Research Paper

PAIN®

Indifference or hypersensitivity? Solving the riddle of the pain profile in individuals with autism

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Abstract

Excitatory–inhibitory (E/I) imbalance is a mechanism that underlies autism spectrum disorder, but it is not systematically tested for pain processing. We hypothesized that the pain modulation profile (PMP) in autistic individuals is characterized by less efficient inhibitory processes together with a facilitative state, indicative of a pronociceptive PMP. Fifty-two adults diagnosed with autism and 52 healthy subjects, age matched and sex matched, underwent quantitative sensory testing to assess the function of the (1) pain facilitatory responses to phasic, repetitive, and tonic heat pain stimuli and (2) pain inhibitory processes of habituation and conditioned pain modulation. Anxiety, pain catastrophizing, sensory, and pain sensitivity were self-reported. The autistic group reported significantly higher pain ratings of suprathreshold single ($P = 0.001$), repetitive (46°C- $P = 0.018$; 49°C- $P = 0.003$; 52°C- $P < 0.001$), and tonic ($P = 0.013$) heat stimuli that were cross correlated ($r = 0.48$-0.83; $P < 0.001$) and associated with sensitivity to daily life pain situations ($r = 0.39$-0.45; $P < 0.005$) but not with psychological distress levels. Hypersensitivity to experimental pain was attributed to greater autism severity and sensory hypersensitivity to daily stimuli. Subjects with autism efficiently inhibited phasic but not tonic heat stimuli during conditioned pain modulation. In conclusion, in line with the E/I imbalance mechanism, autism is associated with a pronociceptive PMP expressed by hypersensitivity to daily stimuli and experimental pain and less-efficient inhibition of tonic pain. The latter is an experimental pain model resembling clinical pain. These results challenge the widely held belief that individuals with autism are indifferent to pain and should raise caregivers' awareness of pain sensitivity in autism.

Keywords: Pain modulation profile, Pronociception, Pain perception, Autism spectrum disorder, Quantitative sensory testing

1. Introduction

Autism spectrum disorder (ASD) is a developmental disability characterized by social and communication impairments, restricted interests, and repetitive behaviors.[2] It is currently estimated to affect 1 in 44 children in the United States.[52] More than 80% of autistic people experience sensory modulating disturbances,[12,40] a phenomenon which in the general population is often associated with sensory and pain hypersensitivity to daily stimuli.[6,7] Autism etiology is not yet fully understood and is probably related to heterogeneous genomic factors.[13,17,23] Indeed, recently, many genetic variations have been associated with autism, some of which play an important role in the functioning of synaptic and presynaptic proteins, including glutamate and γ-aminobutyric acid (GABA) receptors.[83] Deficiencies in synaptic transmission lead to an excitatory–inhibitory (E/I) imbalance at a single cell level that along with compensatory or homeostatic processes is dynamically changed on multiple timescale, affecting global neural circuits activity.[68] Thus, the E/I imbalance is multidimensional and may disrupt the activity of central neural circuits[29,83] and potentially interfere with the pain system function.[37] Namely, neural hyperresponsiveness in the ascending transmitting pathways may cause enhanced facilitatory processes at the spinal and supraspinal levels, whereas reduced neural activity in the inhibitory pathways may interrupt endogenous analgesia.[4] Together, these suggest a pronociceptive profile.[86] Furthermore, the function of additional cortical regions (eg, prefrontal) and the hippocampus is also affected by the E/I imbalance generating pathological switch in circuits function and behaviorly manifested as an emotional/anxiety hypersensitivity,[68] further amplifying the pronociceptive perception.

The prevailing assumption is that autism individuals are hyposensitive to pain. This is supported by the DSM-5 and DSM IV-TR criteria, which describe the sensory atypicality in ASD as having "an apparent indifference to pain/temperature"[2] and "a high threshold for pain".[27] Pain research among autistic people is scarce, largely based on observations and self or parental reports with mixed results. Several previous studies have used quantitative sensory testing (QST) to assess pain sensitivity in autistic

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 164 (2023) 791–803

http://dx.doi.org/10.1097/j.pain.0000000000002767

participants. The majority of these studies found no differences in the pain sensitivity of autistic individuals in response to noxious thermal[19,32] and mechanical[34,77] stimuli and in dynamic tests, including temporal summation[27,34,77] and conditioned pain modulation (CPM),[27,77] compared with healthy control individuals. However, one study found increased sensitivity to noxious thermal stimuli in autistic adults,[31] and one study reported increased sensitivity to pain at the beginning of the temporal summation test.[27] Furthermore, while few studies have assessed sensory thresholds in autistic participants using a variety of methodologies, most have reported no differences in thermal detection,[34,77,82] heat,[31,34,77] cold,[28,34,77] electrical[14] and mechanical[34] pain thresholds, but some have described higher thermal,[28] mechanical[34,77] detection and mechanical pain[77] thresholds or lower heat pain thresholds[18] compared with control groups. Notably, while Dubois[27] and Vaughan[77] conducted comprehensive QST studies, these included small samples, and therefore, the evidence to support an antinociceptive or pronociceptive pain modulation profile (PMP) is limited. Accordingly, whether the PMP in autistic individuals comprises less-efficient inhibitory processes along with a facilitative state, as suggested by an E/I imbalance mechanism,[48] is still a mystery.

We aimed to examine the functioning of facilitatory and inhibitory pain pathways in the largest sample of autistic adults ever tested to better understand the psychophysical characteristics of a potential E/I neuronal imbalance. To this end, we used a comprehensive laboratory pain battery, including static and dynamic tests. In addition, we gathered information about participant psychological distress e.g., anxiety, which interacts with pain processing[78] and is heightened in autism (for review, see Vaughan et al. 2019).[76]

2. Methods

The institutional review board of the Rambam Health Care Campus (no. 0496-17) and the University of Haifa (no. 064/18) approved the study protocol in accordance with the Helsinki Declaration. Each patient signed a written informed consent form prior to commencing the experiment in the presence of a physician.

2.1. Participants

Subjects with autism aged 18 to 55 years, diagnosed according to the requirements of the Israeli Ministry of Health and verified using the Autism Diagnostic Observation Schedule—Second Edition (ADOS-2) interview performed by ADOS-2 certified assessors, as well as age-matched and sex-matched typical developing (TD) subjects were recruited by convenience snowball sampling. Specifically, we sampled all autistic centers in the country, using the snowball sampling to encourage the participation in a laboratory pain study. Participants were asked to avoid the use of analgesics, medication for attention-deficit hyperactivity disorder, and any sedative drugs 24 hours before participation. The TD group consisted of participants with no neurological or psychiatric disorders.

Inclusion criteria for both groups required no language barriers. Exclusion criteria for both groups included reporting on chronic pain diagnoses or pain lasting for more than 3 months, pregnancy, scores lower than 80 on the verbal, performance, and full-scale IQ as measured by the Wechsler Abbreviated Scale of Intelligence—Second Edition (WASI-II), reporting acute pain or use of analgesic medication within the past 24 hours.

2.2. Self-report questionnaires

2.2.1. Sociodemographic and health status

This questionnaire included demographic information (eg, age, gender, years of education), general health conditions, and health-related disabilities (eg, myopia, hearing impairment, etc).

2.2.2. Autism Spectrum Quotient

The Autism Spectrum Quotient (AQ) is a 50-item questionnaire for adults and adolescents aged 16 years and older, intended to assess 5 aspects associated with autism (social skills, attention switching, attention to detail, communication, and imagination). The questionnaire is useful for screening and measuring the degree of autistic symptoms in both clinical practice and laboratory research. The subjects were asked to rate their agreement to each statement on a 4-point Likert scale from 1 "definitely agree" to 4 "definitely disagree". A total score of 32 points or above indicates autistic traits.[11,35]

2.2.3. Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) is a 13-item questionnaire that assesses pain catastrophizing. Each item describes a painful event or situation and is rated on a 5-point Likert scale from 0 "not at all" to 4 "always," that reflects the degree of participant's thoughts or feelings during the event. The PCS generates a total score and 3 subscores that evaluate coping strategies, including rumination, magnification, and helplessness.[38,69]

2.2.4. The Spielberger state-trait anxiety inventory

The state-trait anxiety inventory is a widely used questionnaire that comprises separate scales for assessing state and trait anxiety. The questionnaire includes 2 sections, each with 20 items, rated on a 4-point Likert scale, The state anxiety part assesses the intensity of current emotions and feelings of anxiety using a scale from 1 "not at all" to 4 "very much so". The trait anxiety part assesses the frequency of anxiety feelings, in general, using a scale from 1 "almost never" to 4 "almost always."[64,66]

2.2.5. Pain sensitivity questionnaire

The Pain sensitivity questionnaire (PSQ) is a 17-item questionnaire that assesses pain sensitivity. Fourteen of the 17 items describe daily life situations that are considered painful, the other 3 items describe situations that most healthy subjects rate as nonpainful. Responders are asked to indicate how painful these imagined situations could be using a 0- to 10-point scale (0 "not at all painful" to 10 "most severe pain imaginable"). The PSQ elicits a total score, ie, the mean rating of the 14 painful items and 2 sub scores: (1) pain sensitivity—minor by calculating the mean rating of the 7 painful situations that are usually rated as causing minor pain (mean rating <4), and (2) pain sensitivity—moderate by calculating the mean rating of the 7 painful situations that are usually rated as causing moderate pain (mean rating 4-6).[62]

2.2.6. Sensory Responsiveness Questionnaire—intensity scale

The Sensory Responsiveness Questionnaire—intensity scale (SRQ-IS) includes 58 items representing daily life events referring each to one sensory stimulation and together represent all sensory modalities (tactile, auditory, visual, taste, smell, vestibular,

proprioception) except pain. Each item describes a hedonic (26 items) or an aversive (32 items) valence, and participants are required to rate on a 5-point Likert scale (1 "not at all" to 5 "very much") their response intensity to each of the items.[5] The SRQ-IS provides 2 scale scores, SRQ-aversive and SRQ-hedonic.

2.3. Quantitative sensory testing

2.3.1. Thermal and pain thresholds

To evaluate the function of the peripheral pain system, we applied thermal detection threshold tests using the methods of limits.[87] Cool and warm detection thresholds (CDT and WDT respectively) and heat pain thresholds (HPT) were evaluated on the left volar forearm with a 30 x 30 mm thermode of the Thermal Sensory Analyzer (TSA-II) system (Medoc Ltd, Ramat Yishay, Israel). Each test included a series of 5 stimuli with an interstimulus interval (ISI) of 4 to 6 seconds. For CDT and WDT, the thermode temperature was decreased or increased from the baseline temperature of 32˚C at a rate of 0.5˚C/sec. The participants were asked to press the computer mouse with their right index finger when starting to feel a cold or warm sensation. The thermode temperature returned to baseline at a rate of 8˚C/sec. The mean temperature of the 3 closest stimuli in each series with an interval of less than 0.5˚C was determined as the detection threshold. For the HPT, the thermode temperature increased at a rate of 1˚C/sec, and the participants were asked to press the button when they felt a first sensation of pain. After each stimulus, the thermode was moved to avoid adaptation. The mean temperature of the closest 3 stimuli, preferably with a difference of less than 0.5˚C was used to determine the HPT. Thermal and pain thresholds were also calculated using the z-transform for each individual and adapted for sex and age. The thresholds were based on the German Research Network on Neuropathic Pain DFNS reference: $z\text{-score}_{individual} = [\text{mean threshold}_{individual} - \text{mean threshold}_{reference}]/\text{standard deviation}$.[46] A z-score $> +1.96$ or < -1.96 defined pathological hyposensitivity or hypersensitivity. A logarithmical transformation was performed on the mean values for cold and warm detection thresholds because these parameters demonstrated non-normal distributions in the reference data.[46]

2.3.2. Heat pain sensitivity

Three series of 20 phasic stimuli, at each temperature of 46, 49, and 52˚C with an ISI of 10 seconds and a 5-minute break between the series were delivered to the upper volar aspect of the forearm of the right hand, using the Pathway system for Contact Heat-Evoked Potential Stimulator (CHEPs) delivered by a 27-mm-diameter thermode (Medoc Ltd, Ramat Yishay, Israel). The baseline temperature was 32˚C, the temperature increase rate was 70 ˚C/sec, and the temperature decrease rate was 40˚C/sec. for all stimuli. The average stimulus duration (from onset to offset) was 571 ± 8, 746 ± 8, and 798 ± 8 ms for 46, 49, and 52˚C, respectively. To reduce the risk of an order effect, the first 2 series (46 and 49˚C) were applied randomly. After each stimulus, the thermode was moved to avoid adaptation/sensitization, and the participants were asked to rate their pain on a 0 to 100 numeric pain scale (NPS). The pain ratings were modeled with repeated measures analysis for each series.

2.3.3. Temporal summation of heat pain

Fifteen stimuli at 48 ˚C, each with a 0.7-seconds duration, an ISI of 2 seconds, and a baseline temperature of 39 ˚C were delivered by the CHEPs to the right-hand anterolateral aspect of the base of the thumb. The participants reported their pain levels of the first and last stimuli using the 0 to 100 NPS. The temporal summation value for each individual was calculated by subtracting the first stimulus pain rating from the last stimulus. Accordingly, a positive value indicated temporal summation.

2.3.4. Habituation

The stimulus intensity for the habituation test was individually tailored to evoke a pain of 50 on the 0 to 100 NPS, namely, pain-50_{phasic}. The pain-50_{phasic} was determined by applying a series of 3 CHEPs stimuli with an ISI of 8 seconds to the volar aspect of the forearm of the right hand. The temperature choice was based on the pain ratings in the *heat pain sensitivity* test. that is, 46, 49, and 52˚C. If the reports were above or below 50, the destination temperature was, respectively, decreased or increased at 0.5˚C intervals until the desired pain level of 50 was reached. For subjects not reaching an NPS of 50 at the maximal temperature of 54˚C, stimuli were performed at this temperature. The habituation test was compoed of 2 series of 20 phasic stimuli at the pain-50_{phasic} temperature, an ISI of 8 to 10 seconds, and a 5-minute break between the series, which were delivered by the CHEPs to the volar aspect of the forearm of the right hand. Participants were requested to rate the pain intensity after each stimulus. The mean pain score was calculated for each series. The habituation value was calculated by subtracting the mean pain rating of the first series from the mean pain rating of the second series.

2.3.5. Conditioned pain modulation

2.3.5.1. Conditioning stimulus intensity

The subject was instructed to immerse his left hand in a 46˚C water bath (Heto Cooling Bath, CBN 8-30, Allerod, Denmark) for 10 seconds and to rate the pain intensity on a 0 to 100 NPS. If not tolerated, the temperature was decreased in intervals of 0.5˚C until the water temperature was tolerated. If the NPS was below 40, the water temperature was increased at 0.5˚C intervals up to a maximum of 47˚C.

2.3.5.2. Phasic conditioned pain modulation

The test stimulus for the phasic CPM was calculated by taking the mean of the first 15 stimuli in the second series of the habituation test. After a 5-minute break, the participant was asked to immerse his/her left hand into the water bath and to rate the conditioning stimulus pain intensity after 10 seconds. Immediately afterward, a series of 15 phase stimuli at the pain-50 temperature was applied while the left hand was immersed in the bath (test + conditioning), and the subject was asked to rate each stimulus intensity on a 0 to 100 NPS. After the test stimuli were completed, subjects were asked to rate the pain intensity of the conditioning again. The mean pain intensity for the test + conditioning series was calculated.

2.3.5.3. Tonic conditioned pain modulation

The TSA thermode was introduced to the volar aspect of the right forearm to find the pain-50_{tonic} temperature of the individual, which later was used for the test stimulus. Each participant received 3 7-sec. stimuli at 44, 45, and 46 ˚C in a semirandom order with a 20-second ISI and was asked to rate the pain intensity of each stimulus using the NPS. If a pain rating of 50 was not reached, the stimulus temperature was increased until an

NPS rating of 50 was reached up to a maximal temperature of 49.5°C. The thermode was moved slightly between the stimuli to eliminate adaptation/sensitization.

After a 5-minute break, the 20-second. Test stimulus at the individual pain-50_{tonic} temperature was applied to the volar aspect of the right forearm. The participant was asked to rate the pain intensity at 10 and 20 seconds. using the 0 to 100 NPS (test-stimulus pain ratings). After an additional 10 minutes break, the participant was asked to immerse his left hand into the water bath (ie, the conditioning stimulus) for 30 seconds and to rate the conditioning stimulus pain intensity after 10 seconds. Immediately after rating the conditioning stimulus, the test stimulus was applied on the right forearm for 20 seconds, whereas the left hand was still immersed in the bath. The participant was asked to rate the pain intensity of the test stimulus at 10 and 20 seconds using the 0 to 100 NPS (test + conditioning). After a test stimulus was completed, the subjects were asked to rate again the conditioning. The CPM magnitude was calculated by subtracting the test-stimulus pain ratings at 20 seconds from the test + conditioning ratings at 20 seconds, where the pain-inhibits-pain phenomenon is fully expressed.

2.4. Procedure

Written informed consent was obtained from all participants before experiment enrolment. The experiment was conducted at the Rambam Health Care Campus in 2 sessions. During the first session, the participants underwent the WASI-II assessment and the ADOS-2 interview (only for the autistic individuals) and completed the sociodemographic, health status, and SRQ questionnaires. In the second session, the QST was conducted. Participants were seated in a quiet air-conditioned room in a comfortable armchair. An explanation about the pain rating process and familiarization with the stimuli were given at the beginning of this session. Thereafter, the participants underwent the QST protocol as follows: 1. CDT; 2. WDT; 3. HPT; 4. heat pain sensitivity evaluation; 5 temporal summation; 7. Habituation; 8. Phasic CPM; 8. Tonic CPM (4,5,6 were given in random order).

2.5. Statistical analysis

Statistical analyses were performed in SAS V9.4 (SAS Institute, Cary, NC) and R version 4.1.0. Continuous variables are summarized by the mean and standard deviation (SD) when found normally distributed or the median and inter range quartile when not found normally distributed (data not shown). A *P* value of 0.05 was considered statistically significant. Pain ratings (pain sensitivity, habituation, temporal summation, phasic and tonic CPM) were modeled with repeated-measures analysis of variance. Group and temperature (46, 49, 52°C) or time (first or last stimulus in the temporal summation test) or series (first or second in the habituation test; test or test+ conditioning in the CPM paradigms) were entered as categorical fixed effects as well as an interaction term temperature X group time X group or series X group (depending on the variable), which is the main parameter of interest. Least square means (LSmeans) per temperature or time or series and group and the differences between them were estimated from the model interaction terms with their respective levels of significance and 95% confidence intervals and used to compare both within and between the groups.

Thermal and pain thresholds, and all questionnaire scores were compared between the groups (Autism vs Control groups; psychiatric medication users vs nonusers) using the nonparametric Mann–Whitney test. A secondary analysis aimed at comparing psychiatric medication users, nonuser, and control subjects in QST using one-way analysis of variance followed by a post hoc Tukey test.

3. Results

3.1. Participants

The study participants were composed of 104 adults (84 men; 52 autistic) aged 18 to 50 (median, 25.5) years. No group differences were found in the WASI-II verbal, performance, and full-scale IQ scores (**Table 1**). Group differences were found in the AQ questionnaire scores (**Table 1**). In addition, the autistic group reported higher psychological distress expressed by trait and state anxiety, aversive sensory responsiveness level, pain catastrophizing levels, and greater pain sensitivity to daily life situations, compared with control group (**Table 1**). Routine use of one or more psychiatric medications was reported by 20 autistic participants (10 used selective serotonin reuptake inhibitors (SSRIs), 2 serotonin norepinephrine reuptake inhibitors, 1 norepinephrine–dopamine reuptake inhibitor, 3 benzodiazepines, 3 anticonvulsants, and 9 other antipsychotic drugs), and one healthy control participant (SSRI). No associations were found between these psychiatric medications and the psychological questionnaire scores.

Table 1

Self-report questionnaires scores in autism and controls.

	Autism (n = 52)	Control (n = 52)	*P*
AQ total score			
Median [25th, 75th]	25.0 [20.0, 32.2]	14.5 [11.2, 17.0]	<0.001
Missing data (%)	4 (7.6)	0 (0)	
Total IQ			
Median [25th, 75th]	114.0 [103.5, 121.7]	114.0 [107.0, 119.0]	0.670
Missing data (%)	0 (0)	1 (1.9)	
Performance IQ			
Median [25th, 75th]	116.0 [100.5, 123.0]	118.0 [108.0, 125.0]	0.415
Missing data (%)	0 (0)	1 (1.9)	
Verbal IQ			
Median [25th, 75th]	113.5 [101.2, 122.7]	108.0 [102.0, 115.0]	0.177
Missing data (%)	0 (0)	1 (1.9)	
State anxiety			
Median [25th, 75th]	39.5 [30.0, 50.0]	29.0 [25.2, 35.7]	<0.001
Missing data (%)	2 (3.8)	0 (0)	
Trait anxiety			
Median [25th, 75th]	46.5 [39.5, 59.0]	34.5 [30.2, 41.5]	<0.001
Missing data (%)	2 (3.8)	0 (0)	
PCS total score			
Median [25th, 75th]	27.0 [13.0, 36.0]	18.0 [12.2, 27.0]	0.010
Missing data (%)	1 (1.9)	0 (0)	
PSQ total score			
Median [25th, 75th]	4.8 [3.1, 6.2]	3.7 [2.5, 4.5]	0.002
Missing data (%)	1 (1.9)	0 (0)	
SRQ—aversion			
Median [25th, 75th]	2.0 [1.7, 2.6]	1.6 [1.4, 1.8]	<0.001
Missing data (%)	0 (0)	0 (0)	
SRQ—hedonic			
Median [25th, 75th]	2.2 [1.9, 2.5]	2.1 [1.8, 2.4]	0.453
Missing data (%)	0 (0)	0 (0)	

AQ, autism spectrum quotient; IQ, intelligence quotient; PCS, pain catastrophizing scale; PSQ, pain sensitivity questionnaire; SRQ, sensory responsiveness questionnaire; SD, standard deviation; Min, minimum; Max, maximum.

3.2. Quantitative sensory testing

3.2.1. Thermal and pain thresholds

There were no group differences found in the thermal and pain detection threshold. Raw data comparison yielded no group differences: CDT: (autism: Mdn [25th, 75th] = 30.7 (30.0, 31.3)°C, control: Mdn = 31.1 [30.5, 31.4]°C; $P = 0.196$), WDT: (autism: Mdn = 33.6 [33.2, 34.1]°C, control: Mdn = 33.4 [33.1, 33.9]°C; $P = 0.261$), HPT: (autism: Mdn= 39.6 [36.8, 42.9]°C, control: Mdn = 41.1 [38.1, 43.7]°C; $P = 0.309$).

Chi-square analysis revealed the proportion of participants who demonstrated hypoesthesia or hyperesthesia/hyposensitivity or hypersensitivity. Thermal thresholds that were calculated according to z scores, as described in the methods section, did not differ between the groups (**Table 2**). Pathological somatosensory function pathologies were not indicated (ie, z values $>+1.96$ or <-1.96).

3.2.2. Heat pain sensitivity

A significant main effect of group (F [1, 102] = 10.16, $P = 0.001$) series (F [2, 204] = 959.72, $P < 0.001$), as well as a significant interaction between the group and series (F [2, 204] = 37.18, $P < 0.001$) were found. Post hoc analysis revealed group differences in pain ratings in response to 3 phasic suprathreshold heat stimuli series; the study group demonstrated hypersensitivity compared with control group. In addition, a significant dose response was found within each group. For more details, see **Table 3** and **Figure 1**.

Significant positive correlations were found between the suprathreshold heat pain ratings and PSQ total scores in the study group (46°C, r = 0.39 $P = 0.005$; 49°C, r = 0.40 $P = 0.004$; 52°C, r = 0.45 $P = 0.001$) but not in the control group (46°C, r = 0.10 $P = 0.491$; 49°C, r = 0.11 $P = 0.444$; 52°C, r = 0.18 $P = 0.190$). No significant correlations with other pain-related psychological parameters were found (Supplement 1, available at http://links.lww.com/PAIN/B707).

3.2.3. Temporal summation of pain

A significant effect of group (F [1, 102] = 12.2, $P > 0.001$) was identified demonstrating pain hypersensitivity in the autistic group both for the first (autism: Mdn [25th, 75th] = 45.0 [20.0, 78.7] NPS vs control: Mdn = 20.0 [10.2, 48.7] NPS; $P = 0.001$) and last (autism: Mdn = 40.0 [20.0, 60.0] NPS vs control: Mdn = 23.0 [15.0, 40.0] NPS; $P = 0.001$) stimuli (**Table 4**). Unexpectedly, we did not find a main effect of the stimulus (ie, first vs last stimulus), indicating that both groups did not demonstrate temporal summation of pain (F [1, 100] = 2.01, $P = 0.159$), and there was no significant interaction between group and stimulus (F [1,100] = 0.00, $P = 0.988$).

Because a fixed temperature was used in the temporal summation (TS) test, we decided to perform a subanalysis based on the individual perceived pain intensity of the first stimulus, namely, ≤ 20 NPS rating (mild pain) vs > 20 NPS rating (moderate-to-high pain). Results show that when the pain ratings of the first stimulus were ≤ 20 NPS, both groups demonstrated TS of pain where the main effect of the stimulus was significant (F [1,44] = 14.54, $P < 0.001$). However, no effect of group (F[1,44] = 0.18, $P < 0.672$) or interaction between stimulus and group (F[1,44] = 1.22, $P = 0.272$) were found. In contrast, when the pain ratings were > 20 NPS, both groups demonstrated adaptation where the main effect of the stimulus was significant (F [1,54] = 18.08, $P < 0.001$). In addition, the main effect of group (F [1,56] = 9.27, $P < 0.003$) was identified as autistic individuals showing hypersensitivity to pain stimuli, yet, no interaction between stimulus and group was found (F [1,54] = 0.23, $P = 0.628$), see **Table 4** and **Figure 2**.

3.2.4. Habituation

Most of the subjects did not reach the pain-50_{phasic} intensity even at the highest temperature presented (54°C). Only 18 (45%) subjects from the study group and 12 (23%) subjects from the control group reached the pain-50_{phasic} intensity. Yet, the pain-50_{phasic} temperature was lower in the study group (autism: Mdn [25th, 75th] = 54.0 [52.0, 54.0]°C vs control: Mdn = 54.0 [54.0, 54.0]°C; $P = 0.003$). Subjects from both groups did not demonstrate habituation. Namely, there was no significant decrease in pain ratings in the second series relative to the first series, as expressed by the lack of a main effect of the series (F [1, 95] = 2.14, $P = 0.146$). However, there was a significant main effect of the group (F [(1, 95]) = 8.73, $P = 0.003$). Specifically, in both the first and second series, the NPS pain ratings of the study group were higher than those of the control group, indicating pain hypersensitivity: first series: autism mean = 37.7 ± 21.16, Mdn = 34.7 (0.1-82.0) vs control mean = 26.3 ± 18.24, Mdn = 22.7 (0-68.9); $P = 0.006$. Second series: autism mean =37.0 ± 21.86, Mdn = 35.9 (0.2-83.8) vs control mean = 24.9 ± 19.18, Mdn = 18.3 (0-72.5); $P = 0.004$. However, no significant interaction between series and group was evident (F [1, 95] = 0.19, $P = 0.662$).

Table 2

Thermal and pain detection thresholds.

	Autism N (%) (n = 48)	Control N (%) (n = 52)	Chi-square
CDT			
Normal	39 (81.3)	45 (86.5)	0.756
Hyperesthesia	3 (6.3)	2 (3.8)	
Hypoesthesia	6 (12.5)	5 (9.6)	
WDT			
Normal	44 (91.7)	50 (96.2)	0.423
Hyperesthesia	4 (8.3)	2 (3.8)	
Hypoesthesia	—	—	
HPT			
Normal	32 (66.7)	39 (75)	0.386
Hypersensitivity	16 (33.3)	13 (25)	
Hyposensitivity	—	—	

CDT, cold detection threshold; WDT, warm detection threshold; HPT, heat pain threshold.

Table 3

Pain ratings to phasic suprathreshold stimuli.

	Autism	Control	*P*
46°C			
Mean (SD) NPS	19.8 (20.7)	11.6 (11.6)	0.018
Median [min, max] NPS	14.0 [0.0, 100.0]	9.0 [0.0, 55.0]	
49°C			
Mean (SD) NPS	26.4 (22.4)	16.3 (15.4)	0.003
Median [min, max] NPS	20.0 [0.0, 100.0]	12.0 [0.0, 75.0]	
52°C			
Mean (SD) NPS	38.4 (28.0)	24.2 (20.4)	<0.001
Median [min, max] NPS	33.0 [0.0, 100.0]	20.0 [0.0, 100.0]	

NPS, numeric pain scale; SD, standard deviation; Min, minimum; Max, maximum; N = 1040 stimuli (52 subjects who received 20 stimuli in each series).

3.2.5. Conditioned pain modulation

Autism individuals rated the conditioning stimulus (warm water bath) as more painful on the NPS (autism Mdn = 50.0 [35.0, 65.0] vs control Mdn = 40.0 [25.0, 50.0]; $P = 0.013$), although the adjusted temperature was lower (autism Mdn = 46.0 [45.5, 46.7]°C, control Mdn = 46.5 [46.0, 47.0]°C; $P = 0.001$).

In the phasic CPM, there was a significant main effect of series ($F [1, 95] = 30.16$, $P < 0.001$) and group ($F [1, 95] = 7.13$, $P = 0.008$) but no significant interaction between series and group ($F [1, 95] = 2.50$, $P = 0.116$), demonstrating efficient CPM effects of a similar magnitude in both groups. In accordance with the abovementioned results showing pain hypersensitivity in the study group, autism individuals rated higher the test stimulus and the conditioning stimulus both delivered alone (**Table 5**).

In the tonic CPM, the individual pain-50_{tonic} temperature was lower in the autism group (Mdn = 46.0 [44.5, 48.0]) compared with the control group (Mdn = 48.0 [46.0, 49.0])°C ($P = 0.001$). For the CPM magnitude, we did not find a significant main effect of group: ($F [1, 97] = 1.96$, $P = 0.164$), and no interaction between time and group: ($F [1, 96] = 2.30$, $P = 0.131$). However, we found a main effect for stimulus (the test stimulus given stand-alone vs the test stimulus given under conditioning) ($F [1, 96] = 7.43$, $P = 0.007$). A significant pain-inhibits-pain phenomenon and was demonstrated after 20 seconds of the contact heat stimulation (ie, second pain rating) (LSmean = 7.13, $P = 0.002$) in the control group, but no such effect was identified in the autism group (**Table 5** and **Fig. 3**).

3.2.6. Secondary analyses—psychiatric medications

We further tested whether the pain measures differed between the control individuals and subgroups of autistic individuals based on their intake of psychiatric medications. No differences were found in IQ evaluation, PSQ, PCS, AQ, and anxiety scores between autistic individuals who used psychiatric medications vs those who had no medication intake. However, participants who used psychiatric medications had severe autism based on the ADOS assessment (users: Mdn [25th, 75th] = 10.5 [10.0, 11.7], nonusers: Mdn = 9.0 [7.2, 10.0]; $P = 0.005$) and reported higher scores on the SRQ-aversion scale (users: Mdn = 2.2 [2.1, 2.8], nonusers: Mdn = 1.9 [1.6, 2.3]; $P = 0.004$) and lower scores on the SRQ-hedonic scale (users: Mdn = 2.0 [1.8, 2.2], nonusers: Mdn = 2.3 [2.0, 2.6]; $P = 0.035$). Furthermore, participants in the autism group who received psychiatric medications reported greater pain ratings in the 46, 49, and 52°C stimuli and during the habituation paradigm, and the adjusted temperature used for the conditioning stimulus was lower, compared with nonusers. Furthermore, only those who received psychiatric medication showed pain hypersensitivity compared with control group (**Table 6**).

3.2.7. The response function of the pain facilitatory pathways in autism

Based on our findings suggesting a shift of the stimulus response function toward pain hypersensitivity in the autism group, we performed an exploratory analysis with an aim to test the response function consistency. We correlated, within each group, the responses to various QST variables that significantly differed between autism group and control group. The results are presented in 2 correlation matrices (**Fig. 4**), one for each group, and show moderate to high correlations between responses, suggesting response consistency in autism.

4. Discussion

The study findings indicate a normal functioning of the peripheral nervous system based on the thermal and pain thresholds in autism. Yet, pain sensitivity is evident through the consistent enhanced pain ratings in response to suprathreshold stimuli of different characteristics that cross correlated. Furthermore, we found different response functions to phasic and tonic pain stimuli; while the pain inhibitory system responded efficiently to phasic

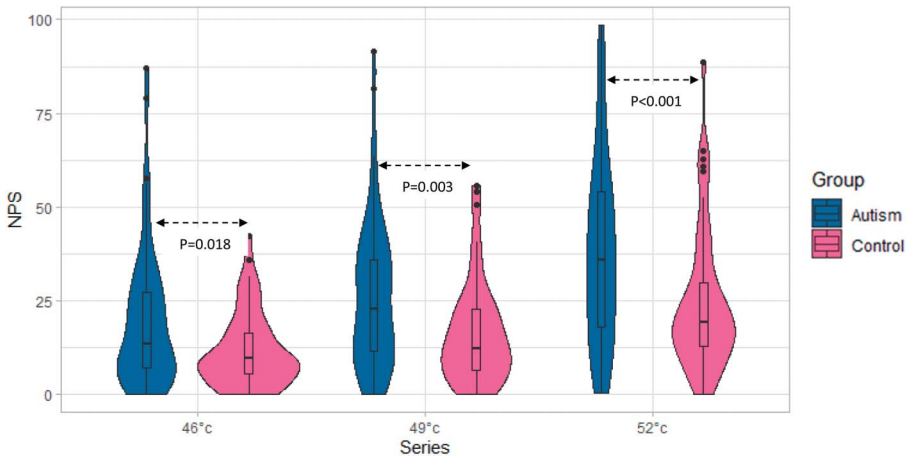

Figure 1. Pain ratings of suprathreshold phasic stimuli. Both autistic and control groups demonstrated an increase in pain ratings with an increase in stimulus intensity. Yet, individuals in the study group showed significant higher pain ratings in response to each of the 3 suprathreshold stimuli. NPS, numeric pain scale.

Table 4

Pain ratings for the temporal summation test.

	First stimulus (N = 52)	Last stimulus (N = 52)	*P*
All subjects			
Autism (N = 52)			
Mean (SD) NPS	47.4 (32.7)	43.5 (29.7)	0.322
Median [min, max] NPS	45.0 [1.0, 100.0]	40.0 [0.0, 100.0]	
Missing data (%)	0 (0)	2 (3.8)	
Control (N = 52)			
Mean (SD) NPS	30.3 (23.9)	27.5 (19.2)	0.323
Median [min, max] NPS	20.0[1.0, 90.0]	23.0 [0.0-75.0]	
Missing data (%)	0(0)	0 (0)	
First pain rating ≤ 20 NPS			
Autism (N = 18)			
Mean (SD) NPS	11.7 (6.7)	22.1 (22.3)	0.003
Median [min, max] NPS	10.0 [1.0, 20.0]	15.0 [0.0, 80.0]	
Missing	0 (0)	0 (0)	
Control (N = 28)			
Mean (SD) NPS	12.7 (6.4)	18.3 (13.2)	0.040
Median [min, max] NPS	12.0 [1.0, 20.0]	15.5 [0.0, 50.0]	
Missing data (%)	0 (0)	0 (0)	
First pain rating > 20 NPS			
Autism (N = 34)			
Mean (SD) NPS	66.2 (23.9)	55.5 (26.5)	0.006
Median [min, max] NPS	65.5 [30.0-100.0]	50.0 [10.0,100.0]	
Missing data (%)	0 (0)	2 (5.8)	
Control (N = 24)			
Mean (SD) NPS	50.8 (20.3)	38.2 (19.8)	0.003
Median [min, max] NPS	50.0 [25.0, 90.0]	35.0 [9.0, 75.0]	
Missing data (%)	0 (0)	0 (0)	

NPS, numeric pain scale; SD, standard deviation; Min, minimum; Max, maximum.

stimuli in both groups, the autism group failed to inhibit tonic pain stimuli. Taken together, based on our in-depth and extensive investigation of the PMP in autism, we conclude that individuals with autism show a pronociceptive PMP comprising pain hypersensitivity along with inefficient inhibition of continuous pain.

The unidimensional view of the E/I imbalance as a dysregulated balance between excitatory and inhibitory neural activity in autism[61,89,90] has been evolved into a multidimensional framework.[68] Neural hyperresponsiveness characterizes the E/I imbalance, manifested in both the timing and level of responses

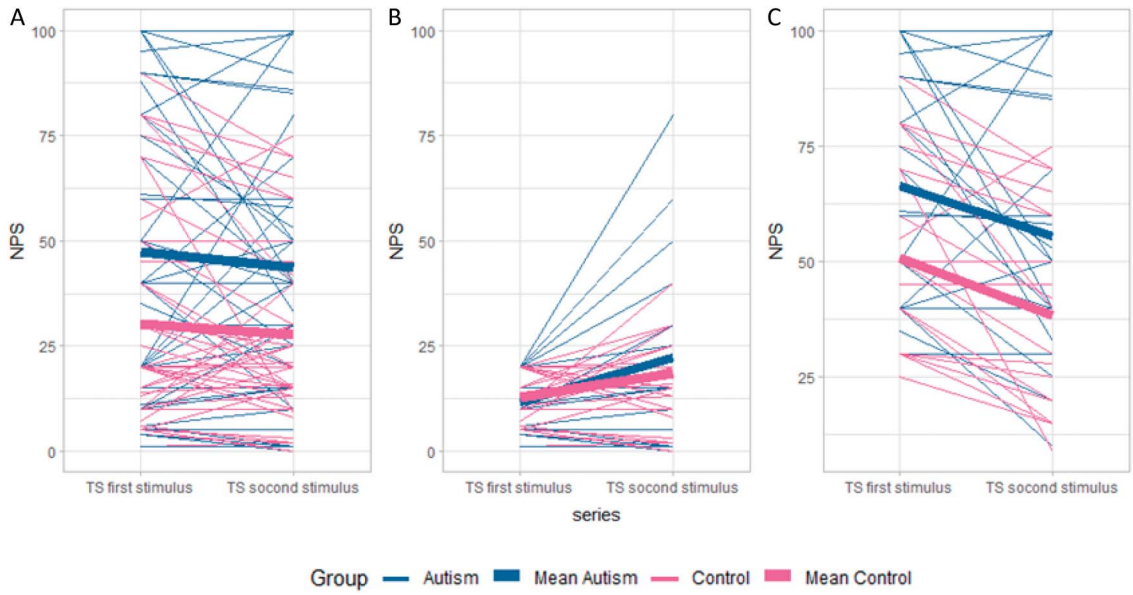

Figure 2. Temporal summation test split based on the perceived pain intensity of the first stimulus. (A) First and last stimulus ratings for the TS test (no split). (B) First and last stimulus ratings for the TS test when the perceived pain rating of the first stimulus was ≤ 20 NPS. Both groups demonstrated TS, no group difference. (C) First and last stimulus rating for the TS test when the perceived pain rating of the first stimulus was > 20 NPS. Both groups demonstrated adaptation, no group difference. TS, temporal summation; NPS, numerical pain scale.

Table 5

Conditioned pain modulation values for tonic and phasic stimuli.

	Autism (N = 52)	Control (N = 52)	Between-group *P*
Phasic CPM T			
Mean (SD) NPS	37.0 (22.0)	24.9 (18.9)	0.003
Median [min, max] NPS	38.3 [0.2, 84.8]	18.5 [0.0, 71.3]	
Missing data (%)	7 (13.5)	0 (0)	
Phasic CPM T+C			
Mean (SD) NPS	29.6 (21.3)	20.8 (18.4)	0.034
Median [min, max] NPS	24.0 [0.0, 80.0]	14.7 [0.0, 66.0]	
Missing data (%)	7 (13.5)	0 (0)	
CPM efficiency *P*value	<0.001	<0.001	
Tonic CPM T 10 sec			
Mean (SD) NPS	49.2 (23.8)	44.0 (19.4)	0.270
Median [min, max] NPS	50.0 [0.0, 100.0]	50.0 [0.0, 80.0]	
Missing data (%)	5 (9.6)	0 (0)	
Tonic CPM T+C 10 sec			
Mean (SD) NPS	49.8 (28.0)	42.6 (20.4)	0.120
Median [min, max] NPS	40.0 [5.0, 100.0]	45.0 [5.0, 80.0]	
Missing data (%)	5 (9.6)	0 (0)	
CPM efficiency *P*value	0.867	0.638	
Tonic CPM T 20 sec			
Mean (SD) NPS	42.5 (23.6)	39.0 (19.3)	0.457
Median [min, max] NPS	40.0 [0.0, 100.0]	41.0 [0.0, 70.0]	
Missing data (%)	5 (9.6)	0 (0)	
Tonic CPM T+C 20 sec			
Mean (SD) NPS	40.5 (30.0)	31.9 (19.1)	0.069
Median [min, max] NPS	40.0 [0.0, 100.0]	30.0 [0.0, 80.0]	
Missing data (%)	6 (11.5)	0 (0)	
CPM efficiency *P*value	0.413	0.002	
Conditioning stimulus intensity -phasic CPM			
Mean (SD) NPS	59.2 (26.6)	44.7 (22.8)	0.003
Median [min, max] NPS	67.0 [1.0, 100.0]	40.0 [5.0,100.0]	
Missing data (%)	7 (13.5)	0 (0)	
Conditioning stimulus intensity—tonic CPM			
Mean (SD) NPS	46.8 (26.2)	38.1 (21.0)	0.094
Median [min, max] NPS	50.0 [0.0, 95.0]	35.5 [2.0, 90.0]	
Missing data (%)	5 (9.6)	0 (0)	

CPM, conditioned pain modulation; T, test stimulus; T + C, test + conditioning stimuli; conditioning stimulus intensity—phasic CPM; pain rating of the warm water bath at the end of the phasic CPM, after 30 ss; conditioning stimulus intensity—tonic CPM, pain rating of the warm water bath at the end of the tonic CPM, after approximately 250 ss; NPS, numeric pain scale; SD, standard deviation; Min, minimum; Max, maximum. In the tonic CPM, secondary analyses were performed using Kruskal–Wallis test.

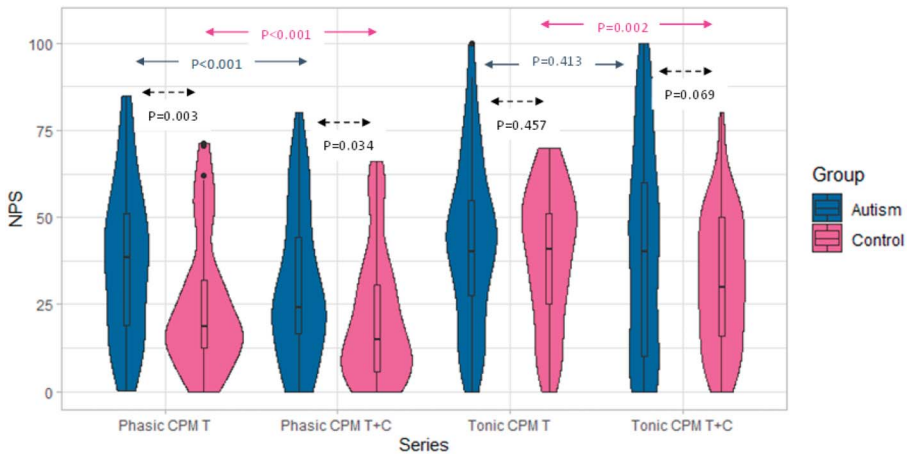

Figure 3. Pain ratings of the test stimulus given alone and concurrently with a conditioning stimulus during the tonic CPM test. While control participants demonstrated a significant inhibition after 20 seconds of the CPM test, individuals with autism did not show the pain inhibits pain phenomenon. CPM, conditioned pain modulation; NPS, numeric pain scale; T, test stimulus, T + C, test + conditioning stimuli.

Table 6

Differences in pain hypersensitivity measures between psychiatric medication users and nonusers in the autism group and the control group.

	Autism: non users (n = 32)	Autism: users (n = 20)	Control (n = 52)	*P*
46°C				
Mean (SD)	15.2 (14.5)*	26.9 (23.6)*#	11.6 (9.9)#	0.001
Median [min, max]	10.0 [0.0, 57.5]	22.5 [1.3, 86.9]	9.3 [0.0, 42.2]	
49°C				
Mean (SD)	20.6 (17.1)*	35.1 (21.7)*#	16.2 (13.6)#	<0.001
Median [min, max]	17.1 [0.0, 63.3]	35.0 [8.5, 91.6]	12.1 [0.0, 55.5]	
52°C				
Mean (SD)	31.1 (26.0)*	49.2 (21.3)*#	24.2 (18.6)#	<0.001
Median [min, max]	22.8 [0.5, 98.5]	46.9 [15.7, 96.8]	19.0 [0.0, 88.5]	
TS first stimulus				
Mean (SD)	41.6 (29.4)	56.7 (36.2)#	30.3 (23.9)#	0.001
Median [min, max]	40.0 [1.0, 100.0]	60.0 [5.0, 100.0]	20.0 [1.0, 90.0]	
TS last stimulus				
Mean (SD)	37.9 (28.0)	53.4 (30.8)#	27.5 (19.2)#	0.002
Median [min, max]	40.0 [0.0, 100.0]	50.0 [5.0, 100.0]	23.0 [0.0, 75.0]	
Missing	0 (0)	2 (10)	0 (0)	
Habituation 1st series				
Mean (SD)	31.8 (20.5)*	46.6 (19.3)*#	26.3 (18.2)#	0.001
Median [min, max]	30.5 [0.1, 72.5]	46.7 [13.2, 82.0]	22.7 [0.0,68.9]	
Missing	5 (15.6)	2 (10.0)	0 (0.0)	
Habituation 2nd series				
Mean (SD)	31.8 (22.5)	44.6 (18.8)#	24.9 (19.1)#	0.002
Median [min, max]	29.0 [0.2, 76.0]	44.7 [13.9, 83.8]	18.3 [0.0, 72.5]	
Missing	5 (15.6)	2 (10.0)	0 (0.0)	
Phasic CPM T				
Mean (SD)	31.9 (22.6)	44.7 (19.2)#	24.9 (18.9)#	0.002
Median [min, max]	28.6 [0.2, 77.3]	44.2 [11.2, 84.8]	18.5 [0.0, 71.3]	
Missing	5 (15.6)	2 (10.0)	0 (0.0)	
Phasic CPM T+C				
Mean (SD)	25.3 (20.9)	36.2 (20.7)#	20.8 (18.4)#	0.019
Median [min, max]	22.3 [0.0, 70.0]	33.3 [1.3, 80.0]	14.7 [0.0, 66.0]	
Missing	5 (15.6)	2 (10.0)	0 (0.0)	
Conditioning temperature				
Mean (SD)	46.2 (0.5)*	45.5 (0.9)*#	46.4 (0.5)#	<0.001
Median [min, max]	46.0 [45.0, 47.0]	45.5 [44.0, 47.0]	46.5 [45.5,47.0]	
Missing	3 (9.4)	0 (0)	0 (0)	
Conditioning NPS				
Mean (SD)	47.0 (27.2)	53.8 (20.2)#	38.8 (20.9)#	0.036
Median [min, max]	50.0 [0.0, 100.0]	54.5 [18.0, 95.0]	40.0 [0.0, 90.0]	
Missing	3 (9.4)	0 (0)	0 (0)	
Phasic pain 50 temperature				
Mean (SD)	53.0 (1.8)	52.0 (3.0)#	53.6 (0.8)#	0.003
Median [min, max]	54.0 [46.0, 54.0]	52.7 [43.5, 54.0]	54.0 [50.0, 54.0]	
Missing	5 (15.6)	2 (10.0)	0 (0.0)	
Tonic pain 50 temperature				
Mean (SD)	46.5 (2.1)	45.2 (2.4)#	47.4 (2.0)#	0.001
Median [min, max]	47.0 [40.0, 49.5]	46.0 [40.0, 49.0]	48.0 [42.0, 49.5]	
Missing	4 (13.3)	1 (5.0)	0 (0.0)	

*Group differences with the autistic group in post hoc analysis; #Differences between control and autistic medication users in post hoc analysis.
TS, temporal summation; CPM, conditioned pain modulation; T, test stimulus; T + C, test + conditioning stimuli; NPS, numeric pain scale; SD, standard deviation; Min, minimum; Max, maximum.

in various locations of the brain including the sensory, attention, and emotional areas (for a review, see 65), and possibly the cause of sensory responsiveness disturbances in autism.[47,61] Moreover, an altered organization of neural networks,[43,47] which normally support social, emotional, and introspective processes, may disable the downregulation of sensory stimuli responses and underlie the deficits seen in autism.[47,65]

At the neurobiology level, an increase in glutamate activity, a decrease in GABA activity, or an imbalance between the 2 neurotransmitters may elicit an E/I imbalance in the brain.[75] Recent studies present mixed results regarding glutamate activity (the main excitatory neurotransmitter) in autism; however, evidence consistently demonstrates disrupted GABA (the main inhibitory transmitter) activity in autism.[48,55] Importantly, GABA

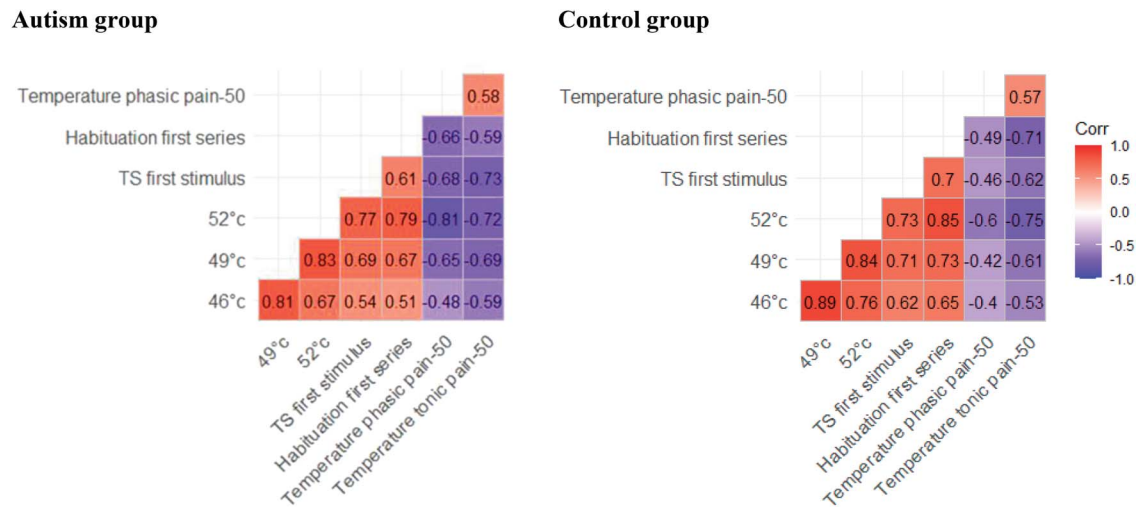

Figure 4. Correlations of pain sensitivity indices in autistic and control groups. Individuals with autism and control participants showed consistent medium to high correlations between quantitative sensory testing indices of facilitatory pathways function that differed between the groups. TS, temporal summation.

and glutamate have an important role in pain processing. Glutamate regulates cell excitability and synaptic transmission at different levels of the pain matrix, serving a pronociceptive role.[37] GABA plays an important antinociceptive role in acute and chronic pain conditions, by adrenergic and dopaminergic suppression at the ascending supra-spinal level and by noradrenergic activation at the spinal level.[37] Thus, decreased GABA activity maintains a pronociceptive pain profile. This is further supported by high levels of brain glutamate[41,54,57] and lower levels of GABA[33,54] in chronic pain conditions. Therefore, the neuropathology and biopathology in autism support our findings that the E/I imbalance may interfere in the pain system, inducing facilitatory processes and altering the endogenous analgesia mechanisms.

We found that autistic participants consistently reported pain ratings across tests, similar to control participants, eliminating the argument of biased pain reporting because of difficulties in communicating socially appropriate pain responses[15,21,74] or to incorrect use of standard pain assessments.[30] Moreover, increased sensitivity to real life pain situations, tested through the PSQ, correlated with the experimental pain ratings, which negates the idea that autistic individuals can express their pain unbiased by attentional and emotional factors in safe laboratory conditions. However, pain sensitivity may be expressed through unusual responses[36,74] mistakenly interpreted by health professions as anxiety, nausea, or delirium in acute pain situations.[44,72]

Autistic individual pain hypersensitivity was manifested in our findings through various suprathreshold heat stimuli: single phasic (first and last stimuli in the TS test), repetitive phasic (at 46, 49, 52°C, and at pain-50_{phasic} determined temperature), and tonic (at pain-50_{tonic} determined temperature and hand immersion in a hot water bath). These results are to some extent similar to those of the recent studies,[27,31] together supporting the E/I imbalance impact on the pain system, specifically the pain pathways transmitting excitation. We cannot conclude whether the abnormal pain processing occurs at the spinal and/or supraspinal level as a result of no observed TS, which evaluates spinal level pain modulation processing. Previous studies in autistic subjects found no difference in the TS magnitude compared with control subjects.[27,34,77] Therefore, because the evidence to draw conclusions regarding abnormal pain processing at the spinal level is restricted, supraspinal pain processing dysfunction is assumed to underlie the pain hypersensitivity in autism. While Failla et al.[32] reported similar pain ratings between autistic and healthy subjects, contrary to our findings, he demonstrated widespread reduced BOLD response in the neural pain network. In line with the E/I imbalance multidimensionality,[68] it is assumed that the expected linear associations between neurophysiological and behavioral pain responses should take a new stance.

As previously reported,[27,77] we found no group differences in the CPM magnitude. However, while in control participants, the pain-inhibits-pain mechanism was successfully activated through the CPM paradigm with the tonic test stimulus, this was not the case in autistic participants, suggesting less-efficient pain inhibition similar to reports in other nonpainful sensory modalities.[12,73] Likewise, our research group has previously found that sensory hyperresponsive individuals, who are otherwise healthy, also expressed hypersensitivity to experimental pain[6–8] and less-efficient CPM, manifested by late pain-inhibits-pain responses,[79] indicating a pronociceptive profile probably because of an E/I imbalance.[4]

The behavioral manifestation of the nonpainful sensory disturbances in autism is due to either hypo responsiveness or hyperresponsiveness in one or more sensory modalities.[12,26,60,65] However, while autistic children demonstrate both types of responsiveness,[9,10,12] reports suggest that autistic adults exhibit more sensory hyperresponsive behaviors.[51,65] Moreover, pain is a threatening stimulus that has a survival significance, and therefore, it might be augmented in adults with autism as a protection mechanism in a world of intensified stimuli that overwhelms their sensory systems. When short-term pain stimuli are perceived as augmented, the endogenous pain inhibitory system successfully activates the pain-inhibits-pain mechanism as manifested in efficient CPM to phasic stimuli. Yet, when long-term pain stimulus is perceptually intensified, the endogenous inhibitory system fails to suppress it, as evident by inefficient CPM to tonic stimuli. Thus, we suggest that preexisting augmented responses and the inability to inhibit tonic pain, considered an experimental model for clinical pain, may lead to the establishment of a pronociceptive profile and the acquisition of pain chronification.[63,81,85] Indeed, a higher incidence of chronic pain conditions is reported in the autistic population[39,80] probably not only due to the preexisting pronociceptive state but

also due to self-injurious behaviors that potentially bias other judgments of pain in autistic individuals.[1,15] Thus, pain is overlooked by caregivers and untreated by physicians.[21] This is crucial in long term because untreated pain can cause plastic changes in the central pain system, amplifying pain sensitivity, and may possibly lead to pain chronicity and suffering.[3,84]

We applied threshold tests to test the functioning of the peripheral nervous system (C and A delta fibers). A recent study has provided evidence of denervation in the peripheral small intra epidermal nerve fibers in skin biopsies of autistic participants,[20,58,67] suggestive of abnormal pain thresholds. Furthermore, inflammatory processes in pain primary afferents because of repeated tissue damage caused by self-injurious behavior may lead to allodynia.[71] However, we did not find group differences in thermal and pain thresholds, suggesting a normal peripheral nervous system functioning in autism. These results are in line with previous studies.[14,28,31,34,77,82] Moreover, increased thresholds found in autistic individuals were explained by cognitive difficulties and not peripheral nervous system pathology.[28,59,88] Hence, we suggest that the central nervous system is solely involved in the improper processing of pain stimuli in autism.

Thirty-eight percent of autistic participants reported routine psychiatric medication use, including tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, anticonvulsants, and benzodiazepines. These drugs are generally indicated for chronic pain conditions, mood disorders, or epilepsy and can have a beneficial effect on pain.[70] However, we found that individuals who used psychiatric medications demonstrated pain hypersensitivity compared with those who did not use psychiatric medication and control individuals. In addition, despite high levels of anxiety in the autistic group compared with control group, no differences were found in anxiety levels between psychiatric users and nonusers, and no correlations were found between levels of pain sensitivity and anxiety in the autism group. Yet, those who used psychiatric medications had greater autism severity and sensory disturbances compared with nonusers. These findings suggest that pain sensitivity in autism may be attributed to autism severity and its accompanied nonpainful sensory disturbances[12] and not to the level of general anxiety, although pain sensitivity was found associated to pain-related anxiety.[31] This is contrary to evidence in nonautistic populations where high anxiety level is associated with greater pain sensitivity,[50] probably as a result of the medication interference. Both autism severity and sensory disturbances have a common denominator mechanism ie, an E/I imbalance,[4,16,22,43] which confirms our assumption that a primary neurophysiological disruption is probably the underlying mechanism of pain sensitivity in autism.

This study had several limitations. Our results can be inferred to the heat pain modality solely. Future studies are warranted to explore the PMP in other pain modalities. Furthermore, we did not control for race. To summarize, based on our in-depth investigation of PMP constituents using thermal QST as well as self-reports, findings suggest normal functioning of the peripheral nervous system, pain hypersensitivity, and pain inhibitory system showing alteration in tonic—but efficiency in phasic—pain stimuli response patterns. Thus, we conclude that individuals with autism show a pronociceptive PMP comprising hypersensitivity along with inefficient functioning of the endogenous inhibition during continuous pain.

The findings contribute to solving the mystery as to whether autistic individuals are indifferent,[14,19,28,31,32,34,77] hyposensitive,[1,53] or hypersensitive[18,27,31] to pain. This evidence demonstrating enhanced pain sensitivity warrants changing the common belief that autistic individuals experience less pain. This misinterpretation can lead to late diagnosis and poor treatment causing suffering and exacerbating the autistic symptoms e.g., sleep disorders, restlessness, and aggressive behaviors.[19,24] Moreover, the latter might increase the incidence of common pain conditions chronicity because of comorbidities and in turn increased propensity for self-injuries.[25,39,49,53] Of note, because throughout the autism spectrum there are shared neural mechanisms, we believe that these results may also apply to people with autism whose cognitive and verbal communication impairments may eliminate their ability to communicate their pain.[19,45] These findings may raise physician, parent, and caregiver awareness to the pain phenomenon in autism and thus lead to early and effective treatment to improve the well-being and quality of life for autistic individuals and their families.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

This study was funded by the Israel Science Foundation grant # 1005/17.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B707.

Article history:
Received 10 May 2022
Received in revised form 21 July 2022
Accepted 16 August 2022
Available online 26 August 2022

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