Atypical Pain Sensitivity in Individuals with Autism Spectrum Disorder: Evidence From Meta-Analysis

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Date: 2021-02-03T00:00:00+00:00

Abstract

This study employed a meta-analytic approach to examine atypical pain sensitivity in individuals with Autism Spectrum Disorder (ASD), using pain threshold, pain-evoked physiological responses, and pain ratings as outcome variables, with the aim of providing reference for the diagnosis and intervention of ASD. The meta-analysis included 16 studies (total sample size N = 822). For pain threshold, no significant difference was found between the ASD group and the control group, but it was moderated by variables such as pain modality; for example, the pressure pain threshold of the ASD group was significantly lower than that of the control group. Regarding pain-evoked physiological responses, the ASD group exhibited stronger physiological responses to real-world medical pain than the control group. However, there was no significant difference in pain ratings between the ASD group and the control group. Future research should combine multimodal pain stimuli and multidimensional pain assessment to systematically investigate pain sensitivity in individuals with ASD and its relationship with core clinical symptoms.

Full Text

Abnormal Pain Sensitivity in Individuals with Autism Spectrum Disorder: Evidence from Meta-Analysis

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Abstract

This study employed meta-analysis to examine abnormal pain sensitivity in individuals with Autism Spectrum Disorder (ASD) using pain threshold, pain-

evoked physiological responses, and pain ratings as outcome variables, aiming to provide insights for ASD diagnosis and intervention. The meta-analysis included 16 studies with a total sample size of N = 822. For pain threshold, no significant difference was found between the ASD and control groups, though this was moderated by variables such as pain modality; specifically, the ASD group exhibited significantly lower pressure pain thresholds than the control group. Regarding pain-evoked physiological responses, the ASD group showed stronger physiological reactions to real-world medical pain than the control group. However, no significant difference in pain ratings was observed between the ASD and control groups. Future research should systematically investigate pain sensitivity in ASD individuals using multimodal pain stimulation and multidimensional pain assessment, examining its relationship with clinical core symptoms.

Keywords: Autism Spectrum Disorder, pain sensitivity, meta-analysis, pain threshold, pain-evoked physiological responses

Received: September 21, 2020
This research was supported by the National Natural Science Foundation of China (31871127), the Characteristic Innovation Project of Guangdong Provincial Universities (2019KTSCX149), and the Shenzhen Basic Research Free Exploration Project (JCYJ20190808154413592).
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Autism Spectrum Disorder (ASD) is a pervasive developmental disorder caused by abnormal nervous system development, with core symptoms including deficits in social communication and interaction, and restricted, repetitive patterns of behavior, interests, or activities. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013), sensory abnormalities are included under the restricted and repetitive behaviors criteria. Statistics indicate that 65%–90% of individuals with ASD exhibit abnormal sensory responses, including over- or under-reactivity to sensory stimuli across different modalities such as specific sounds, lights, odors, and tastes (Leekam et al., 2007). Approximately 95% of children with ASD display sensory abnormalities, such as over-reactivity to loud noises or fascination with spinning or flashing lights and objects (Rogers & Ozonoff, 2005). Among these abnormal sensory responses, Klintwall et al. (2011) found that abnormal reactions to auditory and pain stimuli were the most distinctive features differentiating children with ASD from those with other developmental disorders. Regarding the pain modality, DSM-5 describes pain abnormalities in ASD individuals as "apparent indifference to pain," suggesting lower pain sensitivity compared to typical individuals. However, current research findings exhibit substantial heterogeneity (Allely, 2013): some studies report over-reactivity to pain stimuli in ASD individuals (Rattaz et al., 2013), while others find under-reactivity or normal responses (Li et al., 2015; Fründt et al., 2017).

Abnormal pain responses may be closely related to the clinical core symptoms of ASD. For instance, under-reactivity to pain in ASD individuals may lead to inappropriate restricted and repetitive behaviors, such as self-injurious behaviors

like head-banging or scalp-picking (Summers et al., 2017). Moreover, impairments in the preferentially developing perceptual system may have secondary effects on subsequently developing social-cognitive systems (Bailey et al., 1996), meaning that abnormal pain sensitivity in ASD individuals may affect the development of their social functioning (Fitzgibbon et al., 2013). Animal studies have directly demonstrated the link between abnormal pain sensitivity and ASD core symptoms: when the autism-related gene SHANK3 was knocked out, mutant mice exhibited not only typical ASD core symptoms—including social communication deficits and frequent abnormal movements—but also under-reactivity to thermal pain stimuli (Han et al., 2016). Therefore, understanding abnormal pain sensitivity in ASD individuals can help expand our knowledge of ASD biological mechanisms, such as explaining restricted repetitive behaviors and social dysfunction in ASD individuals from the perspective of abnormal pain sensory information processing.

Pain is defined as an unpleasant subjective sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (Raja et al., 2020). Pain prompts individuals to detect actual or potential threats in the environment and activates defense systems to avoid harm. Clinically, pain is a primary symptom of many diseases and has been regarded as the "fifth vital sign" in addition to respiration, pulse, temperature, and blood pressure (McCaffery & Pasero, 1997). However, different individuals produce different pain responses to the same noxious stimulus or clinical condition, manifesting as individual differences in pain sensitivity. These individual differences can predict the risk of chronic pain development (Meints et al., 2019); for example, individuals with high pain sensitivity have a higher risk of developing chronic pain from acute postoperative pain (Arendt-Nielsen & Yarnitsky, 2009). Furthermore, individual differences in pain sensitivity affect healthcare resource allocation, as patients with low pain sensitivity report lower pain experiences, making it difficult for medical staff to accurately and effectively assess their symptoms. Therefore, from a clinical practice perspective, understanding abnormal pain sensitivity in ASD individuals can facilitate the evaluation and identification of pain responses, guide rational allocation of medical resources and selection of precise treatment plans, and ultimately improve the quality of life for individuals with ASD.

Previous studies have explored abnormal pain sensitivity in ASD individuals. Based on their research methods, these studies can be categorized as case studies, survey methods, and experimental methods. Case studies and survey methods tend to support hyposensitivity to pain in ASD individuals, while experimental studies show high heterogeneity in their findings.

1.1 Case Study Method

Early case studies primarily relied on clinical observations of behavioral manifestations in children with ASD, with most tending to support hyposensitivity to pain. For example, Mahler (1952) documented an ASD child who burned his lips

with a lighter yet remained emotionally calm. Rothenberg (1960) recorded an ASD child named Jonny who felt no pain even after strong impact. Gillberg and Coleman (2000) documented an ASD child named Sally who could run naked in the snow, and another ASD child who could keep his hand in a fireplace without reaction until smelling burning flesh. These behaviors would cause intolerable pain in typical individuals, but ASD individuals appeared pain-insensitive or even pain-absent. Notably, case studies are often based on observations of small samples, and results are susceptible to the observer' s subjective expectations and knowledge.

1.2 Survey Method

Survey research typically employs questionnaires or interviews targeting either ASD individuals or their caregivers. One study administered the Sensory Sensitivity Questionnaire (SSQ; Minshew & Hobson, 2008) to both ASD and typical individuals, finding that ASD individuals reported higher pain sensitivity. Undeniably, as pain is a subjective personal experience, self-report is the most direct pain assessment method, but this requires the reporter to have clear and accurate recall abilities and intact self-reflection capacity (Moore, 2015). Therefore, pain assessment relying on self-report is not suitable for ASD individuals with reading disabilities or intellectual impairments. Caregivers of ASD individuals, such as parents, interact with them daily and understand their behavioral patterns well. Consequently, some studies have indirectly investigated pain sensitivity in ASD individuals through caregiver reports, though results vary considerably. Parents of ASD individuals reported high pain sensitivity on the SSQ (Minshew & Hobson, 2008), but normal pain sensitivity on the Non-Communicating Children' s Pain Checklist (NCCPC; McGrath et al., 1998) (Nader et al., 2004). Another study using the Pre-Linguistic Behavioral Pain Reactivity Scale (PL-BPRS; Tordjman et al., 1999) surveyed parents of 73 ASD individuals, finding that 65.8% reported low pain reactivity, 27.4% normal reactivity, 2.8% high reactivity, 2.8% no reactivity, and 1.4% bizarre reactivity, suggesting that most ASD individuals may have low pain sensitivity (Tordjman et al., 2009). However, these questionnaire results show large discrepancies, possibly related to differences in question formats, items, and response options across questionnaires.

Questionnaire methods are limited by written language, while interview methods offer greater flexibility. In an interview study of 77 parents of ASD children and 32 parents of typical children (Militerni et al., 2000), when parents mentioned abnormal pain responses to noxious stimuli, researchers asked targeted follow-up questions about frequency, stimulus type, and setting. After coding parental responses, results showed 57% of ASD children' s parents reported normal pain reactivity, 22% reported low pain sensitivity, and 21% reported very low pain sensitivity, compared to 91%, 6%, and 3% respectively in the control group, supporting hyposensitivity to pain in ASD individuals. Klintwall et al. (2011) interviewed parents of 208 preschool children with ASD, finding that

43% reported low pain sensitivity in their children regarding the pain modality. Both interview studies support low pain sensitivity in ASD children, though interview methods are susceptible to examiner questioning bias. For example, in Klintwall et al.' s study, questions for auditory and tactile modalities were phrased as "over-reactivity to sounds" and "over-reactivity to touch," while pain questions were phrased as "under-reactivity to pain." Additionally, interview question design and coding methods affect results; for instance, Militerni et al.' s study only included normal and low pain response categories, excluding high pain response.

1.3 Experimental Method

Experimental methods assess pain responses in ASD individuals under controlled conditions and can be divided into natural experiments (involving real medical procedures such as injections, blood draws, or tooth extractions) and laboratory experiments (involving laboratory-induced pain such as cold, heat, or electrical stimulation). Natural experiments primarily examine pain responses in real medical settings. Studies have found that during venipuncture, ASD individuals show stronger heart rate responses than typical individuals (Tordjman et al., 2009; Li et al., 2015), with slower heart rate acceleration and deceleration (Rattaz et al., 2013). Natural experiments have high ecological validity, revealing that ASD individuals exhibit more intense physiological responses during real medical procedures, indicating higher pain sensitivity.

Laboratory pain assessment typically combines standardized noxious stimuli with psychophysical methods to evaluate pain sensitivity, commonly using measures of pain threshold, pain tolerance threshold, and pain ratings. Pain threshold refers to the minimum stimulus intensity at which an individual first perceives pain, such as when a series of closely spaced physical stimuli are delivered in ascending or descending order, with the intensity that first elicits pain sensation defined as the pain threshold. Pain tolerance threshold refers to the maximum pain stimulus an individual can endure, such as when a subject is instructed to immerse their hand in ice water at a constant temperature (e.g., 2°C) and keep it there as long as possible until the pain becomes intolerable, with the duration from immersion to withdrawal defined as cold pain tolerance threshold. Pain intensity rating refers to the perceived pain intensity from a suprathreshold noxious stimulus (exceeding the pain threshold), for example, delivering a 3J laser heat stimulus and asking subjects to report their experienced pain intensity (e.g., on a 0-10 scale: 0 = no pain, 10 = unbearable pain). Notably, these measures relate differently to pain sensitivity: higher pain threshold/tolerance indicates lower pain sensitivity, while higher pain ratings indicate higher pain sensitivity. Regarding pain induction modalities, laboratory experiments involve cold pain, heat pain, pressure pain, electrical stimulation pain, and laser pain. However, current laboratory experimental results show substantial heterogeneity. Some studies find ASD children exhibit lower cold and heat pain thresholds, indicating hypersensitivity (Cascio et al., 2008; Failla et al.,

2019), while others find higher electrical stimulation pain thresholds, indicating hyposensitivity (Li et al., 2015), and still others find no significant differences between ASD and typical individuals in cold, heat, or electrical stimulation pain perception (Fründt et al., 2017; Vaughan et al., 2019; Yasuda et al., 2016).

1.4 Research Purpose

Compared to case studies and survey methods, experimental methods employ strict control of experimental conditions, such as controlling pain stimulus presentation time, intensity, and location, and accurately recording physiological or behavioral responses in ASD individuals, thereby enabling assessment of pain sensitivity under rigorous experimental design and control. However, current experimental findings show high heterogeneity. Therefore, this study used meta-analysis to reorganize and calculate effect sizes from existing experimental studies on pain sensitivity in ASD individuals, systematically examining abnormal pain sensitivity and analyzing moderating variables affecting result heterogeneity, to provide more objective and comprehensive information for existing inconsistent conclusions.

2.1 Literature Search

The literature search covered both Chinese and English publications from January 1, 1900 to August 10, 2020. Chinese literature was searched using the China National Knowledge Infrastructure (CNKI) database, while English literature was searched using PubMed, Web of Science, and PsycInfo. Additionally, reference back-tracking and Google Scholar were used for supplementary searches. Keywords related to "pain" and "autism" were selected. Chinese search terms were ["pain" OR "nociceptive stimulation"] AND ["autism" OR "solitary disease" OR "Asperger syndrome"], while English search terms were ["pain" OR "nociception"] AND ["autis*" OR "ASD" OR "Asperger"].

2.2 Inclusion and Exclusion Criteria

Inclusion criteria were: (1) empirical studies with both experimental and control groups, where the experimental group comprised individuals with Autism Spectrum Disorder (excluding those with high autistic traits) and the control group comprised typical individuals; (2) studies containing pain sensitivity measures such as pain threshold, pain tolerance threshold, pain ratings, and pain-evoked physiological responses; (3) studies with complete data reporting, such as means, standard deviations, and sample sizes (during literature collection, if a study did not report convertible metrics, attempts were made to obtain relevant data through other means; if still unavailable, the sample was excluded).

Exclusion criteria were: (1) literature types including reviews, conference abstracts, patents, theses, observational studies, or survey studies; (2) animal studies; (3) literature with incomplete data that could not be obtained from original sources.

2.3 Literature Screening Process and Results

As shown in [Figure 1: see original paper], literature screening included four stages: search, initial screening, confirmation, and inclusion. Two reviewers (the first and second authors) independently conducted screening based on inclusion and exclusion criteria to determine final studies for the meta-analysis. One Chinese and 15 English studies met the criteria (16 total studies, total sample size = 822 individuals).

[Figure 1: see original paper] Flowchart of literature search and inclusion/exclusion process

2.4 Literature Coding and Effect Size Calculation

Moderating variables were coded for included studies: (1) stimulus modality: cold pain, heat pain, pressure pain, mechanical pain, and electrical stimulation pain (cold pressor and contact cold pain both belong to experimentally evoked cold pain stimulation [Simone & Kajander, 1997] and were combined in the cold pain modality for meta-analysis [Kim et al., 2017]); (2) stimulus location: arm, hand (including palm and dorsum), leg, and multi-site average; (3) ASD group sample size: $n \leq 10$, $10 < n \leq 20$, $20 < n \leq 50$, and $n > 50$; (4) participant population: children only, adolescents only, adolescents and adults combined, and adults only ($ $12 years coded as children, 13-18 years as adolescents, >18 years as adults); (5) study region: Asia, America, and Europe. Detailed coding is shown in .

This study used STATA12.0 for meta-analysis, employing Hedge's g (a corrected version of Cohen' s d) as the effect size for differences between ASD and control groups. If a study included multiple conditions or trials yielding multiple effect sizes, this could overweight the study and bias results (Borenstein et al., 2009). Therefore, for studies with multiple measurements (e.g., pain thresholds across different modalities), we examined whether reported conditions represented important moderating variables for this study: if so, they were treated as separate independent studies with individual effect sizes calculated; otherwise, they were first averaged before inclusion in the overall analysis (Kim et al., 2017).

2.5 Model Selection and Heterogeneity Analysis

Random-effects models are generally more realistic than fixed-effects models, as they account for both within-study and between-study variation, reducing estimation error. Since included studies differed in participants, pain stimulus modalities, and stimulus locations, we selected a random-effects model for meta-analysis (Stubbs et al., 2015). Heterogeneity was assessed using Q tests and I^2 statistics. A significant Q value indicates heterogeneity among studies; I^2 describes the proportion of variance between studies relative to total variance, with $I^2 \leq 25\%$ indicating low heterogeneity and $I^2 \geq 75\%$ indicating high heterogeneity (Huedo-Medina et al., 2006).

2.6 Publication Bias Assessment

Publication bias refers to the tendency for statistically significant results to be published more readily than non-significant results, which are often rejected. This creates systematic differences between included studies and the complete body of research, affecting meta-analysis results. Publication bias is an objective phenomenon for which no adequate correction method currently exists (Reed et al., 2015); researchers typically employ multiple assessment methods. This study used funnel plots, Egger' s linear regression, and trim-and-fill methods to detect publication bias.

As shown in , 16 studies met the criteria and were included in the meta-analysis: 12 involved pain threshold, generating 23 independent effect sizes; 5 involved pain ratings, generating 7 independent effect sizes; 3 involved pain-evoked physiological responses (heart rate changes), generating 3 independent effect sizes; and 2 involved pain tolerance threshold, generating 4 independent effect sizes. Due to the small number of studies on pain tolerance threshold (n = 2), which does not meet meta-analysis requirements ($ $3 studies; Nahman-Averbuch et al., 2018), we conducted meta-analysis only on pain threshold, pain ratings, and pain-evoked physiological responses, with qualitative description only for pain tolerance threshold. Since higher pain ratings or stronger physiological responses indicate higher pain sensitivity, while higher pain threshold indicates lower pain sensitivity, we recoded raw data for the pain threshold outcome variable by multiplying group means by -1 (standard deviations remained unchanged) before meta-analysis (Tesarz et al., 2012). Thus, positive effect sizes indicated higher pain sensitivity in ASD individuals compared to typical individuals, while negative effect sizes indicated lower pain sensitivity.

Information on studies included in the meta-analysis (16 studies)

3.1.1 Pain Threshold

As shown in [Figure 2: see original paper], random-effects model analysis revealed no significant difference in pain threshold between ASD and typical individuals, with Hedge' s g = 0.34 (0.2, 0.5, and 0.8 correspond to small, medium, and large effect sizes, respectively), two-tailed p = 0.16, and 95% confidence interval [−0.14, 0.82]. This indicates comparable pain thresholds between ASD and typical individuals.

[Figure 2: see original paper] Forest plot of pain threshold

3.1.2 Pain Ratings

For the pain ratings outcome variable, involved stimulus modalities included cold pain, heat pain, and electrical stimulation pain. As shown in [Figure 3: see original paper], random-effects model analysis revealed no significant difference in pain ratings between ASD and typical individuals, with Hedge' s g = −0.26,

p = 0.17, and 95% confidence interval [−0.64, 0.11], indicating comparable pain ratings between groups.

[Figure 3: see original paper] Forest plot of pain ratings

3.1.3 Pain-Evoked Physiological Responses

The physiological response indicator was heart rate change during real medical procedures (ΔHR: post-venipuncture minus pre-venipuncture). As shown in [Figure 4: see original paper], random-effects model analysis revealed significantly stronger physiological responses in ASD individuals compared to typical individuals during venipuncture, with Hedge' s g = 2.87, p = 0.002 (p < 0.01), and 95% confidence interval [1.07, 4.67], indicating more pronounced heart rate responses in ASD individuals.

[Figure 4: see original paper] Forest plot of pain-evoked physiological responses

3.1.4 Pain Tolerance Threshold

Due to the small number of studies on pain tolerance threshold (n = 2), meta-analysis was not conducted for this outcome variable. Two experimental studies have examined differences in pain tolerance threshold between ASD and typical individuals (Vaughan et al., 2019; Yasuda et al., 2016), involving cold pain, heat pain, and electrical stimulation pain modalities. As shown in , no significant differences were found between ASD and typical individuals in cold pain, heat pain, or electrical stimulation pain tolerance thresholds.

Information on studies of pain tolerance threshold in ASD individuals

3.2 Heterogeneity Testing

Heterogeneity testing was conducted for pain threshold, pain ratings, and pain-evoked physiological responses. Q tests for pain threshold and pain-evoked physiological responses indicated significant heterogeneity (p < 0.001), with I^2 = 91.0% (p < 0.001) and I^2 = 97.2% (p < 0.001), respectively. The Q test for pain ratings did not reveal significant heterogeneity, with I^2 = 50.4%. High heterogeneity suggests potential moderating variables exert important influences on effect sizes, warranting subgroup analysis to further examine moderating effects (Cooper, 1989).

3.3 Subgroup Analysis

Random-effects model subgroup analysis examined whether stimulus modality, stimulus location, sample size, participant population, and region moderated pain threshold results (see). Due to the small number of studies on pain-evoked physiological responses (n = 3), subsequent subgroup analysis was not conducted for this outcome variable.

Random-effects model analysis of moderating variables

3.3.1 Stimulus Modality Effect sizes for the five modalities were: g (cold pain) = 0.17, p = 0.31; g (heat pain) = −0.05, p = 0.86; g (pressure pain) = 1.62, p = 0.006; g (mechanical pain) = −0.43, p = 0.13; g (electrical stimulation pain) = −0.27, p = 0.63. Within-modality heterogeneity values were I^2 (cold pain) = 19.6%, I^2 (heat pain) = 67.1%, I^2 (pressure pain) = 91.9%, I^2 (mechanical pain) = 0.0%, I^2 (electrical stimulation pain) = 93.2%. Between-modality heterogeneity testing indicated significant differences among the five modalities, QB = 10.9, p = 0.03, suggesting that experimental pain stimulus modality significantly moderates pain threshold abnormalities in ASD individuals.

3.3.2 Stimulus Location Effect sizes for stimulus locations were: g (hand) = 0.41, p = 0.22; g (arm) = 0.78, p = 0.43; g (leg) = 0.22, p = 0.54; g (multi-site average) = 0.93, p = 0.15. Within-location heterogeneity values were I^2 (hand) = 87.9%, I^2 (arm) = 89.1%, I^2 (multi-site average) = 92.0%. Between-location heterogeneity testing indicated no significant differences among the four location conditions, QB = 3.46, p = 0.33, suggesting that stimulus location does not significantly moderate pain threshold abnormalities in ASD individuals.

3.3.3 ASD Group Sample Size Effect sizes for ASD group sample sizes were: g ($n \leq 10$) = 1.54, $p < 0.001$; g ($10 < n \leq 20$) = −0.04, p = 0.65; g ($20 < n \leq 50$) = 1.86, p = 0.01; g ($n > 50$) = −1.61, $p < 0.001$. Within-group heterogeneity values were I^2 ($n \leq 10$) = 0.0%, I^2 ($10 < n \leq 20$) = 14.5%, I^2 ($20 < n \leq 50$) = 94.7%. Between-group heterogeneity testing indicated significant differences among the four sample size categories, QB = 79.26, $p < 0.001$, suggesting that ASD group sample size moderates pain threshold abnormalities in ASD individuals.

3.3.4 Participant Population Effect sizes for different populations were: g (children) = 0.81, p = 0.74; g (adolescents) = −0.28, p = 0.14; g (adolescents and adults) = 0.89, p = 0.04; g (adults) = 0.07, p = 0.66. Within-population heterogeneity values were I^2 (adults) = 55.6%, I^2 (children) = 99.1%, I^2 (adolescents) = 0.0%, I^2 (adolescents and adults) = 88.4%. Between-population heterogeneity testing indicated marginally significant differences among the four populations, QB = 6.90, p = 0.08, suggesting that participant population may moderate pain threshold abnormalities in ASD individuals.

3.3.5 Region Effect sizes for different regions were: g (Asia) = 0.57, p = 0.42; g (America) = 0.14, p = 0.48; g (Europe) = 0.33, p = 0.48. Within-region heterogeneity values were I^2 (Asia) = 96.7%, I^2 (America) = 63.2%, I^2 (Europe) = 90.7%. Between-region heterogeneity testing indicated no significant differences among the three regions, QB = 0.44, p = 0.80, suggesting that study region does not significantly moderate pain threshold abnormalities in ASD individuals.

3.4 Publication Bias Assessment

In a funnel plot, the horizontal axis represents standardized mean difference (effect size) and the vertical axis represents its standard error. Symmetrical distribution of effect sizes around the vertical axis suggests no publication bias, while asymmetry indicates potential bias (Rothstein et al., 2005). As shown in [Figure 5: see original paper], the funnel plot shows asymmetry at the bottom, suggesting possible publication bias. Egger' s linear regression and trim-and-fill methods were further applied. In Egger' s test, intercept values closer to 0 indicate less likelihood of publication bias (Egger et al., 1997). The intercept was 6.96, $p < 0.01$, with 95% confidence interval not including 0, indicating potential publication bias. Based on the assumption that publication bias causes funnel plot asymmetry, the trim-and-fill method uses iterative procedures to estimate the number of missing studies and their impact on the pooled effect size. Trim-and-fill analysis showed that after imputation, g (adjusted) = 0.34, 95% confidence interval [−0.14, 0.82], indicating that publication bias did not significantly affect results.

[Figure 5: see original paper] Funnel plot of publication bias for pain threshold results

4 Summary and Outlook

For the pain threshold outcome variable, no significant difference was found between ASD and typical individuals, though results were moderated by stimulus modality, sample size, and participant population. For pressure pain modality, ASD individuals showed significantly lower pressure pain thresholds than typical individuals, indicating hypersensitivity to pressure pain. For pain-evoked physiological responses, ASD individuals showed stronger physiological reactions during real medical procedures than typical individuals, indicating hypersensitivity to medical pain. For pain ratings, no significant difference was found between ASD and typical individuals. These findings suggest that pain sensitivity abnormalities in ASD individuals may be modality-specific, such as hypersensitivity only to pressure pain and medical pain. Future research should combine multiple pain modalities and multidimensional pain assessment methods to systematically examine pain sensitivity abnormalities in ASD individuals and their relationship with clinical core symptoms, thereby expanding the biological mechanisms of ASD and providing evidence-based guidance for early diagnosis and clinical intervention.

However, due to the 特殊性 of the ASD population and the complexity of psychophysical pain measurement, the number of studies included in the meta-analysis was relatively small, with outcome variables limited to pain threshold, pain ratings, and pain-evoked physiological responses. Additionally, in subgroup analyses, the distribution of samples across moderating variables was unbalanced, with some subgroups containing few studies, which may have affected moderation analysis. As empirical research in this field increases, future

meta-analyses can include more experimental studies and outcome variables (e.g., pain tolerance threshold and pain-evoked brain responses) to deepen understanding of pain sensitivity abnormalities in ASD individuals.

4.1 Sample Selection in ASD Research

This study found that both ASD sample size and participant population moderate pain sensitivity abnormalities in ASD individuals, possibly because the ASD population includes multiple subtypes with large individual differences. Since pain is a subjective experience influenced by biological, psychological, and social factors, and pain expression and responses change with life experiences and social skills, future research should expand sample sizes and comprehensively examine pain sensitivity abnormalities across different age groups in ASD populations.

The meta-analysis found a significant difference in pressure pain threshold between ASD and typical individuals, with Hedge' s g = 1.62. Based on this result, using G*Power software (Faul et al., 2007), the estimated appropriate sample size is no fewer than 11 participants per group (two-tailed test, $\alpha = 0.05$, $1-\beta = 0.95$). However, cross-sectional studies cannot capture the developmental and continuous characteristics of pain processing in ASD individuals. Future research should employ longitudinal designs to examine pain sensitivity abnormalities in ASD individuals from a developmental perspective, characterizing the developmental trajectory of pain sensitivity and its relationship with core symptom development, thereby providing a potential physiological indicator for early diagnosis, disease classification, and severity assessment in ASD.

The cognitive and behavioral characteristics of ASD individuals limit methodological options. For example, due to low experimental compliance and cognitive impairments, recruiting ASD participants for experimental research presents challenges, and some ASD studies have small sample sizes, leading to low replicability. Research suggests that ASD symptoms are continuously distributed in the general population (Hoekstra et al., 2011), meaning everyone has autistic traits to varying degrees. Individuals with high autistic traits exhibit behaviors similar to ASD but below clinical diagnostic thresholds and are therefore considered analogous to ASD individuals (Guan & Zhao, 2015). The Autism Spectrum Quotient (AQ; Baron-Cohen et al., 2001) can be used to screen for high and low autistic trait individuals from the typical population, such as defining the top and bottom 27% of AQ scores as high and low autistic trait groups. Future research could use "quasi-autism" approaches to examine pain sensitivity differences between high and low autistic trait individuals, helping us understand pain information processing and encoding in ASD individuals.

4.2 Pain Assessment in ASD Individuals

Pain is a multidimensional subjective experience comprising sensory-discriminative, affective-motivational, and cognitive-evaluative components

(Tracey, 2011; Wiech et al., 2008). Sensory discrimination involves identifying the quality, location, and intensity of noxious stimuli; affective components include fear, anxiety, and aversion evoked by noxious stimuli; and cognitive evaluation involves attention to and expectation of pain. Pain threshold primarily reflects the sensory-discriminative dimension and is associated with brain regions including the lateral thalamic nuclei and somatosensory cortex (Kuperman et al., 2020; Schnitzler & Ploner, 2000; Vierck et al., 2013). Pain tolerance threshold primarily reflects the affective-motivational dimension and is associated with the medial thalamic nuclei, prefrontal cortex, anterior cingulate cortex, and insula (Bushnell et al., 2013; Peyron et al., 2000). Pain ratings, however, are influenced by multiple dimensions including sensation, motivation, intention, and attitude (Coghill et al., 1999; Rainville et al., 1992) and are associated with somatosensory cortex, bilateral insula, anterior cingulate cortex, and medial prefrontal cortex (Kong et al., 2006). Thus, different psychophysical pain measures involve different dimensions of pain experience and distinct neural mechanisms.

No significant difference was found in pain threshold between ASD and control groups, though moderated by stimulus modality, specifically ASD individuals showed significantly lower pressure pain thresholds than typical individuals. This may be because different physical pain stimulation modalities evoke different pain qualities. For example, electrical stimulation pain primarily activates large-diameter myelinated Aβ fibers (Koga et al., 2005), while pressure pain threshold mainly activates small-diameter myelinated Aδ and unmyelinated C fibers (Vaughan et al., 2019). This suggests that pain sensitivity abnormalities in ASD individuals may be modality-specific, meaning ASD individuals may have processing abnormalities only for certain pain modalities rather than a general processing deficit. Future experimental research should combine multiple physical pain modalities to further investigate whether pain sensitivity abnormalities in ASD individuals are specific to certain modalities, such as using laser pain stimulation that selectively activates Aδ and C fiber terminals in superficial skin layers (Magerl et al., 1999).

Experimental research on pain sensitivity in ASD individuals primarily relies on psychophysical pain measurement, such as subjective experience reports (pain intensity) and behavioral responses (e.g., button press upon pain detection). However, ASD individuals often have intellectual disabilities (difficulty understanding experimental instructions), communication deficits, and alexithymia (inability to appropriately describe and express emotional experiences). Therefore, subjective pain experience reports in ASD individuals may be influenced by their language expression and cognitive comprehension abilities. For example, while approximately 10% of the typical population has varying degrees of alexithymia (Linden et al., 1996), this proportion reaches 50% in ASD populations (Hill et al., 2004). For instance, pain threshold assessment often requires subjects to press a button upon pain detection, but motor or cognitive confounding factors could create apparent "pain sensitivity abnormalities" in ASD individuals. On one hand, ASD individuals may show delayed button responses due to

slow motor responses, manifesting as "low pain sensitivity" ; on the other hand, they may press prematurely due to intolerance of uncertainty, manifesting as "high pain sensitivity." Therefore, some studies have used pain-related physiological indicators (e.g., autonomic nervous system responses such as heart rate) to objectively assess pain sensitivity in ASD individuals (Rattaz et al., 2013; Tordjman et al., 2009). However, these physiological response indicators are not specific to pain experience, as excitement or stress states can also evoke autonomic responses similar to pain (e.g., heart rate acceleration).

To more precisely and effectively probe brain processing and encoding of pain information, some studies have combined psychophysical assessment with functional magnetic resonance imaging to examine cognitive processing of pain in ASD individuals, revealing differences in pain processing patterns between ASD and typical individuals. Failla et al. (2018) found no significant difference between ASD and control groups in intensity ratings of contact heat-evoked persistent pain, and no significant difference in early activation of pain-related brain regions (including somatosensory cortex, thalamus, insula, striatum, anterior cingulate cortex, and supplementary motor cortex). However, during middle and late pain phases, ASD groups showed significantly lower activation in pain-related brain regions (e.g., insula, secondary somatosensory cortex, and thalamus) than controls. This study found a dissociation between behavioral and neural level results: although ASD and typical individuals showed no difference in subjective pain ratings, ASD individuals' pain-evoked response patterns differed from typical individuals. Moreover, because pain experience depends not only on the physical properties of noxious stimuli but also on cortical interpretation of pain, such as differences in processing expected versus unexpected pain stimuli (Price et al., 1999). During anticipation of impending pain, individuals often experience anxiety or fear, with limbic and paralimbic systems closely related to emotional processing showing significant activation, including anterior cingulate, hippocampus, and amygdala (Ploghaus et al., 2001). Therefore, Gu et al. (2018) used an anticipated pain paradigm to compare neural responses between ASD and control groups during pain anticipation and processing stages, finding that during pain anticipation, ASD groups showed significantly higher activation in dorsal and rostral anterior cingulate cortex than controls, while during pain stimulus processing, no significant differences were found between groups in pain-related brain regions (e.g., anterior cingulate and insula). Thus, compared to controls, ASD groups showed enhanced neural responses only during pain anticipation, possibly indicating greater anxiety and fear while waiting for an uncertain pain stimulus.

Pain is a complex subjective experience reflecting not only nociceptive neural impulses transmitted by sensory systems but also influenced by multiple psychological and social factors. This study found that ASD individuals showed higher pain sensitivity in pressure pain threshold but no difference in pain ratings, suggesting that ASD individuals may differ from typical individuals in the sensory-discriminative dimension of pressure pain processing rather than showing global abnormalities across sensory-discriminative, affective-motivational,

and cognitive-evaluative dimensions. Future research should systematically examine different dimensions of pain processing in ASD individuals by combining subjective reports, physiological responses, electrophysiology, and neuroimaging, such as differences between ASD and typical individuals in sensory discrimination, emotional motivation, and cognitive evaluation of pain and their neural mechanisms.

4.3 Link Between Pain Sensitivity Abnormalities and ASD Core Symptoms

Sensory abnormalities in ASD individuals can predict clinical core symptoms; for example, under-responsiveness and sensory seeking can predict social communication deficits in ASD individuals (Foss-Feig et al., 2012; Liss et al., 2006; Watson et al., 2011; Zachor & Ben-Itzchak, 2013). This may represent a compensatory mechanism: social stimuli or interactions lose reward value for ASD individuals (Mundy & Neal, 2001), leading them to seek sensory stimulation to obtain pleasure and reward (Ingersoll et al., 2003). However, excessive focus on sensory information in the environment hinders ASD individuals' detection and processing of other stimulus types, further exacerbating social communication deficits. Additionally, over-responsiveness in ASD individuals can predict their restricted and repetitive behaviors (Boyd et al., 2010; Chen et al., 2009). Sensory abnormalities, restricted repetitive behaviors, and anxiety levels are universally correlated in ASD individuals (Joosten & Bundy, 2010), with anxiety and intolerance of uncertainty mediating the relationship between sensory abnormalities and restricted repetitive behaviors (Wigham et al., 2015). This suggests that restricted repetitive behaviors in ASD individuals may serve as a soothing coping mechanism to alleviate discomfort from sensory information overload.

Pain empathy involves perceiving, judging, and emotionally responding to others' pain. Two studies have examined the link between pain sensitivity and pain empathy in ASD individuals (Chen et al., 2017; Fan et al., 2014). Results showed that ASD individuals' own pain sensitivity could predict abnormalities in pain empathy responses, indicating that abnormal self-pain processing affects the development of higher-order social-cognitive functions. For example, Fan et al. (2014) found that ASD individuals had lower pressure pain thresholds than typical individuals, manifesting as high sensitivity to self-pain. When attention was focused on others' pain cues (judging whether picture materials depicted pain), ASD individuals showed significant differences in event-related potential N2 responses when processing painful versus non-painful pictures, a difference not observed in typical individuals, possibly indicating enhanced neural responses in the early automatic processing stage of pain empathy (e.g., perception and emotional sharing of others' pain). However, when attention was not constrained to pain cues (passive viewing only), ASD individuals showed stronger activation in primary/secondary somatosensory cortex but weaker activation in anterior mid-cingulate and anterior insula—brain regions related to

affective empathy—compared to typical individuals. This may be because ASD individuals' abnormal pain sensitivity (high pain sensitivity) makes them more susceptible to excessive emotional arousal when attentively observing others' pain; when passively viewing others' pain, although ASD individuals show enhanced sensorimotor resonance responses in somatosensory cortex, they tend to use attentional avoidance to prevent excessive emotional distress, resulting in weaker activation in affective empathy brain regions.

Empathy can be divided into cognitive and affective dimensions, where cognitive empathy refers to the ability to understand, explain, and predict others' behavior by inferring their desires, intentions, and beliefs, while affective empathy refers to the capacity to share others' emotions (Decety & Svetlova, 2012). Cognitive and affective empathy for others' pain are influenced by multiple factors, including the observer' s own pain sensitivity and attention (Meng et al., 2010). For example, in typical populations, higher self-pain sensitivity is associated with greater affective and cognitive empathy responses to others (Li et al., 2020; Liu et al., 2019), and this is modulated by attention (Fan & Han, 2008; X. Gu & Han, 2007; Li et al., 2020). However, ASD individuals not only show abnormalities in self-pain processing (e.g., high pain sensitivity) but also have difficulty actively attending to and processing emotional information in complex contexts (Begeer et al., 2008), resulting in inconsistency between self and other pain processing: although ASD individuals may show high sensitivity to self-pain, they exhibit "low empathy" for others' pain, manifesting as indifference and apparent lack of concern. The empathy imbalance hypothesis of ASD posits that ASD individuals show different patterns across cognitive and affective empathy dimensions, specifically high affective empathy and low cognitive empathy (Smith, 2009). High pain sensitivity in ASD individuals may partially explain their high affective empathy.

Since impairments in preferentially developing systems (e.g., perception) may have secondary effects on subsequently developing systems (e.g., social cognition) (Zhang & Yang, 2014), abnormalities in self-pain processing in ASD individuals may further affect social-cognitive functions. This suggests we should examine ASD and its clinical manifestations from a developmental perspective. Future research should characterize pain sensitivity in ASD individuals using different pain induction modalities and multidimensional pain assessment systems, establishing specific relationships between pain response patterns and clinical symptoms or impairments. Research on pain sensitivity in ASD individuals has important theoretical and practical value, as findings can help expand understanding of ASD biological mechanisms—such as explaining their special behavioral manifestations from a perceptual perspective—and facilitate evaluation and identification of pain responses in ASD individuals, guiding rational allocation of medical resources and selection of precise treatment plans.

References marked with an asterisk were included in the meta-analysis.

Note: Figure translations are in progress. See original paper for figures.