons et al. (2010) who found that adults with IDD who had SIB were more facially reactive to a sensory test compared to adults with IDD who did not have SIB. In addition, a survey study of pain experience and expression in children with IDD and SIB found that children with and without SIB did not differ in their ability to express pain (Breau et al., 2003). Because the sensory test used in the Symons et al. study was similar to the sensory testing protocol in the current study, it was expected that a similar result would occur in children with GDD. However, this hypothesis was speculative given there is only one study documenting this relationship and it was conducted with adults with significant intellectual disability.

To determine if children with GDD who had SIB were more reactive to the sensory test, an independent sample *t*-test was used to compare reactivity between children with and without SIB. Children were included in the SIB group if their parent made any endorsement of SIB on the RBS-R self-injurious subscale. In addition, a Pearson's correlation was used to determine if greater severity of SIB (measured by total score on the SIB subscale of the RBS-R) was related to a greater expression of pain behaviors during the sensory test.

9. Is there a relationship between sensory reactivity and peripheral innervation for children with GDD? I hypothesized that children with GDD who had a greater ENF density would exhibit more pain related behaviors during the sensory test. This hypothesis was based on the findings of Symons, Wendelschafer-Crabb, Kennedy, Heeth, and Bodfish (2009) who found that greater ENF density in the skin biopsies of adults with intellectual disabilities was correlated with greater sensory reactivity during a standardized sensory test. A similar relationship was found in a study by Selim et al. (2010) for whom healthy adults with greater ENF density were better/faster at detecting sensation and pain. This relationship holds for adults with large-fiber diabetic neuropathy, for whom a more substantial reduction in ENF density is associated with reduced sensory and pain detection (Sommer & Lauria, 2007). However, the opposite relationship has been found for individuals with diabetic or idiopathic small-fiber neuropathies affecting A delta and C fibers. For individuals with small-fiber neuropathy, reduced ENF density is associated with increased sensitivity to thermal stimuli (Sommer & Lauria, 2007). In addition, individuals with small-fiber neuropathy may experience

allodynia (pain in relation to a stimulus that does not normally provoke pain), hyperalgesia (increased sensitivity to pain), and dysesthesia (abnormal and unpleasant sensations; Sommer & Lauria, 2007).

Given the paucity of related evidence in childhood populations, at this point there is no reason to expect that children with GDD would differ from healthy adults. Selim et al. (2010) found that healthy adults with greater ENF density reported more pin prick applications as painful and were more sensitive to detection of light touch. Based on this evidence, it was expected that children with greater ENF density would be more sensitive to pin prick and light touch in particular; however, given the current study does not test detection thresholds this relationship may not be detected. It should be noted that several studies reviewed found no relationship between ENF density and sensory testing outcomes (Periquet et al., 1999; Holland et al., 1997; Chiang, Chen, Chien, & Hsieh, 2003). Sommer and Lauria (2007) suggest that differences in findings may be related to methodological differences between labs and equipment as well as different populations tested ('normal', clinical, etc.). Given the Selim et al. study was conducted within the same lab where the biopsies for the current study were processed there is increased control over methodological differences between these two studies. For this analysis, a linear regression was used to determine if a predictive model existed between degree of reactivity (i.e., vocal, facial, body pain behaviors) during the sensory test and ENF density quantified from skin biopsies.

Preliminary Analyses and Missing Data

During the pilot work for this study three participants with GDD were enrolled and the sensory test was conducted without having adapted the test stimuli with toy animal (colloquially "kid friendly") coverings. After testing these three participants there was initial concern that the children's reactions to the sensory stimuli were due to fearfulness of the stimuli rather than the actual cutaneous experience of the stimuli. To control for fearfulness of the stimuli the coverings were developed and used for the rest of the participants in both groups. Statistical analyses demonstrated that these three participants (M=86.33, SD=93.43) did not differ significantly in total pain behaviors exhibited during stimuli application from the rest of the children with GDD (M=94.76, SD=50.94; t(18)=-.24, p=.82); therefore, these participants were included in all further data analyses.

The sensory test was terminated prior to completion for three children with GDD and one child in the control group. Reasons for terminating the sensory test for children with GDD included parent request (n=1) and severe pain behaviors; specifically, visible tears, repeatedly moving away from the tester, and loud vocalizations (n=2). One sensory test was terminated in the control group due to visible tears. This resulted in missing data for pressure (n=1), repeated von Frey (n=1), and heat (n=3) stimuli for the GDD group and repeated von Frey (n=1) and heat (n=1) stimuli for the control group. In addition, the heat probe was broken during the sensory test for one child with GDD. A camera malfunctioned during a sensory test for one child in the control group. Because of this, body pain behaviors could not be coded for that child; however, a second camera captured facial video which was used to code vocal and facial pain behaviors. That

child's data were excluded from any between-group analyses of the different types of pain behaviors. After data collection had already begun, it was decided to include a sham stimulus trial. Thus, the sham trial was only instituted for the last 12 participants in the GDD group and the last 5 participants in the control group. This resulted in missing data for each group.

Initial analyses indicated that age ($r = -.13$, $p = .21$) and gender ($t(18) = .91$, $p = .37$) were not significantly related to total pain behaviors exhibited during sensory epochs; thus, these variables were not included as covariates in further data analyses. Initial analyses were conducted to determine if there were differences in the duration of time that the stimuli were applied for each group. An independent samples t-test indicated that the repeated von Frey application was significantly shorter for children with GDD ($M = 46.32$, $SD = 20.23$) compared to the control group ($M = 60.53$, $SD = 7.45$; $t(22.8) = -2.87$, $p < .01$). Consequently, the total mean duration of all stimulus epochs combined was also significantly shorter for children with GDD ($M = 88.40$, $SD = 22.24$) compared to the control group ($M = 104.55$, $SD = 17.85$; $t(38) = -2.53$, $p < .05$; Table 2). The duration of stimulus epochs within each group also differed because all stimulus epochs were 5 seconds with the exception of the repeated von Frey which was applied for 30 seconds. Thus, for any analyses comparing the duration of vocal, facial, or body pain behaviors between participant groups or between stimuli types the duration (in seconds) has been converted to a proportion of each respective stimulus epoch. The three pain behaviors (vocal, facial, and body) were measured separately within each stimulus epoch and combined for total reactivity duration; thus, total mean proportions for each stimulus

epoch may range from 0.00-3.00. A mean proportion of 0.00 indicates that no pain behaviors were measured during the stimulus epoch and a score of 3.00 indicates that all three pain behaviors occurred continuously and simultaneously throughout the stimulus epoch. Mean duration of vocal, facial and body pain behaviors (in seconds and proportions) by group and stimuli are displayed in Table 3. Means and standard deviations were provided in seconds unless specified as a proportion.

Chapter IV: Results

Primary Research Questions

1. Do children with GDD exhibit observable and quantifiable facial, vocal and body signs of reactivity during a standardized sensory test? Means, standard deviations, and ranges for vocal, facial, and body pain behaviors exhibited during each type of stimulus application are provided in Table 3. Similar to children in the control group, children with GDD exhibited behavioral reactivity during each active sensory testing trial suggesting that A beta, delta, and C fibers were functional. On average, children with GDD exhibited 15.35 (SD= 7.24; range= 0-30) distinct episodes of pain behavior that totaled an average duration of 93.50 (SD= 55.80) seconds during all sensory testing epochs combined. Specifically, children with GDD exhibited an average of 4.74 (SD=3.85) episodes of vocal pain behaviors with a total duration of 25.85 (SD=21.01) seconds; 3.65 episodes of facial pain behaviors with a total duration of 23.50 (SD=22.02) seconds; and 6.95 (SD=3.07) episodes of body pain behaviors with a total duration of 43.95 (SD=28.47) seconds. A one-way ANOVA was conducted to determine if children with GDD exhibited more of some pain behaviors compared to other pain behaviors (i.e., vocal, facial, and body) during the sensory test. There was a significant effect for the three pain behaviors ($F(2,57)=4.32$, $p<.05$). Post hoc comparisons using the Tukey HSD test indicated the mean duration for body pain behaviors was significantly greater than the mean duration of facial pain behaviors ($p<.05$; Figure 2a). There were no significant differences between mean duration of facial and vocal or vocal and body pain

behaviors. Overall, children with GDD did exhibit observable and quantifiable vocal, facial, and body pain behaviors during the sensory test.

On average, children in the control group exhibited 8.10 (SD=5.18) distinct pain behaviors that totaled an average duration of 50.90 (SD=56.02) seconds during all sensory testing epochs combined. Specifically, children in the control group exhibited, on average, 1.05 (SD=1.91) episodes of vocal pain behavior with a total duration of 5.90 (SD=15.01) seconds; 2.10 episodes of facial pain behaviors with a total duration of 15.90 (SD=22.11) seconds; and 4.95 (SD=2.96) episodes of body pain behaviors with a total duration of 30.63 (SD=26.32) seconds. A one-way ANOVA revealed a significant effect among the three pain behaviors for the control group ($F(2,56)=6.47$, $p<.01$). Post hoc comparisons using the Tukey HSD test indicated the mean duration of body pain behaviors was significantly greater than the mean duration of vocal pain behaviors ($p<.01$; Figure 2b). There were no significant mean differences for the duration of facial and body or the vocal and facial pain behaviors. For both groups of children, body pain behaviors in relation to sensory stimuli were on average of the greatest duration.

2. Are children with GDD more or less reactive during sensory testing dependent on the modality of the sensory stimuli applied? The multivariate analyses of vocal, facial, and body pain behaviors during each stimulus application (i.e., sham, light touch, pin prick, cool, pressure, repeated von Frey, and heat) demonstrated a significant multivariate effect ($F(18, 331)=2.26$, $p<.01$; Figure 3a). Univariate analyses revealed no significant effect for vocal pain behaviors ($F(6,125)=1.23$, $p=.28$; Figure 3b) but there were significant effects for facial ($F(6, 125)= 2.89$, $p<.05$; Figure 3c) and body

pain behaviors ($F(6, 125)= 4.00$, $p<.01$; Figure 3d). Post-hoc analyses revealed that children with GDD exhibited a significantly greater proportion of facial pain behaviors during the repeated von Frey (M=.43, SD=.42) stimulus trials compared to sham (M=.03, SD=.11; $p<.05$) and heat (M=.09, SD=.16; $p<.05$) stimulus trials. Children with GDD also exhibited a significantly greater proportion of body pain behaviors of reactivity during the repeated von Frey (M=.66, SD=.32) stimulus trials compared to sham (M=.11, SD=.26; $p<.01$), light touch (M=.31, SD=.33; $p<.05$), cool (M=.32, SD=.47; $p<.05$), and pressure (M=.24, SD=.33; $p<.01$) stimulus trials.

For the control group, the multivariate analyses of vocal, facial, and body pain behaviors for each stimulus application produced a significant multivariate effect ($F(18,305)=1.63$, $p=.05$; Figure 4). Univariate analyses indicated a significant effect for body ($F(6, 116)= 3.77$, $p<.01$) but not facial ($F(6, 116)= 1.19$, $p=.32$) or vocal pain behaviors ($F(6,116)=.29$, $p=.94$). Post-hoc analyses revealed that children in the control group exhibited a significantly greater proportion of body pain behaviors during the repeated von Frey (M=.39, SD=.33) stimulus trials compared to light touch (M=.13, SD=.15; $p<.05$), cool (M=.09, SD=.19; $p<.01$), and pressure (M=.15, SD=.22; $p<.05$) stimulus trials.

Children with GDD exhibited longer lasting facial and body pain behaviors during the repeated von Frey stimulus trial. Children in the control group exhibited longer lasting body pain behaviors during the repeated von Frey stimulus trial.

3. Is there a relationship between sensory reactivity and severity of GDD?

A one-way ANOVA was conducted to determine if duration of reactivity was a function of the severity of GDD (severe GDD [n=12], less severe GDD [n=6], controls [n=20]). There was a significant effect for severity of GDD ($F(2,35)=5.31$, $p=.01$). Post hoc comparisons using the Tukey's HSD test indicated children with more severe GDD exhibited a significantly greater duration of reactivity during the sensory test compared to controls ($p<.01$). There were no significant differences between mean duration of reactivity between children with less severe GDD and the other two groups (severe GDD, controls). Descriptively, mean proportions of pain behavior duration for children with more severe delays were greater for all stimulus trials, with the exception of repeated von Frey, compared to children with less severe delays. To summarize, children with more severe delays exhibited significantly more pain behaviors during the sensory test compared to controls; whereas, children with less severe delays did not differ from either of the other two groups.

4. Are children with GDD more or less reactive during the sensory test compared to children in the control group? Mean (SD) duration of reactivity by group (children with GDD, controls) are displayed in Table 3. The multivariate analyses of total duration of reactivity by group (children with GDD, controls) demonstrated a significant multivariate effect ($F(3, 35)= 4.97$, $p=.006$). Univariate analyses revealed significant effects for vocal ($F(1, 37)= 11.13$, $p=.002$) and body pain behaviors ($F(1,37)=6.04$, $p=.02$) and results for facial pain behaviors ($F(1,37)=3.12$, $p=.085$) trended in the same direction (GDD > TD coded facial pain behavior; Figure 6). The two-way ANOVA yielded a main effect for participant group, $F(1,236)=21.74$, $p<.001$ such that children

with GDD exhibited significantly greater duration of reactivity during the sensory test (M=4.88, SD=3.57) compared to controls (M=2.07, SD=1.81). The main effect for sensory modality was significant $F(6,236)=4.25$, $p<.001$. Tukey's HSD post hoc analyses indicated that reactivity was significantly greater during the repeated von Frey trial (M=1.05, SD=0.95) compared to sham (M=0.20, SD=0.52), light touch (M=.44, SD=0.69), pin prick (M=.50, SD=0.59), cool (M=0.49, SD=0.78), pressure (M=0.57, SD=0.77), and heat trials (M=0.55, SD=0.64). The interaction effect between participant group and sensory testing modality was non-significant $F(6,236)=1.16$, $p=.33$. Overall, children with GDD were more reactive to the sensory test, specifically exhibiting more body and vocal behaviors, compared to children in the control group.

Secondary Research Questions

5. Is there a relationship between sensory reactivity and gender in children with and without GDD? For total reactivity during the sensory test, there was no main effect for gender ($F(1,36)=.16$, $p=.69$) and no interaction effect for gender by group ($F(1,36)=.03$, $p=.88$).

6. For children with GDD, is there a relationship between proxy reported pain experience (pain intensity, frequency, duration, interference with functioning) in the previous 7 days and reactivity during the sensory test? Of the 19 participants who completed the DPI, nine participants had pain in the previous week and seven of those were included in the pain group (experienced pain rated ≤4 out of 10 and lasted 5 minutes or longer). Pain types and mean pain intensities are displayed in Table 4. An

independent samples t-test was used to determine if children with GDD exhibited more pain behaviors during the sensory test when they had experienced pain in the previous 7-day period. The total mean pain duration during the sensory test for children with pain (M=70.71, SD=34.73) did not differ significantly from children with no pain (M=110.67, SD=62.22; t(17.0)=1.55, p=.09). Similarly, multivariate analyses revealed no differences in vocal, facial, and body pain behaviors during the sensory test based on pain experience in the previous week (F(3,15)=.22, p=.88).

In the week prior to the study seven children experienced pain that interfered to some extent with the items on the BPI (scored 0 "pain did not interfere at all" to 10 "pain completely interfered"). For those children for whom pain interfered with functioning their mean BPI score was 33.57 out of a possible score of 120 (SD=26.08; range=3-84; n=7). Total BPI scores for all children with GDD did not correlate significantly with total pain expressed during the sensory test (r= -.33, p=.16).

Chronic pain. Four children with GDD experienced chronic pain that had lasted longer than six months. This pain was reported in the form of headaches (n=1), neuro-irritability (n=1), stomach pain (n=1), and sinus pain (n=1). The intensity of chronic pain was reported to fluctuate from day to day. The average pain intensity on a bad day was 3.5 out of 10 (SD=1.29; range 2-5) and on a good day 1 out of 10 (SD=2.00; range 0-4). Mean duration of reactivity during the sensory test for children with chronic pain (M=88.00, SD=47.17; n=4) did not differ significantly from children without chronic pain (M=98.10, SD=59.70; n=15). Multivariate analyses revealed no differences in vocal,

facial, and body pain behaviors during the sensory test based on chronic pain experience ($F(3,15)=.61$, $p=.62$).

Reactivity during the sensory test did not differ significantly based on pain experience in the previous week, pain interference, or chronic pain endorsement.

7. For children with GDD, is there a relationship between sensory reactivity and birth history (i.e., pre-term birth, birth weight, or admittance to the neonatal intensive care unit [NICU])? In this sample, six children with GDD were born pre-term, two children were born at a low birth weight (less than 2500 grams) and four children had been admitted to the NICU (Table 1). Birth weight ranged from 1559 grams (3lbs 7oz) to 4082 grams (8lbs 15oz; $M=3171.85$ grams, $SD=719.32$). Gestational age in weeks did not correlate significantly with overall proportion of reactivity during the sensory test ($r=.25$, $p=.36$). Birth weight significantly correlated with total proportion of pain behaviors exhibited during the sensory test ($r=.38$, $p<.05$). Total length of stay in the NICU was not correlated with total proportion of pain behaviors exhibited during the sensory test ($r=.08$, $p=.73$).

8. Are children with GDD who have self-injurious behavior (SIB) more or less reactive during sensory testing compared to children with GDD who do not have SIB? RBS-R data were available for 14 children with GDD; of those, eight had at least one endorsement of SIB and were included in the SIB group for analyses. All eight children with SIB had some form of SIB that was considered to be a moderate problem and two had SIB that was considered to be a serious problem. Children with SIB exhibited on average five different topographies of SIB, most frequently ‘hits self with

body part', 'hits self against surface or object', and 'pulls hair or skin' were endorsed. The mean score on the SIB subscale of the RBS-R for children with SIB was 9.25 (SD=6.00; range=1-21). Overall, mean total pain behaviors exhibited during the sensory test did not differ significantly between children with SIB (M=84.13, SD=49.29) and children without SIB (M=104.00, SD=73.86; t(12)=.61, p=.56). Children with SIB did not differ significantly in mean vocal (M=24.38, SD=16.04), facial (M=20.25, SD=18.36), or body (M=39.50, SD=33.40) pain behaviors compared to the vocal (M=30.50, SD=27.28; t(12)=.53, p= .61), facial (M=27.50, SD=30.96; t(12)=.55, p=.59) and body (M=46.00, SD=21.50; t(12)=.41, p=.69) pain behaviors of children without SIB. When examined by stimulus modality, mean score differences for proportion of pain behavior during the pin prick stimulus trial was marginally significant for children with SIB (M=.96, SD=.65) compared to children without SIB (M=.43, SD=.42; t(12)= -1.85, p= .089; Figure 8). Total score on the SIB subscale significantly correlated with vocal (r=.58, p=.01) and body (r=.56, p<.05) pain behaviors during the pin prick trial (Figure 9).

Children with SIB did not differ from children without SIB in the duration or types of pain behaviors exhibited during the sensory test. Children with more severe SIB exhibited significantly more vocal and body pain behaviors during the pin prick trial compared to children with less severe or no SIB.

9. Is there a relationship between sensory reactivity and peripheral innervation for children with GDD? Skin biopsies were procured from the calf of 16 children with GDD. Mean ENF density was 92.53 (SD=22.08; range=49.17-141.23).

Children with GDD who had chronic pain had significantly greater ENF density (M=118.34, SD=27.40) compared to children without chronic pain (M=87.09; 21.02; t(13)=-2.06, p<.05) and ENF density negatively correlated with birth weight (r=-.46, p<.05). Birth weight did not correlate with height (r=.22, p=.46), weight (r=.42, p=.16), or body surface area (r=.36, p=.23) at the time the skin biopsy was procured.

Overall ENF density in the skin biopsies did not significantly predict pain expression during the sensory test with (β= -.26, t(14)= -.94, p=.37) or without controlling for birth weight (β= -.46, t(14)= -.85, p=.41). ENF density did not significantly correlate with proportion of pain behaviors exhibited during the sensory test (r=-.38, p=.15). However, when total proportion of pain during the sensory test was dichotomized into high responders (cases in the upper 75th percentile) and average responders (all other cases), an independent samples t-test indicated a significant mean difference in ENF density between high pain behavior responders (M=72.97, SD=13.96; n=4) and average pain behavior responders (M=99.05, SD=28.47; t(11.2)=2.42, p<.05; n=12; Figure 10). ENF density significantly predicted vocal pain behaviors during all sensory testing epochs combined (β= -.51, t(14)= -2.18, p<.05; Figure 11). ENF density also accounted for the variance in vocal pain behaviors (R^2 =.25, F(1,15)= 4.75, p<.05). Specifically, ENF density predicted vocal pain behaviors during the light touch (β= -.58, t(14)= -2.66, p<.05; Figure 12a) and cool touch stimulus applications (β= -.53, t(14)= -2.31, p<.05; Figure 12b). ENF density accounted for the variance in reactivity during light touch (R^2 = .34, F(1,15)=7.05, p<.05) and cool touch (R^2 =.28, F(1,15)=5.31, p<.05).

High pain responders had significantly reduced ENF densities compared to average pain responders. Reduced ENF density accounted for increased vocal pain behaviors overall and specifically during the light touch and cool touch stimulus trials. Children with chronic pain had increased ENF density compared to children without chronic pain. Increased ENF density was associated with comparatively lower birth weight independent of body size at the time of biopsy procurement.

Chapter V: Discussion

This study was the first child-specific study to assess pain behaviors exhibited during a standardized sensory test in a sample of age and gender-matched children with and without GDD. This was also the first study to explore sensory reactivity in relation to severity of developmental delay, SIB, neonatal history, and ENF density in children with GDD. The primary research questions were asked to address the issue of whether pain behaviors during the sensory test would be quantifiable, whether pain behaviors would differ by stimuli or severity of GDD and whether pain behaviors would differ between children with GDD compared to controls.

Sensory Reactivity in GDD

Children with GDD exhibited quantifiable vocal, facial and body pain behaviors during every active stimulus trial of the sensory test. This suggests that this sample of children with GDD had functional A beta, delta, and C fibers transmitting tactile sensory input to the brain. Children with GDD exhibited body pain behaviors most frequently and for the longest duration whereas facial pain behaviors were exhibited least frequently and for the shortest duration. This finding is contrary to the belief that children with GDD (at risk for IDD) would be insensitive or indifferent to tactile or nociceptive input. It should be noted that this was not a pain threshold study and the stimuli would not typically be considered noxious (possibly with the exception of the pin prick and heat trials being mildly noxious). However, given that the children with GDD in this sample exhibited a

repertoire of pain behaviors during the sensory test it seems reasonable to assume they would also exhibit pain behaviors in response to more intense stimuli and are unlikely to be insensitive or indifferent to pain.

Sensory Reactivity and Stimulus Modality

Children with GDD were able to discriminate stimulus intensities by exhibiting more pain behaviors for longer durations during presumably more intense sensory stimuli (i.e., repeated von Frey, heat, and pin prick). It seems reasonable to conclude that these three stimuli were more intense compared to light touch, sham, cool, and pressure because in a previous study pin prick was determined to be mildly painful (Symons et al., 2010) and heat for this study was calibrated at 50°F which is considered heat pain. The 60g monofilament used in the repeated von Frey in a single application is not considered noxious but the repeated nature of the test and the longer duration (30 seconds compared to 5 seconds) may result in a more intense sensory experience compared to light touch, sham, cool, and pressure applications. Using a similar sensory testing protocol Symons et al. (2010) did not find significant differences in facial pain expression in adults with IDD. The differences in findings between the two studies may be due to differences in sample characteristics or sensory testing protocols. The samples differed in chronological age and severity of delay and the Symons et al. study did not include the repeated von Frey stimulus trial and used a warm probe set to a lower temperature (40°C).

This study was the first to use a repeated von Frey stimulus as part of a standardized sensory test in any population at risk for IDD. The repeated von Frey

monofilament was used as a test of temporal summation; an increased pain perception to a repetitive nociceptive stimulus (Coste, Voisin, Luccarini & Dallel, 2008; Eide, 2000). This was a partial test of temporal summation because typically a more intense stimulus is applied repeatedly (e.g., pin prick); however, given the young age and communication impairments of the participants the monofilament was used. Despite this alteration, children with GDD exhibited significant reactivity during the repeated von Frey (controlling for stimulus duration). This test of temporal summation was used as a proxy for central sensitization which is a state of increased sensitivity in the central nervous system leading to amplified processing of nociceptive input (Meeus & Nijs, 2007). Central sensitization has previously been associated with chronic and widespread pain conditions such as fibromyalgia (Staud et al., 2001). However, in this population, increased responsiveness induced by a repeated stimulus may indicate altered or delayed development of the central nervous system (CNS) related to the GDD rather than a specific pain condition or experience. Given an altered or under-developed CNS, the nociceptive system may be less efficient at dampening the pain signal during repeated cutaneous input (Koch & Fitzgerald, 2013). In a study of typically developing children and adolescents, chronologically younger children were more reactive during sensory testing (Blankenburg et al., 2010) suggesting that nociceptive pathways may mature with age similar to other physiological and cognitive systems. For children with GDD many milestones of typical development are altered or delayed; thus, it seems plausible that the nociceptive pathways may also be altered or delayed in maturation.

Sensory Reactivity and Severity of GDD

Children with more severe delays exhibited significantly more pain behaviors during the deep pressure stimulus trial and did not differ in reactivity during other stimulus trials compared to children with less severe delays. Historic perspectives and contemporary conventional wisdom would suggest that greater cognitive impairment would result in more marked sensory deficits (Sobsey, 2006). This finding contradicts that belief, demonstrating that children with more severe delays either did not differ or were more sensitive in some conditions.

Sensory Reactivity in GDD compared to Controls

Overall, children with GDD exhibited significantly more vocal and body pain behaviors compared to controls. Across specific stimulus trials children with GDD exhibited significantly more pain behaviors compared to controls, with the exception of during the sham and heat trials. The two groups did not differ during the sham stimulus trial (sham stimulus was signaled and approached but sensation was absent) which rules out many non-physiological alternative explanations (e.g., fear, anxiety, GDD related behaviors) for between group differences in pain reactivity. There are two possible explanations for why the groups did not differ in reactivity to the heat stimulus trial. First, because heat was applied last children who did not complete the sensory test were not included in this trial. The three most reactive children with GDD and one child in the control group terminated the sensory test prior to experiencing the heat trial. This may have influenced the overall outcome. Second, children with GDD may have been slower

to react to the heat stimulus. Defrin et al., (2009) found that children and adults with IDD and Downs syndrome were more sensitive to heat pain but slower to react. Given the stimulus epoch for coding pain behaviors only extended for the duration of the stimulus application (5 seconds), children with GDD may not have had sufficient time to react to the stimulus within that epoch. When stimulus epochs for the heat trial were extended to 10 seconds, there was a greater but non-significant difference between groups with children with GDD (M=.70, SD=.72) exhibiting a greater proportion of pain behaviors compared to children in the control group (M=0.44, SD=.58; t(33)= 1.18, p=.24; Figure 13). Future work should include longer epochs for measuring response to heat stimulus trials in children with GDD. Specific to the results of the current study, it seems that a combination of the two explanations (i.e., epoch duration, most reactive children with GDD did not experience the heat trial) impacted the heat stimulus trial outcome.

Among this sample, children with GDD were more reactive to an array of calibrated sensory stimuli compared to typically developing children in the control group; however, it is not possible to know from this study why children with GDD in this sample were more behaviorally reactive. One theory would be that children with GDD may experience altered or delayed maturation of the tactile and nociceptive circuitry resulting in amplified mechan-tactile-nociceptive signaling. It is well documented in animal models (Torsney & Fitzgerald, 2002) and human neonate studies (Fitzgerald & Gennings, 1999) that newborns have an immature nociceptive system that results in amplified and unorganized responses to an array of tactile and nociceptive stimuli (Fitzgerald, Shaw & MacIntosh, 1988). With age and experience typically developing

newborns acquire mature nociceptive circuitry resulting in organized and focused nociceptive signaling (Fitzgerald et al., 1988). The process of maturation, however, is complex involving changes in excitatory and inhibitory circuits dependent on a multitude of systematic changes in receptor expression and synaptic pruning.

More specifically, newborns have strong and abundant input from myelinated A fibers to the superficial laminae of the spinal cord's dorsal horn with reduced sensory thresholds and large receptive fields resulting in highly excitable and unfocused responses to tactile stimuli (Fitzgerald, 2005). Maturation of nociceptive circuitry requires a switch from predominantly A fiber input to predominantly C fiber input from the periphery to the dorsal horn (Fitzgerald, 2005). Myelinated A fibers have reduced input to the dorsal horn due to synaptic weakening in the post-natal period. Reduced A fiber input occurs in conjunction with the strengthening of the C-fiber synapses. Thus, mature nociceptive circuitry has strong excitatory and inhibitory input from the C-fibers to spinal cord lamina II neurons and moderate but sparse excitation input from the A-fibers (Fitzgerald, 2005).

Possible mechanisms underlying altered or delayed maturation of the nociceptive circuitry in GDD would include 1) alterations in synaptic connectivity and signaling, and 2) alterations in the balance between inhibition and excitation (Fitzgerald, 2005). These differences in the nociceptive circuitry would result in large and unorganized receptive fields, reduced A-fiber induced synaptic tuning, and reduced mechanical threshold in the dorsal horn. Overall, future research exploring these physiological phenomena may help

to elucidate why some children with GDD may be more reactive to cutaneous sensory input.

Social and environmental influences may contribute to the delayed maturation of the nociceptive circuitry in children with GDD. The World Health Organization's International Classification of Functioning, Disability and Health (ICF: WHO 2001) provides a framework that characterizes body function and structure, activities and participation, and environment in order to integrate medical and social aspects of a health condition. For a child with GDD, there is an underlying pathophysiology responsible for the GDD diagnosis (e.g., chromosomal abnormality, genetic mutation, etc.) possibly accompanied by structural differences in one or more systems (e.g., nervous system, movement, digestive and endocrine systems, voice and speech systems, etc.). As already proposed, the underlying pathophysiology and structural differences related to the GDD may result in altered development of the nociceptive circuitry. Additionally; functional limitations (e.g., cognitive, motor, and communication deficits) and reduced ability to participate in activities of daily living (e.g., self-care, feeding, relationships with friends and family) may exacerbate the altered development of nociceptive circuitry. For example, children with GDD may be at greater risk for early and repeated noxious events (e.g., tissue damage) during critical periods that lead to long term changes in pain circuitry. Children with GDD may also experience differences in early innocuous and noxious tactile input due to limitations in motor function (e.g., fewer falls, reduced exploration of environment). Children with GDD may experience reduced innocuous touch due to differences in the nature of social interactions and communication (e.g.,

reduced maternal holding). Overall, social and environmental influences and their possible contribution to the altered development of nociceptive circuitry is worth speculating on for further study.

Gender, Birth History, and other Possible Covariates

The secondary research questions aimed to explore factors that may influence reactivity during the sensory test: namely, gender, pain experience, neonatal history, SIB, and ENF density. No gender differences were found for either group in this study. While some studies have found gender differences in pain reactivity during sensory testing (Selim et al., 2010; Symons et al., 2010), others have not (Defrin et al., 2004; McArthur et al., 1998; Priano et al., 2009). It is possible that gender differences in pain experience and/or expression develop with increased age due to physiological changes or through increased opportunity for socialization (Dao & LeResche, 2000; Toomey, 2008). The young age of the participants studied may have impacted the opportunity to detect gender effects.

Pain experience in the previous week, pain interference with function, and the experience of chronic pain were not related to sensory reactivity during the sensory test. The lack of relationship between pain experience and sensory reactivity further suggests that the increased reactivity during the repeated von Frey trial was more likely due to delayed or altered development of the CNS rather than a pain condition or experience. While there are physiological reasons why pain experience would influence reactivity during a sensory test (Meeus & Nijs, 2007), there are two possible reasons why this was

not the case in the current study. First, children in this study may not have had significant enough pain experience to impact nociceptive pathways and alter sensory reactivity. Second, pain experience was quantified based on parent proxy report. Previous research has shown that parents are not very accurate at detecting and estimating their child's pain (Hennequin, Faulks, & Roux, 2000; Nader et al., 2004) which is not surprising because assessing another person's internal state is a difficult task (Hadjistavropoulos & Craig, 2002). In addition, other factors such as parental stress or depression may significantly influence proxy-reported pain ratings – possibly even more than the child's actual pain experience (Davis, Mackinnon & Waters, 2011).

Pain behaviors exhibited during the sensory test did not differ based on neonatal history, with the exception of birth weight. In previous studies that found a relationship between premature birth and NICU stay and sensory testing reactivity, the children were born extremely preterm (<27 weeks gestation; Walker et al., 2008) or were admitted to the NICU for over 40 days (Slater et al., 2008). None of the children in the current study met either of those criteria. Children in the current study were born premature (32-36 weeks gestation; n=5) or very premature (28-31 weeks gestation; n=1) and children that had been admitted to the NICU were admitted for an average of 12 days and at most 30 days. Thus, there is likely a magnitude effect such that children born extremely preterm who spend a greater duration of their early existence in an environment prone to painful procedures are more at risk for altered CNS development (Koch & Fitzgerald, 2013). Children in the current study likely did not experience neonatal experiences significantly different from other children with GDD. Therefore, nociceptive pathways were not

impacted or were not impacted to an extent that would be detectable via sensory test. Birth weight, however, was related to sensory reactivity - children were less reactive to the sensory test when they had been born at a comparatively lower birth weight. Walker et al., (2008) found children born preterm were less reactive to sensory stimuli. DeMaio-Feldman et al., (1994) found that school-aged children born at very low birth weights demonstrated significant deficits in their interpretation of sensory integration and praxis tests (i.e., graphesthesia, manual form perception, kinesthesia, finger identification, and localization of tactile stimuli). However, in our sample children with lower birth weights were not deficient in sensory function, but were simply not as reactive to the sensory stimuli as children with comparatively higher birth weights. Given the heterogeneity of the sample it is possible that birth weight is serving as a proxy for different etiologies of GDD.

Overall, children with and without SIB exhibited comparable pain behaviors during the sensory test and children with SIB exhibited greater pain behavior during the pin prick stimulus trial. This finding partially supports that of Symons et al. (2010) who found that adults with IDD and SIB exhibited greater facial pain during a similar sensory test including pin prick. These findings are contrary to models of self-injury that consider individuals with IDD or at risk of IDD to be insensitive or less sensitive to pain (Sandman, 1991; Symons et al., 2010). Given these cumulative findings, there is evidence that children and adults with SIB are as sensitive (possibly more sensitive) to pain than comparable peers without SIB.

Reduced ENF density significantly predicted increased vocal behavioral reactivity to the sensory test. Specifically, children with reduced ENF densities exhibited more vocal pain behaviors during the light touch and cool touch trials. This is contrary to the findings of Symons et al., (2009) and Selim et al., (2010) who found positive correlations between ENF density and reactivity to sensory testing. However, Mancini et al. (2013) compared spatial acuity for pain and intraepidermal nerve fiber density in the fingertip and dorsum of the hand in healthy adults. Fingertips had higher spatial acuity for pain but lower intraepidermal nerve fiber density compared to the dorsum of the hand. Pain acuity may depend not only on the density of nociceptive peripheral innervation but also on the size of the nociceptive receptive fields and the number of multimodal neurons processing the nociceptive input at the spinal and cortical level (Mancini et al.).

PGP staining for ENF density in epidermal skin biopsies quantifies predominantly C fiber afferents and the majority of the stimuli tested were more likely to activate A fibers. The enhanced reactivity of the children with GDD suggests that the A fibers were functioning in this sample. Given what is known about the development of tactile and nociceptive spinal cord circuits, it is plausible to suggest that children with GDD in this sample with reduced C fiber density and enhanced sensory reactivity may have had an underdeveloped sensory system dominated by A fiber afferent input (Koch & Fitzgerald, 2013). Neonatal spinal circuits are similarly highly responsive to tactile inputs that are predominantly transduced via A fiber input. Within the first post-natal weeks C fiber central synaptic inputs become stronger which in turn drives the development of glycinergic inhibition. Maturation of glycinergic inhibition dampens A fiber excitability

and may contribute to reduced receptive field size and align inhibitory and excitatory receptive fields. Previous animal research has demonstrated that C fiber destruction during the critical developmental period resulted in disorganized receptive fields and lack of A fiber inhibition (Wall et al., 1982; Wall, 1982). This disruption in typical sensory circuit development occurred because the glycinergic interneurons failed to mature in these animals due to absent C fiber input. Thus, in our sample of children with GDD with reduced ENF density, there may, in turn, be relative reductions in adequate C fiber input to produce maturation of glycinergic interneurons resulting in a consistent (persistent?) state of A fiber dominance. Typical development of the tactile and nociceptive circuitry requires input from low-threshold A fibers in very early development followed by C fiber input during a later critical period. As discussed previously, some children with GDD may have markedly different sensory experiences that may contribute to altered maturation of tactile and nociceptive circuitry.

Chronic pain and birth weight were significantly related to ENF density in children with GDD. Children with chronic pain had significantly greater ENF densities. This demonstrates that ENF density in this sample was predominantly comprised of functional C fibers because the majority of chronic pain (slow, second pain) is transduced by C fiber input. Birth weight significantly correlated with ENF density independent of body size at the time of biopsy procurement. More research is needed specific to ENF density and nociceptive pathways in children; however, this provides preliminary evidence of altered physiology underlying sensory reactivity differences in some children with GDD.

It should be noted that there are other factors independent of ENF density that influence sensory reactivity in the epidermis. For example, nerve growth factor (NGF) has been shown to play an important role in sensory reactivity independent of ENF density (Hirth et al., 2013) and mast cell degranulation has been linked with increased cutaneous reactivity during a sensory test in adults with intellectual disabilities (Symons et al., 2009). In this sample mast cells were analyzed and found to be predominantly intact and not degranulated. The finding that ENF density and cutaneous reactivity are negatively correlated provides evidence of the complex system that underlies cutaneous sensory reactivity in general and the possible alterations specific to children with GDD. The transduction of sensory information is influenced by many factors external (e.g., environment, learning, behavior) and internal (e.g., genetics, ENF density, neuropeptides, mast cell degranulation, NGF, etc.) to each individual (Fitzgerald, 2005; Koch & Fitzgerald, 2013).

Limitations

There are several study limitations that should be summarized. First, the approach used in this study did not test pain thresholds and therefore implications of this study cannot address the pain thresholds of children with GDD. Most of the sensory stimuli as applied were sub-threshold as noxious stimuli. The implications of the study should therefore be limited to discussion of the duration of pain behaviors exhibited during a standardized array of sensory stimuli. It is important to note that quantification of pain behaviors exhibited during sensory testing cannot be assumed to directly represent pain

experience. Second, although the observational coders of pain behaviors demonstrated strong inter-rater reliability (88-99%) and were blind to the specific research questions, it was not possible to keep the coders blind to each participant's group membership. It was discernible which children had GDD and which children were in the control group because of setting differences and language and behavioral cues. Finally, samples were formed based on convenience; thus, the results should be considered sample specific.

Implications

This study was the first to specifically measure the behavioral response of children with GDD to a calibrated sensory test and in comparison to a typically developing control group. The results of this study provide valuable information about the tactile and nociceptive pathways of children with GDD and their ability to express pain behaviors to signal their internal experience. Opposed to the long-standing belief that individuals with IDD or at risk for IDD are insensitive to pain, the results of this study add to the growing literature demonstrating that these individuals react to tactile sensory stimulation in a typical or even hypersensitive manner (Defrin et al., 2004; Symons et al., 2010). Individuals with IDD or at risk of IDD are capable of expressing their pain and sensory experiences in similar ways to typically developing peers. Thus, there is no reason to exclude individuals with IDD from pain and sensory research that could ultimately improve the care and management of painful conditions and experiences. This is especially important considering painful medical conditions, procedures, and surgeries are more common for these vulnerable individuals.

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Table 1. Children with GDD Group Characteristics

	Total (n= 20)
Diagnosis	
GDD	20 (100%)
Autism spectrum disorder	5 (25%)
Genetic Syndrome	3 (15%)
Motor coordination disorder	1 (5%)
Mixed receptive and expressive language disorder	2 (10%)
Pervasive developmental disorder (NOS)	1 (5%)
Intellectual disability	1 (5%)
Oppositional defiant disorder	1 (5%)
Special education titles for services (n=10)	
Developmental delay	7 (35%)
Autism spectrum disorder	1 (5%)
Deaf and hard of hearing	1 (5%)
Speech and language impairment	4 (20%)
Gross motor delay	1 (5%)
CDI subscale scores -2SD (30%) below age (n=18)	
Developmental score	12 (66.7%)
Expressive language	14 (77.8%)
Language comprehension	13 (72.2%)
Birth History	
Gestation	
Term (range = 37-40+ wks)	14 (70%)
Preterm (range = 32-36 wks)	5 (25%)
Very preterm (range = 28-31 wks)	1 (5%)
Extremely preterm (range = 23-27 wks)	0 (0%)
Birth weight	
Low birth weight (less than 2500 grams)	2 (10%)
Not low birth weight (2500 grams or greater)	18(90%)
NICU admittance	4 (20%)
Mean length of stay in days (SD; n=16)	12.0 (9.0)
Range	1-30 days
Pain experience (n=19)	
Pain in 7 days prior to study	
Yes	9 (47.4%)
No	10 (52.6%)
Chronic pain	
Yes	4 (21.1%)
No	15 (78.9%)

Table 2. Mean duration of Stimulus Epochs in Seconds for Children With and Without GDD

	Children with GDD M(SD; n)	Control Group M(SD)	*p*
Sham	7.00(1.04; n=12)	7.60(1.14; n=5)	.31
Pin Prick	7.50(1.47; n=20)	7.40(1.05; n=20)	.81
Light Touch	8.95(4.69; n=20)	9.05(1.15; n=20)	.93
Cool	9.1(4.33; n=20)	9.45(1.36; n=20)	.73
Pressure	11.68(4.58; n=19)	10.85(2.03; n=20)	.46
Repeated von Frey	46.32(20.23; n=19)	60.53(7.46; n=19)	<.01
Heat	9.69(3.26; n=16)	10.42(2.36; n=19)	.45
Stimuli epochs combined	88.40(22.24)	104.55(17.85)	.025
Total video length	186.10(51.67)	156.70(21.96)	.016

Table 3. Duration of Pain Behaviors Exhibited by Children with and without GDD during the Sensory Test

	Children with GDD M(SD)				Control Group M(SD)			
	Vocal	Facial	Body	Total	Vocal	Facial	Body	Total
Total seconds of pain behavior during combined stimulus epochs								
Sham	.75(2.01)	.25(.87)	.92(2.11)	1.91(4.91)	.00(0.00)	.60(1.34)	.40(.89)	1.00(1.41)
LT	2.30(4.37)	2.60(4.83)	3.20(4.50)	5.95(6.44)	.20(.62)	.50(1.43)	1.11(1.29)	1.85(2.56)
Pin Prick	2.25(3.35)	1.05(2.50)	2.65(2.41)	8.10(12.19)	.25(1.12)	.10(.45)	1.50(1.73)	1.75(2.29)
Cool	3.00(6.33)	2.15(5.87)	3.25(5.67)	8.40(16.59)	.45(2.01)	.90(2.29)	.84(1.74)	2.15(4.31)
Pressure	3.58(5.45)	2.89(4.04)	2.89(4.12)	9.37(11.68)	.50(1.67)	1.00(2.05)	1.53(2.25)	2.95(3.94)
RVF	14.21(14.14)	15.32(15.40)	30.63(23.70)	60.16(40.68)	3.89(12.80)	11.68(19.31)	24.11(20.97)	38.42(46.25)
Heat	1.65(2.60)	.71(1.31)	3.53(3.43)	5.88(6.23)	.84(2.12)	2.42(4.31)	2.89(3.71)	6.00(8.94)
Proportions of pain behavior controlling for duration of stimulus epochs (pain behaviors [s] / stimulus duration [s])								
Sham	.09(.25)	.03(.11)	.11(.26)	.24(.61)	.00(.00)	.08(.17)	.04(.10)	.12(.17)
LT	.17(.33)	.19(34)	.31(.33)	.74(.70)	.02(.07)	.06(.18)	.13(.15)	.25(.31)
Pin Prick	.28(.39)	.13(.11)	.34(.28)	.68(.90)	.03(.12)	.01(.05)	.22(.23)	.20(.27)
Cool	.25(.43)	.17(.32)	.32(.47)	.74(.94)	.05(.22)	.09(.25)	.09(.19)	.23(.47)
Pressure	.30(.38)	.29(.40)	.25(.33)	.84(.93)	.07(.23)	.11(.25)	.15(.22)	.31(.49)
RVF	.40(.40)	.43(.42)	.66(.32)	1.49(.95)	.06(.21)	.18(.31)	.40(.33)	.62(.74)
Heat	.18(29)	.09(.16)	.36(.30)	.60(.63)	.07(.20)	.20(.34)	.25(.27)	.51(.66)

Note. LT = light touch; RVF = repeated von Frey monofilament.

Table 4. Parental Endorsement of Pain Type and Intensity in the 7 days Prior to Study (n=9).

Pain Type	Number of participants experiencing this type of pain (n=)	Median Intensity (rated 0-10)
Accident pain	5 (26.3%)	6
Musculoskeletal pain	3 (15.8%)	5
Gastrointestinal pain	3 (15.8%)	5
Headache pain	1 (5.3%)	4
Other (teeth pain)	1 (5.3%)	5

Figure Captions

Figure 1. Graphical depiction of the methods used to test pain thresholds, including (a) method of limits (MLI) and (b) Method of levels (MLE). MLI is reaction time dependent because a delay in reaction time will artificially inflate the pain threshold, whereas MLE controls for reaction time by removing the stimulus after application to give the participant an opportunity to report if it was experienced as painful.

Figure 2. Mean scores for vocal, facial, and body pain behaviors are presented for (a) children with GDD (n=19) and (b) Children in the control group (n=20). Error bars represent standard deviation.

*p < .05. **p < .05

Figure 3. (a) A multivariate analysis of variance (MANOVA) was performed with post hoc analyses for (b) vocal, (c) facial and (d) body pain behaviors by stimulus trial for children with GDD. Error bars represent standard deviation.

*p <.05. **p <.01

Figure 4. A comparison of pain behaviors by stimulus trial for (a) children with GDD and (b) children in the control group. Error bars represent standard deviation.

*p < .05

Figure 5. A comparison of total pain behaviors during each stimulus trial for children with more severe delays (exceeded -2SD on behavior, expressive, and receptive language subscales of the CDI; n=12), less severe delays (did not exceed -2SD on one or more of the three CDI subscales noted; n=6) and controls (n=20). Error bars represent standard deviation.

*p < .05

Figure 6. Mean comparisons of vocal, facial and body types of pain behaviors exhibited by children with GDD and children in the control group. Error bars represent standard deviation.

*p <.05. **p <.01

Figure 7. Comparisons of mean pain behaviors (vocal, facial, and body types combined) during each stimulus trial for children with GDD and children in the control group. Error bars represent standard deviation.

*p <.05. **p <.01

Figure 8. A comparison of total pain behaviors during each stimulus trial for children with GDD with SIB (parental endorsement on the SIB subscale of the RBS-R; n=8) compared to children with GDD without SIB (n=6).

*p <.05.

Figure 9. Total SIB subscale scores on the RBS-R were positively correlated with (a) vocal and (b) body pain behaviors during the pin prick stimulus trial for children with GDD (n=14).

*p <.05. **p <.01

Figure 10. High responders on the sensory test (upper 75th percentile; n=4) had reduced epidermal nerve fiber (ENF) densities compared to average responders (n=12).

*p <.05.

Figure 11. Duration of vocal pain behavior exhibited during the sensory test negatively correlated with ENF density in children with GDD (n=16).

*p <.05.

Figure 12. Duration of vocal pain behavior during (a) light touch and (b) cool touch negatively correlated with ENF density in children with GDD (n=16).

*p <.05.

Figure 13. Comparisons of mean pain behaviors (vocal, facial, and body types combined) during each stimulus trial for children with GDD and children in the control group. The heat trial epoch was extended to 10 seconds. Error bars represent standard deviation.

*p <.05. **p <.01

Figure 1: Pain threshold testing using method of limits and method of levels.

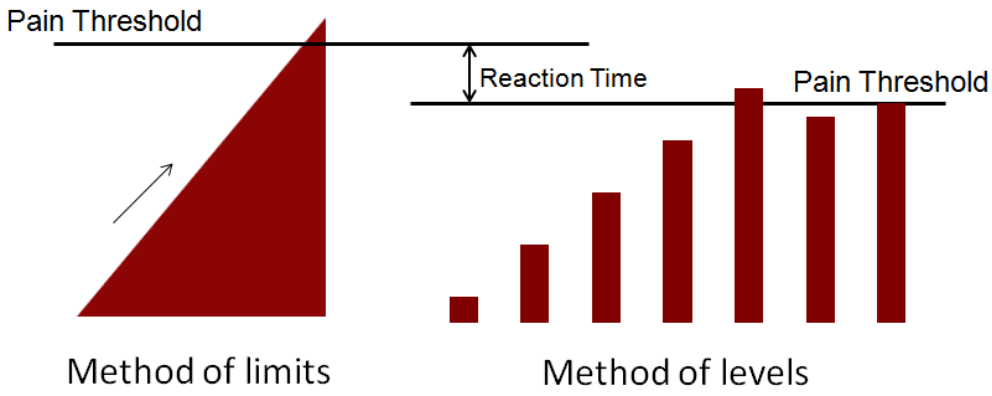
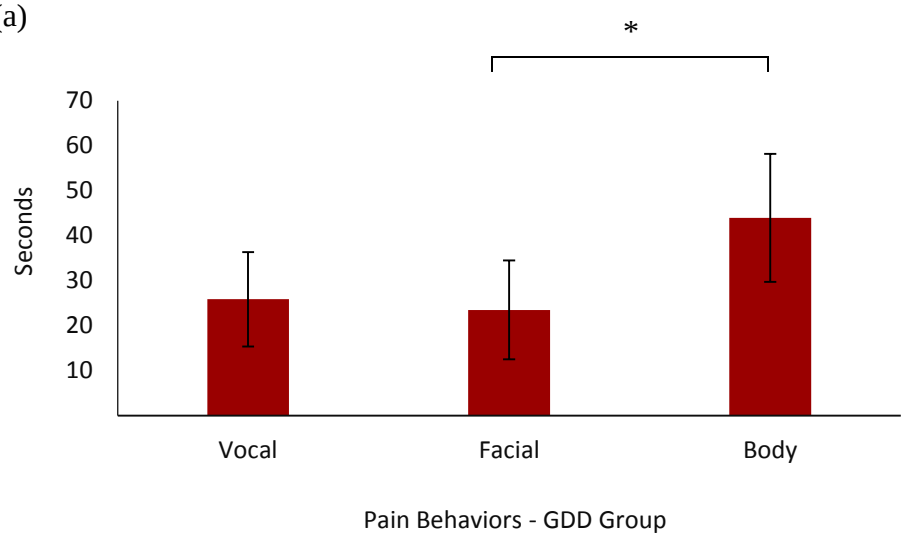


Figure 2: Types of pain behaviors exhibited during sensory testing epochs

(a)



(b)

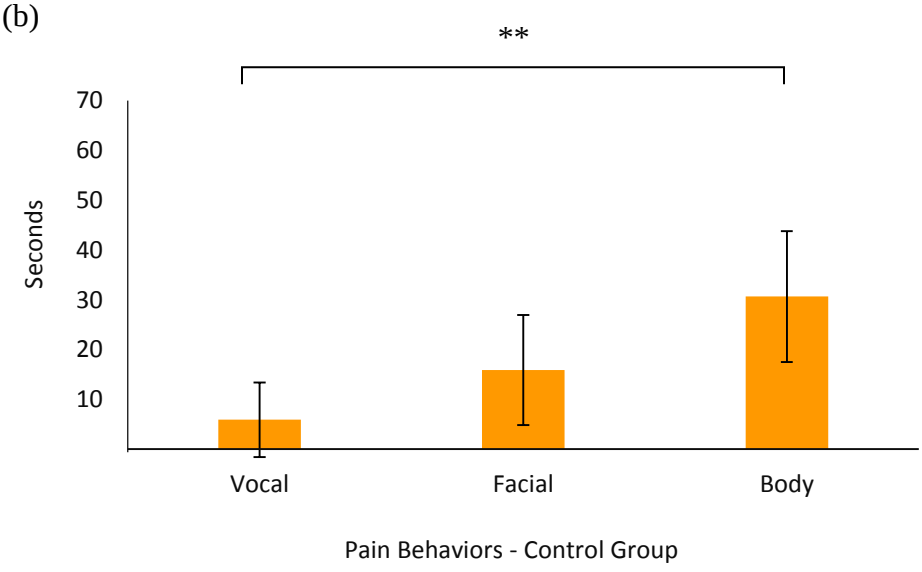
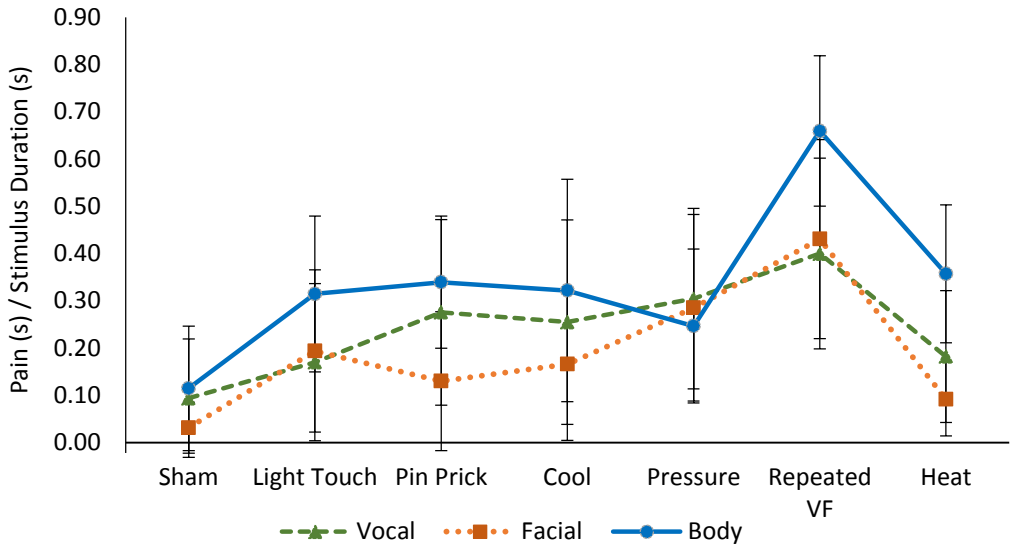
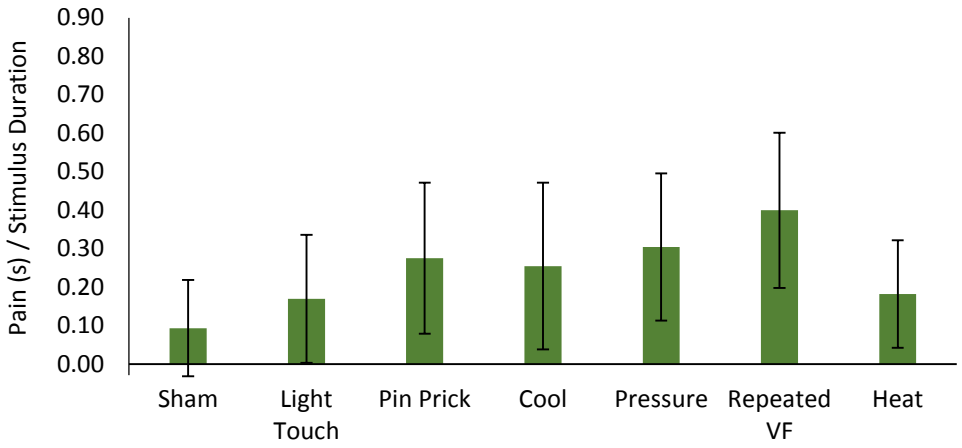


Figure 3: Multivariate analysis of variance (MANOVA) for pain behaviors by stimuli for children with GDD

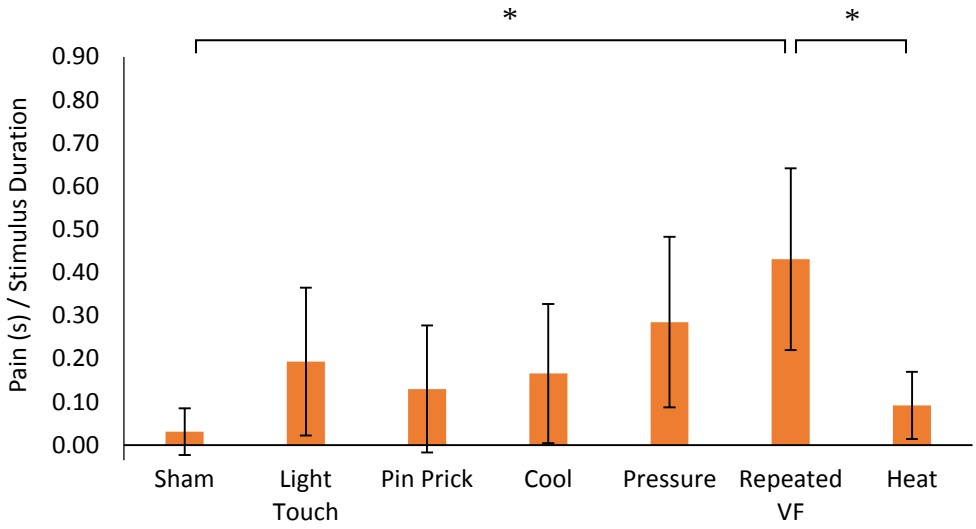
(a)



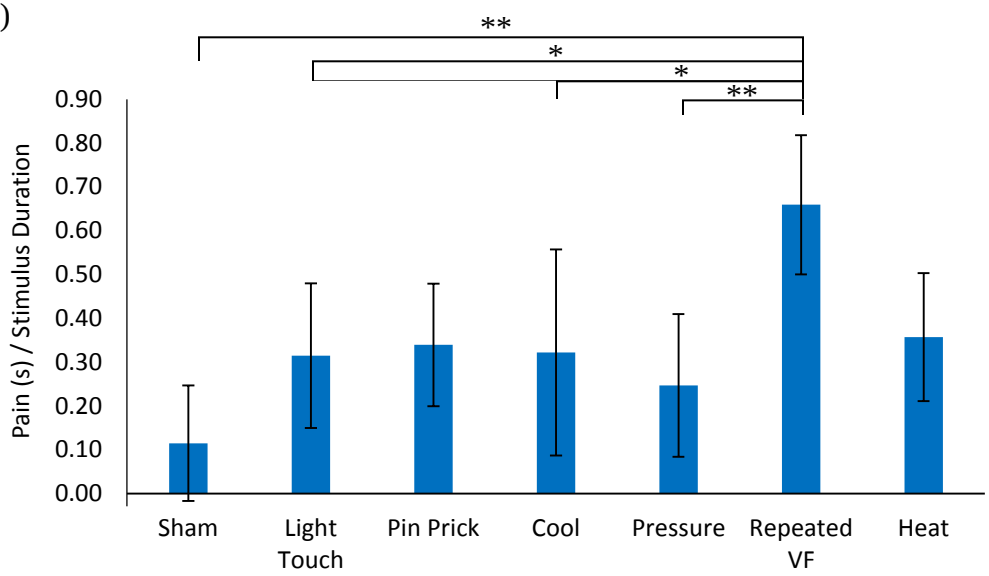
(b)



(c)


*
*
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Pain (s) / Stimulus Duration
Sham
Light Touch
Pin Prick
Cool
Pressure
Repeated VF
Heat

(d)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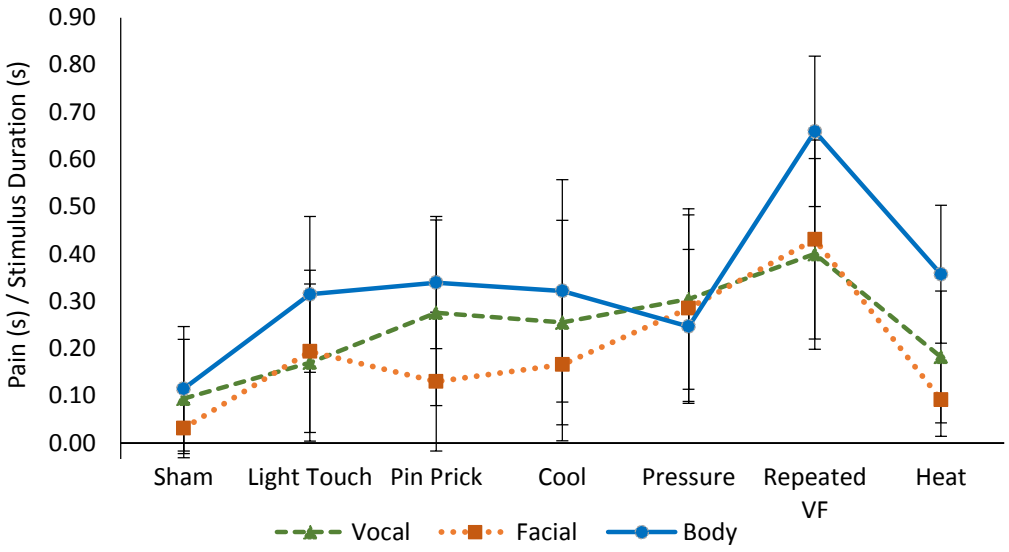
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Pain (s) / Stimulus Duration
Sham
Light Touch
Pin Prick
Cool
Pressure
Repeated VF
Heat

Figure 4: Pain behaviors by stimuli for children with and without GDD

(a)



(b)

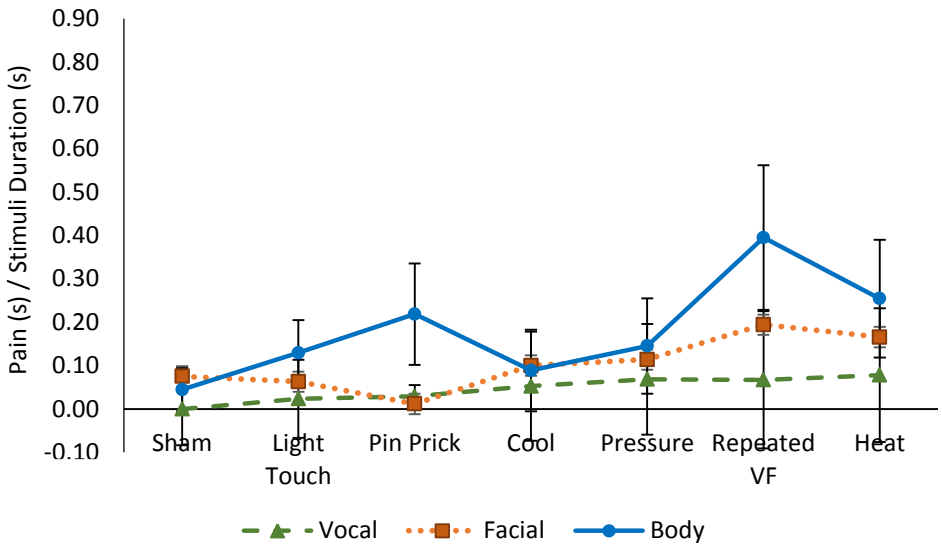


Figure 5: Pain behaviors by stimuli for children with more compared to less severe GDD

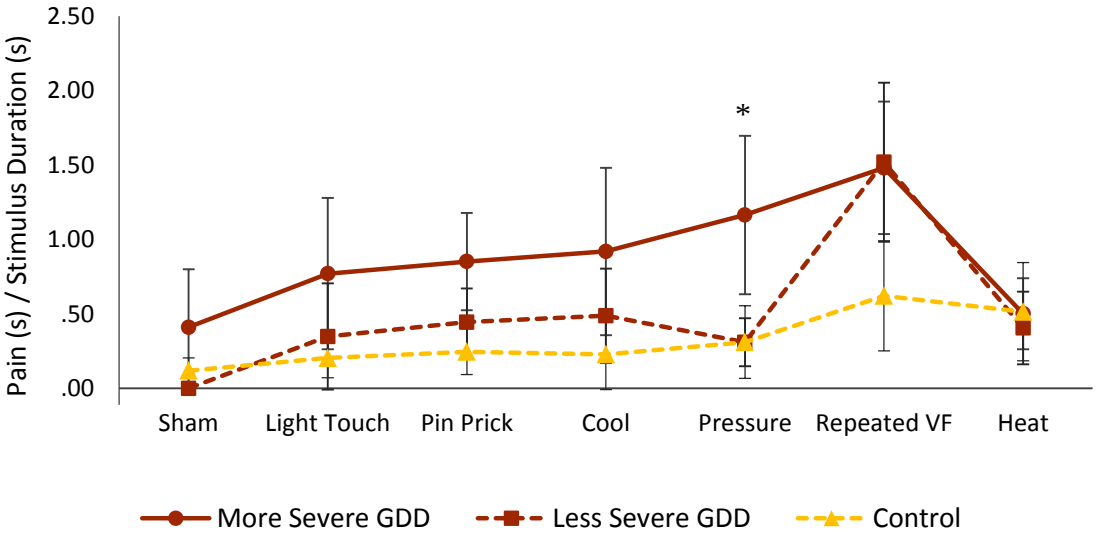


Figure 6: Types of pain behavior exhibited during sensory testing controlling for stimuli duration

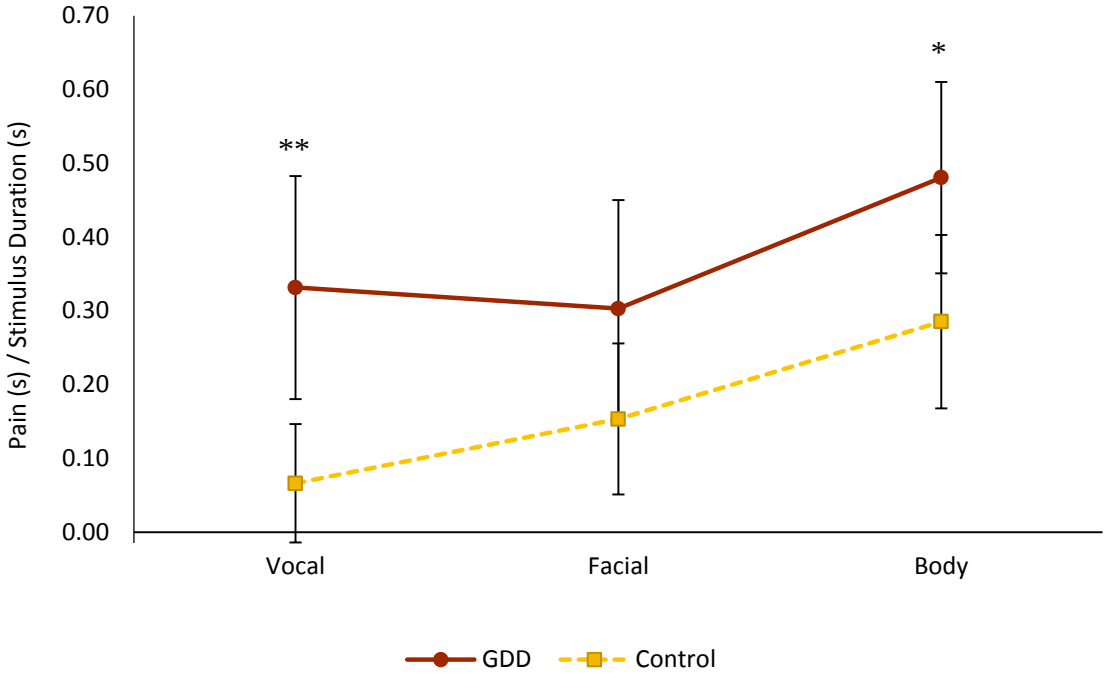


Figure 7: Total pain behaviors by sensory stimuli controlling for stimuli duration for children with and without GDD

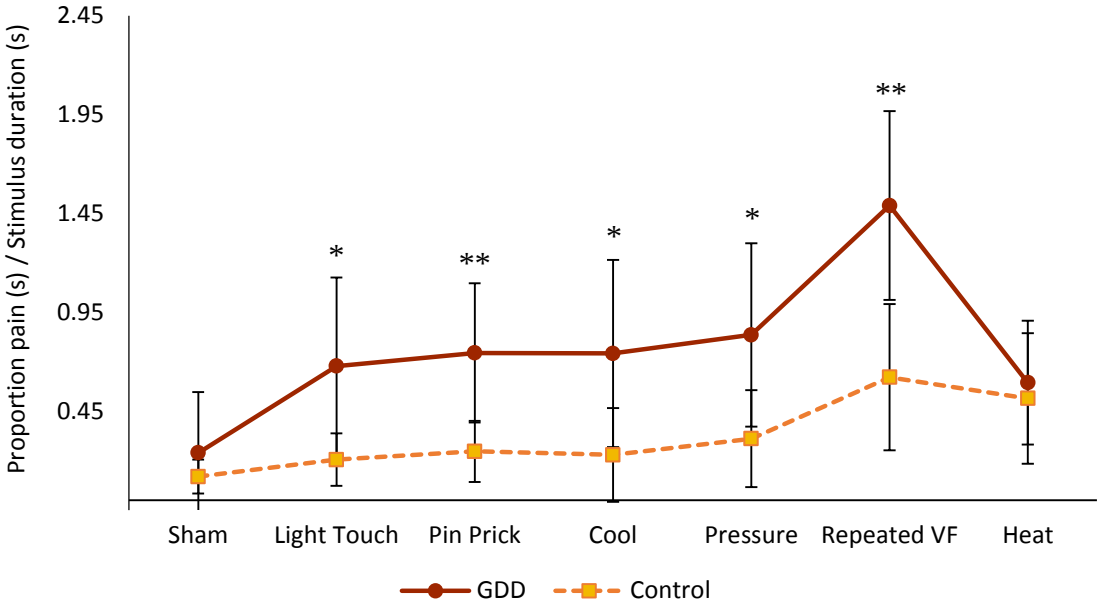


Figure 8: Pain behavior by stimuli for children with GDD with and without SIB

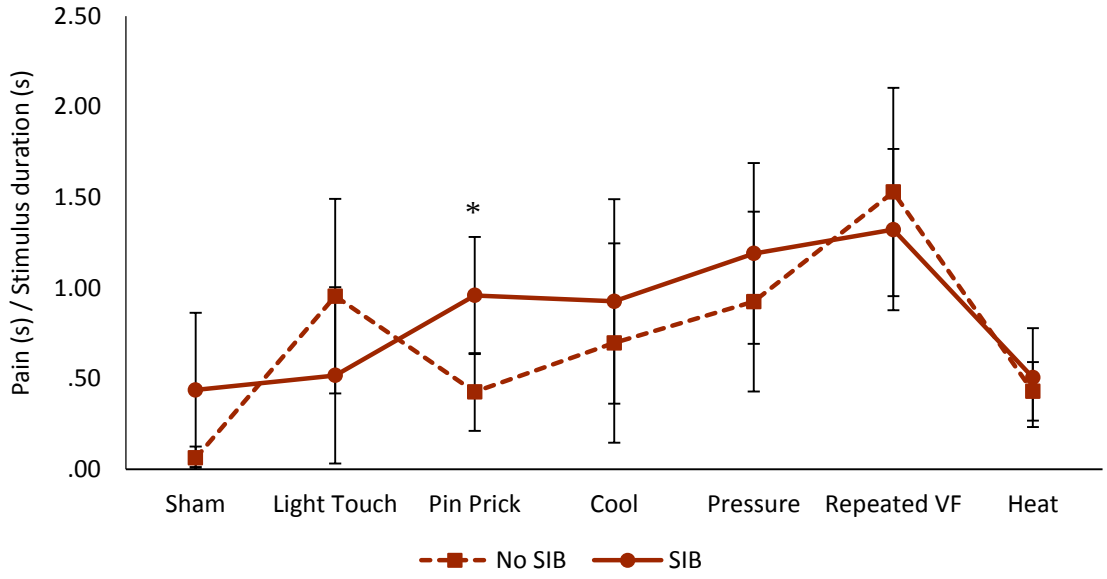
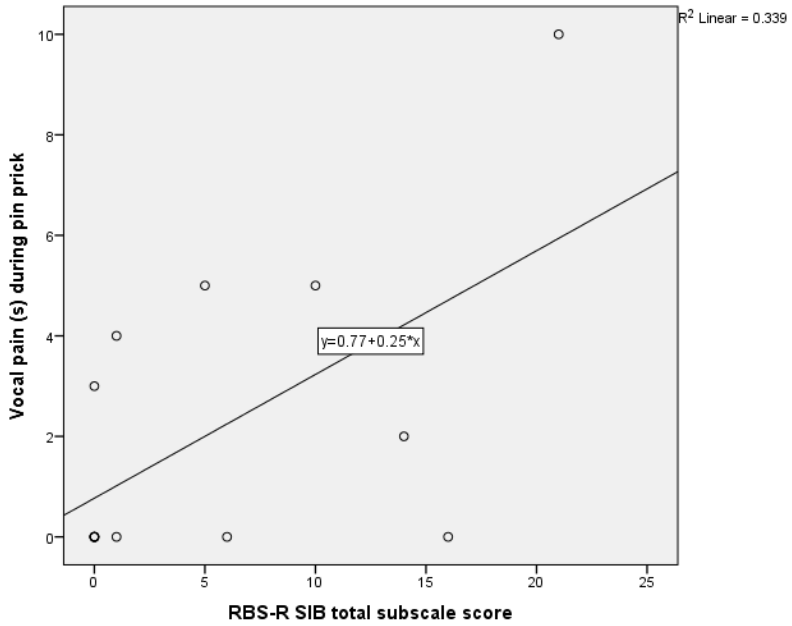


Figure 9: Pearson correlations of vocal and body pain behavior exhibited during the pin prick trial and the severity of SIB for children with GDD

(a)



(b)

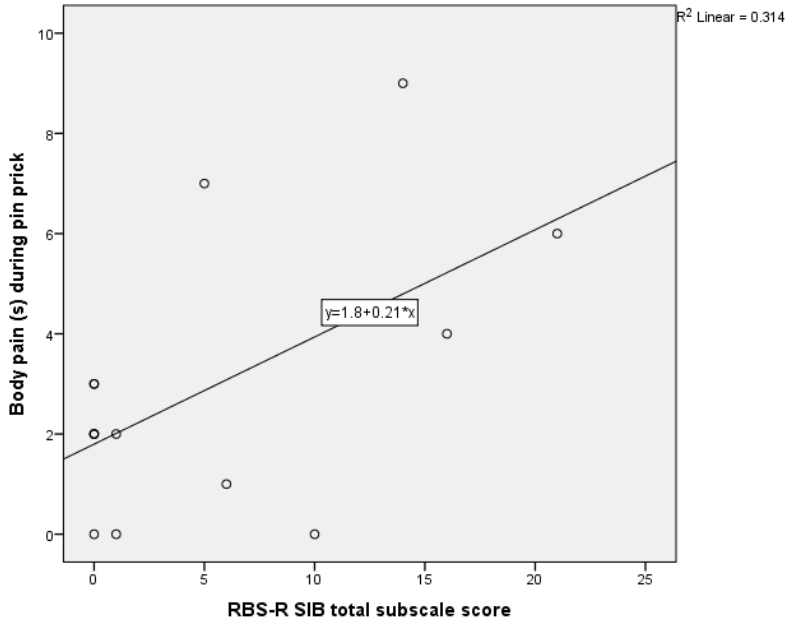


Figure 10: ENF density for average compared to high responders (upper 75th percentile) during the sensory test for children with GDD

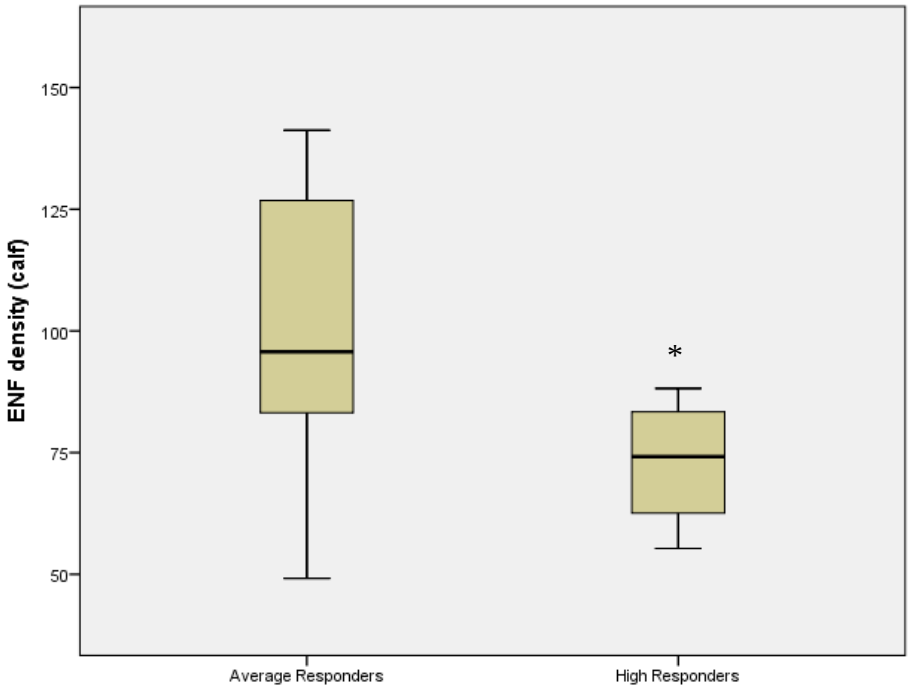


Figure 11: Pearson correlation of total vocal pain exhibited during the sensory test and the ENF density

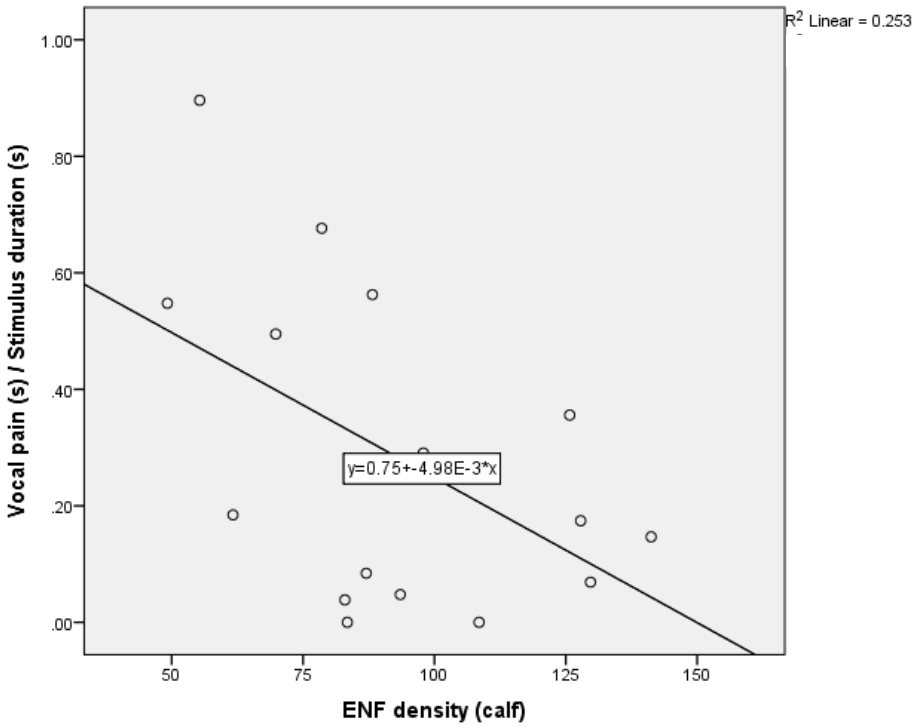
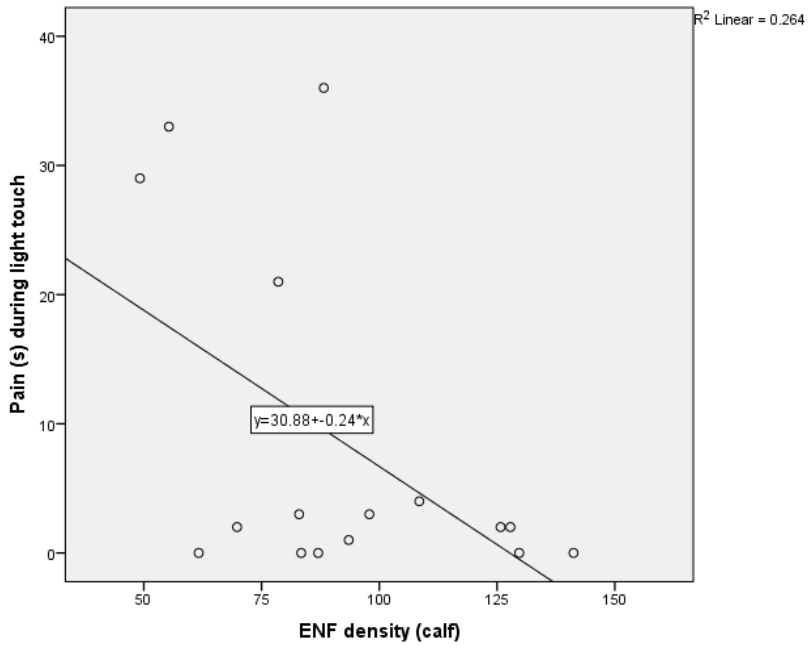


Figure 12: Pearson correlations of vocal pain behavior exhibited during light touch and cool touch trials and ENF density

(a)



(b)

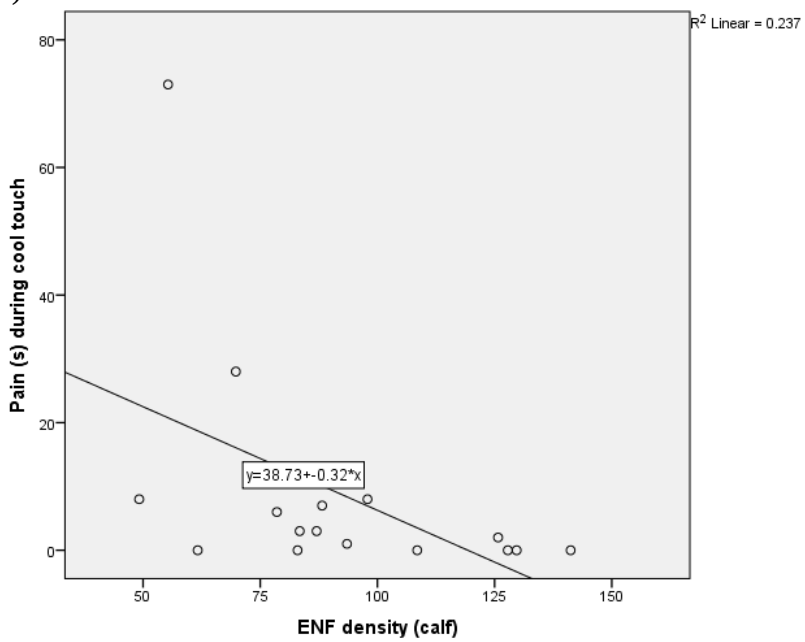
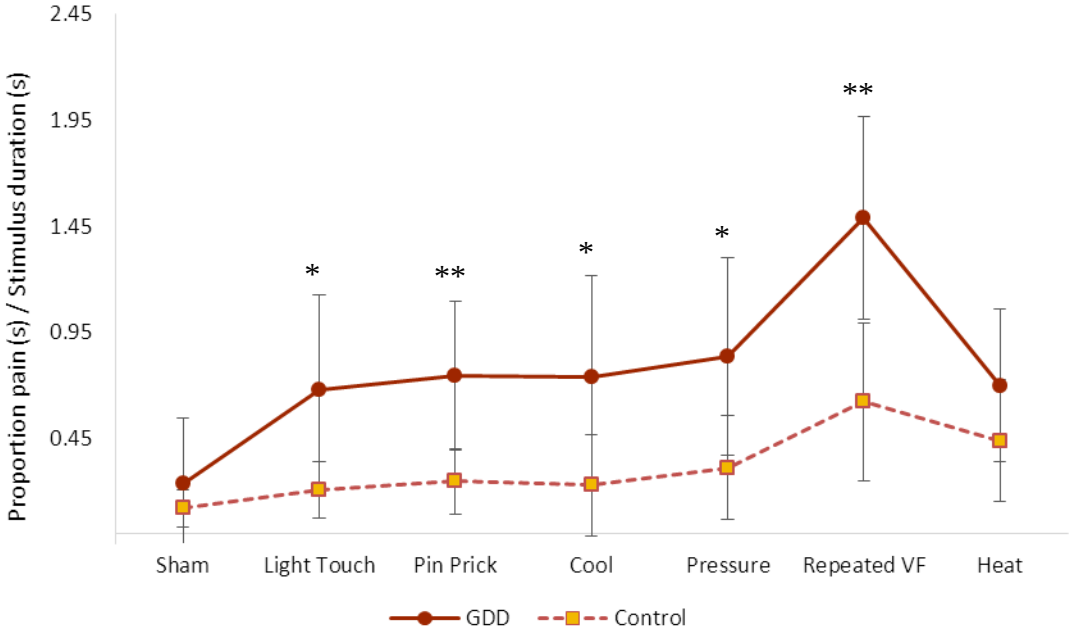


Figure 13: Total pain behaviors by sensory stimuli controlling for stimuli duration for children with and without GDD with the heat trial epoch extended to 10 seconds



Appendix A

Operational Definitions for Behavioral Events and States

Definitions of Pain Behaviors:

1. Vocal – Moaning, whining, whimpering, crying, screaming, yelling, or laughing sounds.

2. Facial – Cringe, grimace, furrowed brow, change in eyes, mouth open, lips puckered, pouting, or quivering, teeth clenched or grinding, or tongue thrust.

3. Body – Protects or favors specific part of body, flinches, or jerks away from examiner.

Operational Definitions of Vocal Pain Behavior:

1. Moaning, whining, whimpering: soft but audible crying-type vocalizations
2. Crying: louder vocalizations made with mouth open or closed, tears may or may not accompany the vocalization
3. Screaming/yelling: very loud vocalization
4. Laughing: burst of repetitive audible vocalizations
5. Vocalization: a statement in English language reporting the experience of pain, discomfort, or an unpleasant sensory experience or state.

Non-examples: Teeth grinding, sneezing, hiccups, spitting, breathing, coughing, sucking.
Examples of vocalization: ouch, this hurts, you're hurting me, my leg is sore
Non-examples of vocalization: that's cold, stop touching me, what are you doing?

Operational Definitions of Facial Pain Behavior:

1. Cringe, grimace: movement of large muscles in face, wrinkling of forehead, pulling back cheeks; causes "crow's feet", bags, or wrinkles to form under eyes; pulling chin in toward neck
2. Furrowed brow: inner and/or central portion of eyebrow lowers; may produce vertical wrinkles between eyebrows; or produces muscle bulge from middle of forehead above middle of eyebrow down to inner corner of eyebrow
3. Change in eyes: eyes may appear glazed; blinking or winking; narrowing of eye opening; eyelid droop; tightening of eyelids; squeezes eyelids together causing wrinkling of eyelid
4. Mouth open: lips vertically separated; jaw dropped; mouth stretched horizontally, lips form "O" ; mouth opened as if tonsils are being examined
5. Lips pucker tight, pout, or quiver: lips form a tight circle; lower lip protrudes; lips tremor
6. Clenches teeth, grinds teeth, thrusts tongue: squeezes teeth together, bites objects or self, rubs teeth together (may be audible), tip of tongue moves past lips

Non-examples: Wrinkling of nose, lifted brow, eyes closed, sucking on object or self, tongue moves in mouth but not past lips.

Operational Definitions of Body Pain Behavior:

1. Protects or favors specific part of body: shields body part with limb or object; actively avoids contact with specific part of body from others or object; limps, or will not bear weight on body part
2. Flinches, sensitive to touch: jerks away when examiner attempts to or touches body part; quick movement when examiner attempts to or actually touches body part

   Non-examples: Participant allows examiner to freely touch body part without attempts to move the body part away. Participant does not guard the body part with an object or self. No startle or jerking movements.