Pain and Sensory Function in Neuronal Ceroid Lipofuscinosis

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Dedication

This thesis is dedicated to my parents Lenn and Sandra Burkitt for instilling in me the importance of education and for their unwavering support both day and night.

Abstract

Aims: In individuals with Neuronal Ceroid Lipofuscinosis (NCL; Batten disease), a rare neurodegenerative disorder, to explore 1) the pain experience, 2) the relationship between pain and self-injurious behavior (SIB), 3) the degree of sensory reactivity, and 4) the degree of sensory reactivity in comparison to individuals without NCL. Method: Following informed consent, eight participants with NCL (*M* age= 14.8 years, range=8-22) were characterized in terms of pain experience (frequency, type, intensity, interference, expression, and coping) and severity of SIB. A brief sensory test (light touch, repeated Von Frey monofilament) was conducted with each participant with NCL as well as with a sibling comparison group without NCL (n=8, *M* age= 23.5 years, range = 8-37). During sensory testing, pain expression was measured using the Battens Observational Pain Scale (BOPS) and infrared thermography (IRT) was used to quantify changes in skin/eye temperature. Results: Individuals with NCL experienced pain frequently and from multiple sources that most negatively impacted enjoyment of life, mood, sleep, and social interactions. Individuals with NCL were significantly more likely to express their pain using vocal/social pain behaviors rather than body and limbs ($p<.05$) or physiological behaviors ($p<.01$). When in pain, individuals tended to seek social support more often. Individuals with NCL who had moderately severe SIB showed significantly more pain behaviors than individuals with mild or no SIB ($p<.05$). Individuals with NCL were reactive to the sensory testing as IRT temperatures significantly increased ($p<.001$). Across combined conditions (light touch, repeated Von Frey), individuals with NCL were significantly more reactive (BOPS total score) to

sensory testing compared to individuals in the sibling comparison group ($p< .05$). Similarly, IRT difference scores between sensory conditions revealed a significant increase in temperature at all face/eye sites for individuals with NCL compared to siblings ($p<.001$). Interpretation: In this sample of individuals with NCL pain was intense and frequent with multiple sources that interfered with a range of daily activities. Individuals with moderately severe SIB may be more sensitive to pain or may experience more pain in general. BOPS scores were elevated prior to sensory testing suggesting that individuals with NCL are living with ongoing pain. The increased pain expression during the repeated application of the Von Frey filament, a partial test of central sensitization, further suggests that the pathophysiology of the ongoing pain individuals with NCL are living with is likely centrally not peripherally mediated.

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The neuronal ceroid lipofuscinosises (NCL) are a rare group of fatal neurodegenerative brain diseases affecting approximately 8 in every 100,000 people worldwide.[1] These autosomal recessive lysosomal storage diseases are marked by the accumulation of autofluorescent lipopigments (ceroid and lipfuscin) in the brain and throughout the body that would normally be degraded.[2,3] Until recently, this accumulation was thought to cause widespread neuron loss which, in NCL, leads to the devastating clinical presentation of the disease (i.e., blindness, epilepsy, dementia) and ultimately death.[2-4] However, more recent research in animal models suggests that increased or decreased accumulation of lipopigments is not closely associated with the progression of neuron loss.[5] Instead, glial activation and synaptic pathology were found to occur early in all forms of NCL and accurately predict which regions and pathways will suffer subsequent neuron loss.[6] The degree of astrocytosis and microglial activation was directly related to the extent of neuron loss in human NCL post mortem analyses.[7] More specifically, the biology of astrocytes and microglia seem to be compromised in NCL and could therefore be responsible for the degradation of neurons.[3]

For all individuals affected with NCL both copies of the CLN gene have a mutation; however, there are at least 8-10 variants of NCL that have different mutations that manifest in a similar phenotype expression.[3] If an individual only has one copy of the mutation then they are a carrier of NCL but they do not have any consequences of the disease. Although there are multiple variants of NCL, there are four types of NCL that are most common and those include infantile (INCL; onset at 6mo-2y), late-infantile (LINCL; onset 2-4y), juvenile-onset (JNCL; onset 4-8y), and adult-onset (ANCL; onset

~30y).[3,9,10] The most common variant, JNCL, is marked by progressive blindness beginning between the ages of four and six, followed by a decline in cognition by age 10.[9] The onset of seizures and dementia occur during the teenage years and can be exacerbated by pubertal hormones. Ataxia is often seen in both JNCL and LINCL; however, in JNCL rigidity and dystonia are also common.[9,11] The physical effects of the disease reduce and eventually terminate the individual's ability to be independently mobile and assistance becomes necessary for daily tasks such as feeding and dressing.[9] Any treatments available are only palliative and do not slow the progression of the disease[10] which ultimately results in death by the second or third decade of life.[12]

From a psycho-social perspective, the symptoms of the disease make it difficult for the affected individual to maintain peer relationships.[9] Depression is often apparent during the adolescent years likely due to the stressful adjustment to the progression of the disease, understanding the fatal nature of the disease, isolation from peers, or possibly due to the natural course of an underlying psychiatric disorder. [9,13,14] In one study, significant proportions of the sample had problems with restlessness (35%), aggression (40%), fear (45%), pain (23%), difficulty falling asleep (32%) and staying asleep (34%).[14] In another study, the majority of individuals with JNCL (74%) had a symptom score at clinical or borderline range for psychiatric disturbance, including such symptoms as thought and attention problems, aggression, somatic complaints, sleep disturbances, and speech problems.[13] Females showed more psychiatric symptoms than males and those on psychotropic medications showed more symptoms than those that were not on medication.[13] Because multiple children in a family may be affected, younger siblings are

often fearful of the future.[9] As the disease progresses it becomes increasingly more challenging for adolescents with JNCL to keep up with their peers academically. Speech impediments, echolalia and perseveration become noticeable and cognitive skills are lost as the disease worsens.[13] This symptom cluster creates obvious issues for day-to-day activities of daily living and unique challenges within educational contexts. It is imperative that educators and school psychologists work closely with the child, their family, and healthcare professionals to provide adequate support and accommodations to ensure the child is as comfortable as possible in the educational environment.[8] The parent and child's unique wishes to receive special education services, to remain in the general education program, or to cease school attendance all together should be discussed and supported. Especially given the neurodegenerative and fatal nature of the condition, health and palliative needs should be given highest priority even within the educational context.

Pain and NCL.

Few studies have examined the pain experience of children with NCL. Mannerkoski and colleagues studied the use of transdermal fentanyl patches to alleviate pain of central origin in young children with INCL.[15] The five participants involved all had persistent pain that was reduced at least partially by the low doses of transdermal fentanyl. A reduction in pain was determined based on observation of pain signs using a visual analogue scale of pain. Santavuori et al., conducted a survey of parents of whom 9 out of the 42 reported their child with NCL had pain.[14] Parents also reported that their

children had problems with restlessness, aggressive behavior, falling asleep, and staying asleep. Breau et al., also asked parents to report on their child's pain experience using a pain and health questionnaire.[16] Eight of the 35 parents reported that their child had persistent pain. One child experienced 2 hours of pain daily, four children experienced 4-10 hours of pain weekly, three children experienced 5-7 hours of pain monthly.

Although there is limited scientific documentation of the pain experience of individuals with NCL, there is reason to suspect that pain is a problem based on the symptoms associated with the rapid degeneration known to occur in this disease. Spasticity, gastrointestinal complications, and decline of respiratory function, for example, are all associated with NCL and are known to cause pain in other populations.[14, 17-19] The experience of pain itself is distressing and in addition, ongoing pain can lead to other negative consequences. In other populations pain has been associated with a decline in overall quality of life, [20] depression, [21,22] and a decrease in functional and cognitive ability.[23] Unfortunately, diagnosing the cause of pain and providing effective treatment can be especially problematic when language abilities are compromised as in the case of individuals with NCL as the disease progresses.[24] These challenges can exacerbate the financial and emotional burden on the family caring for the individual.[25,26] There is no reason to assume individuals with NCL and their families might be spared these negative consequences of pain. Therefore, it would be beneficial to understand more about the pain experience of individuals with NCL and how pain impacts their lives.

Sensory Function and NCL

Pain perception depends, in part, on the functioning of the peripheral nerve fibers and their ability to detect thermal, mechanical or chemical stimuli and transmit the message to the central nervous system.[27, 28] The cell bodies of peripheral nerve fibers are located in the dorsal root ganglia and have a peripheral axonal branch that innervates their target organ and a central axonal branch that innervates the spinal cord. When the peripheral nerve fiber is activated by an intense stimulus (thermal, mechanical, chemical) the message is relayed to the central nervous system. There are two types of nerve fibers that relay this message; medium diameter myelinated Aδ fibers transmit fast pain that is well-localized whereas the small diameter unmyelinated C-fibers transmit slow pain that is poorly localized. These fibers differ from the larger diameter myelinated Aβ fibers that conduct non-painful sensations resulting from mechanical stimuli such as light touch.[27]

Calibrated stimuli have been developed to non-invasively determine the functional integrity and proficiency of the sensory nerve fiber afferents in conducting the message to the central nervous system.[29] The stimulus (thermal, mechanical, chemical) is applied and the response of the individual to the stimulus is measured. A pain threshold can be determined using quantitative sensory testing by applying a noxious stimulus at an increasing intensity until there is a pain response. The intensity of the stimulus at the time there is a pain response is considered the pain threshold. If thresholds are higher than would typically be expected there may be small nerve fiber loss and sensory dysfunction; similarly, a low pain threshold may signal hyperalgesia (amplified pain response to a painful stimulus).[30] Quantitative sensory testing can also be used to

determine the reactivity of individuals to sub-threshold sensory stimuli. In this case, the stimulus is applied and withdrawn and the response of the subject is measured. This type of sensory testing aims to determine if the individual detected the stimulus but does not determine a pain threshold. Another form of sensory testing involves the use of a constant repetitive stimulus (e.g., Von Frey filament, pin prick) applied to the same location and the response of the individual is measured. In animal models this is known as a test of 'wind-up' and is considered to be the progressively increasing activity in dorsal horn cells due to repetitive activation of primary afferent C-fibers.[31] In humans this is considered a test of temporal summation which is thought to be a psychological correlate of wind-up that involves an increased pain perception to the repetitive stimulus.[31, 32] Temporal summation is a proxy for central sensitization that is thought to play a role in the pathophysiology of chronic pain and has been explored in chronic pain conditions such as fibromyalgia,[33] temporomandibular joint disorders,[34] and migraine pain.[35]

Although sensory testing of the kinds described above has not previously been conducted in the NCL population, there has been some limited research in sensory testing conducted with individuals with intellectual and/or developmental disabilities (I/DD). In some respects, individuals with NCL and individuals with I/DD are similar in that their limited communication and neurological impairment require adaptations to typical methods of sensory testing that use verbal self-report. Defrin et al. and Priano et al. used thermal probes to determine the pain threshold for individuals with unspecified intellectual disabilities, Down's syndrome, or Prader-Willi syndrome. [36, 37] Observations of behavior were used to determine the pain threshold rather than verbal self-report. The

results suggested that individuals with I/DD had markedly altered pain thresholds, and in some cases lower heat pain thresholds, meaning they were more sensitive to heat pain. Other researchers have used a battery of sensory stimuli to determine the degree to which individuals with I/DD were reactive to tactile stimuli. [38-40] Each study included some combination of deep pressure, light touch, pin prick, warm and cool stimuli. In all three studies the authors concluded that the individuals with I/DD were sensitive and reactive to the stimuli presented.

These studies demonstrate that sensory testing is possible and important in documenting the sensory capacities of individuals with various neurological impairments and limited communication abilities. Considering the degeneration of the central nervous system and the neuronal damage known to occur during the progression of NCL [2,3] there is reason to speculate that there may be sensory differences experienced by these individuals and that these sensory differences may relate to the pain experienced by individuals with NCL as the disease progresses.[14]

Research Questions

This study aimed to better understand 1) what is the pain experience of individuals with NCL, specifically 1a) what is the intensity, frequency, and type of pain experienced, 1b) in what ways does pain interfere with daily life for individuals with NCL, 1c) what pain behaviors do parents most recognize in their child with NCL, and 1d) what coping styles are used by individuals with NCL, 2) What is the relationship between pain and self-injurious behavior (SIB) in NCL, specifically 2a) does pain

behavior/expression and pain intensity differ in individuals with NCL who have moderate SIB compared to those who have mild or no SIB, 2b) are individuals with NCL who have moderate SIB more reactive to sensory stimuli compared to those who have mild or no SIB?,), 3) are individuals with NCL reactive to sensory stimuli, and 4) do individuals with NCL react differently to sensory stimuli compared with carrier or unaffected siblings?

Methods

Sample Characteristics

A convenience sample of 8 individuals with NCL (4 male, 4 female; mean age = 14.8 years, range = 8-22). One participant was diagnosed with late infantile NCL and seven were diagnosed with juvenile NCL. All participants lived at home with their parents and six participants were still attending school at the time of the study. Seven parents reported on their child's health issues such as seizures (n=6), vision impairment (n=7), musculoskeletal challenges (n=5), and constipation (n=4). One participant was fed by G-tube. Gross motor function classification system (GMFCS) levels were I (n=1), II (n=2), III (n=0), IV (n=1), V (n=3) with I meaning the most self-initiated mobility and V meaning the least self-initiated mobility. A comparison group consisted of 8 individuals who had siblings with NCL but who were themselves either unaffected by NCL (n=2) or were known to be NCL carriers (n=6). The sibling comparison group did not exhibit any signs or symptoms of NCL. Data was originally collected on 12 siblings; however, four of those 12 siblings were excluded from analyses because they had not had genetic

testing to determine if they would develop NCL, were carriers, or if they were unaffected. Thus, all analyses were conducted with eight siblings in the comparison condition. The sibling group's mean age was 23.5 years (range = 8-37). Following IRB approval all participants were recruited during a national parent and family conference of the Batten's Disease Support and Research Association (BDSRA). Parents provided informed consent for all individuals with NCL and those in the sibling comparison group who were under 18 years of age. Participants without NCL who were over 18 provided their own informed consent.

Measures

Parents of seven individuals with NCL completed questionnaires related to the health and pain status of their child. One parent did not return the questionnaire for their child. The specific measures used included the Batten's Observational Pain Scale, a pain questionnaire, the Brief Pain Inventory, the self-injury subscale of the Repetitive Behavior Scale – Revised, the Pediatric Pain Coping Inventory, and the Gross Motor Function Classification System (described below).

The Batten's Observational Pain Scale (BOPS) was used as a measure of parent's recall of pain behaviors demonstrated by the individuals with NCL in the previous week.[41] The BOPS was derived from the Non-Communicative Children's Pain Checklist – Revised (NCCPC-R) and specifically adapted for individuals with NCL. In the initial validation of the scale during 10-minute observation periods the scores on the BOPS significantly correlated with the visual analogue scale of pain for the same observation

times (r = .57). The BOPS also showed strong sensitivity (92%) and specificity (89%) to pain behaviors. The cut off scores were determined to be 4 (pain is present), 7 (moderate pain is present), and 23 (severe pain is present).[41]

A pain questionnaire was adapted based on a questionnaire previously used for eliciting pain information about girls with Rett Syndrome [42] which was originally based on a questionnaire created for the National Fragile X Survey.[43] Specifically, responses were elicited for overall frequency of pain or discomfort, severity of pain (How would you describe the severity of your child's pain compared to that of children without disabilities? Less than, about the same as, more than other children), pain types (e.g., Is your child regularly affected by these types of pain? Gastrointestinal, musculoskeletal pain, etc.), and the pain intensity of each type of pain reported (scored 0-10).

The Brief Pain Inventory (BPI) was used to determine the extent to which pain interfered with daily life.[44] For the BPI parents report the extent that pain has interfered with activities such as sleeping, communication, mobility, and enjoyment of life in the previous week. Parents can rate the extent of pain interference from 0 meaning "does not interfere" to 10 "interferes completely". The BPI has shown excellent internal consistency (.89) and a significant correlation to pain intensity ratings when reported by adults with cerebral palsy (r = .66, p < .01).[40]

The Repetitive Behavior Scale – Revised (RBS-R) is a clinical rating scale used to measure the presence and severity of repetitive behaviors that are typically displayed by individuals with autism spectrum disorder (ASD) and related I/DD conditions.[45] The RBS-R has multiple subscales including compulsive behavior, routine behavior, and

stereotyped behavior. For this study, the self-injurious behavior subscale of the RBS – R was used to quantify self-injurious behavior in individuals with NCL. Parents reported for each self-injurious behavior if the behavior was a mild, moderate, or severe problem. There is evidence and ongoing work exploring the relationship between pain and self-injurious behavior, and so this association was explored in NCL.[46, 47]

The Pediatric Pain Coping Inventory (PPCI) – parent version was used to assess pain coping mechanisms used by individuals with NCL.[48] The PPCI includes 41 questions about coping styles which are rated 0 for "Never", 1 for "Sometimes" or 2 for "Often" depending on how frequently that coping mechanism applies. Individual coping style scores can be calculated to determine which coping styles (Cognitive Self-Instruction, Problem Solving, Distraction, Seeks Social Support, and Catastrophizing/Helplessness) are used. The PPCI is designed for children as young as age five and the items are observable by parents which makes the scale appropriate for use by parents of individuals with NCL. For example, the PPCI asks whether the individual "gets angry, irritable or cranky" and whether they "sleep it off" when in pain. The PPCI has shown good internal consistency and validity and has been used with multiple pediatric populations [48-50] including children with cognitive and language limitations.[51, 52]

The Gross Motor Function Classification System (GMFCS) was used to determine the mobility status of individuals with NCL.[53] The GMFCS is based on self-initiated movement especially sitting, standing, and wheeled mobility. The GMFCS is designed for use with individuals with cerebral palsy; however, individuals with NCL

have similar mobility limitations including spasticity, ataxia, dystonia, and rigidity. [9,11] The GMFCS is a 5-level classification system with level I indicating the least motor involvement and level V indicating the most motor involvement. The distinction between levels is based on functional limitations, the need for assistive devices for mobility, and the quality of movement. The GMFCS has shown excellent reliability and content validity in previous research studies.[54]

Individuals with NCL participated in a brief sensory test to determine the extent to which they were sensitive and reactive to an array of tactile stimuli. A comparison group also participated in the sensory test to determine if individuals with NCL reacted to stimuli differently than individuals without NCL. The sensory test included first, a light touch with a cotton swab on the palms, forearms, shins, and top of the feet. This test was used as a partial test of allodynia (pain reaction to a stimulus that does not typically cause pain). [27] This test also determined the functioning of Aβ fibers and was used as baseline measurement against which to compare the other sensory tests. Second, sharp and dull sensory stimuli were randomly applied to the same body locations to determine if participants could distinguish between the sensations. For this test the sharp end of the toothpick and the flat end of a cotton swab were used. This test aimed to determine if participants could differentiate between Aδ/C- and Aβ fiber activity. Finally, a 60g Von Frey monofilament was touched repeatedly to two body locations at 1 Hz for 30 seconds. This temporal summation test was used as a proxy for central sensitization. The two body locations were determined based on a pain site and a contra lateral non-pain location. When there was no pain location identified or if there was no contra lateral non-pain

location available the temporal summation test was conducted at two body locations consistent across participants, 1) the front of the wrist and 2) the mid to upper portion of the trapezius muscle. These locations were chosen in part, because they were accessible on every participant regardless of clothing, wheelchair position, contractures or braces. Multiple research protocols have specified the use of the palm for sensory testing as well as the trapezius muscle which has been shown to be useful for detecting deep muscle pain as well as chronic musculoskeletal pain.[55-57] Contractures often cause the hands of individuals with NCL to maintain a fisted position and therefore the palm of the hand can be inaccessible. The front of the wrist was chosen because it is in close proximity to the palm of the hand and this site ensured consistency in location across participants regardless of contracture.

For the sensory test, verbal self-report was too difficult for the participants with NCL as the disease had progressed to the point where language was either totally or partially compromised. Instead of using verbal responses which were deemed to be either absent or unreliable, observational methods were employed as the outcome variable in order to characterize physical responses to the sensory stimuli. To keep the outcome variable consistent and comparable across groups, observational methods were used to code the sensory reactivity of those with NCL and the sibling comparison group. The BOPS was used to code pain behaviors (i.e., moaning, tears, furrowed brow) observed from video recorded during the sensory test. The 17 pain behavior items on the BOPS were coded 0 “not at all”, 1”just a little”, 2 “fairly often” and 3 “very often”. The scores for each item were summed to create a total pain score for the time period

associated with each sensory test for each participant. Because the sharp and dull portion of the sensory test was designed specifically to require the use of language to differentiate between stimuli and because the duration of each trial was deemed too short to use observational methods for coding, this portion of the sensory battery was excluded from further analyses. A portion of the videos (~ 28%) were coded by a second coder to ensure coding accuracy. The mean inter-observer agreement (IOA; calculated as the number of agreements/total number of items) between the two coders was 92.8%.

Infrared thermography (IRT) was used as a novel approach to quantify changes in eye and face temperatures to indirectly characterize changes in autonomic function during the sensory testing. To the best of our knowledge IRT has not previously been used for characterizing sensory reactivity in NCL; however it has been used in non-human studies.[58] In one study researchers used IRT to measure eye temperature in cattle during castration which is known to cause deep visceral pain. The eye temperature of the cattle increased following castration possibly demonstrating vasodilation due to increased parasympathetic activity. Although the mechanisms underlying these changes in autonomic functions are not currently well understood, it appears that IRT is a useful method of quantifying surface temperature changes associated with increased or decreased blood flow in the superficial capillaries surrounding the eye that are under autonomic nervous system control. The methodology for analyzing the IRT data was based on the methods used by previous IRT non-human research.[58] The temperature of the skin surrounding each eye was collected for 1) a point directly above the thickest part of the eyebrow toward the midline of the face, and 2) a point associated with the tear duct

on the inside corner of the eye. The temperature of each entire eyeball was collected in the form of 1) the average temperature of the ellipse associated with the eyeball and 2) the maximum temperature within the ellipse associated with the eyeball. Total body temperature was taken using a standard ear thermometer.

Statistical analysis

Data were analyzed using SPSS version 19 (SPSS Inc, Chicago IL, USA). Descriptive statistics (frequencies, means, and medians,) were generated, as appropriate, to describe pain intensity, frequency, and type as well as the way in which pain interferes with daily life. Means and standard deviations were calculated for the subscale scores on the BOPS (vocal/social, facial, body and limbs, and physiological) and an analysis of variance (ANOVA) was conducted to determine if pain was expressed more among some pain subscales than others. Means and standard deviations were calculated for each pain coping subscale (Cognitive self-instruction, Distraction, Problem Solving, Seeks Social Support, and Catastrophizing/ Helplessness) and an ANOVA was calculated to determine if coping was demonstrated significantly more within some coping subscales than others.

A series of analyses were conducted to explore the relationship between pain and self-injurious behavior (SIB) in individuals with NCL. Mean pain intensity (sum of pain intensity scores [0-10] for each type of pain reported) and mean pain expression scores (BOPS total score) for pain in the previous week are reported for 1) individuals with moderate SIB, and 2) individuals with mild or no SIB. An independent samples t-test was used to determine if the means differed significantly between SIB groups. A non-

parametric correlation was used to explore the degree to which pain intensity and pain expression in the previous week were related to degree of SIB without assuming normality. Finally chi square analyses were conducted to determine if there were differences in pain intensity and pain expression between individuals who had more severe SIB and individuals who had mild or no SIB. For the chi square analyses the cut score for dichotomizing self-injurious behavior was made based on the participant having at least one topography of self-injurious behavior reported to be a moderate problem. The cut score for dichotomizing pain intensity and pain expression was based on the individual having a pain score at or above the 75^{th} percentile. Finally, to determine if individuals with moderate SIB were more reactive to the sensory test compared to individuals with mild or no SIB, an independent samples t-test was used to determine if pain expression (total BOPS score) differed significantly between the two groups.

Two outcome measures were used (BOPS, IRT) to determine if individuals with NCL were reactive to the two types of sensory stimuli (light touch [baseline], repeated Von Frey monofilament test [partial test of central sensitization]). The IRT data was analyzed using two different approaches; creating, 1) a mean temperature score for each participant (IRT sites collapsed), and 2) a mean temperature score for each IRT site on the face/eyes (individual participant data collapsed). BOPS total scores (observational measure of pain expression) were calculated for each participant during the light touch condition and the repeated Von Frey monofilament condition. A repeated measures t-test was conducted to determine if the change in BOPS scores were significant from one sensory test to the other. IRT data was analyzed first by calculating mean temperature

scores (IRT face/eye sites collapsed) for each participant. A repeated measures t-test was conducted to determine if the mean temperature change in IRT was significantly different between the light touch and the repeated Von Frey monofilament conditions. Second, mean temperature scores were calculated for each IRT site on the face and eyes (individual temperatures collapsed). A repeated measures *t*-test was conducted to determine if the change in IRT temperature at each site was significantly different. The same calculations described above were also done for the sibling comparison group.

In order to compare sensory reactivity between groups (NCL, sibling comparison group); first, an independent samples *t*-test was conducted to determine if individuals with NCL were more or less reactive (BOPS) across both sensory testing conditions (light touch, repeated Von Frey) combined compared to the sibling comparison group. Second, difference scores were calculated for both outcome measures (BOPS, IRT) to determine if individuals with NCL reacted differently to each sensory stimuli (light touch, repeated Von Frey) compared to the sibling comparison group. Means and standard deviations were calculated for the difference scores. Finally, independent samples *t*-tests were conducted to determine if the difference scores of each outcome measure (BOPS, IRT) were significantly different between the two groups (individuals with NCL, sibling comparison group).

Movement artifacts in the IRT data meant that for some participants not all eight IRT sites included usable data. Any missing IRT temperatures were replaced by the mean temperature for that IRT site based on temperature scores from participants in the same group (NCL, sibling). For one participant with NCL there was no usable IRT data

available during the light touch condition due to excessive movement, therefore this participant was excluded from individual IRT analyses.

Results

Pain Experience of Individuals with NCL

Pain experience was determined based on parent reported questionnaires. One parent did not return the questionnaires. Parents reported that their child with NCL experienced pain about once a week (n=3), almost every day (n=2), and every day (n=2). Parents reported that their child's pain severity was less than other children (n=3), about the same as other children (n=2), and more than other children (n=2). Parents reported the type and intensity of their child's pain (see Table 1). Pain interfered most with enjoyment of life (*M*=2.86, *SD*=4.02), mood (*M*=2.71, *SD*= 3.30), sleep (*M*=2.43, *SD*=3.40), and social abilities (*M*=2.43, *SD*=3.55). BOPS mean scores (based on a 1-week recall) were calculated for each subscale of the BOPS based on the subscale categories used in the NCCPC-R from which the BOPS was derived. There was a significant main effect of pain expression type on the degree of pain reported [$F(3, 24)= 4.77$, $p= .01$]. Tukey's post hoc comparisons indicated that individuals with NCL used significantly more Vocal/Social pain behaviors (*M*= 6.29, *SD*= 3.68), than Body and Limbs (*M*= 2.43, *SD*= 2.51, $p < .05$) or Physiological (*M*= 1.29, *SD*= 0.95, $p < .01$) pain behaviors. The Facial subscale did not differ significantly from the other groups (*M*= 3.14, *SD*=2.48). Based on the cut off scores established for individual total scores reported on the BOPS, there is a

94% chance that 5 participants were experiencing moderate pain, and an 80% chance that one participant was experiencing severe pain in the previous week.

Participants were most likely to cope by seeking social support (*M*= 4.86, *SD*= 3.48). This subscale included items that describe the child seeking comfort from parents, peers, or others, such as "asks for a hug" and "has a parent or friend with him/her". Participants were least likely to cope using cognitive self instruction (*M*= 2.00, *SD*= 2.08) which includes items that involve the child dealing with the pain cognitively such as "Pretends that he/she doesn't have any pain" and "knows that he/she can do something to make his/her pain feel better". There was no significant effect of coping style in individuals with NCL between the five coping styles [$F(4,30)= 0.98$, $p= .43$].

The Relationship between Pain and SIB in NCL

On the self-injurious subscale of the RBS-R three participants were reported to engage in some form of SIB. One participant had occurrences of skin picking that were considered to be a mild problem. A second participant had occurrences of hitting self against a surface or object that was a mild problem and had occurrences of skin picking that were considered to be a moderate problem. A third participant had occurrences of biting self, pulling hair or skin, and poking self (eye-poking, ear-poking) that were considered to be mild problems as well as rubbing or scratching self and skin picking, which were considered to be moderate problems. Individuals with NCL were grouped according to the severity of their SIB. The first participant described had mild SIB and was grouped with the participants who had no SIB to make up the mild or no SIB group.

The second and third participants described each had SIB considered to be a moderate problem so these two participants made up the moderate SIB group. The two participants with moderately severe SIB had non-significantly higher pain intensity scores (M= 11.00, SD= 2.83) compared to individuals who had mild or no SIB (M= 6.00, SD= 9.17; $t(5)$= -.72, p= .50). Individuals with NCL who had moderate SIB showed significantly more pain expression (M= 22.50, SD= 9.19) in the previous week compared to individuals who had mild or no SIB (M= 9.40, SD= 4.16; $t(5)$= -2.82, p< .05). The occurrence of moderately severe SIB was significantly correlated with pain expression (r= .80, p< .05), but not pain intensity (r= .48, p= .27). Similarly, pain expression (X^2= 7.00, n=7, p< .05) but not pain intensity (X^2= 3.73, n= 7, p= .52) was significantly related to moderately severe SIB. Pain reactivity during sensory testing was non-significantly greater for individuals with moderate SIB (M= 12.5, SD= 12.02) compared to those with mild or no SIB (M= 7.40, SD= 9.99; $t(5)$= -.59, p= .58)

Pain Reactivity of Individuals with NCL

Seven participants with NCL had elevated BOPS scores during the light touch condition and five of those participants showed an increase in pain behavior during the repeated monofilament stimulus. One participant showed no pain behaviors during either condition and one participant showed the same frequency of pain behaviors during both conditions and one participant showed fewer pain behaviors during the repeated monofilament compared to light touch. Overall mean BOPS score increased from the light touch condition (m = 4.5, SD = 4.41) compared to the repeated Von Frey (m = 7.25,

SD = 6.80) condition, however this change was not significant (*t*(7)= -1.50, *p*= .18). Overall mean temperature for each participant increased from the light touch condition (*m* = 91.57, *SD* = 7.18) compared to the repeated Von Frey (*m* = 92.67, *SD* = 5.42) condition, however this change was not significant (*t*(6)= -.55, *p*= .60). Mean scores for all IRT sites (above eye brow, tear duct, eye maximum, eye minimum) on both the left and right sides significantly increased from the light touch condition (*m* = 91.57, *SD* = 1.24) to the repeated Von Frey (*m* = 92.67, *SD* = 1.09) condition; (*t*(7)= -6.75, *p*<.001).

Pain Reactivity of Sibling Control Group

The sibling group showed very few pain behaviors during both the light touch and the repeated monofilament conditions. For the sibling group the overall mean BOPS scores increased non significantly from the light touch condition (*m* = 0.38, *SD* = 0.52) compared to the repeated Von Frey (*m* = 0.88, *SD* = 1.46) condition; (*t*(7)= -0.88, *p*= .41). Overall mean temperature for each sibling participant decreased slightly from the light touch condition (*m* = 96.31, *SD* = 2.64) compared to the repeated Von Frey (*m* = 96.22, *SD* = 1.45) condition; this change was not significant (*t*(7)= 0.07, *p*= .94). For the sibling group the mean scores for all IRT sites (above eye brow, tear duct, eye maximum, eye minimum) on both the left and right sides decreased slightly but not significantly from the light touch condition (*m* = 96.31, *SD* = 1.02) compared to the repeated Von Frey (*m* = 96.22, *SD* = 0.99) condition, (*t*(7)= 1.16, *p*= .28).

Pain Reactivity of individuals with NCL Compared to Sibling Control Group

Across combined conditions (light touch, repeated Von Frey), individuals with NCL were significantly more reactive (BOPS total score) to sensory testing (M= 9.25, SD= 9.17) compared to individuals in the sibling comparison group (M=1.25, SD=1.49; $t(7.37)= 2.43$, $p< .05$).

The mean BOPS scores for the participants with NCL and siblings are depicted in Figure 1(a & b). The difference scores between conditions were calculated for participants with NCL (m = -2.75, SD = 5.20) and siblings (m = -0.50, SD = 1.60). The difference scores were not significantly different between groups ($t(14)= 1.17$, $p= .26$; Figure 1c).

The total body temperature (measured with a standard ear thermometer) of individuals with NCL (m = 97.6, SD = 0.93) did not differ from the sibling comparison group (m = 97.8, SD = 0.99; $t(14)= -0.36$, $p= .72$). The mean IRT temperatures for each individual participant within each condition (light touch, repeated Von Frey) are depicted in Figure 2 (a & b). For this calculation temperatures for all eight IRT sites were collapsed into one mean temperature for each individual participant. The difference scores between the two conditions for all participants were calculated for the participants with NCL (m = -1.09, SD = 5.29) and siblings (m = 0.09, SD = 3.45); with no statistically significant difference ($t(13)= -0.52$, $p= .61$; Figure 2c). The mean IRT temperatures for each IRT site (above eye brow, tear duct, eye maximum, eye minimum for each side of the face) are depicted in Figure 3 (a & b). For this calculation temperatures for all participants were collapsed into one mean temperature for each IRT site. The difference scores between the two conditions for all IRT sites were calculated for the participants

with NCL (m = -2.00, SD = 0.97) and siblings (m = 0.13, SD = 0.26) and were significantly different ($t(14)$= -5.98, p<.001; Figure 3c).

Discussion

The results presented here indicate that individuals with NCL experience a great deal of pain from multiple sources (musculoskeletal, gastrointestinal, headache, daily living pain) and with significant intensity. Considering medication is typically administered in a clinical setting when pain intensity is rated 4 out of 10, the multiple pain intensity ratings for individuals with NCL of well over 4/10 are alarming. The frequency of pain is also disconcerting given that no participant was reported to have pain less than once a week. Pain was clinically significant enough that it interfered with daily activities especially enjoyment of life, mood, sleep, and social abilities.

The BOPS scores demonstrated that individuals with NCL do show observable signs of pain that can be quantified by parents as well as researchers who are unfamiliar with the individual. BOPS scores calculated based on a one-week parent recall were above the cut off score for moderate or severe pain for six of the seven participants who completed the BOPS. Further, BOPS scores were elevated during the light touch portion of the sensory test. This suggests that individuals with NCL are living with ongoing pain that at least in this sample has not been well controlled. The positive is that this pain was quantifiable using the BOPS and therefore this measure may helpful when used by caregivers and healthcare providers to determine when an individual with NCL is in pain and provide a strong rationale for administering treatment for that pain. The effectiveness

of the treatment provided can be determined based on a subsequent decrease in BOPS total score.

Individuals with NCL who had moderately severe self-injurious behavior showed significantly more pain expression in the previous week compared to individuals with NCL who did not self-injure. While this is counter-intuitive to the conventional belief that individuals who self-injure are insensitive or indifferent to pain, this result is in line with recent research suggesting that other populations with cognitive and communication limitations who self-injure show signs of increased sensitivity to pain. [46, 59-61] Recent findings in individuals with neurodevelopmental disabilities suggest that at least some individuals who self-injure may be in a neuropathic-like pain state.[61] The repeated tissue damage may elicit inflammatory, immune, and nociceptive system activity that contribute to pain hypersensitivity.[61] Given that individuals with NCL demonstrated an elevated pain response to the light touch stimulus further suggests that some individuals with NCL may be hypersensitive to pain.

Individuals with NCL were most likely to cope by 'Seeking Social Support' which is considered in the typical population to be a negative form of coping that is associated with greater pain suffering;[48] however, research with other populations with cognitive and communication limitations have also shown a preference for this style of coping.[51,52] Seeking social support may be an effective means of coping for individuals who are limited in their ability to care for themselves and who may lack the cognitive ability to use other more difficult coping strategies such as cognitive self-instruction and distraction.[62]

Combined pain expression scores across both sensory tests (light touch, repeated Von Frey) demonstrated that individuals with NCL were significantly more sensitive and reactive to tactile stimuli compared to the sibling comparison group. This elevated sensitivity is another indicator that not only are the nerve fibers of individuals with NCL intact, they may actually be hypersensitive to touch. This evidence opposes a belief held by some that individuals with cognitive limitations are insensitive or unresponsive to pain.[59] Other recent research studies including tactile sensory testing have also demonstrated observable responsiveness in similar populations.[38-40]

The repeated Von Frey monofilament was used as a test of temporal summation; an increased pain perception to a repetitive nociceptive stimulus.[31, 32] Based on BOPS scores, individuals with NCL showed greater reactivity to the repeated Von Frey monofilament compared to the sibling comparison group. For four individuals with NCL the BOPS total score during the repeated Von Frey test was great enough (>4) that the individual would be considered to be in pain according to the cut off scores for the BOPS. This is surprising given that the 60g monofilament is not typically considered to be a nociceptive stimulus. Individuals with NCL also reacted differently compared to the sibling comparison group according to IRT outcomes. Those with NCL showed a significant increase in temperature on all face and eye IRT sites whereas siblings showed a slight decrease in temperature. Although IRT has not been used to measure sensory reactivity in humans, in the animal literature an increase in eye temperature was documented in cattle during castration, a procedure known to be associated with deep visceral pain.[58] The authors suggested this may demonstrate vasodilation associated with

increased parasympathetic activity. Whether there is or was altered parasympathetic activity among this NCL sample was unknown.

The test of temporal summation was used as a proxy for central sensitization. Central sensitization results when repeated or long term pain experience results in increased neuronal responsiveness.[64] Central sensitization has previously been associated with chronic and widespread pain conditions.[33-35] The increased pain expression and change in autonomic function during the repeated application of the Von Frey filament, a partial test of central sensitization, further suggests that the pathophysiology of the ongoing pain individuals with NCL are living with is likely centrally not peripherally mediated. Given that activation of astrocytes and microglia is associated with neuron loss and the progression of NCL and that the specific biology of these cells are suspected to be altered, [3] it is interesting to consider that astrocytes and microglia are activated during spinal nociceptive transmission and central sensitization.[65,66] Microglia and astrocytes are known to play a key role in neuropathic and inflammatory pain, respectively. When activation of these specific cells in the spinal cord is blocked the development of allodynia and hyperalgesia is delayed or prevented.[67-71] In a rat model it has been shown that glia-mediated central sensitization is a mechanism for pain hypersensitivity.[72] The current research specifically associating microglia and astrocytes with central sensitization has only been conducted in animal models; however, this basic science does provide insight into the possibility that the glial cell activation associated with the natural course of the disease may predispose individuals with NCL to develop pain of central origin.

Limitations

The study has several limitations. First, the results presented here are based on a small sample size of convenience that may not be representative of all children and adolescents living with NCL and so the results are specific to the sample; however, this issue is difficult to overcome given the rarity of the disease and how dispersed the individuals with this disease are across the country. Sensory testing requires being physically present with the participants so mailing and telecommunication with families was not an option for this study. Second, although the BOPS shows promise for use with individuals with NCL and is derived from a well validated scale (NCCPC-R) [73] there is limited data demonstrating the reliability and validity of this tool beyond the initial test group.[41] Further, the initial validation of the BOPS was scored after a 10 minute observation period whereas in this study the BOPS was scored after a brief 2-5 minute observation period. The BOPS has not previously been validated for shorter observation times; however the NCCPC-R (from which the BOPS was derived) has been shown to be valid and reliable for observations as short as 5 minutes in length.[74] Third, IRT was used in a preliminary way to identify possible changes in autonomic function; however, the mechanisms underlying the changes demonstrated in this study are not well understood at this time. Fourth, the data presented here are not confirmatory but are preliminary and descriptive and intended to provide the first steps toward characterizing pain experience and potential sensory differences in individuals with NCL.

Implications

The methodology of this study used a novel approach to quantify pain experience and expression in individuals with compromised cognitive and language abilities with NCL. While self-report is often considered the 'gold standard' in pain research in typical populations, [75] this type of pain reporting is either unfeasible or unreliable due to cognitive and language limitations.[76] Research in similar populations often relies solely on parent proxy report. Considering the self-report of pain relies on one's own ability to determine an internal state, it seems unlikely that parents are always able to determine the internal state of their child.[77] Further, parent ratings may be biased because of parent-related factors (i.e., stress, depression, guilt) that likely influence reporting. This study, along with other resent research, [36,37,39,40] demonstrates that there are objective methods of testing the sensory reactivity as an indirect non-invasive method to explore underlying sensory nerve fiber function.

The clinical application of this study suggests that clinicians and caregivers must consider that individuals with NCL likely experience a great deal of pain that likely worsens with the progression of the disease. The results presented here suggest that this pain may be chronic and of a central rather than peripheral origin, making treatment more challenging. The BOPS was shown to be able to detect pain expression in individuals with NCL and seems to be useful when completed by parents and also by those who are unfamiliar with the individual. This may prove to be a valuable tool for use at home and in healthcare settings to identify and measure pain and determine the effectiveness of treatment approaches aimed to improve comfort of individuals with NCL.

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Table 1: Parental endorsement of pain type and intensity (n=7).

Pain Type	Number of participants experiencing this type of pain (n=)	Median Intensity
Musculoskeletal pain	5	6.5
Gastrointestinal pain	5	6.5
Headache pain	4	2
Everyday pain	4	1
Seizure pain	2	3.5
Equipment related pain	2	3.5
Daily living	2	4

Figure captions

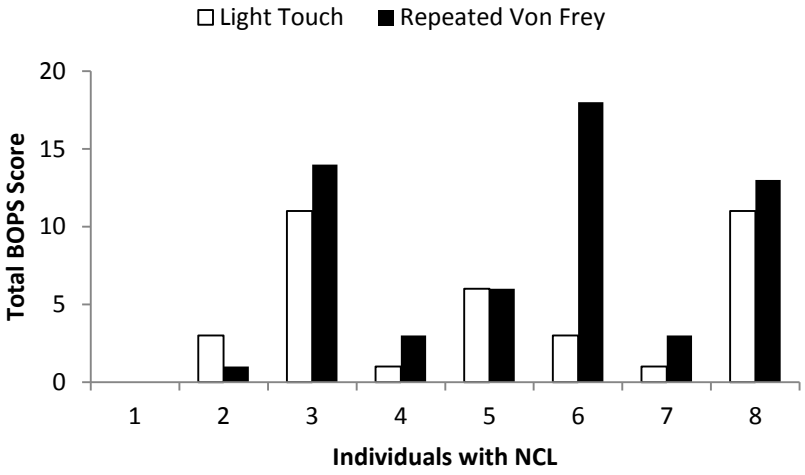
Figure 1: Total BOPS scores depicting pain expression in each of the two sensory testing conditions (light touch, repeated Von Frey) are shown for (a) individuals with NCL, and (b) the sibling comparison group. Difference scores were calculated between participant groups (c) to demonstrate how these groups differed in pain expression.

Figure 2: Mean IRT temperatures for each participant during each of the two sensory testing conditions (light touch, repeated Von Frey) are shown for (a) individuals with NCL, and (b) the sibling comparison group. Difference scores were calculated between participant groups (c) to demonstrate how these groups differed in IRT temperatures across participants.

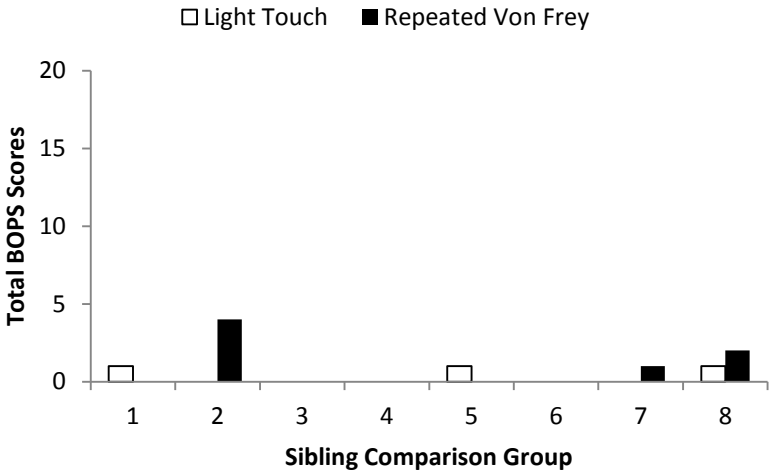
Figure 3: Mean IRT temperatures for each IRT site during each of the two sensory testing conditions (light touch, repeated Von Frey) are shown for (a) individuals with NCL, and (b) the sibling comparison group. Difference scores were calculated between participant groups (c) to demonstrate how these groups significantly differed in IRT temperatures for eye and face sites ($p < .001$).

Figure 1: Pain expression during sensory testing

a)



b)



c)

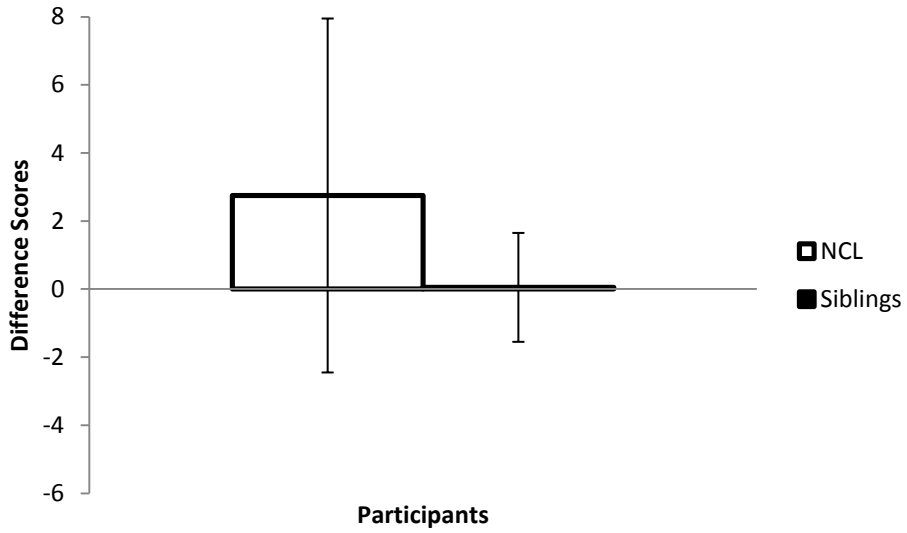
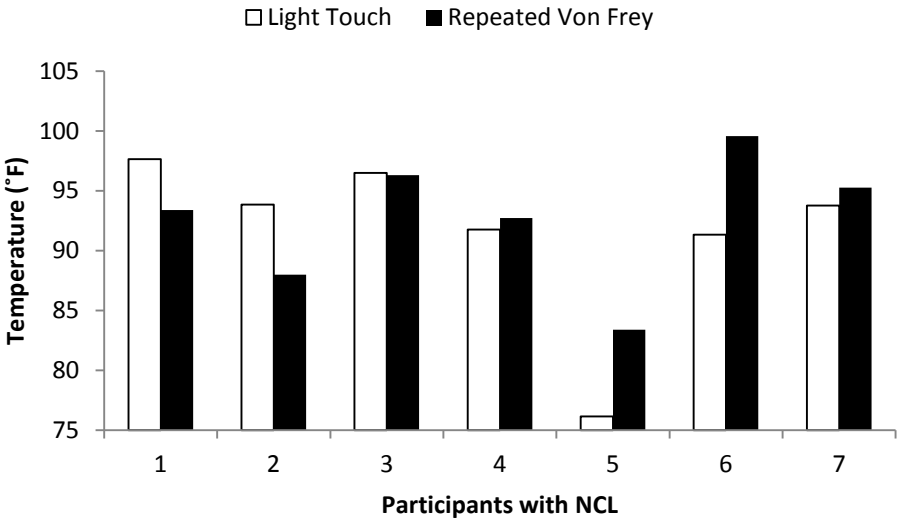
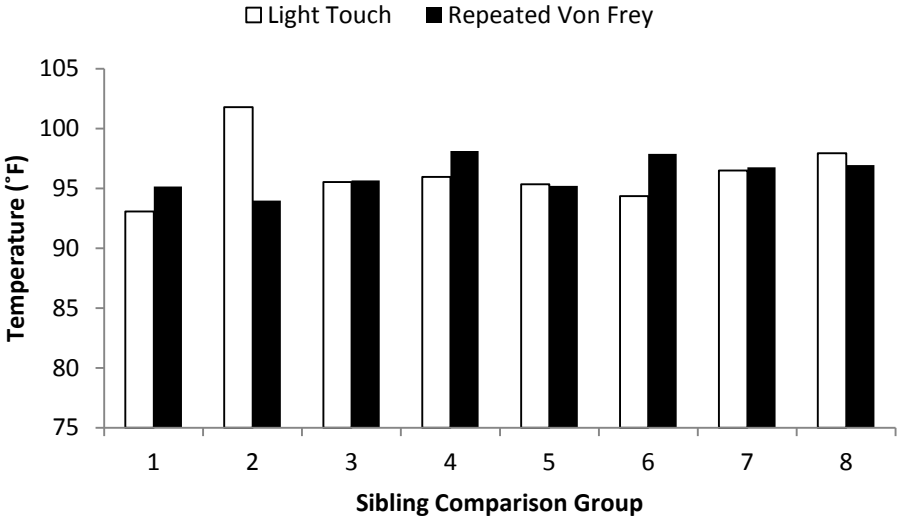


Figure 2: IRT participant temperatures during sensory testing

a)



b)



c)

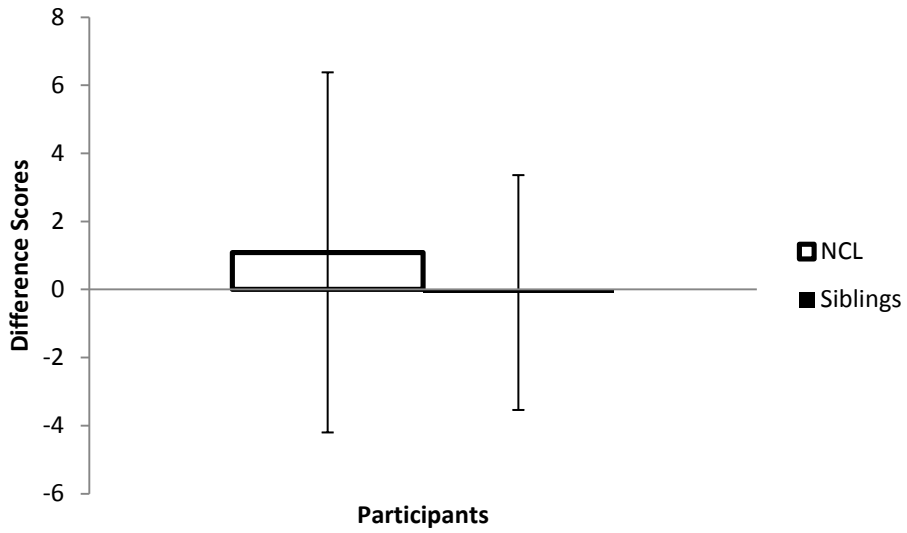
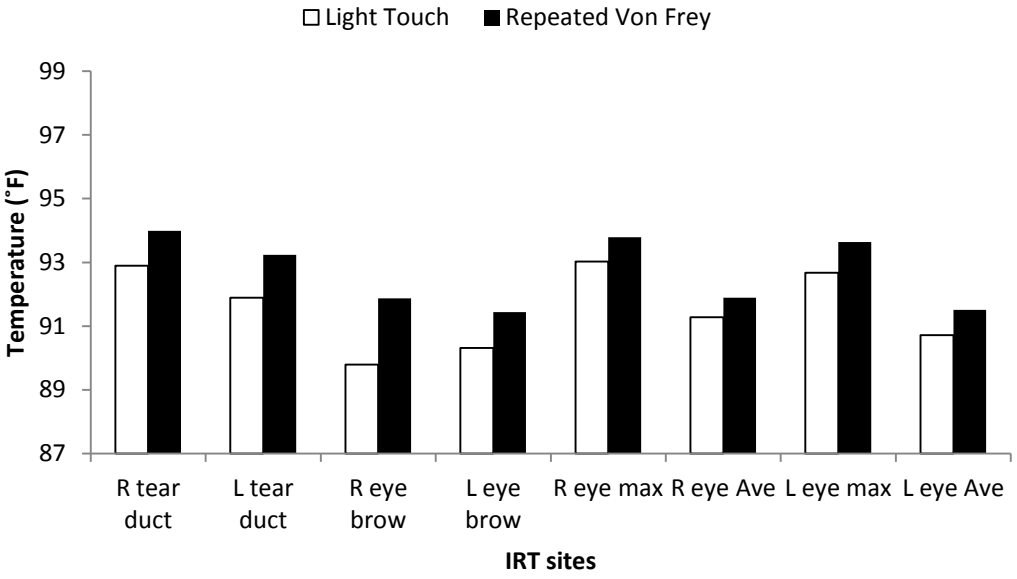
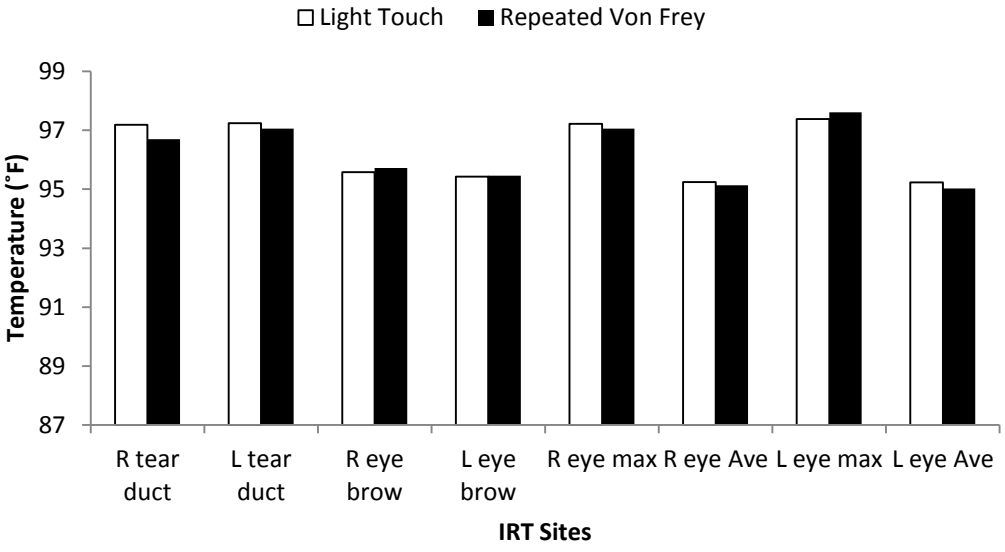


Figure 3: IRT site temperatures during sensory testing

a) Participants with NCL



b) Sibling Comparison Condition



c)