Contextual Information Modulates Pupil Size in Autistic and Non-Autistic Children.

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Research

Abstract

Background. Recent Bayesian models suggest that perception is more "data-driven" and less dependent on contextual information in autistic individuals than others. However, experimental tests of this hypothesis have given mixed results, possibly due to the lack of objectivity of the self-report methods typically employed. Here we introduce an objective no-report paradigm based on pupillometry to assess the processing of contextual information in autistic children and a comparison clinical group.

Methods. After validating (in a group of neurotypical adults) a child-friendly pupillometric paradigm, in which we embedded test images within an animation movie that participants watched passively, we compared pupillary response to images of the sun and meaningless control images in children with autism versus age- and IQ-matched children presenting developmental disorders unrelated to the autistic spectrum.

Results. Both clinical groups showed stronger pupillary constriction for the sun images compared with control images, like the neurotypical adults. There was no detectable difference between autistic children and the comparison group (in spite of a significant difference in pupillary light responses, enhanced in the autistic group).

Limitations: Having found no statistically significant differences between groups, we cannot exclude that group differences existed but were too small to be detected – a critique that applies to most negative findings. Additional limitations concern the heterogeneous composition of the comparison group and the types of stimuli tested, which only allowed for studying the effect of context on relatively complex perceptual processes.

Conclusions: Our report introduces an objective technique for studying perception in clinical samples and children. The lack of statistically significant group differences in our tests suggests that autistic children and the comparison group do not show large differences in perception of these stimuli. This opens the way to further studies testing contextual processing at other levels of perception.

Background

Although atypical perception is not a diagnostic criterion for Autism Spectrum Disorders, there is growing evidence that autism is associated with different perceptual styles [1–4]. The idiosyncrasies in visual perception include a preference for local over global perceptual features [5–7], reduced susceptibility to visual illusions [8], and deficits in the processing of contextual information for social cues [9], face processing [10] and perceptual grouping [11]. Several recent theories link autistic perception with Bayesian models of sensory integration [12–19]. The fundamental idea is that perception is more "data-driven" in autistics than in neurotypicals, less dependent on contextual information that is known to strongly influence perception under many circumstances.

Experimental tests of susceptibility to illusions have produced mixed results. Some behavioral studies found reduced susceptibility to illusions in autistic individuals [8, 20, 21], but others failed to detect significant differences in the strength of illusory effects between autistic and controls [22–26]. For example, using the method-of-adjustment (where participants adjust one stimulus until it is perceptually identical to another), Ropar and Mitchell [25] found that autistic children are generally similarly susceptible to illusions as children from a range of comparison groups, including individuals with moderate learning difficulties and typically developing children and adults. Similarly, autistic participants have been reported to perceive the orientation of low-level stimuli in a qualitatively similar manner as control participants, with no evidence of superior processing in the precision or accuracy of orientation perception [27, 28].

A number of confounding factors might explain inconsistencies in earlier work. Perseverative behaviors, anxiety, and understanding of task instructions are difficult to control for. Compounding this problem, many studies used behavioral paradigms that may be influenced by strategies in reporting what they perceive. Previous studies assessing visual illusions in autism have confounded sensitivity to an illusion with the subjective criterion for reporting the illusion. Therefore, group differences in illusion susceptibility estimates may reflect differences in decision criteria or bias, with no underlying differences in perception (a possibility that is particularly likely when groups differ in cognitive and affective factors [29]).

For these and other reasons, it would be useful to measure objective and quantitative indices of perception and perceptual styles. Recent work suggests that pupillometry may serve this purpose. Pupillary constriction in response to light increment is probably the simplest visually evoked response. However, higher order visual processes such as attention [30–33], visual awareness [34–38], mental imagery [39] and brightness illusions [40, 41] can also contribute to determining pupil size [42, 43]. For example, contextual cues associated with high light levels, such as an image of the sun, cause pupillary constriction compared with a more neutral luminance-matched image [38, 44–46]. These results show that pupillary constriction typically reflects the interpretation of light in a scene, not just the amount of physical energy entering the eye, suggesting that pupillary responses can be informative about an individual's perception. Indeed, pupillometry has been shown to track inter-individual differences in perception, and it may even be more reliable than behavioral measures and other physiological responses [47–50].

In the present study, we used a no-report pupillometry paradigm to assess processing of contextual information in autistic children and a comparison group. Specifically, we tested whether a pictorial representation of the sun would lead to pupillary constriction when compared with control images, using the same stimuli as in Binda et al. [45]. After validating a novel child-friendly paradigm in a group of neurotypical adults (Experiment 1), we measured pupillary response to images of the sun (and meaningless images matched in luminance and contrast) for two groups of children: one group with autism and one matched by age and IQ, presenting developmental disorders unrelated to the autistic spectrum (Experiment 2). The results show that both groups had larger pupillary constrictions for the sun images compared with control images (like the neurotypical adults), with no significant difference

between the groups. Our observations do not support the hypothesis of reduced use of contextual information in autism.

Materials And Methods

Participants

Experiment 1 was conducted on 40 neurotypical adults (32 females; age [mean ± SD]: 29.42 ± 1.93), with no diagnosed neurological condition. For Experiment 2, we recruited 40 children with developmental disorders, including 18 autistics (3 females; age 6.2–15.6 years; mean ± SD: 10.77 ± 3.02 years). Note that we often use the wording "autistic" throughout the paper, aligning with the preference for identity-first language expressed by the autistic community [51]. The other children (22 (7 females); age 6.8–15.5 years; mean ± SD: 10.88 ± 2.34 years) were diagnosed with disorders considered to be outside the autism spectrum, specifically: learning disabilities (LD) (n = 7), developmental language disorder (DLD) (n = 7), behavioral disorder (BD) (n = 3), or attention deficit hyperactivity disorder (ADHD) (n = 5).

Autistic children had received a diagnosis of autism according to DSM-5 criteria [52], or of autistic disorder, Asperger disorder, and pervasive developmental disorder-not otherwise specified according to DSM-IV criteria [53] (Table 1). In all cases, the diagnosis had been made prior to admission in the study, by a multidisciplinary team that included a senior child psychiatrist and an experienced clinically trained research child psychologist. The autistic and comparison groups were matched by chronological age (two-sample t-test on age in years: $t_{(39)}$ = 0.51, p = 0.60, lgBF = − 1.07) and Performance IQ ($t_{(39)}$ = 0.23, p = 0.81, lgBF = − 1.04), as measured by standardized tests (Leiter International Performance Scale-Revised or Leiter- R, [54]; Wechsler Preschool and Primary Scale of Intelligence WPPSI, Italian version [55]; Wechsler Intelligence Scale for Children [56]), chosen for each participant based on their varying levels of verbal functioning. All children had a Performance IQ score above 70 and were thus considered "cognitively able". No child in either group had additional medical or developmental conditions, as reported by parents, and no child was on medication at the time of the study.

Using G*Power [57], we computed the sensitivity of our tests given the sample size, a set power of 80% and a type I error probability of 5%. This indicated that the smallest between-group difference we would be able to detect was 0.9 as measured with Cohen's d metrics, a large effect size.

Table 1. *Mean (standard deviations) in each group of participants; the last column gives the comparison between the two groups of children*

	Adults	Autistics	Controls	A-C Comparison
Gender (F:M)	32:8	3:15	7:15	X^2=1.21, p = 0.27
Age	29.78 (1.61)	10.95 (2.35)	10.51 (2.94)	$t_{(39)}$ = 0.51, p = 0.60
Performance IQ	-	99.00 (17.00)	100.40 (14.06)	$t_{(39)}$ = 0.27, p = 0.78
Ados-2 Total Score	-	12.20 (3.30)	-	
AQ Total Score	14.25 (8.01)	27.56 (7.81)	18.18 (7.55)	$t_{(39)}$ = 3.84, p < 0.0001

All participants had normal or corrected-to-normal visual acuity. Experimental procedures were approved by the regional ethics committee *Comitato Etico Pediatrico Regionale—Azienda Ospedaliero-Universitaria Meyer—Firenze (FI)* and are in accordance with the declaration of Helsinki; participants (and their legal guardian, where appropriate) gave written informed consent.

AQ score

All neurotypical adult participants filled out an on-line or paper version of the Autism-spectrum Quotient questionnaire, using the validated Italian version [58, 59]. The test comprises 50 items. Responses are made on a 4-point Likert scale: "strongly agree", "slightly agree", "slightly disagree", and "strongly disagree". Items were scored as described in the original paper [58]: 1 when the participant's response was characteristic of autism (slightly or strongly), 0 otherwise. Total scores ranged between 0 and 50, with higher scores indicating higher degrees of autistic traits. AQ scores for children are parent-reported, and were collected using the age-appropriate form [60]. For one child participant the AQ score was not collected (the parent filled out only part of the questionnaire and could not be re-contacted to complete the task).

Stimuli and Procedure

The experiment was conducted in a dark room with no illumination other than the display screen. For adults (Experiment 1) the display was a CRT (Cathode-ray tube) monitor (40 × 30 cm, Barco Calibrator with resolution 1024 × 768; maximum-minimum luminance 53 – 0.1 cd/m^2). Children (Experiment 2) were tested with a more portable device (53 × 32.8 cm LCD color monitor Acer, with resolution 1920 × 1080; maximum-minimum luminance 110 – 0.1 cd/m^2). In both cases, the screen was placed 57 cm from the participant, whose head was stabilized by chin rest. Visual stimuli were generated in Matlab (Mathworks) using the Psychophysics Toolbox[61]. Total testing time (for both adults and children) was about 30 min, including the time for initial adjustment of the apparatus to match each participant's eye-level.

Top: images (sun, moon and meaningless control images) were presented for 1s each in random order, embedded within an animation movie. Bottom: the same protocol was used for the presentation of full-screen maximum or minimum luminance squares, for testing the pupillary light or dark response.

During experimental sessions participants observed a clip extracted from an animation movie [62], displayed at screen center within a window of 17 × 9.1 deg. Stimulus presentation blanked out the movie (with no interruption of the soundtrack) for 1 s, and occurred every 4 s on average (Fig. 1). When testing adults (Experiment 1), three types of images were used: photographs of the sun; photographs of the moon, adjusted to match the mean luminance of the sun images; and phase-scrambled images of the sun that preserved mean luminance, power spectrum, and root mean square contrast [63]. There were 13 images per category, all 10 X 10 cm (subtending 10 × 10 deg at 57 cm viewing distance). Each image was presented twice, over two sessions, in pseudorandomized order. For children (Experiment 2), only sun and phase-scrambled images of the sun were used, which yielded the strongest differences in pupillary response in adults. In addition, in separate sessions, full-screen white or black squares were shown for 1 s and 13 repetitions to estimate each child's pupillary light/dark responses.

Pupil diameter was monitored at 500 Hz with an EyeLink 1000 system (SR Research) with infrared camera mounted below the screen, recording from the left eye. Pupil measures were calibrated by an artificial 4-mm pupil placed at the approximate position of the participants' eye. Synchronization between eye recordings and visual presentations was ensured by the Eyelink toolbox for MATLAB [61]

Analysis of pupillometry and eye-tracking data

Eye-tracking data were preprocessed using custom Matlab scripts that implemented the following steps:

1. Identification and removal of gross artifacts: removal of time-points with unrealistically small or large pupil size (more than 2 mm from the mean of the trial or < 0.1 mm, corresponding to blinks or other signal losses).
2. Identification and removal of finer artifacts: identification of samples where pupil size varied at unrealistically high speeds (> 25 mm per second, beyond the physiological range) and removal of the 20 ms epoch surrounding this disturbance.
3. Down-sampling of data at 100 Hz, by averaging the retained time-points in non-overlapping 100 ms windows. If no retained sample was present in a window, that window was set to "NaN" (MATLAB code for "not a number").

Pupil traces were transformed into changes from baseline by subtracting the average pupil diameter in the first 200 ms after stimulus onset (i.e. during the latency of the pupillary light response). After averaging all traces per subject and image type, we took the maximum dilation (for dark images) or the maximum constriction (for all other images) after the stimulus presentation to index the size of the response, which we submitted to statistical tests. Due to the preprocessing described above, trials with blinks or artifacts yielded traces with several missing values; we excluded these from our analyses by eliminating all trials for which no sample was available over the stimulus presentation window (mean ± s.e.m in adults: 1.5 ± 0.23%; autistic group: 19.40 ± 3.22%; control group: 7.20 ± 1.53%).

Statistical Analysis

Data were analyzed using custom Matlab code and JASP [64]. We used a repeated-measures approach, computing average per-participant responses and comparing them across stimulus types and (for children) across participant groups. Data from Experiment 1 were analyzed with a One-way ANOVA for repeated measures, with 'stimulus category' as within-subject factor; subsequent paired t-tests tested pairwise differences between sun, moon and phase-scrambled stimuli. Data from Experiment 2 were analyzed with a mixed design ANOVA for repeated-measures. This had a within-subject factor 'stimulus category' (sun versus phase-scrambled or bright versus dark) and a between-subject factor 'group' (autistic versus comparison group). Pupillometric results from both the experiments were correlated with participants' AQ scores using Pearson's correlation coefficient.

Each analysis was complemented with a Bayesian Repeated Measures ANOVA, which estimated Bayes Factors for each of the F-terms [65]. Statistical significance was evaluated using both p-values and log-transformed Bayes Factors. The Bayes Factor is the ratio of the likelihood of the two models H_1/H_0, where H_1 assumes an effect (e.g. correlation between two variables or difference between two means) and H_0 assumes no effect. By convention, when the base 10 logarithm of the Bayes Factor (lgBF) > 0.5 is considered substantial evidence in favor of H_1, and lgBF < − 0.5 substantial evidence in favor of H_0.

Results

Experiment 1: Pupillary responses to Sun and Moon pictures in neurotypical adults

We measured pupil-size modulations with contextual information processing using a child-friendly paradigm, where the images (pictures of the sun, moon and phase-scrambled images) were embedded within an animated movie, which participants watched passively. We validated this approach by measuring pupillary responses to the three image categories in 40 neurotypical adult participants. **Figure 2A** shows the average time course of pupil size (in mm) for each image category; **Figure 2B** shows the peak pupil constriction during the stimulus presentation window. Although all images were matched in luminance, pupil responses were clearly modulated by image category (one-way ANOVA for repeated measures, F = 25.55, p < 0.001, lgBF = 6.49). Post-hoc t-tests showed that the sun images evoked the strongest pupillary constriction, stronger than meaningless images obtained by phase-scrambling the sun images (t(39) = 9.846, p < 0.001, lgBF = 9.35) and stronger than moon pictures (t(39) = 3.545, p = 0.001, lgBF = 1.47). Moon pictures also evoked stronger constriction than meaningless images (t(39) = 2.82, p = 0.008, lgBF = 0.71). This pattern of results essentially replicates previous findings [44, 45], indicating that the animation movie did not interfere with the processing of contextual information, which is presumably responsible for the modulation of the pupillary responses.

Experiment 2: Pupillary Light Response in children with and without autism.

As a preliminary step towards evaluating responses to the sun images in autistic participants and age- and IQ-matched participants, we measured the sensitivity of their pupillary system to simple light/dark stimuli (**Figure 3A**). A mixed-design ANOVA revealed a significant interaction between factors: image

category (bright, dark screen: within-subjects) and autism diagnosis (interaction term: $F(1,39) = 8.73$, p = 0.005, lgBF = 1.19). Post-hoc tests showed that the autistic group had a stronger pupillary response to light than the comparison group (two-sample t-test: $t(39) = 2.37$, p = 0.02, lgBF = 0.43). However, the amplitude of the pupillary dark response was indistinguishable between groups (two-sample t-test: $t(39) = 0.50$, p = 0.62, lgBF = −0.47), as was the overall shape of both responses, with no apparent differences in dynamics or latency (not shown). Autistic participants also had slightly but significantly more dilated resting pupil diameter measured in the pre-stimulus interval (mean ± standard error of the mean, autistic group: 4.07 ± 0.15; comparison group: 4.14 ± 0.15; $t(39) = 2.11$, p = 0.04, lgBF = 0.23).

Pupillary responses to contextual images in children with and without autism

Finally, we probed contextual information processing in our children participants by focusing on responses to the sun and phase-scrambled images, those most distinct in the adult data. Figure 3B shows average pupil constriction during the stimulus presentation window. Again, these were analyzed with a mixed-design ANOVA with factors: image category (sun, phase-scrambled: within-subjects) and diagnosis (autism and non-autism, between-subjects). Both image categories evoked marginally stronger pupillary constriction in the autistic than the comparison group (main effect of diagnosis: $F(1,39) = 4.11$, p = 0.049, lgBF = 0.14), confirming the enhanced pupillary response to light seen in **Fig. 3A**. Like in the neurotypical adults, pictures of the sun systematically evoked a stronger constriction than the meaningless phase-scrambled images (main effect of image category: $F(1,39) = 55.24$, p < 0.001, lgBF = 6.23). However, this effect was similar in the autistic and comparison groups (no image x diagnosis interaction: $F(1,39) = 0.59$, p = 0.44, lgBF = 0.05), as confirmed by the non-significant difference between the two ($t(39) = 0.77$, p = 0.45, lgBF = − 0.41).

Taking into account the enhanced pupil responsivity in the autistic group did not change the pattern of results: even after normalizing each individual's response by their pupillary light response, the amplitude of the response to the sun pictures was indistinguishable between groups ($t(39) = 0.03$; p = 0.98; lgBF = − 0.51).

As children in the comparison group had heterogeneous diagnoses, we checked that pupillary responses did not differ across sub-groups (ADHD, LD, DLD, BD) with a one-way ANOVA on pupillary responses to the sun pictures ($F(3,19) = 0.46$, p = 0.71, lgBF = − 0.53).

Contextual Pupil Response and Autistic Traits

Previous reports of reliable associations between pupillometry results and inter-individual differences in perceptual styles [47-50] motivated us to investigate the relationship between the effects of contextual information on pupillary responses and autistic-like traits measured by the Autism-Spectrum Quotient [58]. However, we found no association between AQ and the pupil difference for sun pictures and phase-scrambled images, neither in neurotypical adults (**Figure 4A**: $r(40) = −0.10$; p = 0.53; lgBF = −0.83) nor in the groups of children (**Figure 4B**: $r(40) = −0.12$; p=0.48; lgBF = −0.80).

Discussion

We measured pupil size changes in response to images of the sun, moon and phase-scrambled images, all matched in average luminance. Previous studies showed that each of these images evokes a different pupillary constriction response in adults, despite being matched in luminance, indicative of an effect of contextual information on pupillary responses. Here we replicated the findings by Binda et al [45] in a group of neurotypical adults (Experiment 1), using a novel, child-friendly setup, without requiring participants to respond: the high-luminance context implied by the sun image caused pupillary constriction, even when embedded within an attention-grabbing animation movie. We then measured the effect in two groups of 6–15 years old children (Experiment 2), one comprising children with autism diagnosis, the other with diagnosis of unrelated development disorders. Both groups showed strong contextual effects, with pupils constricting significantly more for the sun than for the phase-scrambled control image. However, there was no measurable difference between the two groups.

It is now established that pupil diameter is sensitive to top-down modulation, implying that it is modulated by cortical pathways other than the subcortical PLR system [42, 66]. A recent experiment using continuous flash suppression [38] demonstrated that extra-retinal pupillary modulation requires visual awareness: the pupillary response to the sun and phase-scrambled images differed only when participants were aware of the images, not when the images were successfully suppressed from awareness. This is clear evidence that the pupil modulation evoked by pictures of the sun reflects high-level perceptual processing and the contents of conscious perception. Our results suggest that this form of perceptual processing, albeit relatively high-level, is not affected in autistic individuals. This negative finding is in line with a recent study that also used pupillometry to compare perceptual processing in autistic individuals and controls and failed to reveal systematic differences in pupillary constriction to illusory bright stimuli [67].

On the other hand, the literature reports multiple instances of differences in basic pupillary responses to light or dark in autism, including reports of enhanced pupillary responses to light in autistic individuals compared to controls [68, 69]; our findings are in line with this pattern (Fig. 3A) and they might be linked to hypersensitivity phenomena that are often associated with autism [70, 71]. However, the literature presents discordant findings, with some studies reporting no differences with autism, or reporting differences in latency but not in amplitude [72, 73]; some studies even show the opposite pattern [74, 75]. For example, Fan et al. reported that pupils of autistic children took longer to respond to short (0.1 s) light stimuli, and constricted less and more slowly than those with typical development [75]. We also found a marginally larger pre-stimulus pupil diameter in the autistic group, in line with studies by Anderson et al. [74, 76, 77]. Also in this case, however, the literature includes conflicting reports, some of which found a weak [78] or null [68, 69, 75] steady-state pupil size difference between autistic individuals and controls.

We take these findings to suggest that although pupillary light responses and steady-state pupil diameter are perhaps the easiest pupillometry parameters to estimate, they are not necessarily the most informative, being unable to systematically differentiate autistic individuals from controls (at least not

consistently across the varying testing conditions in different studies). Thus, measuring pupil size modulations related to more complex aspects of visual processing may provide a more informative index – one that may be able to track the contents of perception or cognition. We submit that the negative findings in the present and previous report [67] should not discourage this pursuit but may rather testify to its selectivity.

LIMITATIONS

One limitation of the study is that we probed contextual processing with one type of stimulus, known to involve relatively complex visual processing. We found no differences between the autistic group and the comparison group, and this leaves open the possibility that the group differences exist, but they are too small to be detected with this type of stimulus. The composition of the comparison group may be an additional limitation, as its heterogeneity might in principle have inflated the variance of our measurements, decreasing our ability to measure group differences. In future studies, the recruitment of neurotypical controls and the use of a larger range of stimuli may address these concerns.

Conclusions

Previous studies have stressed the importance of minimizing the effects of decision biases when assessing inter-individual differences in perceptual experience – such as those that may emerge between individuals with and without autism. The child-friendly no-report paradigm presented here might serve this purpose in future studies. Specifically, it may help determine whether atypical perception (as previously reported in autistic persons for visual illusions or local/global hierarchical images) reflect real perceptual differences between autistic and neurotypical individuals. Also, it may be useful to identify which (if any) of these functions is selectively altered in autism.

Declarations

Ethics approval and consent to participate

All participants had normal or corrected-to-normal visual acuity. Experimental procedures were approved by the regional ethics committee *Comitato Etico Pediatrico Regionale—Azienda Ospedaliero-Universitaria Meyer—Firenze (FI)* and are in accordance with the declaration of Helsinki; participants (and their legal guardian, where appropriate) gave written informed consent.

Consent for publication

Not Applicable

Availability of data and materials

Experimental data have been uploaded to Zenodo at the following doi: 10.5281/zenodo.4608371

Competing interests

Funding

Authors' contributions

All authors contributed to the conceptualization of the research, and the design, analysis and interpretation of the results. CT and AP conducted to the data acquisition, RI and MT the selection of participants. All authors contributed to, and read and approved the final manuscript.

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Figures
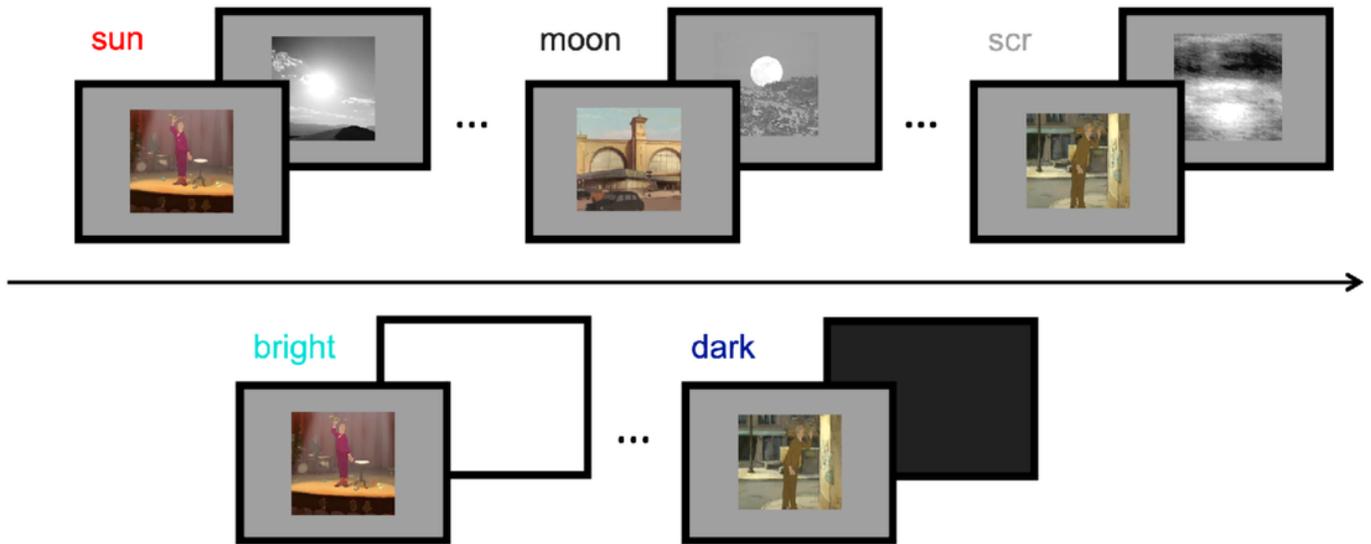
Figure 1

Schematics of the experimental stimuli and procedure.
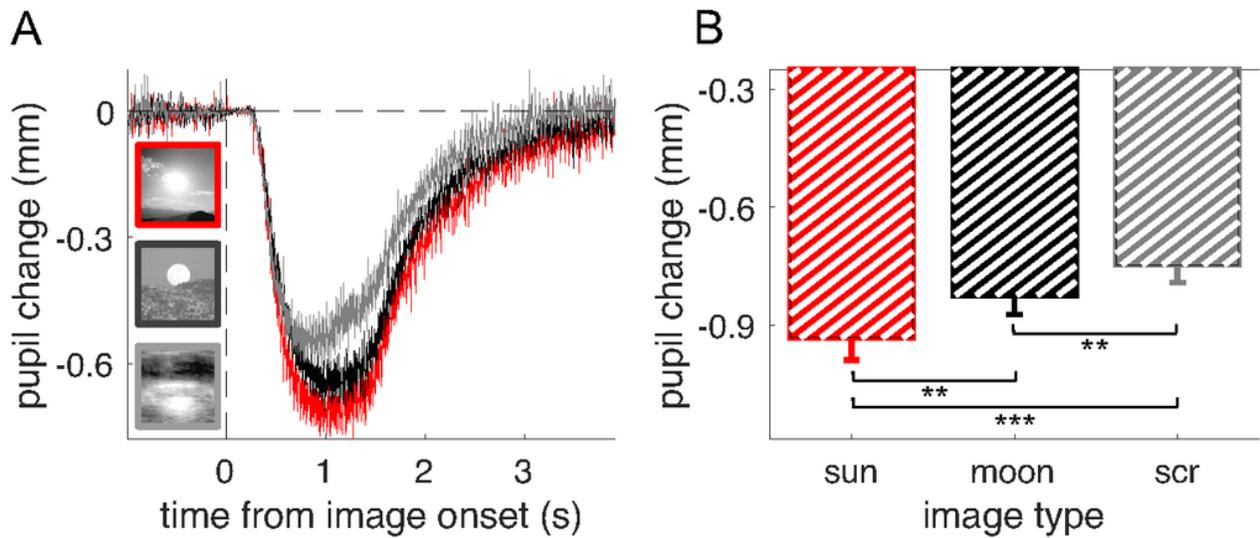
Figure 2

Results from Experiment 1 (neurotypical adults). A: timecourses of pupil constrictions (referenced to pre-stimulus baseline) evoked by the three image categories: pictures of the sun, of the moon and meaningless control images obtained by phase-scrambling the sun pictures ('scr'); thin lines straddling the timecourse give s.e.m. at each timepoint. B: peak constriction for the three image categories,

averaged across participants. Error-bars show ±1 s.e.m. across participants. Stars indicate significance of the post-hoc t-tests (** for p < 0.01, *** for p < 0.001).
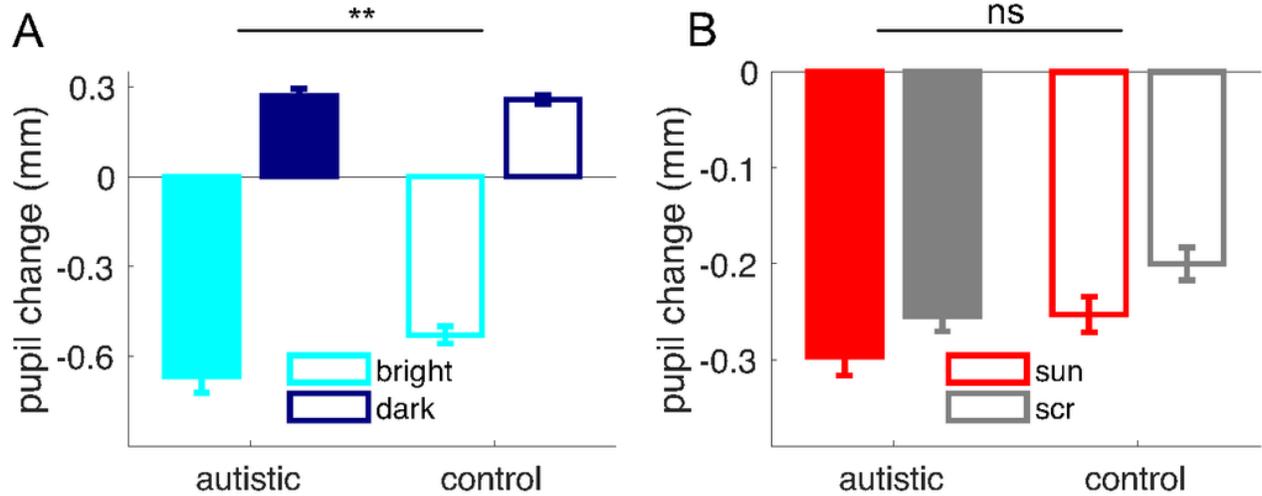

Figure 3

Results from Experiment 2 (autistic and comparison children). A: peak pupil response to luminance increments and decrements, averaged across observers in each group. B: peak pupil response to sun pictures and meaningless images ('scr'), averaged across observers in each group. In both panels, error bars indicate ±1 s.e.m. across participants and the symbols on the top indicate the significance of the group × image category interaction term in the mixed-design ANOVA (** = p<0.01, ns = non-significant).
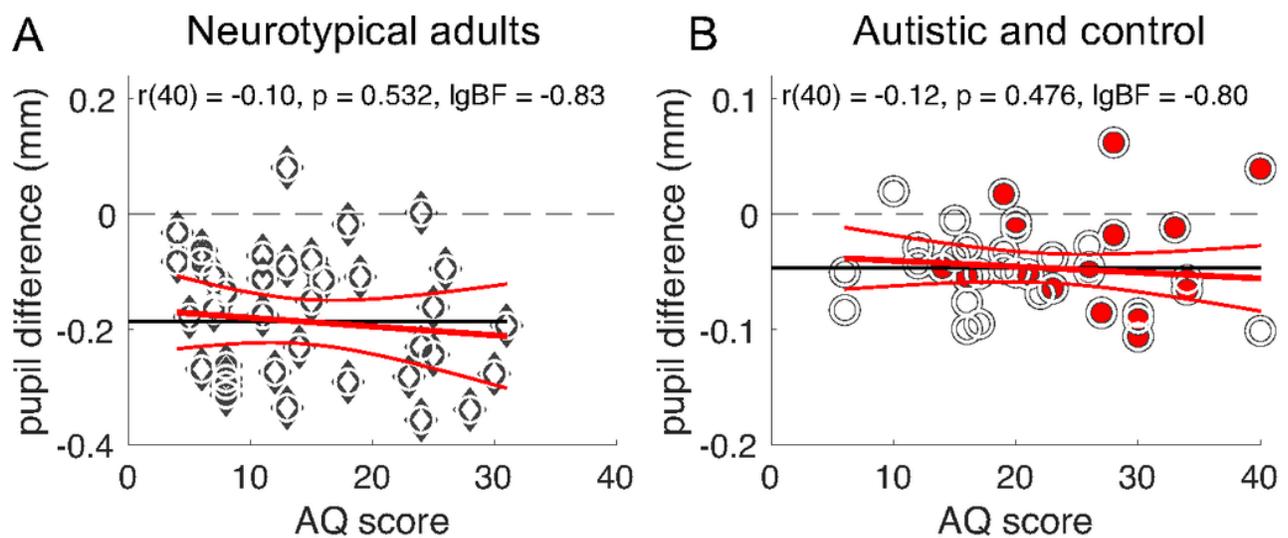

Figure 4

Lack of association between autistic-like traits, as measured by the Autism-spectrum Quotient questionnaire (AQ score), and the difference in pupil response evoked by the sun images and the meaningless control images obtained by phase scrambling. A: data from neurotypical adults. B: data from children, from both the autistic (filled symbols) and the comparison groups (empty circles). The horizontal continuous black line shows the mean, and the red lines show the best-fit linear regression with its 95% confidence interval. Text insets give the Pearson's correlation (with sample size) and associated p-value and log Bayes Factor.