Neurological Sciences (2023) 44:3853–3861
https://doi.org/10.1007/s10072-023-06942-2

REVIEW ARTICLE

Pain assessment in autism: updating the ethical and methodological challenges through a state-of-the-art review

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Received: 14 June 2023 / Accepted: 3 July 2023 / Published online: 12 July 2023

Abstract
Sensory features of autism include hypo- or hyper-reactivity to pain; however, previous studies on pain in autism lead to conflicting results. Here, we present the state of the art and the methodological challenges concerning pain perception in autism, focusing on studies that used standardized protocol as Quantitative Sensory Testing (QST) to measure perception. Despite there are still scant evidences found with the use of QST, they have challenged the presumed hyposensitivity to pain in autisms, which emerged from parents' reports. Both, peripheral and central mechanisms, have been found involved in typical features of perception in autism. Nonetheless, evidences with controlled protocols are still scarce, and even scarcer are studies focused on children. Overall, complex ethical challenges have to be overcome in order to collect subjective and objective measures from autistic children. With heterogeneous neurodevelopmental features, or intellectual disability, novel or modified protocols are needed.

Keywords Pain · Autism · Neurodevelopment · Quantitative Sensory Testing (QST) · Sensory processing

Introduction

Differences on sensory, cognitive, and emotional features characterize neurodevelopment with autism compared with the typical neurodevelopment [1–3]. Indeed, since 2013, novel diagnostic criteria include "hyper-or–hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment" [4]. Proff and colleagues [5] highlight the heterogeneity of sensory perception among people with autism and the different methodological approaches used to investigate it. A distinction, between hypo- and hyper-responsivity, has been proposed [6], and it has been found how these two profiles were associated with different behaviors and developmental outcomes [7]. In a recent study, on a large sample of children and adults with autism [8], the authors identify five sensory phenotypes. However, patients with autism, and with intellectual disability, were under-represented. Overall, still knowledge is missing about subjective perceptual features of autism at early neurodevelopmental stages, and still fewer studies included children compared to adult and late adolescence.

Pain perception is a complex and multifaceted experience characterized by sensory-discriminative (e.g., localization, duration, and intensity of the noxious stimulus), affective-motivational (e.g., unpleasantness of the noxious stimulus), and cognitive-evaluative processes (e.g., expectations, coping, context appraisal). How is pain perceived and communicated among people with autism? Despite the recent updates in the literature about autism and perception, this is still an open question [9, 10]. The International Association for the Study of Pain defines it as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [11]. Recently updated, six points have been added to the original version. Point six, in particular, touch a crucial topic for neurodivergent people, who might fell in the described category:

"Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain."

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Furthermore, people with autism could be largely exposed to pain during their life, as everyone does, or they could have a higher risk for self-injurious behaviors [3], and last but not least, they may present co-morbidity with health problems associated with pain [12]. Methodological differences in the study of pain perception in autism, such as different measures (for example, part reports vs self-report or objective measures, electro-cutaneous vs pressure pain thresholds measures), the lack of control groups, and the use of nonstandard pain measures, contributed to contrasting results. Results from parent reports showed hyposensitivity to pain; however, normal or hypersensitive responses have been found from medical and experimental procedures as well [13–15].

Until 2015, according to Moore [13], the most systematic examination of pain thresholds was provided by Cascio and colleagues [16], using a standardized Quantitative Sensory Testing (QST) protocol to induce the thermal sensations and measure thermal pain threshold. In particular, QST is aimed at studying and quantifying sensory function through the measurement of detection thresholds of calibrated sensory stimuli [17].

Cascio and colleagues [16] measured and reported pain threshold together with tactile sensation and reported hypersensitivity, in line with Fan [14, 16]. Moreover, recent evidences from a meta-analysis [18] showed that people with autism have a lower pain threshold for pressure pain particularly and greater physiological responses to medical procedures than controls, while pain ratings showed to be comparable with the control group. Furthermore, it has been proposed that people with autism could share a pain modulation profile, characterized by less inhibitory processes and pain facilitation, compatible with the pronociceptive profile, i.e., low pain conditioned modulation, and enhanced temporal summation of repeated nociceptive stimulation [19, 20]. These differences in conceptualization of pain perception are due to the high heterogeneity in methodology and population. The authors found higher pain ratings for the neurodivergent group, supporting the idea of a pronociceptive profile shared by this population, with hypersensitivity attributed to autism severity [19]. Overall, these results challenge the belief that people with autism are indifferent to pain, by using a highly reproducible methodology as the QST.

The picture concerning pain perception in autism appears blurred from the recent literature, and one of the reasons for this is the scarce use of controlled and reproducible tests and measures for pain. The QST responds to the methodological challenge of determining accurate and reproducible sensory thresholds in a reasonable amount of time. Moreover, when looking for pain thresholds, the additional challenge is to minimize the unpleasantness to the patient [21]. It has the great advantage of using calibrated sensory inputs delivered through a highly reproducible protocol. The use of controlled peripheral inputs is crucial when studying perception, together with the mutual influences of individual and contextual factors, respectively, over pain perception and pain responses [22–27]. In this vein, QST could be the elective instrument to face the challenge of studying pain in autism in a way that is controlled and reproducible. To date, two recent reviews [13, 18] considered the broader topic concerning pain in autism, recollecting several studies addressing this issue. However, a mixture of methodologies, pain stimuli, and pain measures are considered under the big umbrella label of pain in autism. Indeed, there is a high heterogeneity in methodology in the study of pain, as well as the samples used and the near total absence of direct measures of pain. Here, among the methodological limitations that emerged from previous reviews, we claim that the need for standardized and reproducible pain assessment is a priority to understand pain in autism. Thus, we reviewed how many studies, after Moore's review [13], have used quantitative sensory testing to study pain in autism. We aimed to summarize the state-of-the-art in a narrative perspective.

Methods

Two researchers independently conducted a literature research, on Pubmed and Scopus, to identify researches that used quantitative sensory testing in autism from 2008 until 2023, according to the following criteria. An additional search was conducted on Scholar with the same criteria. Studies were eligible if they were (i) original article, (ii) published between 2008 and 2023 in a peer-reviewed journal written in English, and (iii) using QST to investigate pain perception in a population with autism. Research on animal models, papers relying on qualitative measures, questionnaires, and parents reports that were not including QST, studies using QST to investigate non-noxious inputs only, and studies on generic clinical populations, such as developmental delay, not specifically with autism, were excluded. The words considered for this research were "quantitative sensory testing, autism"; "sensory testing, autism"; "quantitative sensory testing, autism spectrum disorder"; and "sensory testing, autism spectrum disorder." The search and selection process is summarized in Fig. 1 (PRISMA flow diagram). From 2015 until now, five studies have been included according to eligibility criteria; studies features are summarized in Table 1. Studies were sorted by methodological aspects such as sample features, dependent variables included, and reported results; we also included a specific focus on sensory features that emerged from the population with autism, when it was reported in the results, and finally limitations.

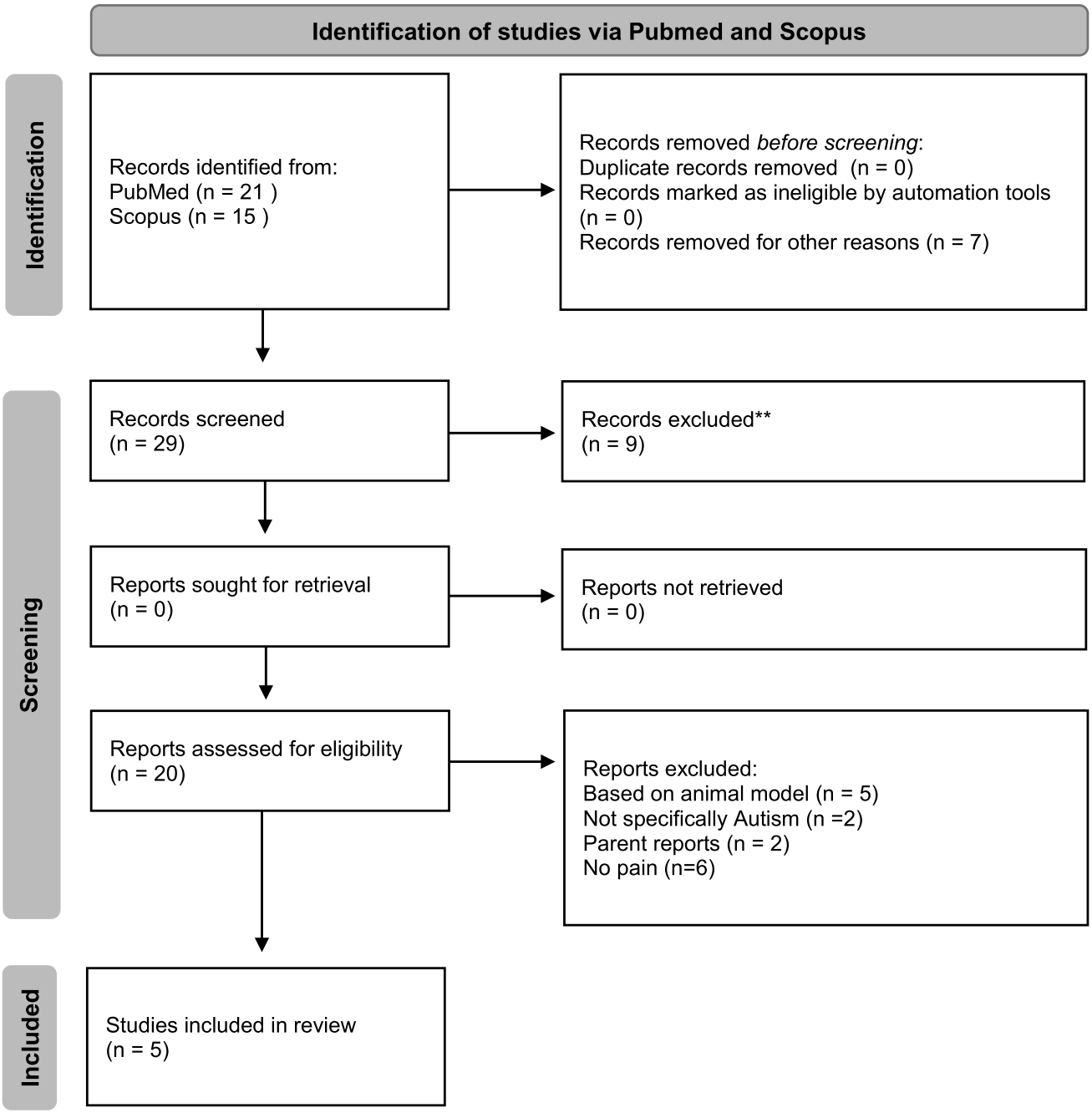

Fig. 1 Flow diagram, according to PRISMA guidelines 2020 for systematic reviews. The diagram shows the process of article selection. Searching the words "quantitative sensory testing, autism"; "sensory testing, autism"; "quantitative sensory testing, autism spectrum disorder"; "sensory testing, autism spectrum disorder," we have found 21 articles in Pubmed and 15 in Scopus. After excluding 7 studies pre-screening because they were not pertinent to the topic and the word we used, we also excluded other 9 articles for the same reason, but after the screening. The remained 20 articles underwent eligibility assessment. Five articles were excluded because they were based on animal model; other two were excluded because they considered neurodevelopmental disorders without specific distinction for autism; other two were excluded because there were considering parents reports only to infer pain; and finally, six studies were excluded because they not assessing pain perception

Results

The first study is from Duerden and colleagues [28]; it aimed to investigate sensitivity to noxious stimuli in adolescent with autism. The authors measured warm and cool detection thresholds and heat and cold pain thresholds in a sample of 20 adolescents with IQ > 70 according to the Wechsler Abbreviated Scale of Intelligence, compared with

Table 1 Summary of literature research concerning the use of quantitative sensory testing to study pain in autisms. From 2008 until 2023, five studies met the selection criteria. Studies have been summarized according to the included samples, dependent variables, results, specific sensory features reported in their results, and limitations, respectively

Study	Autism sample	Neurotypical sample	Dependent variables (for pain)	Results	Reported sensory features in autism	Limitations
Duerden et al. 2015 [28]	20 adolescents with IQ > 70	55 gender-matched neurotypical adolescents	Heat and cold pain thresholds	Higher threshold for warm detection, and a lower temperature for cool detection, commented as less sensitivity to warm and cold in autistic people.	_____	Methods of limits based on RTs
Fründt et al. 2017 [29]	In 13 adults, matched for IQ >70	13 neurotypical adults matched by age and gender	Pain threshold	Differences only for mechanical detection thresholds.	Paradoxical pain perception and allodynia	Sample size for the variability reported in the autism group
Vaughan et al. 2020 [30]	13 adults	13 age, gender-matched adults	Pain threshold and cold-pressor test	Group difference for mechanical stimuli only: hyposensitivity to mechanical stimuli for the autism group	Three people showed paradoxical heat sensation and dynamic mechanical allodynia	Sample size and not matched for IQ
Chien et al. 2020 [32]	32 men	27 age-matched adults	Small fiber density; CHEP; pain threshold; large fiber	17/32 of the autism group had reduced small fiber density; this was associated with higher thermal threshold, higher CHEP amplitude, and tactile peculiarities	See results	Sample size and not matched for IQ
Hoffman et al. 2022 [19]	52 adults	52 age and sex-matched adults	Pain threshold and ratings for repeated stimuli	Hypersensitivity to experimental pain in autism related to autism severity. Comparable inhibition of phasic but not tonic heat stimuli to controls.	See results	Sample not matched for IQ

55 neurotypical adolescents. The authors found individuals with autism to have a higher threshold for warm detection and a lower temperature for cool detection, commented as less sensitivity to warm and cold in people with autism. However, the method of limits has been used to determine the detection threshold, which is based on reaction times and thus related to cognitive abilities. The authors commented that this result could reflect slower response time in the population with autism, more than an actual loss of sensitivity, even if a physiological basis of this between-group difference could be present as well [28]. In 2017, Fründt and colleagues [29] aimed at investigating the 13 sensory parameters of the QST, including pain threshold, in 13 adults with autism, matched for IQ (higher than 70), compared with 13 neurotypical adults, matched by age and gender as well. Overall, except for mechanical detection thresholds, none of the investigated parameters resulted in differences between the two groups; however, the authors reported higher variability in reports from people with autism, as well as distinctive sensory features for some patients like paradoxical pain perception and allodynia. They commented that, for such a variability, probably a larger sample should have been considered [29].

In 2020, also Vaughan and colleagues [30] aimed to characterize sensory differences between people with autism and neurotypical people. They administered QST (testing all the 13 parameters of the QST) and cold pressor test as well, to 13 adults with autism and 13 neurotypical participants, matched for age and gender. Results showed hyposensitivity to mechanical stimuli for participants with autism, compared to neurotypical. Moreover, they also reported high variability for the group with autism, and three participants showed distinct sensory features such as paradoxical heat sensation and dynamic mechanical allodynia. The authors commented that, in line with previous findings [16, 28, 29], a peripheral mechanism could be implied in the observed alteration for mechanical stimuli that involve C-tactile fiber that typically convey pleasant touch sensation (low force and slow stroking, see also Fusaro et al. [31] about pleasant touch). However, out of 13 parameters, this is the only confirmed difference across different studies, indicating that there is no systematic fiber dysfunction in the population with autism and leading to the conclusion that central mechanisms could be responsible for the sensory and behavioral differences observed in autism [30]. In the same year, Chien and colleagues [32] investigated if peripheral mechanism could characterize responses to sensory thermal stimuli in autism. They studied small fiber assessments through skin biopsy, intraepidermal nerve fiber (IENF) density, contact heat-evoked potentials (CHEPs) collected through EEG, quantitative sensory testing, and the large-fiber physiology of nerve conduction. They found 17, out of 32 of the group with autism, with reduced small fiber density, while in the remaining 15, this aspect was not present. Within the 17 people subgroup, the fiber density was associated with elevation of thermal threshold, higher CHEP amplitude, and correlated with tactile peculiarities such as "dislike to be touched" and "are uncomfortable with some texture of clothes." These results provide evidence of differences in the pathology and physiology of nociceptive processing at the peripheral (fiber density) and central (CHEP amplitude) levels in a subgroup of people with autism. This evidence supports the hypothesis that altered peripheral mechanisms are involved in sensory and behavioral features of autism; however, it is also interesting that only a subgroup of people within the autism spectrum showed these differences, thus the mechanisms involved in peculiarities of the other patients remain unclear. Finally, the last study investigating specifically pain in autism with QST was recently published by Hoffman and colleagues [19], and it has been described in details above in this review. The authors were testing a specific central mechanism behind peculiarities observed in pain perception in autism: the excitatory–inhibitory (E/I) imbalance. On a larger sample compared to the previously presented, they found a pain modulation profile in the autism sample that is compatible with pro-nociceptive profile, characterized by low pain-conditioned modulation and enhanced temporal summation of repeated nociceptive stimulation, with hypersensitivity attributed to autism severity. A limitation of this study is that within this bigger sample, participants were not matched for IQ; nonetheless, due to the high variability of physiological and subjective measures reported in autism, large sample have to be considered to characterize specific mechanisms of sensory processing in this population.

Discussion

To date, we have found only five studies specifically investigating pain with QST methodology, of which only one study considered adolescents and none considered children. While all the studies share the use of QST in the methods, they also investigated different hypotheses and considered different dependent variables on very different samples as well. Nonetheless, communalities are present between the studies from Fründt and colleagues [29] and Vaughan and colleagues [30]. They both found between-group differences for mechanical stimuli only, also describing within their samples the sensory features of a few patients as paradoxical heat perception and mechanical allodynia. Interestingly, they both converge on the idea that peripheral afferent function, specifically related to C-tactile fiber, could be involved in these differences between autism and neurotypical perception. This requires further investigation concerning also the study of

C-tactile fiber in this population, investigating touch and pain together, and specifically affective touch in autism. Interestingly, some groups already investigated responses to affective touch within this population and found different brain processing and top-down modulation with respect to the neurotypical sample [33–35]. It has been also suggested that the effect of affective touch on different domains, like emotion and perception, even when experienced vicariously in virtual environments [36], would be interesting to deepen the relation between affective touch and pain, extending it to the autism spectrum as well. Looking instead at the studies from Duerden and colleagues [28] and Chien and colleagues [32], they both reported lower sensitivity on some perceptual parameters for people with autism. However, only Chien and colleagues collected other measures than QST, being able to characterize sensory fiber density decrease. This decreased density can explain sensory features in Chien's samples, and we could speculate that the same mechanism could be at play for results reported by Duerden and colleagues as well. However, differences in methodologies do not allow to claim this conclusion and to directly compare these results. Moreover, even for Chien's sample, decreased fiber density was present in a subgroup of people only leading to the conclusion that peripheral mechanism can only partially explain perceptual feature in autism, and further investigation is needed.

Finally, some common limitations of these studies concerned the sample size and the need to match neurotypical and neurodivergent samples on many features at the same time as age, gender, and QI, as well as to increase sample size, to not fell in misleading results due to low statistical power.

Moreover, it emerges the necessity to quantify pain perception taking into consideration methodological features concerning:

- The pain modality. The best would be to characterize responses to different pain modalities within the same sample, as indicated by the results from Zhang et al. [18].
- The pain measure and response to pain. A first consideration concerns the way to analyze pain measures, considering that pain is characterized by high inter- and intra-individual variability of subjective reports. Thus, a statistical approach is needed to account for such variability (i.e., ANCOVA instead of ANOVA, using subject as a covariate, or linear mixed models with at least random intercept, or even more complex models) [24, 25, 37]. Moreover, such variability has been reported to be higher for pain threshold than for other pain measures, such as ratings or physiological measures [18]. Considering these aspects together, we auspicate that in future research would be considered different pain measures within the same sample and that statistical approaches would be chosen in order to account for the variability of pain as a dependent variable.
- The sample. As emerged from Moore's work [13], many groups that collected data regarding pain in autisms did not compare their data with a control group, even if this was more frequent among clinical reports and parent reports. Moreover, another important feature is the heterogeneity within the sample with autism from the genetic aspects [38] to behavioral outcomes, such as motor coordination, in which the degree of autistic traits (high or low) differentiates the motor coordination [39]. Finally, there is also the heterogeneity of investigated samples in the literature, which lead to difficulties in comparing results from different studies, as emerged from the recent reviews [13, 18]. Indeed, some studies matched samples for age and IQ as well [3, 15, 40], while some others, such as Cascio and colleagues [16] and Hoffman and colleagues [19], did not match for IQ. Future studies could take into account these considerations, including not only the control group, but also matching samples for age, gender, and IQ, as well as monitoring individual differences in cognitive/emotional/behavioral peculiarity (as autistic traits), and account for their effect in the statistics as well.

Methodological features are illustrated in Fig. 2.

According to recent findings [14, 15, 40], beliefs about reduced sensitivity to pain in people with autism have been challenged. However, other important questions are still open: how can we measure pain perception in neurodivergent people? How can we overcome differences in communication by using novel or modified assessment methods?

Indeed, a limitation of the actual QST is that it is not meant for the neurodivergent population, for minimally verbal people, or with severe cognitive/motor/communicative disabilities. As highlighted already by Duerden and colleagues [28], the use of the method of limits to measure perceptive thresholds, as relying on reaction times, could be affected by different motor reactivity and thus produce a biased result in certain population. Moreover, when including samples with neurodivergent children, especially with disabilities or communicative peculiarities, a different ethical complexity has to be considered. To date, collaborative partnership, scientific validity, risk-benefit ratio for the patient, and informed consent are still open challenges in research with intellectual disabilities, especially to study pain, where it could be difficult to control stimuli unpleasantness and tolerability with non-verbal patients [41, 42]. At the same time, the risk is to exclude these patients from research, contributing to social inequity [43]. In line with these considerations, Symons and colleagues [44, 45] modified the QST in order to study perception in children

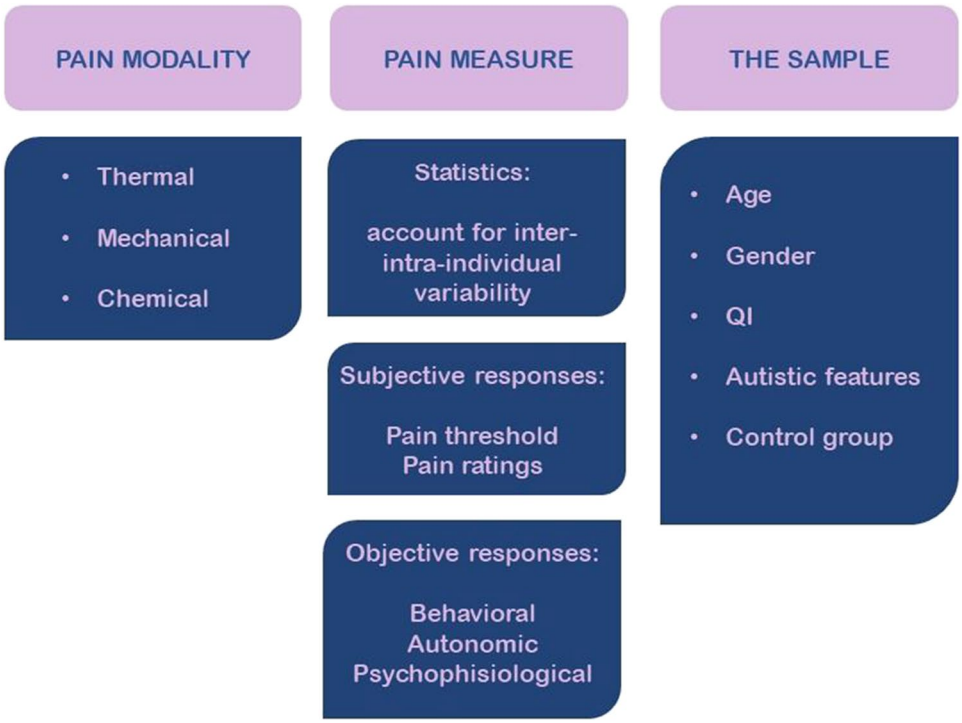

Fig. 2 Summary of the methodological considerations emerged from recent literature. According to the recent literature, the main reasons preventing direct comparison among different studies concern differences regarding pain modality, pain measures and responses to pain, and the sample, listed in the upper part of the figure. Below each of the three pink boxes, the main issues to be considered are listed in the blue boxes

with global developmental delay. To approach non-verbal patients, they recorded behavioral reactivity, including any vocal response, while to reduce discomfort, they collected ratings immediately after the stimulus, avoiding stimuli repetition. However, these modifications prevented to measure sensory thresholds of different modalities, for example, they were not interested in measuring pain threshold [44, 45]. Thus, despite advancement related to recent modifications, a protocol suitable to study pain perception in the neurodivergent population is still absent. Moreover, considering that pain in people with autism has been often underestimated, deepening such an issue in children would have clinical implication concerning pain management in daily life and clinical practice, as well as would increase common knowledge concerning basic mechanisms involved in neurodivergency since early stages of life.

Conclusions

Many years after Moore's review [13], evidences concerning pain in autism through QST are still scant, and methodological limitations concerning sample sizes, sample heterogeneity, and testing protocols are still present. Despite this, an important update is the challenge to the presumed hyposensitivity to pain in autism. As much as reasonable could be to rely on parents' reports, they seem not fully descriptive of the actual patients' experience and should be at least correlated with other measures. On which measure to rely on, in case of very divergent communicative skills, is still an open question. Moreover, while recent studies with QST showed peripheral fibers functioning to be involved in autistic features, also central mechanisms could explain differences in sensory processing and social behavior, in line with recent theoretical framework based on Bayesian and predictive coding principles [5, 46]. However, evidences from children, which could help in targeting crucial and early mechanisms, are almost inexistent. This could be due to the intrinsic limitation of QST with neuroatypical population and ethical complexity. Nonetheless, it is possible, and needed, to change existent protocols and increase controlled and reproducible testing of sensory features in autism.

Acknowledgements This work was supported by the Italian Ministry of Health (Ricerca Corrente Program 2023).

Author contribution All authors contributed to the review conception and design. Preliminary searches, literature search, and data analysis were performed by Valentina Nicolardi and Antonio Trabacca. The first draft of the manuscript was written by Valentina Nicolardi, further revised by Giuseppe Accogli and Antonio Trabacca, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethical approval Not applicable.

Informed consent Not applicable.

Consent for publication This manuscript has been approved for publication by all authors.

Conflict of interest The authors declare no competing interests.

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