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Increased pain sensitivity and pain-related anxiety in individuals with autism

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Abstract

Introduction: Individuals with autism spectrum disorder (ASD) often exhibit differences in pain responsivity. This altered responsivity could be related to ASD-related social communication difficulties, sensory differences, or altered processing of pain stimuli. Previous neuroimaging work suggests altered pain evaluation could contribute to pain-related anxiety in ASD.

Objectives: We hypothesized that individuals with ASD would report increased pain sensitivity and endorse more pain-related anxiety, compared to typically developing controls.

Methods: We recruited 43 adults (ASD, n = 24; typically developing, n = 19) for 3 heat pain tasks (applied to the calf). We measured heat pain thresholds using a method of limits approach, a pain-rating curve (7 temperatures between 40 and 48°C, 5 seconds, 5 trials each), and a sustained heat pain task with alternating low (42°C) and high (46°C) temperatures (21 seconds, 6 trials each). Individual differences in pain-related anxiety, fear of pain, situational pain catastrophizing, depressive symptoms, and autism-related social communication were assessed by self-report.

Results: There were no group differences in pain thresholds. For suprathreshold tasks, mean pain ratings were higher in ASD across both the pain-rating curve and the sustained heat pain tasks, but responses in the ASD group were more varied. Pain anxiety (PASS-Total) and pain-related fear (FOP-III-Total) were higher in the ASD group and were positively associated with pain ratings.

Conclusions: Our results suggest that both sensory and cognitive experiences of pain are heightened and interact reciprocally in adults with ASD. Future studies are needed to evaluate the impact of pain-related anxiety on treatment-seeking and pain behaviors, given higher levels of pain-related anxiety in ASD.

Keywords: Pain, Autism, Anxiety, Psychophysics

1. Introduction

Autism spectrum disorder (ASD) is characterized by social communication difficulties and restricted and repetitive

behaviors.[2] Insensitivity to pain is used as an example of sensory sensitivity in the diagnostic criteria for ASD,[2] and clinicians have described "reduced pain sensitivity" in ASD[5,23] since the earliest clinical report.[31] Furthermore, the presence of self-injurious behaviors in most individuals with ASD has also led to an assumption of reduced pain sensitivity.[53] There is a paucity of empirical pain research in ASD, yet recent data suggest children with ASD experience more painful conditions compared to their peers.[61] Complicating pain assessment in ASD is the fact that verbal, self-report of pain is still the "gold standard," thus, for individuals with ASD or similar communication difficulties, accurate assessment of pain can be challenging. As pain is a complex sensory, emotional, and social experience,[12] there are many possible reasons for altered pain behaviors and responses in ASD.

Recent reviews of acute pain in ASD highlight contradictory data from observational, parent-report data, and the few experimental studies.[40,57] Most studies in ASD have only assessed pain thresholds (with mixed results[7,8,16,19,52,56]). Two recent studies investigated temporal summation and central pain modulation in ASD, suggesting both excitatory and inhibitory mechanisms may be intact in ASD.[15,56] Our previous functional magnetic resonance imaging work investigated responses to sustained heat pain in verbal adults with ASD.[17] In that study, neural responses were initially intact but dramatically diminished

before the end of the painful stimulus, even while participants continued to report pain. This response was observed across pain-related somatosensory (thalamus, primary and secondary somatosensory regions) and emotional processing brain regions (insula, dorsal anterior cingulate). Intact early responses suggest similar processing of pain intensity, but diminished late responses to pain could reflect altered pain coping or evaluation in ASD.[41] This temporally unique neural response to pain could in part account for the coexistence of both hyporesponsiveness and hyperresponsiveness to pain in ASD.[40] Yet, it remains unclear whether reactivity differences reflect sensory vs communication symptoms. Given limited evidence of altered pain thresholds in ASD, yet temporally distinct neural responses to sustained painful stimuli, we investigated pain responses in verbal adults with ASD in 3 temporally different pain stimuli, ranging from less than a second to 21 seconds for each presentation.

In the current study, we also assess pain-related anxiety and depressive symptoms with the hypothesis that increased negative affect could result in more pain sensitivity in ASD. Both anxiety[29,43,60] and depression[29] are highly comorbid in ASD, and recent data suggest affective states in ASD can predict pain behaviors[22] similar to other populations.[4,35] As our previous neuroimaging study demonstrated different neural responses to later phases of pain processing,[17] consistent with emotional processing of pain, this could be a possible mechanism for altered pain evaluation in ASD that could contribute to pain-related anxiety. We also examined autism-related social communication difficulties, which could directly impact pain reporting and contribute to anxiety about painful events. Because we expanded this study beyond pain thresholds to assess targeted psychophysics of pain and pain-related symptoms specifically relevant to ASD, this study represents one of the richest characterizations of pain responsivity in ASD to date.

2. Methods

2.1. Participants

The Vanderbilt University Medical Center Institutional Review Board approved this study. All participants provided informed consent before participating in the study. We recruited 24 participants with an ASD and 19 participants in a typically developing comparison (TD) group. Participants were recruited from the community, using posters and social media postings, as well as from a pool of participants from previous studies in the lab, all who consented to be recontacted. All participants had a full-scale intelligence quotient (IQ) > 70, as measured by Wechsler Abbreviated Scales of Intelligence—Second Edition.[59] All ASD diagnoses were confirmed by the judgment of a licensed clinical psychologist based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria and research-reliable administration of the Autism Diagnostic Observation Schedule—Second Edition-2.[36] TD individuals were excluded if they had a history of any psychiatric or learning disorder or had a first-degree relative with ASD. All participants had normal or corrected-to-normal vision. For all participants, exclusion criteria included genetic conditions, neurological disorders, significant head injuries, current chronic pain (defined as significant daily to near-daily pain for more than 3 months), or current prescribed medication for pain.

2.2. Heat pain testing

For all testing that required a pain rating, participants rated their pain immediately after each trial using a visual analogue scale

(VAS) (No Pain, Worst Pain anchors). Given the potential influence of social communication difficulties associated with ASD, all VAS ratings were collected on a laptop to minimize social interactions during pain ratings, with specifically less verbal conversation and eye contact because these may be stressors for individuals with ASD.[25] The VAS was programmed to appear with PsychoPy v1.85.3.[45] Participants used a Current Designs (Philadepia, PA) scroll click response device connected to a laptop to move a tick mark across the VAS line. The tick mark was initialized at "No Pain"; participants had to push the scroll wheel down to respond, thus, "No Pain" was never recorded without a response from the participant.

Heat pain was administered using a Peltier stimulator (30 × 30 mm thermoconducting surface; TSA II, Medoc, Ramat Yishai, Israel) to the side of the calf, alternating legs, starting on the left calf, alternating legs for each task. To manage anxiety regarding the pain testing, before any testing, participants were instructed that the thermode "*will heat up and cool down to different temperatures. It has safety mechanisms that control these temperatures. Some temperatures in these tasks may be painful to you, but none of the temperatures you will feel can cause any lasting damage*." Before study testing began, participants were presented with 4 "preview" stimuli for 5 seconds each at 40, 44, 48, and 40°C temperature. This preview was used to ensure that all participants had a full understanding of how the stimuli would feel, ensuring clear consent and high-quality data even from the beginning of the pain testing. The preview was separated from pain testing by 15–45 minutes during which participants filled out surveys. The waiting period was implemented to minimize the effects of the preview on pain testing. Five participants in the TD group did not receive the preview stimuli. The preview phase of the research was added after these participants had been tested and was introduced following recommendations of a panel of ASD self-advocates who were consulted for the study. These 5 participants' pain responses did not differ significantly from the remaining group.

After the waiting period, all participants were tested in the same order: (1) pain thresholds, (2) pain-rating curve, and (3) sustained heat pain task. The preview, pain-rating curve, and sustained pain task were conducted in PsychoPy v1.85.3.[45]

Pain thresholds were determined using a method of limits approach, with 5 trials starting at ambient temperature (32°C) with a 1°C/s ramp rate, up to the maximum of 50.5°C for each trial. The thermode was strapped to the calf for this testing using an elasticated strap fitted with Velcro as instructed within the Medoc TSA II manual. To begin each trial, participants were instructed "*You will hear a beep each time when the temperature begins to change. Please pay attention to this sensation.*" Participants were instructed to respond by button press "*as soon as you feel any pain.*" To reduce anxiety regarding the pain stimulus, participants were told that the temperature would increase gradually, that they could remove their leg at any time, and that responding by button push would stop the heat immediately.

The pain-rating curve was assessed using a method of constant stimuli using 7 temperatures (40, 42, 44, 45, 46, 47, and 48°C), presented for 5 seconds, 5 trials each, in pseudo-andomized order (between consecutive trials, the temperature always differed by >2°C), with a 4-8s intertrial interval. Participants were instructed that they would "*feel a range of temperatures for a short period of a few seconds each.*" The thermode was held to the calf by a research assistant and manually rotated between 5 adjacent sites on the calf to minimize sensitization to the heat stimuli. For the sustained heat pain task, trials with alternating low (42°C) and high (46°C) temperatures (21

seconds, 6 trials each, 30-second intertrial interval) were presented at the same site, with the thermode strapped stationary on the calf. Participants were instructed that they would "*feel a range of temperatures, but these will last a bit longer than the previous experiment, but less than 30 seconds.*" For both the pain-rating curve and sustained pain task, participants rated their pain immediately after each trial using the VAS. For ratings, participants were instructed, "*Pay attention to each temperature. At the end of each temperature, you will be asked to rate your pain on the scale of "No Pain" to "Worst Pain."*"

Although our pain-rating curve task was not designed to calculate a threshold, we performed a post hoc analysis to approximate a threshold from the curve, with the idea that this protocol was similar to a method of constant stimuli approach and could thus be informative to compare with the thresholds derived using the method of limits.[28] For each trial of the pain-rating curve, ratings were binarized (no pain, 0 = 0 VAS; pain, 1 = greater than 0 VAS score), and then for each temperature, the percentage of painful trials was calculated. We then plotted temperature by the percentage of painful responses and fit a sigmoid curve to the data. Heat pain threshold was considered the point of the curve where $y = 0.5$, or 50% of trials were reported as painful. For individuals where a sigmoid curve fit was not applicable, the threshold was considered the midpoint between the lowest temperature at which responses were above 50% and the previously tested temperature. For participants who never found any stimuli painful more than 50% of the time (ie, floor effect), the threshold was approximated as the highest available temperature of 48°C (ASD = 1, TD = 1), whereas those that reported over 50% pain at every temperature (ie, ceiling effect), the threshold was approximated as the lowest available temperature of 40°C (ASD = 7, TD = 1).

2.3. Self-report autism-related traits

2.3.1. Social Responsiveness Scale

All participants were administered the Social Responsiveness Scale (SRS), a 65-question self-reported survey assessing traits relevant for ASD[9] to provide a continuous measure of ASD traits. The psychometric properties of the SRS have been validated in large samples with a one-factor structure and intraclass correlation coefficients for retest reliability of ~0.80.[10]

2.4. Self-report pain questionnaires

2.4.1. Pain Anxiety Symptoms Scale

The Pain Anxiety Symptoms Scale-20 (PASS-20)[1,37] is a 20-item self-report measure of pain-related fear and anxiety, which assesses cognitive anxiety, escape and avoidance, fearful appraisals of pain, and physiological symptoms. Participants are asked how frequently they engage in a range of behaviours when in pain, eg, avoiding activities when hurt. The 4 subscales of the Pain Anxiety Symptom Scale were also calculated: Cognitive, Fear, Avoidance, and Physiological anxiety symptoms. The internal consistency of the total and the subscales is adequate to excellent, Cronbach alpha = 0.67 to 0.92.[1,11]

2.4.2. Fear of Pain Questionnaire-III

The Fear of Pain Questionnaire (FPQ-III)[38] is a 30-item self-report questionnaire to assess fear of different causes of pain. Participants are asked how much they fear the pain associated with a range of injuries, such as breaking one's arm. Score on 3

subscales were also calculated: Severe, Minor, and Medical-related pain. The FPQ-III has an excellent Cronbach alpha ($\alpha = 0.92$) indicating high internal reliability, and good test–retest reliability ($r = 0.74$).

2.4.3. Situational Pain Catastrophizing Scale

Pain catastrophizing was assessed immediately after the sustained pain task using a Situational short form of the Pain Catastrophizing Scale (S-PCS).[39] The S-PCS includes 6 items related to thoughts and feelings while experiencing pain related to magnifying the pain or helplessness during the experience. Participants were instructed to think of the sustained heat pain they had just experienced. This measure has been shown to have a Cronbach alpha of 0.96.[55]

2.4.4. Brief Pain Inventory

Physical pain experience in the 24 hours before pain testing was assessed using the Brief Pain Inventory.[13,54] This measure asks participants to report the nature and intensity of any current pain. The item "pain at its worst in the last 24 hours" has high internal consistency (Cronbach alpha coefficient of 0.77–0.90).[3]

2.5. Depression symptoms

Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI).[6] The BDI consists of 21-items assessing psychological and somatic aspects of depression over the previous two-week period. The BDI was given to participants before any pain testing and was not immediately followed by pain testing. The BDI has an internal consistency, as measured by Cronbach alpha coefficient, of greater than 0.90[14] and test–retest reliability reported from 0.73 to 0.96.[58]

2.6. Statistical analysis

All statistics were run in R v.3.5.2.[50] Parametric and non-parametric tests were considered. Nonparametric tests were used when any of the parametric test assumptions were violated or where nonparametric tests were deemed more appropriate based on variable distribution (kurtosis and/or skewness were evaluated and visual inspection of the distribution). Group differences in demographic variables (age, sex, and IQ) were investigated using a Mann–Whitney test or a χ^2 test where appropriate. Heat pain thresholds were determined by dropping the highest and lowest trials and then averaging the remaining 3 trials.[30] To determine group differences in pain thresholds and in pain ratings from individual conditions from the sustained pain task, we used a Mann–Whitney test. To examine group differences in the pain-rating curve, we fit linear mixed-effects models (using the R package lmerTest, with Satterthwaite degrees of freedom method) with participant as a random effect and temperature as a fixed effect. Linear effects were examined for diagnostic group and a diagnostic group by temperature interaction. Post hoc testing was conducted using a multivariate t distribution correction based on the model's covariance structure (using the R package mvtnorm). Linear models were also fit to each participant's pain-rating curve to extract slope as an individual measure of the pain-rating curve to use in correlations with pain, anxiety, depression, and autism measures. To analyze group differences in the sustained heat task, a two-way analysis of variance (ANOVA) was used, with condition (low and high heat) and diagnostic group as factors, and an interaction between

Study demographics

	ASD (N = 24)	TD (N = 19)	P	Effect size*
Age, mean (SD)	29.29 ± 9.49	30.42 ± 7.44	0.254	−0.206
Gender			0.632	1.601*
Women, n (%)	13 (54)	8 (42)		
Men, n (%)	11 (46)	11 (58)		
Full IQ, mean (SD)	100.46 ± 14.78	109.11 ± 12.76	0.068	−0.329
Verbal IQ, mean (SD)	104.04 ± 13.39	110.42 ± 17.48	0.152	−0.259
Performance IQ, mean (SD)	97.54 ± 19.17	106.26 ± 12.67	0.186	−0.239
Social responsiveness scale, mean (SD)	69.71 ± 9.60	45.74 ± 6.32	**<0.001**	**0.919**
Beck depression inventory, mean (SD)	12.75 ± 8.02	1.71 ± 2.79	**<0.001**	**0.821**

* Cliff's delta is reported, except for gender, where the odds ratio is reported. Bold designates significance of p<0.05.
ASD, autism spectrum disorder.

condition and group was tested. To examine differences in variability of pain ratings within groups during the sustained heat task, Levene test was used. To examine group differences on the PASS-20, FPQ-III, BDI-II, S-PCS, and the SRS-2, we used a Mann–Whitney test. For correlations between variables from psychophysical testing and behavioral data (pain, anxiety, depression, and autism measures), Spearman rho was calculated.

3. Results

This study recruited n = 19 TD participants (8 women and 11 men) and n = 24 ASD participants (13 women and 11 men). In the ASD group, 2 participants were unable to complete any part of the heat pain protocol; both participants declined to continue after the preview of the pain stimuli. In addition, 3 ASD participants and 1 TD participant were unable to complete the pain curve and sustained pain tasks and asked to stop during testing. The final sample size for each heat pain task is reported with each statistical test. There were no significant group differences in age, sex, or IQ (**Table 1**); however, participants with ASD endorsed more depressive symptoms on the BDI compared to TD participants (W = 255, $P < 0.001$). Consistent with an ASD diagnosis, participants with ASD also scored higher on the SRS-2 compared to the TD group (W = 437.5, $P < 0.001$).

3.1. Pain testing

Average pain thresholds derived from the method of limits protocol were not significantly different by diagnostic group (Mean$_{ASD}$ = 47.555 ± 2.607°C, N$_{ASD}$ = 22, Mean$_{TD}$ = 47.556 ± 3.099°C, N$_{TD}$ = 19, w = 204.5, P = 0.916, **Fig. 1**) or by sex (Mean$_{Women}$ = 47.816 ± 1.712, Mean$_{Men}$ = 47.282 ± 3.656, w = 192, P = 0.646). Pain ratings differed by group across a range of temperatures and durations. We analyzed pain-rating curves (pseudorandomized presentation of temperatures for 5 seconds) using a mixed-effects model by including only participants who completed pain-rating curve testing (N$_{ASD}$ = 20, N$_{TD}$ = 17). There were significant main effects of diagnostic group (□ = −0.512, F = 5.34; df = 1,34.78; P = 0.027) and temperature (□ = 0.026, F = 154.9; df = 1,34.8; $P < 0.001$), as well as a significant interaction of temperature*group (□ = 0.014, F = 7.00; df = 1,34.8; P = 0.009, **Fig. 2**), such that pain ratings were higher in the ASD group, specifically in temperatures over 44°C. In contrast to the method of limits-based protocol, approximated pain thresholds calculated from the pain-rating curve data

demonstrated that the ASD group had a lower heat pain threshold compared to the TD group (Mean$_{ASD}$ = 42.463 ± 2.723°C, N$_{ASD}$ = 20, Mean$_{TD}$ = 44.956 ± 2.386°C, N$_{TD}$ = 17, w = 258, P = 0.007, Supplemental Figure 1, available at http://links.lww.com/PR9/A82). There was no significant correlation between heat pain thresholds derived from the method of limits protocol and the post hoc threshold calculation from the pain-rating curve (r = 0.178, P = 0.293).

We also tested if pain ratings were elevated in individuals with ASD in a sustained (21 seconds) heat task with low (42°C) and high (46°C) heat conditions (N$_{ASD}$ = 19, N$_{TD}$ = 18, **Fig. 3**). In a 2-way ANOVA, there was a significant effect of group, where the ASD group reported more pain than the TD group F(1,68) = 8.048, P = 0.006, but there was no significant effect of heat level F(1,68) = 0.107, P = 0.745. There was no significant interaction between diagnostic group and heat level F(1,68) = 2.149,
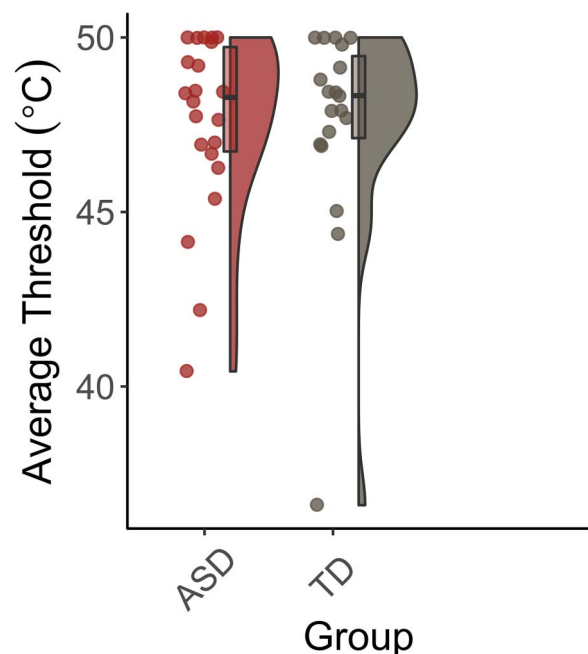
Figure 1. Pain thresholds derived from the method of limits were not different by diagnostic group, Mean$_{ASD}$ = 47.555 ± 2.607°C, N$_{ASD}$ = 22, Mean$_{TD}$ = 47.556 ± 3.099°C, N$_{TD}$ = 19, w = 204.5, P = 0.916. For each group, boxplot of interquartile range, with mean at center line, is overlaid on the group's distribution. ASD, autism spectrum disorder.
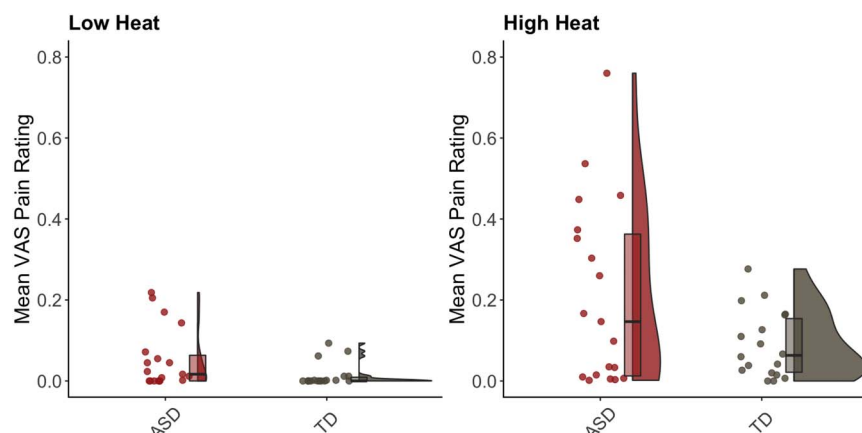
Pain Rating Curve
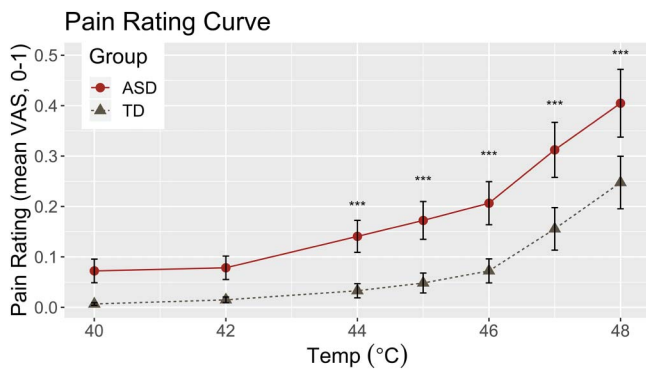
Figure 2. Mean pain ratings during quantitative sensory testing by temperature and group. Error bars represent SEM. Ratings are captured using a VAS, scored on a 0 to 1 scale. Ratings were averaged for temperature, ranging 40 to 48°C. In the mixed effects model, there were significant main effects of diagnostic group ($\beta = -0.512$, $F = 5.34$; $df = 1$, 34.78; $P = 0.027$) and temperature ($\beta = 0.026$, $F = 154.9$; $df = 1$, 34.8; $P < 0.001$), as well as a group × temperature interaction ($F = 7.00$; $df = 1$, 34.8; $P = 0.012$). In post hoc testing, group differences were significant at 44°C, $P = 0.021$; 45°C, $P = 0.015$; 46°C, $P = 0.012$; 47°C, $P = 0.011$; and 48°C, $P = 0.001$; P value adjustment using multivariate t-distribution.

$P = 0.147$. Notably, pain ratings in the ASD group were significantly more variable during both the low (Levene test, $F(1,35) = 4.64$, $P = 0.038$) and high heat trials ($F(1,35) = 10.24$, $P = 0.003$) compared to the TD group. Post hoc testing within group showed that pain ratings were significantly higher during the high heat compared to low heat for both groups: in TD, low heat = 0.014 ± 0.030 and high heat = 0.090 ± 0.08, $t = -3.63$, $df = 21$, $P = 0.002$; and in ASD, low heat = 0.053 ± 0.074 and high heat = 0.211 ± 0.225, $t = -2.90$, $df = 22$, $P = 0.008$.

3.2. Self-report Pain Questionnaires

On the Brief Pain Questionnaire, 7 individuals reported some pain in the last 24 hours (3 TD, 4 ASD). One individual in the ASD group who reported recent pain did not complete the pain testing. Average pain in the last 24 hours ranged from 1 to 6, Mean = 2.50 ± 2.07, whereas pain reported at the time of testing ranged from 0 to 3, Mean = 0.75 ± 1.04.
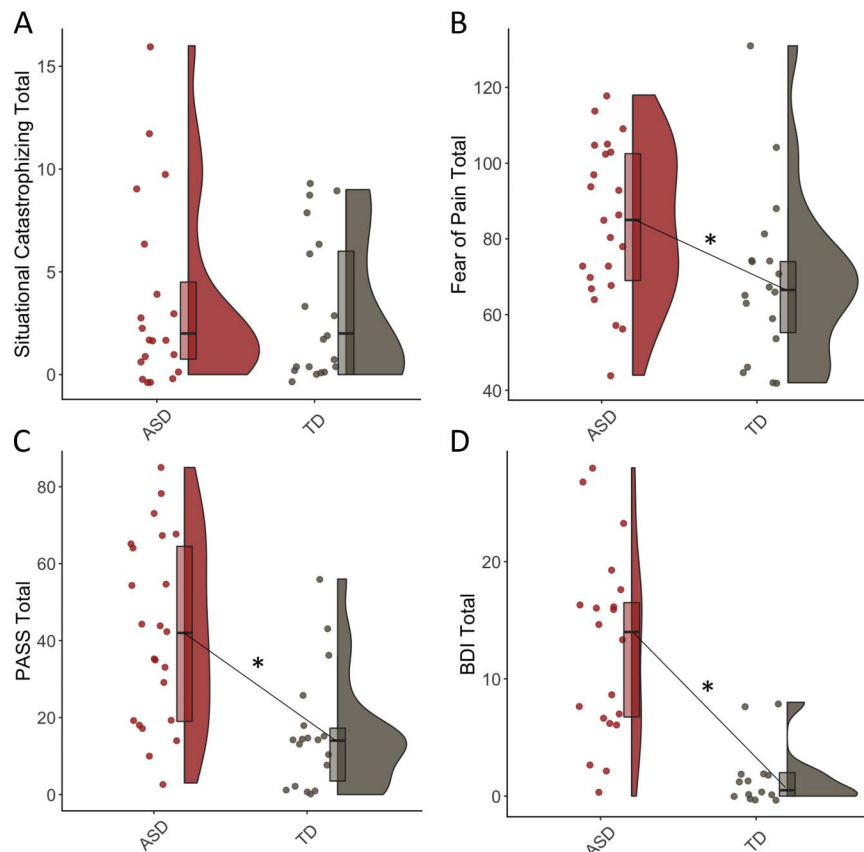
Figure 4 summarizes data from pain questionnaires. There were no group differences in situational pain catastrophizing on the S-PCS ($W = 186.5$, $P = 0.265$). Participants with ASD reported more fear of pain on the FPQ-III ($W = 246.5$, $P = 0.006$) and more pain anxiety symptoms on the PASS-20 compared to the TD group ($W = 279$, $P < 0.001$). Participants with ASD reported more pain-related anxiety across all 4 domains of the PASS-20 but only on the medical subscale of the FPQ-III (**Table 2**).

In a secondary analysis, we explored correlations between psychophysical measures and pain-related anxiety, autism-related social communication, and depressive symptoms (see **Table 3** for all tests). Specifically, we tested individual heat pain threshold, slope from the pain-rating curve, and average pain rating during the low and high heat conditions of the sustained heat pain task. We hypothesized that pain anxiety may explain elevated pain ratings in the ASD group. In the ASD group, more pain-related anxiety symptoms on the PASS-20 were associated with pain threshold, slope from the pain-rating curve (**Fig. 5**), and pain ratings during high heat on the sustained pain task, but were not correlated in the TD group. Depressive symptoms were not associated with any psychophysical testing. Social communication symptoms as measured on the SRS-2 were associated with slope of the pain-rating curve and ratings on the sustained heat across both groups. Situational catastrophizing on the S-PCS was associated with higher slopes on the pain-rating curve and higher ratings during the sustained heat task; these relationships were significant across groups and in the ASD group alone (see **Table 3** for all tests).

4. Discussion

In this study, verbal adults with ASD report more sensitivity to both subthreshold and suprathreshold pain stimuli. Individuals with ASD had elevated pain ratings compared to the typical control group in the pain-rating curve, especially at higher temperatures. In the more sustained pain task, there was a significant effect of group, with individuals with ASD reporting more pain across temperatures. Individuals with ASD also reported more pain-related anxiety compared to the typical group. These results suggest that individuals with ASD may experience more pain-related anxiety and thus, report more pain sensitivity, especially in unpredictable and novel painful situations.

Figure 3. Pain ratings in sustained (21 seconds) heat pain, low (42°C) and high (46°C) heat conditions ($N_{ASD} = 19$, $N_{TD} = 18$). In a 2-way ANOVA, a significant effect of group $F(1,68) = 8.048$, $P = 0.006$, but not heat level $F(1,68) = 0.107$, $P = 0.745$. There was no significant interaction between diagnostic group and heat level $F(1,68) = 2.149$, $P = 0.147$. For each group, boxplot of interquartile range, with mean at center line, is overlaid on the group's distribution. ASD, autism spectrum disorder.

Figure 4. There were no group differences in situational catastrophizing total scores (A, W = 186.5, P = 0.265). Participants with ASD reported more fear of pain (B, W = 246.5, P = 0.006), more pain anxiety symptoms (C, W = 279, P < 0.001), and endorsed more depressive symptoms on the Beck Depression Inventory (D, W = 255, P < 0.001) compared to TD participants. For each group, boxplot of interquartile range, with mean at center line, is overlaid on the group's distribution. ASD, autism spectrum disorder.

Consistent with previous studies,[40,57] we found no differences in pain thresholds in verbal adults with ASD using a method of limits approach. However, pain thresholds calculated using methods of limits depend, in some part, on processing and response times.[28] Psychophysical studies in ASD suggest slowed or variable response times could confound threshold measurements significantly in ASD.[63] Responses to pain threshold testing involve perceptual decisions, influenced by prior beliefs,[62] thus, specific ASD-related slowing of perceptual decisions[26,47] could impact pain thresholds. Several studies report no differences in heat pain thresholds in autism,[16,21,56,65] but none of these studies have used a time-independent method for threshold assessment, nor have they assessed or corrected for individual reaction or processing time differences. We specifically added a pain-rating curve (similar to a method of constant stimuli) task to this study because we hypothesized this method might help differentiate pain reporting in ASD compared to previous approaches, including providing pain ratings to suprathreshold stimuli. Post hoc threshold approximation using this method suggests individuals with ASD could have lower heat pain thresholds that are obscured in method of limits testing. The processing of the stimuli, decision that it should be categorized as painful, and then subsequent reaction time in executing the response may all be slowed in ASD,[34,47] potentially leading to compounded delays. We have previously reported increased intertrial variability in thermal threshold testing using methods of limits in ASD, suggesting potential instability in perceptual processing time.[63] Because our study was not designed to

calculate thresholds with method of constant stimuli, further investigation using this method a priori is needed to support our findings. To reduce the impact of social communication difficulties on pain ratings, we collected ratings on a laptop with no verbal or social component to our pain rating. This was designed to minimize verbal conversation and eye contact during pain testing because these may be stressors for individuals with ASD.[25] Future studies are needed to explicitly test methods of threshold assessment in ASD as well as different pain rating systems to aid pain assessment in this population.

We report increased pain sensitivity in ASD, across a range of temperatures in the pain-rating curve and in sustained heat pain

Table 2

Group differences on subscales of pain anxiety measures.

	ASD (N = 23)	TD (N = 18)	P	Cliff's delta
Pain anxiety symptom scale Subscales, mean (SD)				
Cognitive	14.00 ± 7.19	4.72 ± 5.09	**0.002**	**0.691**
Fear	8.21 ± 6.82	2.72 ± 3.64	**0.007**	**0.495**
Avoidance	10.48 ± 5.95	5.00 ± 4.24	**0.004**	**0.519**
Physiological	9.52 ± 6.22	3.50 ± 3.68	**0.002**	**0.585**
Fear of Pain Questionnaire Subscales, mean (SD)				
Severe	34.61 ± 8.70	30.50 ± 8.79	0.109	0.297
Minor	22.26 ± 7.23	17.83 ± 6.78	0.053	0.357
Medical	27.52 ± 8.37	20.89 ± 8.42	**0.007**	**0.500**

Bold designates significance of p<0.05.

Table 3

Correlations in sample and by group between pain sensitivity and behavioral measures.

	Heat pain Threshold	Pain-rating curve Slope	Sustained heat Low	High
SRS-2				
All	−0.112	0.437†	0.453†	0.386*
TD	0.212	0.131	0.322	0.185
ASD	−0.308	0.516*	0.359	0.565*
BDI-II				
All	0.114	0.268	0.281	0.298
TD	0.055	0.087	0.251	0.191
ASD	0.167	0.161	0.221	0.206
PASS-20				
All	−0.281	0.366*	0.384*	0.455†
TD	−0.081	−0.201	0.118	0.255
ASD	−0.454*	0.626†	0.385	0.590†
FPQ-III				
All	0.056	0.313	0.399*	0.333*
TD	0.231	−0.197	0.265	0.219
ASD	−0.040	0.473*	0.399	0.360
S-PCS				
All	−0.145	0.594‡	0.385*	0.591‡
TD	−0.113	0.309	−0.016	0.355
ASD	−0.124	0.768‡	0.794‡	0.699‡

* Spearman's r. $P < 0.05$.
† Spearman's r. $P < 0.01$.
‡ Spearman's r. $P < 0.001$.
ASD, autism spectrum disorder; BDI, Beck Depression Inventory; FPQ-III, Fear of Pain Questionnaire-III; PASS, Pain Anxiety Symptoms Scale; S-PCS, Situational Pain Catastrophizing Scale; SRS, Social Responsiveness Scale.

Figure 5. Pain-related anxiety (as measured by PASS-Total score) was correlated with the slope from the pain-rating curve in participants with ASD (red line, $r = 0.626$, $P = 0.003$), but not in the TD group (gray line, $r = −0.201$, $P = 0.455$). ASD, autism spectrum disorder; PASS, Pain Anxiety Symptoms Scale.

testing. In the pain-rating curve, there is a main effect of group and temperature, as well as an interaction of group by temperature. This interaction is due to increased pain sensitivity in ASD at higher temperatures, suggesting this group effect becomes magnified during more painful temperatures in the pain-rating curve. In the sustained heat pain test, there is only a main effect of group, but not temperature in the model. We expected a main effect of temperature, and post hoc testing did show a significant effect of temperature within each group. The lack of a temperature main effect in our larger model could be due to significant variation in the ASD group, as we report the variability was significantly higher in the ASD group. The longer stimulus time could allow for potential effects of coping skills or habituation to the stimuli that could be different by diagnostic group. Importantly, in both pain tasks, people with autism consistently report more pain sensitivity. Results from this study suggest that people with autism may be more sensitive to pain, which calls into question previous literature that supported reduced pain responsivity in autism.

We also report evidence of a clinically significant pain anxiety phenotype in autism. Although social communication difficulties likely impact pain behaviors and verbal pain ratings, pain-related anxiety may also be an important component to assess in ASD. Anxiety is a common comorbidity in ASD (estimated 11%–84%),[60] which can heavily impact daily functioning and exacerbate ASD core symptoms.[42] Although general anxiety is highly prevalent, this is the first study to examine pain-related anxiety in ASD. Several studies have documented effects of anxiety on neural processing and reporting of pain.[32,48,64] Pain-related anxiety in ASD could contribute to or arise due to altered neural processing of pain. In ASD, reports of heightened responses in the anterior cingulate during pain anticipation[24] and substantial late phase suppression of the neural pain signature during a painful stimulus[17] are consistent with
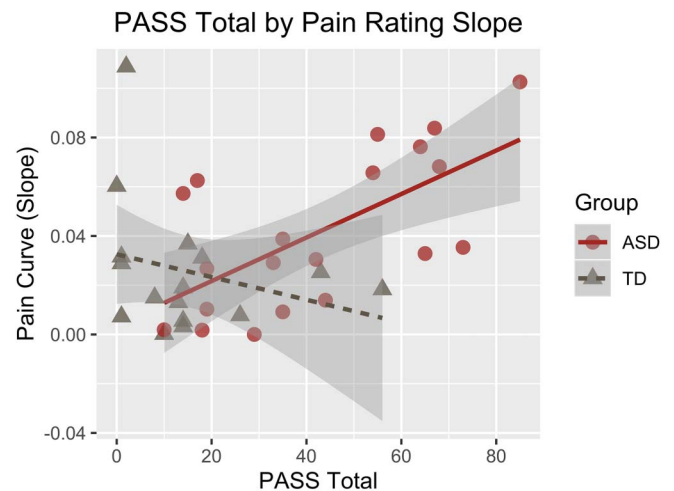
increased pain-related anxiety and varying profiles of pain sensitivity based on the temporal profile of the stimuli as reported in this study. However, specific mechanisms for altered pain-related processing in ASD have not been identified and it is not clear how they might interact with pain-related anxiety in ASD.

Pain-related anxiety in ASD was increased across domains of the PASS-20 and in the medical pain subscale of the FPQ-III. On the PASS-20, items related to ruminative thought patterns in the cognitive domain were often endorsed, which could reflect the increased presence of depressive symptoms reported in our ASD group. Depression is a common comorbidity in ASD.[27,29] Depressive symptoms were not correlated with pain psychophysics in this study, consistent with recent work in ASD.[15] Elevation of fear in the medical subtest of the FPQ-III could be due to several factors. Medical pain often involves either implicit "Receiving stitches..." or explicit "Having an eye doctor remove a foreign particle..." social interactions and can elicit reminders of a complex sensory environment (ie, bright lights), which can be anxiety-inducing for people with ASD.[42,46] Individuals with ASD may also have comorbid medical conditions[18] that could result in painful procedures, perpetuating specific anxieties. Medical pain-related anxiety represents a significant target for interventions in this population. Yet, it will also be critical to assess pain-related anxiety in ASD in the face of comorbid anxiety and depression. Similarly, it is important to note that these pain-related anxiety measures have not been validated in ASD; thus, future work should assess specific population effects.

Pain-related anxiety and situational catastrophizing were associated with pain ratings in the ASD group. We did not observe an association in the TD group; however, anxiety is most related to affective qualities of pain,[35,49] which we did not measure in this study. Our data suggest a consistent effect of anxiety on pain ratings in ASD, regardless of stimulus length. Although we examined pain sensitivity across different temporal stimuli, these methods differed in their predictability. In the pain-rating curve, with shorter stimuli, different temperatures were pseudorandomized and thus, unpredictable to the participant. In the longer, sustained paradigm, low and high temperatures alternated. Given the unpredictability of the pain-rating curve, pain-related anxiety could have elevated ratings more

systematically in the pain-rating curve compared to the sustained pain task. In addition, in shorter time frames, there may be a larger effect of pain-related anxiety and/or anticipation. Pain ratings tend to increase during continuous noxious heat stimuli for the first 10–12 seconds and then may stabilize, increase, or decrease depending on a number of factors.[33] In recent work by Dubois et al.,[15] initial pain ratings during temporal summation were elevated in ASD, which could be consistent with increased pain-related anxiety. Yet, in our longer sustained stimulus, a number of other factors could have contributed to increased variability in the ASD group's pain ratings. Future work will need to compare continuous pain ratings with poststimulus ratings in the ASD population.

The International Association for the Study of Pain highlighted pain in vulnerable populations in their 2019–2020 global year. In populations like ASD, where social communication is difficult, it is critical to develop best practices for pain assessment. This is especially true when clinical assumptions exist that suggest reduced pain sensitivity in people with ASD. This notion likely arose for 2 reasons: (1) salient case reports and anecdotes of moderate to severe injury without a typical pain reaction in children with ASD and (2) the presence of self-injurious behaviors in people with ASD. The presence of self-injurious behaviors has led many to believe that individuals with ASD must have reduced pain sensitivity to engage in highly repetitive, painful stimulation, but recent experimental work contradicts this idea.[51] In fact, empirical studies of pain in ASD tend to report *increased* pain sensitivity[57] and our work adds more data that challenge these old assumptions. Also, because many individuals with ASD have a number of comorbid medical conditions that could cause or exacerbate pain,[18,61] accurate assessment and management of pain is imperative in this population.

There are several points to consider when interpreting this study. This study was conducted with a relatively small sample, and several psychophysical and psychological measures were given to the same individuals. Given the sample size and the heterogeneity in ASD, replication in larger samples is necessary to confirm the findings we report. In fact, there was greater variation in pain ratings in the ASD group compared to the TD group, consistent with previous work in ASD.[15] Heterogeneity in core ASD symptoms could impact this variability. We did not evaluate self-injurious behaviors, but these behaviors could also affect pain sensitivity. Almost half (~45%) of individuals with ASD engage in repetitive self-injurious behaviors; however, the type and severity of these behaviors varies across the ASD spectrum, with more severe and frequent behaviors occurring in individuals with lower cognitive ability than the adults in our sample.[51] Similarly, some participants endorsed pain on the Brief Pain Inventory over the previous 24 hours, but it is not clear how previous acute or chronic pain impacts our findings.

This study offers a significant expansion of pain sensitivity research in ASD and the first study to examine pain-related anxiety and fear in this population. In ASD, pain is likely a complicated phenomenon, with both reduced and increased pain sensitivity across individuals and/or situations without clear mechanisms for these responses. Work in mouse models of ASD demonstrates the potential of peripheral somatosensation as a contributor to aberrant pain behaviors.[44] Yet, from our work, we suggest pain-related anxiety, in light of delayed suppression of neural responses to pain, could reflect altered emotional processing of painful stimuli in ASD. More studies are needed to tease apart effects of primary somatosensory and affect-related effects on pain-reporting in ASD. We also found

evidence that this pain-related anxiety could have a specific medical or social component in ASD, which could have significant effects on treatment seeking behaviors and, thus, a global impact on overall health in these individuals. For example, if individuals with autism decline to seek care early in a condition, this delay could result in increased risk for complications, even for routine or common conditions. In one study of appendicitis presentation, children with ASD tended to present with more complicated cases, suggesting potential barriers in assessing this group for a condition that often is identified by pain.[20] Work is needed to understand the role of social communication difficulties in development of pain-related anxiety in ASD as well as other populations with social communication difficulties.

Disclosures

The authors have no conflicts of interest to declare.

Acknowledgements

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A82.

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