Methodological Principles and Mechanisms of Pupil-Measurement-Assisted Screening and Diagnosis of Children with Autism*

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Abstract

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder, and early diagnosis is crucial for intervention and prognosis. Pupillometry, as a technique for assessing unconscious neural responses, can evaluate atypical neural responses in children before behavioral characteristics emerge. Children with autism exhibit atypical pupillary response patterns: in pupillary light reflex tasks, they show longer constriction latency and smaller relative constriction amplitude; in complex visual stimulation tasks, they show smaller pupil dilation to social stimuli and greater pupil dilation to nonsocial stimuli or no difference from typically developing children; in attentional orienting tasks, they show greater pupil dilation. These findings suggest that children with autism have weaker parasympathetic regulatory function and dysregulated tonic–phasic dynamic coupling of the locus coeruleus–norepinephrine system. Pupillary parameters can not only effectively distinguish diagnosed children with autism from typically developing children, but some parameters are also associated with the core symptoms of autism; pupillary parameters collected during infancy and toddlerhood also have predictive value for symptom severity at later diagnosis. Future research should focus on longitudinal follow-up of high-risk infant and toddler populations and establish a standardized multimodal assessment system to clarify the early predictive function of pupillometry before the emergence of behavioral symptoms of autism, and to promote its translation into a clinical auxiliary screening tool.

Full Text

Methodological Principles and Mechanisms of Pupil-Measurement-Assisted Screening and Diagnosis of Children with Autism*

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Abstract Autism spectrum disorder (ASD) is a common neurodevelopmental disorder, and early diagnosis is of crucial importance for intervention and prognosis. As a technique for assessing unconscious neural responses, pupil measurement can evaluate children' s abnormal neural responses before behavioral features become apparent. Children with autism show atypical pupillary response patterns: in pupillary light-reflex tasks, they have a longer contraction latency and a smaller relative contraction amplitude; in complex visual-

stimulation tasks, their pupil dilation to social stimuli is smaller, whereas their pupil dilation to nonsocial stimuli is larger or does not differ from that of typically developing children; in attention-orienting tasks, their pupil dilation is larger. These findings suggest that children with autism have relatively weak autonomic nervous regulation, dysfunction in dynamic coupling of the tonic-phasic activity of the locus coeruleus–norepinephrine system, and other problems. Pupil parameters can not only effectively distinguish diagnosed children with autism from typically developing children, but some parameters are also associated with the core symptoms of autism; pupil parameters collected during infancy and toddlerhood also have predictive value for the severity of symptoms at later diagnosis. Future research should focus on longitudinal tracking of high-risk infant and toddler populations, establish standardized multimodal assessment systems, clarify the early predictive function of pupil measurement before autistic behavioral symptoms appear, and promote its transformation into a clinical auxiliary screening tool.

Keywords autism spectrum disorder, pupil measurement, screening and diagnosis, early prediction, autonomic nervous system

1 Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized chiefly by social-communication impairments, repetitive stereotyped behaviors, and sensory abnormalities (Hirota & King, 2023). Globally, the number of people with autism is showing an increasing trend year by year (Zeidan et al., 2022). Zhou et al. (2020) conducted a large-scale epidemiological survey in eight representative cities in China; the results showed that among 120,000 children aged 6–12 years, the prevalence of autism was approximately 0.70%. Although the core symptoms of autism already begin to appear in early childhood (Macari et al., 2012), they are often overlooked because young children' s behavioral features are ambiguous, their language abilities are immature, and parents lack experience (Yuan Yuhuan, Luo Fang, 2022). Large numbers of children later diagnosed with autism are already attending regular schools before diagnosis (Zhou et al., 2020), missing the critical opportunity for early intervention and making it difficult to obtain targeted educational support and professional assistance. Therefore, improving

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Early identification and screening techniques for autism are of critical importance. However, current mainstream methods for early diagnosis of autism—

such as standardized tools based on clinical behavioral observation and developmental assessment—still have limitations. First, they rely heavily on interviews or questionnaire information provided by caregivers; such subjective reports may affect the objectivity and accuracy of the assessment results. Second, because early behavioral and language expressions are ambiguous, many core features of autism, such as deficits in social interaction and restricted, repetitive behaviors, are difficult to identify clearly at younger ages, further increasing the difficulty of early diagnosis.

Pupillometry, as a noninvasive neurophysiological assessment technique, can indirectly reflect the activity of an individual' s internal neural circuits by presenting visual stimuli and accurately recording dynamic changes in pupil diameter. This technique is objective, noninvasive, and rapid, and is especially suitable for infants and toddlers (Dinalankara et al., 2017), providing a distinctive pathway for the early prediction of autism. A growing body of evidence indicates that children with autism exhibit atypical pupillary responses that differ significantly from those of Typically Developing (TD) children; this difference may stem from atypical neurophysiological mechanisms in children with autism. For example, the autonomic nervous system (ANS) function of individuals with autism is impaired, manifested as increased sympathetic nervous activity (Hirstein et al., 2001), leading them to continually seek external stimulation for self-regulation and thereby display repetitive stereotyped behaviors. Compared with other autonomic measures such as Heart Rate Variability (HRV) and Skin Conductance Response (SCR), pupillometry is more convenient and easier to operate (de Vries et al., 2020).

At present, empirical research and theoretical discussion in China on the application of pupillometry to autism remain relatively limited. Existing studies have mostly focused on the general application of pupillometry in psychological research (Yang Xiaomeng et al., 2020), and no studies have yet systematically reviewed the potential applications and core value of pupillometry in early identification, auxiliary screening, and clinical diagnosis of autism. In view of this, it is necessary to systematically review relevant studies from recent years, elucidate the value of pupillometry in revealing dysregulation of autonomic nervous regulation, attention, and arousal functions in children with autism, as well as its potential for early prediction of autism, with the aim of providing theoretical support and practical evidence for objective assessment and clinical diagnosis in the early stage of autism.

2 Principles and Methods of Pupillometry

2.1 Physiological and Neural Basis of Pupillary Responses

Pupil constriction and dilation are jointly regulated mainly by the sympathetic and parasympathetic pathways of the autonomic nervous system. The constriction pathway relies primarily on the parasympathetic pathway: when light stimulates the retina, signals are transmitted via the optic nerve to the pretec-

tal olivary nucleus in the midbrain, activating the E-W nucleus (Edinger–Westphal Nucleus, EWN), which then releases acetylcholine (Acetyl Choline, ACh) through the oculomotor nerve, causing contraction of the iris sphincter muscle. Pupil dilation primarily reflects activity of the locus coeruleus–norepinephrine (LC-NE) system: the blue

The locus coeruleus (LC), by indirectly inhibiting the E–W nucleus and reducing parasympathetic activity, cooperates with the hypothalamus to project signals to the intermediolateral column (IML) of the spinal cord, and then activates the sympathetic nervous system via the superior cervical ganglion (SCG). The sympathetic nerves transmit signals to the pupillary dilator muscle, ultimately producing pupil dilation (Mathôt, 2018; Ferencova et al., 2021).

The pupil response regulated by the locus coeruleus has two modes: tonic and phasic (Aston-Jones & Cohen, 2005). Tonic pupil size, also called tonic pupil diameter, refers to the baseline pupil diameter in the absence of task stimulation. Tonic activity reflects the baseline firing level of the locus coeruleus, and its firing amplitude is relatively small. Phasic pupil size refers to pupil dilation induced by specific stimuli; it is usually associated with bursts of cortical activity or task-related decision-making processes, and is closely related to highly accurate behavioral responses (Aston-Jones & Cohen, 2005; Bast et al., 2018). According to the adaptive-gain theory, a moderate level of tonic activity can provide the optimal state for subsequent phasic activity, whereas tonic activity that is too high or too low weakens the effectiveness of phasic responses, similar to the classic inverted-U motivational curve of Yerkes–Dodson (Aston-Jones & Cohen, 2005).

In screening studies of autism, the above mechanisms have direct clinical relevance. Autistic children often show parasympathetic/sympathetic imbalance (Bufo et al., 2025; Arora et al., 2021; Vidal-Zaborski et al., 2026) and abnormalities in the function of the locus coeruleus–noradrenergic system (Kim et al., 2022). Therefore, the parameters extracted from pupillometry can serve as objective indicators for evaluating abnormalities in autonomic nerves and attentional function in autistic individuals.

2.2 Indicators and Parameters of Pupillometry

The principle of pupillometry is to achieve precise capture of dynamic changes in the pupil through infrared pupillometry—corneal-reflection technology.

Rubin (1961) first used flash-photography equipment to examine pupil changes in autistic children, typically developing children, and typically developing adults. The results showed that, compared with typically developing children, autistic children had lower levels of pupil dilation, slower constriction speed, and no difference in absolute constriction amplitude; compared with typically developing adults, autistic children had higher levels of pupil dilation, with no difference in constriction speed or absolute constriction amplitude. With the development of eye-movement equipment, eye trackers (such as Tobii, Eyelink,

Figure 1. Schematic waveform of the pupillary light reflex (PLR).

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etc.) have become the choice of more researchers. Pupil responses cover the types induced by visual, auditory, and tactile stimuli. Among them, pupil responses induced by visual stimuli can be divided into two major categories: light-stimulus-induced pupil responses, namely the pupillary light reflex (PLR), and pupil responses to complex visual stimuli (PRC) (de Vries et al., 2020). Compared with auditory or tactile stimuli, pupil responses induced by visual stimuli are more universal and constitute the core research direction in this field.

The pupil response to light stimulation includes three stages (see Figure 1): rapid constriction–rapid dilation–slower dilation (Wang et al., 2016). The persistence of constriction is affected by factors such as the duration and intensity of the light (Hall & Chilcott,

2018), and can directly reflect basic autonomic nervous function. Pupil diameter can constrict from 8 mm to 1.5 mm (McDougal & Gamlin, 2014), and the constriction process is considered to be purely parasympathetic activity that is not affected by sympathetic nerves (Wang et al., 2016). In studies of the pupillary light reflex in individuals with autism, the most commonly reported pupil parameters include baseline pupil diameter (baseline), constriction latency (latency), and constriction amplitude (de Vries et al., 2020). Among these, baseline pupil diameter refers to the mean pupil diameter before light stimulation; obtaining baseline pupil diameter requires ensuring consistency in the ambient light and dark levels. Constriction latency refers to the period from the light stimulus reaching the pupil to the onset of any pupil response. Constriction amplitude includes maximum constriction amplitude and relative constriction amplitude: maximum constriction amplitude is the absolute difference obtained by subtracting the minimum constricted value from the baseline pupil diameter; relative constriction amplitude is a baseline-corrected maximum constriction amplitude, converting the absolute difference into a percentage of the baseline diameter. This parameter can effectively control for the influence of individual differences in baseline diameter. Overall, maximum constriction amplitude is more suitable for comparing constriction differences in the same participant across different tasks, whereas relative constriction amplitude is more suitable for comparing pupillary constriction ability across different groups. In addition, latency is considered the parameter that best distinguishes differences in pupil size between individuals with autism and typically developing individuals (de Vries et al., 2020).

Figure 1 Schematic waveform of the pupillary light reflex (PLR): before light stimulation, the pupil maintains a stable baseline diameter (baseline). After the onset of light stimulation, following a brief latency, the pupil rapidly constricts at the maximum constriction velocity, reaches the minimum pupil diameter

within the constriction time, and the difference between the baseline and minimum diameter is the maximum constriction amplitude. After the end of light stimulation, the pupil enters the recovery phase, first rapidly dilating and then slowly dilating until it recovers to the baseline diameter; the duration of this process is called the recovery time. The figure is adapted from Hall and Chilcott (2018).

Pupil changes induced by complex visual stimuli (such as social emotions, complex patterns, multiple-object tracking, etc.) can indicate pupil dia

diameter is used as a real-time index for processing cognitive load, emotional arousal, attentional allocation, and sensory salience. In individuals with autism, the most commonly reported pupillary parameters in studies of pupil responses induced by complex visual stimuli include baseline pupil diameter and relative dilation amplitude. At present, there is no unified standard for selecting the time window of baseline pupil diameter. Depending on the research purpose, experimental paradigm, and stimulus type, researchers may choose 50 ms before stimulus presentation (Kim et al., 2022), 200 ms (Hogan et al., 2022), 250 ms (Polzer et al., 2022), 400 ms (Camero et al., 2021), 500 ms (Polzer et al., 2024; Rudling et al., 2021), or 1000 ms (Segers et al., 2020) as the baseline pupil diameter. Relative dilation amplitude is calculated by first calibrating the baseline to remove individual differences, and then subtracting the baseline value from the dilation value. Overall, in studies of the pupillary light reflex, researchers tend to focus more on constriction indices, whereas in studies of pupil responses induced by complex stimuli, they tend to focus more on dilation indices. Baseline indices are important in both types of research, because the amplitudes of both constriction and dilation require baseline diameter as a reference.

3 Abnormal Pupil Responses in Children with Autism

3.1 Baseline Pupil Diameter

Baseline pupil diameter, also known as tonic pupil diameter or resting pupil diameter, refers to the initial pupil diameter under no-task conditions. Pupil dilation in the resting state reflects the level of arousal, and may in turn affect subsequent task engagement and adaptation to the environment (Arora et al., 2021). In studies concerning children with autism, the direction of abnormalities in baseline pupil diameter remains highly controversial. Some studies have reported that the baseline pupil diameter of children with autism is larger than that of typically developing children (Anderson & Colombo, 2009; Blaser et al., 2014; Keehn et al., 2021; Kim et al., 2022), or that the baseline pupil diameter of children with autism is smaller than that of typically developing children (Martineau et al., 2011; Zhao et al., 2022), whereas other studies have reported no between-group differences in baseline pupil diameter between children with autism and typically developing children (Fan et al., 2009; Daluwatte et al., 2012; Nuske, Vivanti & Dissanayake, 2014; Daluwatte et al., 2015; Nyström et al., 2015; Aguillon-Hernandez et al., 2019; Boxhoorn et al., 2019; Jiang & Liu,

2025). Through meta-analysis, de Vries et al. (2020) found that there was no between-group difference in baseline pupil diameter between individuals with autism and typically developing individuals.

Taken together, the above evidence suggests that pupil differences between children with autism and typically developing children may mainly be reflected in dynamic responses induced by different stimuli, rather than at the baseline level (Stefanelli et al., 2024). Inconsistent baseline findings may also be attributable to differences in participants' ages, sample heterogeneity, and measurement methods (de Vries et al., 2020; Dinalankara et al., 2017; Arora et al., 2021). One study found that the baseline pupil diameter of typically developing children aged 2–6 years increased with age, whereas the baseline pupil diameter of children with autism showed no age-related trend before age 4 and a slight decreasing trend with age after age 4 (Dinalankara et al., 2017). Another study found that the baseline pupil diameter of typically developing children aged 6–12 years increased with age ···

increases with age, but this age trend has not been observed in children with autism (Daluwatte et al., 2012). This result suggests that the development of baseline pupil diameter in children with autism may show stagnation or deviation from the trajectory. Because the meta-analysis combined sample data from different age groups, such opposing age effects may offset one another, leading the overall effect size to approach zero. On the other hand, because intellectual level and symptom severity differ, there are different subtypes within the autism population, which may obscure true between-group differences (de Vries et al., 2020). In addition, studies differ in how baseline is measured. For example, some studies required participants to fixate on the center of the screen in order to obtain the initial pupil diameter (Boxhoorn et al., 2019; Keehn et al., 2021), whereas others took the initial pupil diameter when participants were not engaged in any activity (Daluwatte et al., 2012). Arora et al. (2021) suggested that between-group differences under a purely resting (inactive) condition may be easier to observe than those under an active-fixation (fixating on the screen) condition. Thus, whether there are differences in baseline pupil diameter between children with autism and typically developing children remains to be further tested by controlling for sample characteristics, environment, and measurement methods.

3.2 Pupil Responses Induced by Light Stimulation

In studies of pupil responses induced by light stimulation, constriction latency and relative constriction amplitude are the indices most commonly reported as abnormal; they respectively reflect the conduction speed of the reflex pathway and the modulatory strength of the parasympathetic nervous system.

3.2.1 Prolonged Latency

The pupil constriction latency of children with autism is significantly prolonged. Latency refers to the period from light stimulation of the pupil to the onset of a pupil response. In typically developing individuals, the shortest latency can reach 180–230 ms (Hall & Chilcott, 2018). Under both light-adapted and dark-adapted conditions, autistic individuals aged 2–19 years all show longer latency than typically developing individuals of the same age (Fan et al., 2009; Daluwatte et al., 2012; Daluwatte et al., 2015; Dinalankara et al., 2017), and deviations in the developmental trajectory of latency have even been observed among high-risk infants aged 6–24 months (Fish et al., 2021). With increasing age, the latency of typically developing children begins to show a decreasing trend, reflecting the maturation of neural conduction pathways; however, this normal shortening of latency has not been observed in children with autism, whose latency remains at a relatively long and stable level (Daluwatte et al., 2012). This pattern of developmental stagnation may become an important clue for the early identification of neurodevelopmental disorders. Prolonged latency suggests that children with autism may have dysfunction in the parasympathetic efferent pathway from the retina to the midbrain E–W nucleus.

3.2.2 Reduced Relative Constriction Amplitude

Relative constriction amplitude refers to the amount of constriction from the baseline diameter to the minimum diameter as a percentage of the baseline diameter, and is an important parameter reflecting whether parasympathetic activity is normal in the pupillary light reflex. Some studies have found that the relative constriction amplitude of children with autism is significantly smaller than that of typically developing children only under dark-adapted conditions (Fan et al., 2009), while other studies have found that, regardless of whether under light-adapted ···

whether under dark-adapted conditions, differences in pupillary constriction between the two groups of children were stably present (Daluwatte et al., 2012; Daluwatte et al., 2015), suggesting that children with autism have weaker parasympathetic regulatory function. In studies on the developmental trajectory of pupillary light reflex in infants and toddlers, several longitudinal studies have revealed its complexity. Kercher et al. (2020) conducted a longitudinal follow-up study of infants aged 6–24 months and found that the relative constriction amplitude of both high-risk and low-risk infants showed a tendency to increase with age, but the relative constriction amplitude of high-risk infants was significantly smaller than that of low-risk infants at all ages. Another study observed the opposite response pattern among high-risk infants: infants later diagnosed with autism showed greater relative constriction amplitude than low-risk infants at 9–10 months of age (Nyström et al., 2018). This difference may stem from differences in experimental design and testing conditions: the age ranges of infants observed in the two studies differed, with the former covering the full period from 6 to 24 months, whereas the latter focused only on the

specific developmental time point of 9–10 months. In addition, wavelength and ambient illumination also directly affect the amplitude of pupillary constriction. There are significant differences in the reflex intensity induced by white light and green light, and low-illumination environments significantly amplify the pupillary light reflex effect (Lobato-Rincón et al., 2014). This abnormality not only has group specificity but also good classification efficacy. For example, Fan et al. (2009) found that the single index of relative constriction amplitude alone could correctly distinguish 94% of children with autism from typically developing children. Combining multiple pupillary light reflex indices can achieve a classification accuracy of 81.5% (Daluwatte et al., 2012).

3.3 Pupil Responses Induced by Complex Visual Stimulation

Unlike the pupillary light reflex, which reflects basic autonomic nervous system function, pupil dilation induced by complex visual stimulation mainly points to cognitive processing, emotional arousal, and attentional allocation processes, and is a core indicator for assessing social information processing in individuals with autism.

3.3.1 Abnormal Pupil Responses to Social and Non-Social Stimuli

Using the baseline pupil diameter before stimulus presentation as a reference, studies have found that children with autism and typically developing children show markedly different directions of pupil response when facing social stimuli. Typically developing children show pupil dilation when viewing human faces—especially internal features: the eyes, nose, and mouth—whereas the pupils of children with autism show constriction in the same context (Anderson et al., 2006). Compared with control groups, individuals with autism show smaller pupil dilation when viewing social scenes and fewer fixations on faces (Bast et al., 2023), as well as weaker fixation preference for dynamic real faces and smaller pupil dilation (Aguillon-Hernandez et al., 2019; Polzer et al., 2022), and this weaker fixation preference for social stimuli persists into adulthood (Matyjek et al., 2025). In addition, adding emotional and linguistic stimuli to social stimuli does not change the pupil responses of children with autism; compared with control groups, their pupil dilation remains smaller (Segers et al., 2020). When the line of sight is shifted from geometric figures to face images, typically developing individuals show significantly greater pupil dilation than individuals with autism, indicating that individuals with autism show weaker arousal and attentional intensity toward face images (Murofushi et al., 2021). Stefanelli et al. (2024) found that typically developing individuals showed significant differences in pupil responses to social and non-social stimuli, whereas auti

The pupil responses of autistic individuals to these two types of stimuli show no significant difference, indicating that typically developing individuals have already established, at the physiological level, stable anticipatory arousal to

social stimuli, whereas autistic individuals show systematic abnormalities in physiological arousal when processing social information.

In addition to social stimuli eliciting abnormal responses in autistic individuals, nonsocial stimuli likewise elicit abnormal responses. Autistic children' s pupil dilation to nonsocial stimuli is often larger, or does not differ significantly from that of typically developing children. For example, studies have found that, compared with typically developing children, autistic children show greater pupil dilation to dynamic geometric figures (Polzer et al., 2022) and nonsocial scenes (Bast et al., 2023). Segers et al. (2020) found that there were no between-group differences in pupil dilation to nonsocial stimuli between autistic children and typically developing children. Some scholars have speculated that autistic individuals' preference for nonsocial stimuli may stem not only from a weakened response to social stimuli, but may also be related to the category of nonsocial stimuli. Specifically, stimuli related to circumscribed interests (CI)—for example, geometric figures, machines, and repetitive structures—may be more capable of inducing strong pupil responses in autistic children (Hinz et al., 2024). However, more studies are still needed in the future to test this inference by controlling the type of nonsocial stimuli.

3.3.2 Abnormal pupil responses to emotional faces

In emotional processing, the abnormalities indicated by pupil measurements in autistic individuals do not follow a single pattern; rather, they are influenced by multiple factors, including emotional valence, stimulus familiarity, level of processing awareness, and social context, and they exhibit highly heterogeneous arousal characteristics. Research using standardized images of unfamiliar emotional faces has found that autistic children show significantly greater pupil dilation than typically developing children when viewing happy faces, whereas their pupil responses to fearful faces do not differ significantly from those of typically developing children (Reisinger et al., 2020). However, when familiarity is taken into account, autistic children show less pupil dilation to unfamiliar fearful faces than typically developing children, and also less pupil dilation than when viewing fearful faces of familiar adults; yet their pupil responses to fearful faces of familiar adults do not differ significantly from those of typically developing children (Nuske, Vivanti & Dissanayake, 2014). This result suggests that emotional valence may be influenced by familiarity, and that autistic children may have insufficient arousal in processing negative emotions from unfamiliar people. In terms of social-emotional calibration, Nuske et al. (2016) asked children to watch two videos in which an actor opened a box and displayed either fear or happiness toward the object inside; before and after the scene, visually identical box close-ups were presented. The results showed that typically developing children exhibited significantly greater pupil dilation to the later box than to the earlier box, whereas autistic children showed no such difference in pupil response, indicating that autistic children are unable to achieve emotional calibration. At the same time, autistic children are also insensitive to the social

signal of others' gaze direction. For example, autistic children showed no significant differences in pupil dilation elicited by happy, fearful, angry, and neutral faces with direct gaze versus averted gaze, whereas typically developing children showed different levels of pupil dilation to emotional faces in the two gaze directions, especially stronger pupil dilation to happy faces with direct gaze (Sepeta et al., 2012). In addition, pupil responses are also influenced by the level of awareness in emotional processing; compared with typically developing children

In contrast, autistic children spend less time fixating on the eyes, show smaller pupil dilation under unconscious conditions, and maintain relatively intact emotion processing under conscious conditions. This result suggests that there may be a specific abnormality in the subcortical rapid automatic emotional pathway in autistic children (Nuske, Vivanti, Hudry & Dissanayake, 2014). Painful faces induce automatic pupil dilation, which is an unconscious physiological empathic response. Studies have found that the stronger the autistic traits, the weaker this empathic response—that is, the smaller the pupil dilation (Zhang et al., 2025). Polzer et al. (2024) used naturalistic dynamic emotional videos, extracted pupil-dilation levels during the early, middle, and late stages of fixation through principal component analysis (PCA), and combined this with growth curve analysis (GCA). They found that although there was no significant difference in the overall dynamic change of pupil size between autistic children and typically developing children, autistic children showed less fixation on the eye region in the early phase of the task and a compensatory increase in dynamic fixation in the late phase. This result suggests abnormal arousal in emotional-face processing among autistic children.

Notably, this abnormal arousal related to emotional processing already appears in infancy. In a longitudinal study of 9-month-old infants, Wagner et al. (2016) found that although high-risk and low-risk infants did not differ significantly in their face-fixation patterns, high-risk infants showed significantly higher levels of pupil dilation in response to emotional faces, and this degree of dilation negatively predicted social communication ability at 18 months. This finding suggests that abnormal arousal to emotion early in life may be a potential risk marker before behavioral symptoms emerge, highlighting the unique value of pupillometry in tracking early atypical trajectories of emotional processing in autism.

3.3.3 Abnormal pupil responses in attention-orienting tasks

Attention orienting refers to the selective allocation of visual attention to a specific region or object (Sara & Bouret, 2012), and attention-orienting tasks reveal the attentional control ability of autistic individuals. Stimuli in attention-orienting tasks can be divided into exogenous and endogenous stimuli. Exogenous stimuli are mostly peripheral and unpredictable (for example, passively viewing pictures without advance preparation, and recording orienting responses to suddenly appearing peripheral stimuli); endogenous stimuli are usually central, expected, and bound to task goals (for example, actively and consciously

focusing gaze on an object) (Bast et al., 2018). Compared with typically developing children, autistic children show impaired orienting to exogenous stimuli (Boxhoorn et al., 2019; Keehn et al., 2021; Hou et al., 2024), but their orienting to endogenous stimuli is normal or even stronger than that of typically developing children (Blaser et al., 2014; Keehn et al., 2023; Bu Fanshuai et al., 2016). Boxhoorn et al. (2019) asked children to press a button when they saw a butterfly and to make no response when they saw a fish. Before each stimulus was presented, an arrow cue was given, and the direction of the arrow was unpredictable. The results showed that autistic children responded more slowly than the control group under direction-inconsistent conditions, and had greater pupil dilation (Boxhoorn et al., 2019). Another study similarly found that, for stimuli with social attributes, autistic children' s saccadic responses were slower than those of typically developing children; moreover, regardless of whether the stimulus was social or nonsocial, and whether the direction of appearance was consistent or inconsistent with the cue, their overall pupil dilation was greater than that of typically developing children (Hou et al., 2024). Other studies have used the gap-overlap paradigm to examine attention orienting in autistic children.

whether the difficulty lies in shifting attention or disengaging attention. Specifically, children were asked to fixate on a stimulus at the center of the screen, and their saccadic responses and pupillary responses were recorded when peripheral stimuli appeared. When new stimuli appeared on both sides of the screen but the central stimulus disappeared, this was an attention-shifting task; when new stimuli appeared on both sides of the screen but the central stimulus did not disappear, this was an attention-disengagement task. The results showed that, regardless of whether the task was visual or auditory, autistic children exhibited delayed saccadic responses and greater pupil dilation only under the overlap condition that required active disengagement from the central stimulus, whereas under the gap condition, in which the central stimulus had disappeared in advance, they did not differ significantly from typically developing children (Keehn et al., 2021). This result indicates that autistic children' s difficulty in attentional orienting mainly originates from impaired attentional disengagement rather than from problems in attention shifting (Landry & Bryson, 2004; Keehn et al., 2021). Moreover, this abnormality is essentially distinct from that in children with attention deficit and hyperactivity disorder (ADHD): children with ADHD show shorter dilation latency and faster responses to target stimuli, but poorer sustained attention (Boxhoorn et al., 2019). Bast et al. (2021) used a visuospatial reaction time task to examine differences in activity of the locus coeruleus–noradrenergic system between children with ADHD and autistic children. The task included two conditions: low reward (stimulus interval 8 s, slow event rate, and no immediate reward for responses) and high reward (stimulus interval 1 s, fast event rate, and smiley-face feedback rewards for continuous rapid responses). The results showed that children with ADHD did not exhibit abnormalities in baseline arousal level or in arousal dynamics between high- and low-reward conditions, whereas autistic traits were positively corre-

lated with baseline arousal under the low-reward condition, and autistic children showed a marked deficit in the ability to regulate arousal when switching from the low-reward to the high-reward task. This finding provides valuable clues for early prediction and differentiation of autism and ADHD.

Autistic children' s orienting ability to endogenous stimuli is relatively intact or even stronger, manifested as better search ability than typically developing children (Blaser et al., 2014; Keehn et al., 2023). Visual search tasks are one of the classic paradigms for studying children' s cognitive abilities; they require children to actively search for a target stimulus among a set of distractors. Individuals with autism show faster and more accurate search ability than the control group in this task, and this advantage becomes more evident as task difficulty increases (Blaser et al., 2014; Keehn et al., 2023; Bu Fanshu et al., 2016). Blaser et al. (2014) examined pupillary performance in autistic children during a visual search task and found that their level of pupil dilation was significantly greater than that of typically developing children, and that their search efficiency was higher. Domestic scholars using similar research methods likewise found that autistic children searched faster, took less time to first fixate the target, and had a larger baseline pupil diameter than typically developing children (Bu Fanshu et al., 2016). Keehn et al. (2023) further confirmed that the larger baseline pupil diameter of autistic children was associated with their better search ability.

4 Pupil Measurements Reveal the Neural Mechanisms of Abnormalities in Autistic Children

4.1 Imbalance in autonomic nervous regulation: abnormal sensory processing

A synthesis of existing evidence shows that, in studies of the pupillary light reflex, individuals diagnosed with autism may exhibit characteristics such as a longer constriction latency and a relatively smaller constriction amplitude. Latency shows an obvious age-related trend in typically developing children; in

In children with autism, however, this trend is absent (Daluwatte et al., 2012). This atypical developmental trajectory may be related to abnormal white-matter maturation in children with autism (Weinstein et al., 2010). A study using electron microscopy to analyze occipital white-matter specimens from typically developing individuals and individuals with autism aged 2–44 years found that myelin thickness in individuals with autism was significantly lower than in the control group, and that myelin thickness did not increase with age (Hanson et al., 2025). In other words, the cerebral white matter of individuals with autism stagnates in the early stage of development and cannot, as in typically developing individuals, increase with age to achieve accelerated neural-signal transmission; instead, it shows a latent period that remains consistently long and does not decline. A study of people with multiple sclerosis (a chronic inflammatory demyelinating disease of the central nervous system, manifested as damage

to the myelin sheath of already mature cerebral white matter) found that, in studies of the pupillary light reflex, the contraction latency in this population was generally longer than that in the control group (Van Diemen et al., 1992). Although the autism group does not have typical demyelinating symptoms, this finding provides key evidence for exploring the relationship between pupillary constriction latency and white-matter abnormalities. In addition, a prolonged latency may also be associated with abnormalities of cerebellar pathways (Fan et al., 2009). The cerebellar fastigial nucleus can regulate the midbrain E-W nucleus through descending projections, thereby modulating the parasympathetic output pathway that innervates the pupillary sphincter muscle (Hultborn et al., 1978). In animal anatomical studies, after removal of the cat cerebellum, a significantly prolonged constriction latency can be observed during pupillary light-reflex tasks (Ijichi et al., 1977). A study using diffusion tensor imaging (Diffusion Tensor Imaging, DTI) further showed that some cerebellar neural pathways are abnormal in individuals with autism, and that these abnormalities may lead to damage of output pathways and local circuits (Catani et al., 2008). Taken together, the above evidence suggests that although the cerebellum is not an inherent component of the pupillary light-reflex pathway, it can exert a regulatory role (Fan et al., 2009). Therefore, abnormal cerebellar function may weaken its regulatory function over the E-W nucleus, thereby leading to prolonged pupillary constriction latency.

Multiple studies of the pupillary light reflex have indicated that children diagnosed with autism show significantly smaller relative constriction amplitude than typically developing children, and that this difference is stable under both light-stimulation and dark-stimulation conditions. Reduced relative constriction amplitude mainly reflects lower efficiency of the parasympathetic efferent pathway (Fan et al., 2009; Daluwatte et al., 2012; Daluwatte et al., 2015), which cannot effectively control the activity of the sphincter muscle. Pupillary constriction is mediated by acetylcholine released from parasympathetic nerves acting on the iris sphincter muscle; therefore, constriction amplitude has become one of the key peripheral indicators for evaluating parasympathetic nervous function. The study by Daluwatte et al. (2015) linked relative constriction amplitude with sensory behavior and suggested that, in children with autism, smaller relative constriction amplitude is associated with more pronounced atypical sensory behavior, indicating that parasympathetic dysfunction may be a potential neural basis of atypical sensory processing in autism. However, infancy shows a complex response pattern. A study of high-risk infants at 10 months of age found that children later diagnosed with autism showed greater relative constriction amplitude than the control group (Nyström et al., 2018); whereas a longitudinal study of infants aged 6–24 months found that the relative constriction amplitude of high-risk infants was consistently smaller than that of low-risk infants (Kercher et al., 2020). Pupillary constriction induced by strong light depends highly on the acetylcholine system in the neural pathway behind it (Fotiou et al., 2009), and the sensitivity of high-risk infants' pupils to light stimulation suggests that their acetylcholine system may be disorganized, and that abnor-

malities in sensory processing may already appear in early childhood. Whether the constriction amplitude is "increased" or "decreased," what they point to in common is parasympathetic

abnormalities in neural regulation. It is noteworthy that, in infancy, this pupil response to light stimulation suggests that abnormalities in pupillary light reflex may already be present before behavioral symptoms appear, and thus has important value for early screening.

To verify the relationship between atypical pupil responses and the autonomic nervous system in individuals with autism, some studies measured average heart rate (Average Heart Rate, AHR) and heart-rate variability while collecting pupillary light-reflex data. The former reflects the basal arousal level of the autonomic nervous system, whereas the latter quantifies the dynamic regulatory capacity of the autonomic nervous system; together, they help assess whether autonomic function is normal. The results found that individuals with autism had a higher average heart rate than the control group and lower heart-rate variability. More importantly, individuals with autism had a longer constriction latency and a relatively smaller constriction amplitude (Daluwatte et al., 2012). A higher average heart rate indicates more pronounced sympathetic inhibition, whereas lower heart-rate variability suggests reduced flexibility in autonomic regulation (Arora et al., 2021). Together, these pieces of evidence demonstrate that autonomic nervous function is abnormal in individuals with autism and that this abnormality can be manifested through pupil responses.

4.2 Dysregulation of the locus coeruleus–norepinephrine (LC-NE) system

Pupil responses have long been regarded as related to attention and information processing (Hess & Polt, 1964; Bast et al., 2018), and the arousal state reflected by the pupil can directly regulate attentional processing. Manipulating arousal level through external cues can directly change an individual' s attentional-orienting efficiency, demonstrating a causal relationship between arousal and attention (Kleberg et al., 2016a; Kleberg et al., 2016b). As a core nucleus for neural regulation in the brainstem, the locus coeruleus has an activity level that is a response indicator for physiological arousal, allocation of attentional resources, and the perception of external stimulus salience (Sara & Bouret, 2012). Changes in its activity can be sensitively reflected in pupil diameter, and because the locus coeruleus plays an important regulatory role in the coordinated functioning of the sympathetic and parasympathetic nervous systems, it is regarded as an effective peripheral indicator of autonomic nervous system function (Wass et al., 2015). With the aid of pupillometry, researchers can clearly reveal differences between children with autism and typically developing children in social information processing, attentional orienting, and arousal regulation, thereby providing key evidence for understanding the neurophysiological basis of social-communication impairments.

4.2.1 Abnormal salience processing of social information

In typically developing individuals, preferential and prioritized processing of social information has been widely confirmed to be an early automatic processing process (Rösler et al., 2017; Griffin et al., 2024). This process can be explained by the phasic alerting response regulated by the locus coeruleus–norepinephrine system: when social stimuli (such as faces) appear, sensory signals are transmitted via the ascending thalamus–amygdala pathway to the salience network composed of the anterior insula (anterior insula, AI) and anterior cingulate cortex (anterior cingulate cortex, ACC), thereby conducting salience evaluation of the stimulus (Uddin et al., 2013; Seeley et al., 2007). This signal transmission via the subcortical pathway can complete rapid encoding of the physical salience of a stimulus within 150 ms after the stimulus appears (Liddell et al., 2005), enabling social stimuli to preferentially enter the brain' s attentional-resource allocation window. In this process, the anterior insula, as an integrative hub for the limbic system and sensory information, is responsible for evaluating the degree of prominence of the stimulus; the anterior cingulate cortex then assigns the expected attentional-control value of the stimulus (Shenhav et al., 2013). Once a stimulus is evaluated as salient, the anterior insula and anterior cingulate cortex transmit driving signals to the locus coeruleus from top to bottom, thereby enhancing target-loop signals through projections to norepinephrine, preferentially processing salient information while suppressing irrelevant information (Mather et al., 2015). This circuit, in which signals are transmitted from bottom to top and then amplified and regulated from top to bottom, constitutes the neural basis for automatic preference and prioritized processing of social information in typically developing individuals.

However, in individuals with autism, this regulatory circuit for social stimuli shows functional abnormalities, leading to marked changes in the automatic priority assigned to social stimuli. Specifically, compared with typically developing children, autistic children show smaller relative pupil dilation to social stimuli (such as faces and social scenes), shorter fixation durations, but larger relative pupil dilation to non-social stimuli (such as geometric figures and non-social scenes) and longer fixation durations (Polzer et al., 2022; Bast et al., 2023). Bast et al. (2018) proposed the core hypothesis that autistic children' s weaker attention to social stimuli originates from weaker bottom-up sensory signals caused by abnormal phasic activity in the locus coeruleus–norepinephrine system; this deficit may further reduce the brain' s top-down salience evaluation of social stimuli and the attribution of predictive reward (Bast et al., 2018). Specifically, in individuals with autism, the signals for social stimuli transmitted by the superior colliculus–pulvinar pathway to the salience network are insufficiently strong, causing the anterior insula and anterior cingulate cortex to be unable to assign normal salience levels and expected attentional-control values to these stimuli, which in turn weakens their ability to send driving signals top-down to the locus coeruleus. Bast et al. (2023) used principal component analysis to extract an early-weighted pupillary response (PR1) from the pupil-

response process; this index reflects rapid, bottom-up processing by the locus coeruleus–norepinephrine system. The study found that this early pupillary component was negatively correlated with fixation time on faces, and that this negative correlation was more pronounced in autistic children, indicating that the sensory-input strength represented by pupillary responses may be a key factor determining face-fixation behavior (Bast et al., 2023). Recent research shows that autistic children have a significantly lower frequency of preferential fixation on faces during early visual processing than typically developing children (Griffin et al., 2024), and, compared with social stimuli, autistic children show greater pupil dilation to geometric figures (Polzer et al., 2022). It can therefore be inferred that abnormal early bottom-up sensory processing in autistic children may be a marker of reduced attention to social information: that is, social stimuli fail to obtain sufficient rapid physical-salience encoding through subcortical pathways, resulting in insufficient signal strength transmitted to the salience network and ultimately producing different patterns of salience attribution to social and non-social stimuli (Polzer et al., 2022; Bast et al., 2023).

4.2.2 Difficulty disengaging attention in exogenous attention-orienting tasks

Attention functions include alerting, orienting, and attentional control (Fan et al., 2002). Alerting includes tonic alerting and phasic alerting. Tonic alerting controls baseline arousal, whereas phasic alerting refers to the early peak of pupil dilation 200–300 ms after stimulus onset (Bast et al., 2018). This process is associated with rapid alerting responses to stimuli and directly reflects the initial activation of the locus coeruleus by salient stimuli.

(Petersen & Posner, 2012). Oriented pupil dilation in response to social stimuli depends on the interaction between the locus coeruleus and orienting networks, a process that occurs approximately 400–600 ms after stimulus presentation (Bast et al., 2018). The orienting network is divided into two subnetworks, the ventral frontoparietal network and the dorsal frontoparietal network: orienting to exogenous stimuli depends on activation of the ventral frontoparietal attention network; orienting to endogenous stimuli depends on activation of the dorsal frontoparietal attention network (Corbetta et al., 2008). Studies have found that autistic children show impaired ability to orient to exogenous stimuli and exhibit greater pupil dilation than typically developing children (Boxhoorn et al., 2019; Keehn et al., 2021). The fundamental reason for this abnormality is that excessive phasic activity of the locus coeruleus–norepinephrine system weakens signals to the temporoparietal junction (TPJ), preventing normal activation of the ventral frontoparietal attention network, leading to reduced phasic alertness; individuals therefore have difficulty disengaging from the currently attended target, thereby delaying orienting responses to exogenous stimuli (Boxhoorn et al., 2019; Keehn et al., 2021). Kleberg et al. (2016a) attempted to present auditory alerting signals before visual targets appeared in order to activate phasic alertness, and found that this manipulation improved the attentional orienting

efficiency of autistic children, with acceleration comparable to that of typically developing children. Because the salience of social stimuli is weakened in autistic children, they are more likely to show difficulty disengaging attention from such stimuli (Hou et al., 2024). However, auditory alerting signals can likewise enhance autistic children' s salience evaluation of social stimuli (such as eye images) and increase the speed of attentional orienting (Kleberg et al., 2016b). This means that although autistic children show the deficit of difficulty in attentional disengagement, the phasic alerting function of their locus coeruleus–norepinephrine system can be normally triggered by unexpected auditory cues, thereby improving their orienting efficiency; the problem of difficulty in attentional disengagement may instead stem more from excessive tonic activity, which affects spontaneous arousal ability.

On the other hand, in a series of endogenous tasks requiring active attentional engagement, the attentional orienting ability of autistic individuals is not impaired and may even be better. For example, autistic children' s search efficiency is superior to that of typically developing children, and the dilation of their pupils —whether tonic pupil dilation reflecting sustained arousal (Keehn et al., 2023) or task-evoked phasic pupil dilation (Blaser et al., 2014)—is significantly greater than that of typically developing children. Some researchers have inferred that enhanced phasic activity of the locus coeruleus in autistic individuals produces an over-focused attentional state, giving them stronger inhibition of irrelevant distracting stimuli and making them less distractible, thus leading to better performance in complex visual search tasks (Blaser et al., 2014; Kaldy et al., 2016). Another explanation is that the better search ability in autism may be related to a more even distribution of attention. For example, the study by Keehn et al. (2023) found that the natural left visual-field bias of autistic children was significantly reduced, and that this feature was directly related to higher resting-state locus coeruleus activity. Typically developing individuals generally show a scanning habit with left visual-field dominance, whereas autistic individuals are not constrained by this bias and can distribute visual attention more evenly across the entire visual field (Keehn & Joseph, 2016).

In sum, the atypical pupil responses of autistic children essentially reflect dysregulated tonic–phasic coupling in the locus coeruleus–norepinephrine system. Although the baseline pupil diameter reflecting tonic activity shows directional heterogeneity across existing studies,

However, extensive evidence indicates that the stability of this phasic response pattern is abnormal. According to adaptive gain theory, either excessively high or excessively low tonic activity can prevent flexible and appropriate phasic responses to external stimuli (Aston-Jones & Cohen, 2005), thereby manifesting as a series of abnormal responses such as significantly weakened processing of social information and difficulty disengaging attention. The weakened processing of social stimuli and abnormal attentional responses caused by functional disruption of the locus coeruleus–noradrenergic system may constitute an important neurophysiological basis for social-communication difficulties in autism

(Matyjek et al., 2025), providing key evidence for early physiological-marker screening and targeted intervention.

4.3 Amygdala–Prefrontal Regulation Abnormalities: Imbalance in Emotional-Arousal Regulation

Pupillary response has been shown to be a reliable indicator of emotional arousal (Bradley et al., 2008; Mathôt, 2018; Wende et al., 2026), and is functionally related to the amygdala: the amygdala can induce pupil dilation through the extended descending sympathetic pathway (Graur & Siegle, 2013). For typically developing individuals, both positive and negative emotions elicit pupil dilation (Yang Xiaomeng et al., 2020), but for individuals with autism, the level of arousal elicited by emotion and the degree of pupil dilation are more complex.

On the one hand, individuals with autism show functional deficits in low arousal and subcortical emotional pathways. Autistic children exhibit significantly lower pupil dilation during unconscious emotional processing than typically developing children, whereas conscious emotional processing is relatively preserved, indicating that abnormalities may exist in their rapid, automated subcortical emotional-processing pathway (Nuske, Vivanti, Hudry & Dissanayake, 2014). Reduced subcortical participation during unconscious emotional processing may further weaken a series of cognitive processes influenced by emotion, such as attentional capture, perceptual bias, behavioral decision-making, and affective resonance in social interaction (Tamietto & Gelder, 2010). In addition, the characteristics of emotional responses in individuals with autism have a certain genetic basis; their parents likewise show delayed peak pupillary responses to emotional faces (Hogan et al., 2022). Sepeta et al. (2012) found that, compared with typically developing individuals' rewarding responses to directly gazed happy faces, individuals with autism show markedly different responses to happy faces: their pupillary responses to happy faces do not differ as a function of gaze direction (direct gaze vs. averted gaze), suggesting that individuals with autism may have deficits in integrating social signals and reward value. Functional magnetic resonance imaging (functional magnetic resonance imaging, fMRI) studies have found that, for typically developing individuals, viewing attractive faces significantly activates reward-related brain regions, especially increasing activation of the ventral striatum (Ventral Striatum), whereas gaze aversion reduces the degree of activation (Kampe et al., 2001). In addition, this difference may also be related to attention to the eyes; compared with typically developing individuals, individuals with autism fixate the eye region significantly less often (Reisinger et al., 2020). The emotional responses of autistic children are influenced by familiarity: for fearful expressions displayed by familiar individuals, their pupillary responses are similar to those of typically developing children, but for fearful expressions displayed by strangers, their level of pupil dilation is significantly lower than that of typically developing children. This feature is closely related to insufficient amygdala activation (Nuske, Vivanti & Dissanayake, 2014). The amygdala has been shown to be a core brain region that promotes the process-

ing of fearful expressions (Wende et al., 2026), indicating that when autistic children face unfamiliar faces, the amygdala

nuclear activation is insufficient, whereas they can be activated normally when facing familiar faces.

On the other hand, some studies have found that individuals with autism show high arousal to emotional stimuli and excessive activation of the autonomic nervous system. For example, Reisinger et al. (2020) found that individuals with autism exhibited greater pupil dilation when viewing happy faces, while their pupillary responses to fearful faces did not differ significantly from those of typically developing individuals. A longitudinal study of infants showed that, at 9 months of age, high-risk infants had significantly greater pupil dilation to emotional faces than low-risk infants, reflecting possible congenital autonomic overarousal and abnormal amygdala responses (Wagner et al., 2016). Functional magnetic resonance imaging studies have found that individuals with autism show overactivation of the right amygdala during emotional processing, accompanied by enhanced functional connectivity between the amygdala and the ventromedial prefrontal cortex and weakened connectivity with facial processing regions in the occipital lobe. This finding suggests abnormal regulation of the amygdala by the prefrontal cortex in individuals with autism, which in turn leads to excessive responses to emotional stimuli (Monk et al., 2010). Nuske et al. (2015) found that children with autism showed greater pupil dilation to emotional faces of unfamiliar people than to emotional faces of familiar adults, and that this phenomenon was associated with their internalizing symptoms (such as anxiety and withdrawal), indicating that emotion-regulation ability is an important factor affecting pupillary responses. Recent studies using growth-curve analysis have shown that individuals with autism initially look less at the eyes, but as task duration increases they display delayed compensatory gaze, suggesting that abnormal arousal patterns in individuals with autism may be closely related to abnormalities in the dynamic allocation of visual attention (Polzer et al., 2024).

In summary, the pupillary response patterns of individuals with autism during emotional-face processing show a high degree of heterogeneity. These seemingly contradictory response characteristics are not mutually opposed, but are influenced by multiple factors (Yi et al., 2022). Among them, the visual fixation region is a key influencing factor: Stuart et al. (2022) systematically reviewed relevant neuroimaging evidence and argued that individuals with autism show abnormally high arousal when fixating on the eye region of faces, whereas they show insufficient arousal when fixating on non-eye regions. Emotional valence likewise elicits differentiated levels of arousal: when individuals with autism process fearful faces, they more often show a state of low pupillary arousal (Nuske, Vivanti & Dissanayake, 2014), whereas when they face happy faces, they show high-arousal features characterized by excessive pupil dilation (Reisinger et al., 2020). In addition, facial familiarity, gaze direction, the dynamic allocation of attention, and level of processing awareness all regulate pupillary responses; at

the same time, they also reflect the internal heterogeneity of individuals with autism in emotional sensitivity, neural regulation, and developmental trajectories. Pupillary indices can serve as potential physiological markers for the early identification of autism, while also providing an important neurophysiological basis for elucidating the impairments in social-emotional communication.

5 Summary and Prospects

As an important method for assessing the nervous system, pupil measurement is expected to evaluate abnormal neural responses before behavioral symptoms appear in children with autism, thereby assisting in screening and diagnosis. There are significant differences in pupillary responses between children with autism and typically developing children: in pupil light-reflex tasks, they have a longer constriction latency and a smaller relative constriction amplitude, reflecting abnormalities in sensory processing; in complex

In visual-stimulation tasks, pupil dilation to social stimuli is smaller, pupil dilation to nonsocial stimuli is larger, pupil-response heterogeneity to emotional stimuli is greater, and pupil dilation is larger in orienting tasks, reflecting problems such as abnormal salience processing, difficulty disengaging attention, and impairments in social-emotional communication.

5.1 Implementation Pathways for Pupil Measurement to Assist Screening and Diagnosis of Children with Autism

At the level of clinical application, pupil-measurement-assisted screening and diagnosis can be implemented through the following two pathways. First, early warning before symptom onset. For high-risk infants aged 6–24 months, priority can be given to measuring parameters such as the constriction latency of the pupillary light reflex, relative constriction amplitude, and resting pupil size, using these as preliminary screening cues for identifying the risk of neurodevelopmental deviation. Longitudinal studies have shown that high-risk infants in this age range already exhibit larger resting pupil diameters than low-risk infants (Kercher et al., 2020), as well as greater relative constriction amplitude (Nyström et al., 2018). Second, auxiliary diagnosis at the time of initial symptom presentation. For children who seek medical attention because of social-communication problems but whose behavioral manifestations remain atypical and only suggest autism, pupil responses elicited by stimuli such as social stimuli can serve as objective supplementary conditions for existing behavioral assessments, helping to support and shorten the time to a definite diagnosis. Existing studies have found that preschool children with autism show smaller pupil dilation to dynamic faces and greater pupil dilation to dynamic geometric figures (Polzer et al., 2022). Preschool children with autism show significantly greater pupil dilation when viewing inverted faces than when viewing upright faces, whereas typically developing preschool children show no significant difference in pupil responses across different orientations (Falck-Ytter, 2008).

5.2 Limitations of Pupil Measurement in Assisting Screening and Diagnosis of Children with Autism

Pupil measurement shows great potential in revealing the abnormal neural mechanisms of children with autism and in assisting screening and diagnosis, but it also has many limitations. First, the pupil response is the combined product of many factors, including illumination, cognitive load, and autonomic nervous activity (Mathôt, 2018). Attributing its specificity to the relative activity of the locus coeruleus-norepinephrine system may still require cross-validation with methods such as pharmacological blockade. Second, pupil measurement is highly dependent on standardized baseline acquisition; data are easily subject to artifacts such as blinking and head movement, and for autistic individuals who are young or have intellectual disability, their data must be handled with caution. Finally, variables that are common among autistic individuals—such as sensory hypersensitivity, anxiety states, and history of psychotropic medication use—constitute potential confounding factors that are difficult to control completely (Daluwatte et al., 2015).

5.3 Future Directions for Pupil Measurement to Assist Screening and Diagnosis of Children with Autism

Promoting the transformation of pupil-measurement technology from a basic research tool into a standardized clinical auxiliary tool requires efforts in the following areas. First, standardized paradigms should be established to measure baseline pupil diameter. In studies of pupil measurement in children with autism, the current divergence in baseline pupil diameter is relatively large, while interpretation of pupil dilation and constriction depends highly on baseline diameter. For example, in attention-orienting tasks, existing studies often attribute larger relative pupil size to excessively large tonic pupil diameter (Keehn et al., 2021; Hou et al., 2024), but some studies have not found differences in tonic pupil diameter between autistic individuals and typically developing individuals.

differences (Boxhoorn et al., 2019). Given that abnormalities in attentional function may be among the earliest features to appear in infants at risk for autism (Keehn et al., 2023), future research should place greater emphasis on how baseline pupil diameter is measured and should establish standardized protocols for data collection and analysis. Second, longitudinal follow-up studies of high-risk infants should be strengthened. On the one hand, it is necessary to construct a causal chain linking "pupillary abnormality—neural mechanism —autistic behavioral symptoms." A large body of research has confirmed that atypical pupil responses in autistic children are significantly associated with the core symptoms of autism (Nyström et al., 2018; Wagner et al., 2016), but causal relationships remain insufficiently explored. As a result, it is not yet possible to determine whether early neural abnormalities can influence pupil responses independently of later social experience, or whether early neural abnormalities lead to social avoidance, thereby causing insufficient social experience and ulti-

mately exacerbating atypical processing of social stimuli by the pupil. On the other hand, such research would help clarify the early predictive utility of pupillometry before autistic behavioral symptoms become manifest. For example, future studies could establish standardized, multimodal stimulus libraries and validate their reliability and validity; expand the analytic indices for pupillometry; identify the optimal predictive indicators and abnormal-value ranges; and thereby provide support for screening and diagnosing autistic children.

Third, the age range of participants should be narrowed (de Vries et al., 2020), and typically developing control children matched to autistic children in intellectual level should be included, so as to improve the comparability of research findings. In most current studies, the participant age range is relatively broad (for example, from childhood to adulthood). As age increases, physiological functions also change continuously; this not only interferes with comparisons within a study, but also poses substantial challenges for comparisons across studies. Controlling the age range of participants would also help determine at which developmental stage pupillary data are more stable and thus more suitable for screening and diagnosis. Fourth, pupillometry should be deeply integrated with technologies such as brain imaging and electrophysiology to construct multimodal neurophysiological markers. Future studies should not be limited to single-modality behavioral or physiological indicators, but should promote the simultaneous collection and integrative analysis of multimodal data. Existing studies show that dynamic changes in the pupil are closely related to activation of the locus coeruleus–norepinephrine system (Joshi & Gold, 2020) and are also associated with activity in specific brain regions (such as the amygdala and prefrontal cortex) (Peinkhofer et al., 2019). However, most interpretations of the atypical neural mechanisms underlying autistic pupillary responses rely on indirect inference. Therefore, future research should synchronously collect multimodal data such as pupil measures, electroencephalography, and functional near-infrared spectroscopy (fNIRS), so as to more precisely locate the neural circuits responsible for atypical pupil responses and explain the pathophysiological significance of pupillary markers at the mechanistic level (Bast et al., 2018). Fifth, cross-cultural research should be conducted to clarify whether the atypical neural mechanisms revealed by pupillometry in autistic children are universal. Current studies applying pupillometry to autistic children are concentrated mainly in Western countries, and it remains unclear whether their findings can be directly generalized to infants and young children from different ethnic and cultural backgrounds. Therefore, clarifying the universality of this method is crucial for supporting screening, diagnosis, and intervention in autistic populations. Through systematic efforts to advance the transformation of this technology from a research tool into a standardized clinical auxiliary tool, it can not only provide objective evidence for the early prediction and diagnosis of autism, but also open new perspectives for understanding its neurodevelopmental mechanisms.

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Methodological principles and mechanisms of pupillometry-assisted screening and diagnosis in children with autism

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Abstract Autism spectrum disorder (ASD) is a prevalent neurodevelopmental disorder, and early diagnosis is critical for intervention and prognosis. Pupillometry is an objective, non-invasive, and rapid technique that can detect atypical neural responses in children before behavioral symptoms emerge. Evidence indicates that children with ASD exhibit atypical pupillary response patterns. In the pupillary light reflex, they show prolonged contraction latency and reduced relative contraction amplitude, suggesting weakened parasympathetic regulation. In complex visual stimulation tasks, they show reduced pupil dilation in response to social stimuli, whereas their responses to non-social stimuli are either enhanced or comparable to those of typically developing children. In attentional orienting tasks, they show exaggerated pupil dilation, suggesting impaired dynamic coupling between the tonic and phasic components of the locus coeruleus-norepinephrine system. Pupillary parameters not only distinguish children with ASD from typically developing children but are also associated with core symptom domains of ASD. Importantly, pupillary measures collected during infancy and early childhood predict later symptom severity at the time of diagnosis. Future research should prioritize longitudinal follow-up of high-risk infant and toddler cohorts and the establishment of standardized multimodal assessment frameworks, with the aim of clarifying the early predictive utility of pupillometry before the emergence of behavioral symptoms and facilitating its translation into clinical screening tools.

Keywords children with autism spectrum disorder, pupillometry, screening and diagnosis, early prediction, autonomic nervous system

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