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Autism spectrum disorder, but not amygdala lesions, impairs social attention in visual search

Shuo Wang^{a,*}, Juan Xu^{b,1}, Ming Jiang^b, Qi Zhao^b, Rene Hurlemann^c, and Ralph Adolphs^{a,d}

^aComputation and Neural Systems, California Institute of Technology, Pasadena, CA 91125, USA

^bDepartment of Electrical and Computer Engineering, National University of Singapore, 117583 Singapore, Singapore

^cDepartment of Psychiatry, University of Bonn, 53105 Bonn, Germany

^dHumanities and Social Sciences, California Institute of Technology, Pasadena, CA 91125, USA

Abstract

People with autism spectrum disorders (ASD) have pervasive impairments in social interactions, a diagnostic component that may have its roots in atypical social motivation and attention. One of the brain structures implicated in the social abnormalities seen in ASD is the amygdala. To further characterize the impairment of people with ASD in social attention, and to explore the possible role of the amygdala, we employed a series of visual search tasks with both social (faces and people with different postures, emotions, ages, and genders) and non-social stimuli (e.g., electronics, food, and utensils). We first conducted trial-wise analyses of fixation properties and elucidated visual search mechanisms. We found that an attentional mechanism of initial orientation could explain the detection advantage of non-social targets. We then zoomed into fixation-wise analyses. We defined target-relevant effects as the difference in the percentage of fixations that fell on target-congruent vs. target-incongruent items in the array. In Experiment 1, we tested 8 high-functioning adults with ASD, 3 adults with focal bilateral amygdala lesions, and 19 controls. Controls rapidly oriented to target-congruent items and showed a strong and sustained preference for fixating them. Strikingly, people with ASD oriented significantly less and more slowly to target-congruent items, an attentional deficit especially with social targets. By contrast, patients with amygdala lesions performed indistinguishably from controls. In Experiment 2, we recruited a different sample of 13 people with ASD and 8 healthy controls, and tested them on the same search arrays but with all array items equalized for low-level saliency. The results replicated those of Experiment 1. In Experiment 3, we recruited 13 people with ASD, 8 healthy controls, 3 amygdala lesion patients and another group of 11 controls and tested them on a simpler array.

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*Correspondence to: 114-96, 1200 E California Blvd. Pasadena, CA 91125, USA. Tel.: +1 626 395 3898; fax: +1 626 395 2000. wangshuo45@gmail.com (S. Wang).

¹Equal contributions.

Author contributions

S.W. and R.A. designed experiments and wrote the paper. R.H. provided two of the patients with bilateral amygdala lesions. S.W. and J.X. performed experiments. S.W., J.X., M.J. and Q.Z. analyzed data. All authors discussed the results and contributed toward the manuscript.

Here our group effect for ASD strongly diminished and all four subject groups showed similar target-relevant effects. These findings argue for an attentional deficit in ASD that is disproportionate for social stimuli, cannot be explained by low-level visual properties of the stimuli, and is more severe with high-load top-down task demands. Furthermore, this deficit appears to be independent of the amygdala, and not evident from general social bias independent of the target-directed search.

Keywords

Visual search; Autism; Amygdala; Saliency; Social

1. Introduction

People with autism spectrum disorders (ASD) are characterized by pervasive impairments in social interaction and communication, together with restricted interests and repetitive behaviors (American Psychiatric Association, 2013). Laboratory-based measures reflecting the social impairments have documented abnormal eye tracking to social videos (Klin, Jones, Schultz, Volkmar, & Cohen, 2002) as well as static faces (Pelphrey et al., 2002). Work from our laboratory has argued for an increased tendency in adults with ASD to saccade away from the eye region of faces when information is present in those regions (Spezio, Adolphs, Hurley, & Piven, 2007b), and instead an increased preference to fixate the location of the mouth (Neumann, Spezio, Piven, & Adolphs, 2006), together with reliance of information from the mouth (Spezio, Adolphs, Hurley, & Piven, 2007a). Similarly, other eye tracking studies have found active avoidance of fixating the eyes in faces in people with ASD (Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010). However, many other studies have shown normal social orienting and eye attention in people with ASD (see Guillon, Hadjikhani, Baduel, and Rogé, (2014) for a recent review); infants who later develop autism show an equally strong face orienting response (Elsabbagh et al., 2013) and adults with ASD demonstrate a similar looking-time to faces as controls (Kuhn, Kourkoulou, & Leekam, 2010; Nakano et al., 2010). Young children with ASD show similar pattern of attention to the eyes and the mouth as typically developing controls (de Wit, Falck-Ytter, & von Hofsten, 2008; Falck-Ytter, Fernell, Gillberg, & Von Hofsten, 2010) and so do adolescents with ASD (McPartland, Webb, Keehn, & Dawson, 2011)—the story about reduced social orienting and eye attention in ASD is far from clear.

The findings showing abnormalities in how eyes are fixated by people with ASD may be related to the more subtle and heterogeneous findings in the literature regarding face processing. In particular, several studies have found reliable, but weak, deficits in the ability to recognize emotions from facial expressions (Kennedy & Adolphs, 2012; Law Smith, Montagne, Perrett, Gill, & Gallagher, 2010; Philip et al., 2010; Wallace et al., 2011) (for review, see Harms, Martin, and Wallace (2010)). The recognition of more complex mental states from faces may show a more reliable impairment in ASD, particularly if only the eye region of faces is shown (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Interestingly, abnormal fixations onto faces (Adolphs et al., 2005), abnormal recognition of emotion from facial expressions (Adolphs et al., 1999), and abnormal recognition of mental

states from the eye region of faces (Adolphs, Baron-Cohen, & Tranel, 2002) have also all been reported in rare patients with amygdala lesions, providing some support for a long-standing hypothesis about the amygdala's involvement in ASD (Baron-Cohen et al., 2000).

Although there is evidence for global dysfunction at the level of the whole brain in ASD (Amaral, Schumann, & Nordahl, 2008; Anderson et al., 2011; Geschwind & Levitt, 2007; Piven et al., 1995), several studies emphasize abnormalities in the amygdala both morphometrically (Ecker et al., 2012) and in terms of functional connectivity (Gotts et al., 2012). Tying together the abnormal eye fixations onto faces in ASD mentioned above, and a correlation with amygdala processing, functional neuroimaging studies have found associations between abnormal fixation behavior and abnormal amygdala activation in people with ASD (Dalton et al., 2005; Kliemann, Dziobek, Hatri, Baudewig, & Heekeren, 2012). One recent study even found evidence for abnormal processing of information from the eye region of faces in single cells recorded from the amygdala in neurosurgical patients with ASD (Rutishauser et al., 2013). Despite considerable variability in reports of abnormal face processing in ASD, and despite the fact that there is brain dysfunction at a more global level in ASD, studies largely support (a) abnormal processing of faces in ASD, and (b) a link between this abnormality and amygdala function.

The human amygdala has been quite broadly implicated in processing emotionally salient and socially relevant stimuli (Adolphs, 2010; Kling & Brothers, 1992). Studies of a patient with bilateral amygdala lesions demonstrated a selective impairment in recognizing fearful faces (Adolphs, Tranel, Damasio, & Damasio, 1994), congruent with early neuroimaging studies (Morris et al., 1996). A distinctive aspect of our studies was the direct comparison between subjects with ASD, and rare patients with bilateral amygdala lesions.

Much of the work cited above has focused on abnormal social processing in ASD in relation to the features of faces. Yet it is clear that the impairment is broader than this: two-year-olds with autism orient to non-social contingencies rather than biological motion (Klin, Lin, Gorrindo, Ramsay, & Jones, 2009), and attention to pictures of people is reduced in relation to pictures that are non-social when these compete for visual attention (Sasson, Turner-Brown, Holtzclaw, Lam, & Bodfish, 2008; Sasson, Elison, Turner-Brown, Dichter, & Bodfish, 2011; Sasson & Touchstone, 2014). We capitalized on these prior findings, and used the stimuli developed in these prior studies, with slight modification (see *Methods* for further details). Notably, these images provided stimuli that fell into three categories: social, non-social, and special interest. The prior findings had shown, both in children and adolescents (Sasson et al., 2008), as well as in 2–5 year-olds (Sasson et al., 2011), that participants with ASD fixated social images less than controls when freely viewing the arrays. Our approach here extends this prior work in four important respects, with social attention defined as fixating and attending to social stimuli:

1. We assessed high-functioning adults with ASD, and also manipulated the difficulty of our task (number of items in the array) to test whether abnormal social attention would be revealed even in high-functioning adults.

2. We provided a comparison to a small sample (three) of subjects with bilateral amygdala lesions, to enable comparisons between these two populations in light of the prior findings we reviewed above.
3. We modified the experiment so that all subjects were performing a uniform search task for either social or non-social targets (rather than free viewing).
4. We added a control experiment that equates the items in the search array for low-level visual properties (standard saliency, size, and distance to center).

Visual search tasks are not new to autism research. Several studies have suggested superior visual search skills in individuals with ASD (Kemner, van Ewijk, van Engeland, & Hooge, 2008; Plaisted, O’Riordan, & Baron-Cohen, 1998; O’Riordan & Plaisted, 2001; O’Riordan, Plaisted, Driver, & Baron-Cohen, 2001; O’Riordan, 2004), particularly in relatively difficult tasks. Among various efforts to explain the differences, O’Riordan and Plaisted (2001) proposed two processing differences that could potentially explain the performance advantage: (1) enhanced memory for distractor locations already inspected, and (2) enhanced ability to discriminate between target and distractor stimulus features. Later, Joseph, Keehn, Connolly, Wolfe, and Horowitz (2009) argued that the superiority is due to the anomalously enhanced perception of stimulus features.

While a sizable literature in ASD has investigated search for simple, non-social stimuli (shapes, letters, etc.) and only manipulated low-level attributes of the stimuli (Kemner et al., 2008; Manjaly et al., 2007; Plaisted et al., 1998; O’Riordan & Plaisted, 2001; O’Riordan et al., 2001; O’Riordan, 2004), far fewer studies have examined visual search with social stimuli. In the present study, we used a more general framework that does not restrict the stimuli to specific facial emotions, or investigate internal features of faces, but tests competition for attention between natural social (faces and people with various emotions and poses) and non-social (e.g., furniture, toys and food) stimuli when presented simultaneously in a search array. Given the reduced orientation towards social images in young children and adolescents with ASD when freely viewing the arrays (Sasson et al., 2008, 2011), we hypothesized that adults with ASD would have reduced attention to socially relevant items during visual search, while the deficits for attention to non-social items would be less pronounced. In a series of studies, we here explore whether the possible deficit depends on the amygdala (by comparisons with amygdala lesion patients tested on the identical tasks), and whether it depends on low-level visual properties of the search stimuli (by equating stimuli for their low-level visual properties in some of the studies). Since task demands such as the number of distractors can influence visual search performance (Lavie, Hirst, de Fockert, & Viding, 2004; Wolfe, 1998), we also test a variation of the search array with fewer distractors and test whether the possible deficit in ASD is disproportionate for higher cognitive loads (larger numbers of distractors), which would in turn suggest a possible working memory deficit in ASD. Our specific hypotheses tested in the studies were thus that (1) people with ASD would be impaired in visual search; (2) this deficit would be greater for social than for non-social stimuli; (3) this deficit would not be attributable solely to the low-level visual properties of the stimuli, but (4) possibly interact with cognitive load.

2. Methods

2.1. Subjects

Subjects gave written informed consent and the experiments were approved by the Caltech and NUS Institutional Review Boards. All subjects had normal or corrected-to-normal visual acuity.

In Experiment 1, eight high-functioning people with ASD were recruited (see Supplemental Tables 1 and 2). All ASD participants met DSM-IV/ICD-10 diagnostic criteria for autism, and all met the cutoff scores for ASD on both the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989) and the Autism Diagnostic Interview-Revised (ADI-R) (LeCouteur, Rutter, & Lord, 1989) (Supplemental Table 1). We assessed IQ for participants using the Wechsler Abbreviated Scale of Intelligence (WASI™). The ASD group had a full scale IQ of 106.9 ± 11.8 (mean \pm SD).

AP, AM and BG are three patients with selective bilateral amygdala lesions as a result of Urbach–Wiethe disease (Hofer, 1973). AM and BG are monozygotic twins. The details of these patients have been described previously (Buchanan, Tranel, & Adolphs, 2009; Becker et al., 2012). The detailed pattern of abilities and disabilities in the amygdala lesion patients is somewhat variable and complex, given the different tasks and stimuli on which they have been tested, often across different laboratories. However, in an attentional change detection task used in our own laboratory, AP, AM and BG all showed intact preferential attention to animals and people (Wang, Tsuchiya, New, Hurlemann, & Adolphs, 2014a), consistent with the normal pattern of performances in the present paper. By contrast, there is a substantial literature documenting deficits on more spontaneous or passive emotion recognition and social judgment tasks (Adolphs et al., 1994; Adolphs, Tranel, & Damasio, 1998; Adolphs et al., 1999, 2005), albeit tested in a set of subjects with amygdala lesions that did not include AP, AM or BG. Taken together, the patterns across studies of patients with amygdala lesions are suggestive of the most prominent impairments in spontaneous and passive viewing tasks, with largely preserved abilities on explicit and goal directed tasks, a dissociation that will be important to compare eventually in more detail to ASD. The anatomical scans of the lesions are shown in Supplemental Fig. 1. The amygdala group had a full scale IQ of 98.3 ± 2.5 (mean \pm SD), comparable to people with ASD (*t*-test: $p=0.26$ for Experiment 1, $p=0.45$ for Experiment 2, and $p=0.44$ for Experiment 3).

Eight healthy subjects were recruited as general controls for both people with ASD and amygdala lesion patients, matched on IQ (full scale: 104.7 ± 6.1 (mean \pm SD); *t*-test: $p=0.68$ for people with ASD and $p=0.13$ for amygdala patients) and education (Supplemental Table 3).

Eleven students from the National University of Singapore (NUS) were tested for all three versions of the task (Experiments 1–3) to provide an independent reference group. By testing NUS controls as an independent healthy comparison sample to which both the patient (amygdala and ASD) and their control groups could be compared, we could show that our results were not sensitive to experimental locations, experimenters and eye tracker systems, but were robust across populations (general population vs. college undergraduates) and

different cultures. Furthermore, NUS controls performed all three experiments, and this thus facilitated cross-experiment comparisons.

In Experiment 2, we tested 13 high-functioning people with ASD (different from those who participated in Experiment 1; see Supplemental Tables 1 and 2), eight healthy ASD controls (Supplemental Table 2) and 11 NUS control subjects (the same as Experiment 1; experiment order counterbalanced). The ASD group had a full scale IQ of 108.7 ± 22.3 (mean \pm SD) and ASD controls had a comparable full scale IQ of 111.3 ± 9.8 (t -test, $p=0.76$). The ASD group had a mean age of 29.7 ± 8.6 years and ASD controls had a mean age of 35.9 ± 11.8 years (t -test, $p=0.18$). ASD controls also matched on gender, race and education.

In Experiment 3, we tested the same three amygdala lesion patients from Experiment 1 (AP, AM and BG), 13 high-functioning people with ASD (see Supplemental Tables 1 and 2), eight healthy ASD controls (the same as Experiment 2; Supplemental Table 2), and 11 NUS control subjects (the same as Experiments 1 and 2; experiment order counterbalanced). The ASD group had a full scale IQ of 108.8 ± 22.1 (mean \pm SD) and ASD controls had a comparable full scale IQ of 111.3 ± 9.8 (t -test, $p=0.78$). The ASD group had a mean age of 28.8 ± 7.6 years and ASD controls had a mean age of 35.9 ± 11.8 years (t -test, $p=0.11$). ASD controls also matched on gender, race and education.

2.2. Stimuli and apparatus

In Experiment 1, we used 20 distinct visual search arrays. In each array there were 24 items whose spatial locations were randomized between the 20 arrays. 12 items were social (faces and people with different postures, emotions, ages, genders, etc.) and 12 items were non-social (furniture, toys, food, etc.). Items comprising the search arrays were obtained from two prior studies that investigated visual attention in infants and children with ASD (Sasson et al., 2008, 2011). Items were cropped and reassembled from search arrays used by Sasson et al. (2008), and the search arrays were further modified into gray scale to minimize the bottom-up effects of colors. By such reassembling, we could create more arrays than Sasson et al. (2008) to ensure that subjects would not likely memorize any particular arrays during visual search, and have different number of items in arrays than Sasson et al. (2008) to manipulate task load. The social and non-social items composing the array stimuli have been characterized and described previously (Sasson, Dichter, & Bodfish, 2012). From each array stimulus, we randomly assigned 4 social items and 4 non-social items as targets (on 8 distinct trials). For each array, we also had 2 catch trials, i.e., the target was not among the items in the search array (one catch trial with a social target, and one with a non-social target). Therefore, in total we had 100 trials with social targets and 100 trials with non-social targets, and 20% of trials were catch trials.

The experimental setup of Experiment 2 was identical to Experiment 1 except that low-level properties of social and non-social items were equalized within each search array. Low-level properties included standard low-level saliency as quantified by the Itti-Koch saliency model (Itti, Koch, & Niebur, 1998; Itti & Koch, 2001), size subtended on the screen, and distance to the screen center. The Itti-Koch saliency model included channels of color, orientation and pixel intensity. High saliency value indicated high local contrast, which in turn tended to attract more fixations. The saliency value was computed for each array item

and averaged separately for social and non-social items. Similarly, we calculated size and distance to the screen center for each array item (the larger the size, the easier to attract fixations; the closer to the screen center, the faster to attract fixations). We adjusted item color, intensity, size and distance to the screen center to ensure that on average the social and non-social items did not differ in these low-level properties (all $ps > 0.79$; Supplemental Fig. 2A–C). An exemplar standard array with fixations is shown in Fig. 1B (left).

The experimental setup of Experiment 3 was identical to Experiment 2 except that there were only 12 items in total in each search array (6 social and 6 non-social). Low-level properties of social and non-social items were also equalized within each search array, as we had done for Experiment 2 (Supplemental Fig. 2D–F). The social and non-social items did not differ in standard low-level saliency, distance to center, or size (all $ps > 0.34$). An exemplar simple array with fixations is shown in Fig. 1B (right).

Subjects sat approximately 65 cm from an LCD display with a 23-inch screen (screen resolution: 1920×1080). The refresh rate of the display was 60 Hz and the stimuli occupied the center of the display ($14.9 \times 11.2^\circ$ visual angle). Stimuli were presented using MATLAB with the Psychtoolbox 3 (Brainard, 1997) (<http://psychtoolbox.org>).

2.3. Task

We used a standard visual search task (Fig. 1A). A target was presented for 1 s followed by the search array. Subjects were instructed to find the item in the array that matched the target and explicitly told that the array might or might not contain the target. The search array stayed up for at most 14 s, or until the subject responded, either by pushing the space bar to indicate that the target was found in the array, or by pushing the button ‘N’ to indicate that the target was absent in the array. If they pushed the space bar in target-present trials, subjects were asked to click on the target item in the array with a mouse. If subjects clicked on the correct target, a message ‘Correct’ was displayed to the subjects for 1 s. Otherwise, a message ‘Incorrect’ was displayed for 1 s. Subjects were instructed to respond as quickly and accurately as possible. If subjects did not respond within 14 s after array onset, a message ‘Time Out’ was displayed. An inter-trial-interval (ITI) was jittered between 1 and 2 s. The array and target orders were completely randomized for each subject. Subjects practiced 5 trials before the experiment to familiarize themselves with the task.

2.4. Eye tracking

Eye tracking was carried out using a non-invasive infrared remote Tobii X300 system which recorded binocular gaze at 300 Hz. The Tobii visualization software (Tobii Studio™ 2.2) was used to record eye movements and perform gaze analysis. Fixations were detected by Tobii Fixation Filter implemented in Tobii Studio. The Tobii Fixation Filter is a classification algorithm proposed by Olsson (2007) and detects quick changes in the gaze point using a sliding window averaging method. Velocity threshold was set to 35 [pixels/samples] and distance threshold was set to 35 [pixels] in our study.

NUS control subjects were recorded with a noninvasive infrared Eyelink 1000 system (SR Research, Canada). One of the eyes was tracked at 2000 Hz. The eye tracker was calibrated with the built-in 9-point grid method.

2.5. Data analysis

Prior to data collection, we defined a rectangular region that encompassed each target as the target region to define acceptable mouse click locations for each search. In Experiment 1, out of 4800 target-present trials, in 4547 trials (94.73%) subjects found the target by pushing the space bar and subsequently clicked within the pre-defined areas (correct detection trials). Subjects missed targets altogether (judged target-present trials as target-absent) in 183 trials (3.81%) and correctly reported target presence but clicked outside the target rectangle in 69 trials (1.44%) (both are incorrect trials). Subjects did not respond within 14 s after array onset (time-out trials) in only 1 trial (0.021%). Out of 1200 target-absent trials, subjects had 1129 (94.08%) correct trials, 70 (5.83%) false-alarm trials (reported target presence in target-absent trials), and 1 (0.08%) time-out trial. We found similar percentages of correct, incorrect, time-out and false-alarm trials for Experiment 2 and Experiment 3. We only analyzed correct target-present trials (correct target-present response followed by correct identification of the target) unless otherwise specified. Further, we only included trials with reaction times (RTs, with respect to search array onset) within ± 2.5 standard deviations for all analyses (in Experiment 1, 114 trials were excluded, 2.51%). There was no difference between participants with ASD, amygdala patients and control subjects in any of the above proportions (all $ps > 0.10$).

We performed fixation-by-fixation analysis on the first 10 fixations in fixation serial order. As can be seen in Fig. 3A–C, most target-present trials had less than 10 fixations before target detection (percentage of target-present trials that had 10 or more fixations averaged across all conditions: Experiment 1: 19.10%, Experiment 2: 21.91%, Experiment 3: 4.95%; for target-absent trials: Experiment 1: 78.00%, Experiment 2: 85.31%, Experiment 3: 35.29%; see Fig. 3D–F for average number of fixations for each condition). We truncated trials with more than 10 fixations, and for trials with less than 10 fixations, we only averaged up to their last fixation (thus, there were fewer trials being averaged at later fixations). We chose 10 fixations for analyses because this could capture most of the visual search process on the one hand, and would not leave the average at later data points too noisy on the other hand. Statistics were performed from the second fixation due to the random start of the first fixation. In all fixation-wise analyses, we corrected for multiple comparisons with false discovery rate (FDR) of 0.05 (Benjamini & Hochberg, 1995).

Note that array items were defined by rectangular regions of interest (ROIs) that tightly encompassed the items and all our fixation-wise analyses included fixations occurring within the margins between the item ROIs (note that due to this the percentage of fixations on social items and non-social items did not add up to 100% in Fig. 5, Supplemental Figs. 4 and 5), except that in Supplemental Fig. 3 we excluded fixations in the margins and only included fixations fully within the item ROIs. Also note that the 10 fixations involved in the fixation-by-fixation analyses could include multiple consecutive fixations within the same array item.

3. Results

3.1. Behavioral performance: accuracy and reaction time

We first analyzed the behavioral performance of all subject groups. Across all three experiments, all subject groups (ASD, ASD controls, amygdala lesions, general controls and NUS students) had an average performance above 90%, indicating that they were able to perform the task without difficulty. Only a slight difference was found in accuracy between target-present trials and target-absent trials, or between subject groups (two-way mixed ANOVA (target presence \times subject group); main effect of target presence: Experiment 1: $F(1,26)=9.28$, $p=0.0053$, $\eta^2=0.095$; Experiment 2: $F(1,29)=3.12$, $p=0.088$, $\eta^2=0.043$; Experiment 3: $F(1,31)=2.17$, $p=0.15$, $\eta^2=0.027$; main effect of subject group: Experiment 1: $F(3,26)=1.26$, $p=0.31$, $\eta^2=0.075$; Experiment 2: $F(2,29)=3.48$, $p=0.044$, $\eta^2=0.095$; Experiment 3: $F(3,31)=0.58$, $p=0.63$, $\eta^2=0.030$; interaction: Experiment 1: $F(3,26)=1.73$, $p=0.19$, $\eta^2=0.053$; Experiment 2: $F(2,29)=2.33$, $p=0.12$, $\eta^2=0.065$; Experiment 3: $F(3,31)=0.74$, $p=0.53$, $\eta^2=0.028$), indicating no detection bias towards target presence or absence, and that subjects could perform the task equally well. Further analysis within target-present trials showed no difference in accuracy between social targets and non-social targets nor between subject groups (see Supplemental Results and Fig. 2 for details).

As expected, we observed shorter reaction times (RTs) in target-present trials, as subjects needed more time for exhaustive search in order to confirm target absence, while we observed little difference in subject groups or interactions (two-way mixed ANOVA (target presence \times subject group); main effect of target presence: Experiment 1: $F(1,26)=180.0$, $p=3.39 \times 10^{-13}$, $\eta^2=0.66$; Experiment 2: $F(1,29)=197.8$, $p=1.75 \times 10^{-14}$, $\eta^2=0.61$; Experiment 3: $F(1,31)=197.8$, $p=5.33 \times 10^{-15}$, $\eta^2=0.56$; main effect of subject group: Experiment 1: $F(3,26)=1.77$, $p=0.18$, $\eta^2=0.042$; Experiment 2: $F(2,29)=2.56$, $p=0.094$, $\eta^2=0.044$; Experiment 3: $F(3,31)=3.14$, $p=0.039$, $\eta^2=0.077$; interaction: Experiment 1: $F(3,26)=0.29$, $p=0.83$, $\eta^2=0.0031$; Experiment 2: $F(2,29)=1.37$, $p=0.27$, $\eta^2=0.0084$; Experiment 3: $F(3,31)=2.83$, $p=0.055$, $\eta^2=0.024$). We subsequently analyzed target-present trials only. Across experiments, non-social targets, which were more distinct from one another than was the case for social targets, were detected more quickly by all subject groups. Detailed results are shown in Supplemental Results and Fig. 2. Note that all results shown in Fig. 2 were from target-present trials only.

3.2. Eye tracking: quantification of fixation properties and analysis of visual search mechanisms

3.2.1. The number of fixations before target detection mirrors RT results—In the eye movement analysis, we first quantified the number of fixations taken to detect targets (Fig. 3A–C and D–F). In Experiment 1, non-social targets were detected with fewer fixations by all subject groups (Fig. 3D; two-way mixed ANOVA (target type \times subject group); main effect of target type: $F(1,26)=122.9$, $p=2.37 \times 10^{-11}$, $\eta^2=0.10$), yet without any interaction with subject group ($F(3,26)=1.42$, $p=0.26$, $\eta^2=0.0036$). General controls and NUS controls had overall fewer fixations to detect targets (main effect of subject group: $F(3,26)=5.50$, $p=0.0046$, $\eta^2=0.34$), but there was no difference between amygdala patients

vs. general controls, amygdala patients vs. people with ASD, or people with ASD vs. general controls (two-tailed *t*-test, all *ps*>0.05). These results all mirrored the RT results.

In Experiment 2, non-social targets still featured fewer fixations for target detection, which also mirrored the RT results (Fig. 3E; main effect of target type: $F(1,29)=99.4, p=7.09 \times 10^{-11}, \eta^2=0.039$), but there was no interaction with subject group ($F(2,29)=0.69, p=0.51, \eta^2=5.38 \times 10^{-4}$). ASD controls and NUS controls still had overall fewer fixations to detect targets compared to people with ASD (main effect of subject group: $F(2,29)=3.64, p=0.039, \eta^2=0.19$).

With simpler arrays in Experiment 3, non-social targets that were more distinct from one another retained their advantage to be detected faster (Fig. 3F; main effect of target type: $F(1,31)=11.5, p=0.0019, \eta^2=0.016$). ASD controls and NUS controls showed faster detection of targets (main effect of subject group: $F(3,31)=3.48, p=0.027, \eta^2=0.24$), but there was no interaction ($F(3,31)=0.30, p=0.82, \eta^2=0.0013$). These results all mirrored the RT results.

3.2.2. Shorter fixation duration on social items—We next compared the fixation duration on social vs. non-social items during visual search (Fig. 3G–I). In Experiments 1 and 2 but not Experiment 3, we found significantly shorter fixation durations when fixations were on social items compared to non-social items (Experiment 1: social: 396.3 ± 18.4 ms (mean \pm SEM), non-social: 472.7 ± 25.0 ; two-way mixed ANOVA (item type \times subject group); main effect of item type: $F(1,26)=37.9, p=1.64 \times 10^{-6}, \eta^2=0.095$; Experiment 2: social: 457.4 ± 31.9 , non-social: $577.5 \pm 43.7, F(1,29)=63.5, p=8.70 \times 10^{-9}, \eta^2=0.074$; Experiment 3: social: 515.1 ± 32.8 , non-social: $533.8 \pm 30.9, F(1,31)=1.70, p=0.20, \eta^2=0.0025$), indicating a faster and more efficient processing of social stimuli than non-social stimuli during visual search, especially when task demand was high. A subject group effect was not evident in Experiment 1, but was prominent in Experiments 2 and 3, due to shorter fixation durations in NUS controls (Experiment 1: ASD: 462.1 ± 48.4 , amygdala: 495.7 ± 122.0 , general control: 441.9 ± 35.4 , NUS control: 361.8 ± 13.7 ; main effect of subject group: $F(3,26)=2.22, p=0.11, \eta^2=0.17$; Experiment 2: ASD: 472.4 ± 52.0 , ASD control: 570.9 ± 47.0 , NUS control: $346.5 \pm 14.9, F(2,29)=7.19, p=0.0029, \eta^2=0.29$; Experiment 3: ASD: 570.1 ± 49.6 , amygdala: 673.9 ± 332.3 , ASD control: 674.3 ± 73.7 , NUS control: $402.0 \pm 22.6, F(3,31)=4.85, p=0.0070, \eta^2=0.30$; unpaired two-tailed *t*-test: $p < 0.05$ for all comparisons between NUS controls and other subject groups in Experiments 2 and 3). Furthermore, we only observed a weak interaction in Experiment 2 (Experiment 1: $F(3,26)=2.31, p=0.099, \eta^2=0.017$; Experiment 2: $F(2,29)=4.21, p=0.025, \eta^2=0.0098$; Experiment 3: $F(3,31)=0.73, p=0.54, \eta^2=0.0033$). Overall, our results indicated a faster processing of social stimuli than non-social stimuli.

3.2.3. Initial orientation to targets—an attentional mechanism—We further explored the gaze patterns to elucidate the mechanism underlying advantageous target detection, either between target types or between subject groups. Two possible mechanisms could explain the advantage in target detection: (1) a subject could look at a certain type of target faster (an attentional mechanism of faster orienting); (2) having fixated a target, it could be detected more rapidly and/or efficiently (a conscious detectability mechanism that

could in principle be distinct from (1) (Koch & Tsuchiya, 2007)). We next analyzed these mechanisms and their interplay separately.

We quantified the attentional mechanism by computing the serial order of fixation that first landed on the target (Fig. 3J–L). In all three experiments, non-social targets attracted faster fixations (Experiment 1: social: 6.22 ± 0.32 (mean \pm SEM), non-social: 5.02 ± 0.24 ; two-way mixed ANOVA (target type \times subject group); main effect of target type: $F(1,26)=72.1$, $p=5.69 \times 10^{-9}$, $\eta^2=0.14$; Experiment 2: social: 6.81 ± 0.39 , non-social: 5.42 ± 0.33 , $F(1,29)=57.6$, $p=2.28 \times 10^{-8}$, $\eta^2=0.11$; Experiment 3: social: 3.89 ± 0.10 , non-social: 3.67 ± 0.11 , $F(1,31)=11.0$, $p=0.0023$, $\eta^2=0.030$), which explained the faster detection of non-social targets due to their distinctiveness from one another. We also observed faster orientation to targets in control subjects, although this effect was relatively smaller (Experiment 1: ASD: 6.72 ± 0.82 , amygdala: 6.07 ± 0.60 , general control: 5.65 ± 0.31 , NUS control: 4.77 ± 0.15 ; main effect of subject group: $F(3,26)=3.36$, $p=0.034$, $\eta^2=0.23$; Experiment 2: ASD: 7.15 ± 0.77 , ASD control: 5.57 ± 0.22 , NUS control: 5.36 ± 0.18 , $F(2,29)=3.18$, $p=0.056$, $\eta^2=0.15$; Experiment 3: ASD: 4.03 ± 0.18 , amygdala: 4.28 ± 0.53 , ASD control: 3.72 ± 0.15 , NUS control: 3.42 ± 0.099 , $F(3,31)=3.34$, $p=0.032$, $\eta^2=0.22$). Yet, we observed no interactions (Experiment 1: $F(3,26)=0.21$, $p=0.89$, $\eta^2=0.0012$; Experiment 2: $F(2,29)=0.56$, $p=0.58$, $\eta^2=0.0021$; Experiment 3: $F(3,31)=0.66$, $p=0.59$, $\eta^2=0.0053$). These results showed that faster initial orientation to targets could explain the faster detection of targets for non-social targets and in control subjects.

3.2.4. Missing detection of targets—a conscious detectability mechanism—We next investigated our second possible mechanism: a failure to consciously detect targets, conditional on them having been fixated first. In some trials, targets failed to be detected even if the subject looked at the target item in the array. We explored this mechanism by computing the percentage of trials having ‘misses’, which were defined as fixations that landed on the target even though the target was not detected. We excluded the last 3 fixations landing on the target for misses since they corresponded to target detection.

Across experiments, we found that missing detection of targets did not differ between subject groups, nor between social vs. non-social targets (see Supplemental Results and Fig. 3M–O for details), suggesting that the conscious detectability mechanism could not explain the faster detection of targets for non-social targets and in control subjects. Notably, missing detection of targets was not prominent in amygdala lesion patients, suggesting that the amygdala is not essential for preferential coding of biologically relevant stimuli into conscious perception in this visual search task. Interestingly, we found that missing detection of targets was positively correlated with task difficulty (reaction time) (see Supplemental Results and Supplemental Discussion).

3.2.5. Interplay between the attentional and conscious detectability mechanisms—How do the attentional mechanism and the conscious detectability mechanism interplay? We observed that faster detection of non-social targets came from more rapid orientation towards non-social targets (Fig. 3J–L). This was the first step towards target detection. To further establish the conscious mechanism, we lastly analyzed the latency starting from having first fixated onto the target to detecting the target (Fig. 3P–R).

Once subjects looked at the target, this latency was primarily driven by the conscious detectability mechanism.

We only observed a mild advantage to detect non-social targets as a shorter latency in Experiment 1, but not in Experiment 2 or 3 (Experiment 1: social: 491.8±37.4 ms (mean ±SEM), non-social: 459.0±36.4; two-way mixed ANOVA (target type × subject group); main effect of target type: $F(1,26)=9.24$, $p=0.0053$, $\eta^2=0.0068$; Experiment 2: social: 591.1±45.1, non-social: 563.7±53.1, $F(1,29)=1.94$, $p=0.17$, $\eta^2=0.025$; Experiment 3: social: 386.0±28.2, non-social: 382.3±28.3, $F(1,31)=0.42$, $p=0.52$, $\eta^2=1.23 \times 10^{-4}$). However, the shorter latency was consistent with faster detection of targets in control subjects (Experiment 1: ASD: 648.2±77.1, amygdala: 605.6±63.0, general control: 460.1±53.1, NUS control: 328.9±32.8; main effect of subject group: $F(3,26)=7.26$, $p=0.0011$, $\eta^2=0.44$; Experiment 2: ASD: 737.3±90.6, ASD control: 517.5±67.3, NUS control: 434.7±43.9, $F(2,29)=4.68$, $p=0.017$, $\eta^2=0.23$; Experiment 3: ASD: 466.1±52.1, amygdala: 432.6±122.8, ASD control: 364.7±51.1, NUS control: 289.2±27.9, $F(3,31)=2.71$, $p=0.062$, $\eta^2=0.21$), although no interactions were found between subject group and target type (Experiment 1: $F(3,26)=0.70$, $p=0.56$, $\eta^2=0.0015$; Experiment 2: $F(2,29)=0.26$, $p=0.77$, $\eta^2=6.75 \times 10^{-4}$; Experiment 3: $F(3,31)=2.23$, $p=0.59$, $\eta^2=0.0020$). These results showed an interplay between the attentional mechanism and conscious detectability mechanism as a latency effect only for subject groups but not for target types, and confirmed that the conscious detectability mechanism played a minimal role in advantageous detection of non-social targets.

3.3. Eye tracking: general social preference does not differ between subject groups after controlling for low-level saliency

In the above analysis, we have illustrated the mechanisms underlying visual search—although social stimuli featured a more rapid processing speed, non-social stimuli were detected faster due to a faster initial orientation mechanism. But do people have different preference to social vs. non-social items? In particular, do people with ASD have altered preference to social stimuli compared to controls? We next analyzed the differential preference between social and non-social items and its dependence on subject groups.

We first computed the number of fixations landing on social vs. non-social items before target detection regardless of target types (Fig. 3S–U). As can be seen clearly, across experiments social items attracted more fixations in general (Experiment 1: social: 2.19±0.10 (mean±SEM), non-social: 1.67±0.069; two-way mixed ANOVA (item type × subject group); main effect of item type: $F(1,26)=115.0$, $p=4.84 \times 10^{-11}$, $\eta^2=0.24$; Experiment 2: social: 2.11±0.098, non-social: 1.67±0.094, $F(1,29)=59.7$, $p=1.60 \times 10^{-8}$, $\eta^2=0.15$; Experiment 3: social: 1.11±0.057, non-social: 0.91±0.049, $F(1,31)=72.1$, $p=1.36 \times 10^{-9}$, $\eta^2=0.095$), showing a general social bias. Only Experiment 1 showed a difference between subject groups (Experiment 1: ASD: 2.09±0.19, amygdala: 2.29±0.19, general control: 2.06±0.13, NUS control: 1.63±0.095; main effect of subject group: $F(3,26)=3.56$, $p=0.028$, $\eta^2=0.20$; Experiment 2: ASD: 2.01±0.19, ASD control: 1.73±0.11, NUS control: 1.86±0.11, $F(2,29)=0.75$, $p=0.48$, $\eta^2=0.038$; Experiment 3: ASD: 1.12±0.11, amygdala: 1.03±0.23, ASD control: 0.93±0.073, NUS control: 0.92±0.051, $F(3,31)=1.09$, $p=0.37$, $\eta^2=0.082$).

Importantly, Experiment 1 showed an interaction between item type and subject group (Experiment 1: $F(3,26)=3.28$, $p=0.037$, $\eta^2=0.020$; Experiment 2: $F(2,29)=0.91$, $p=0.42$, $\eta^2=0.0045$; Experiment 3: $F(3,31)=0.36$, $p=0.78$, $\eta^2=0.0014$), suggesting a difference in social bias between subject groups that we will turn to next.

We next performed fixation-by-fixation analysis, which had a better temporal resolution and allowed us to study the time course of decisions in visual search. Did subjects in general look at social items first or non-social items first? If there was a social bias, when did this bias start and how did it evolve over time? Fixation-by-fixation analysis could help to answer these questions.

Given the difference in social bias between subject groups, we tested whether people with ASD had reduced global preference to look at social items in the search array. For each fixation in a serial order, we calculated a social bias in attention as the difference between the percentage of fixations on social items as compared to non-social items (Fig. 4). In Experiment 1 (Fig. 4A), we observed an overall reduced proportion of fixations onto social items for people with ASD (one-way ANOVA across four subject groups on the average social bias of fixations 2–10: ASD: 5.97 ± 2.31 (mean \pm SEM), amygdala: 15.10 ± 4.91 , general control: 17.24 ± 1.39 , NUS control: 14.06 ± 1.96 ; $F(3,26)=5.02$, $p=0.007$, $\eta^2=0.37$; two-tailed t -test compared to general controls: $t(14)=-4.18$, $p=9.17\times 10^{-4}$, $g=-1.98$). This reduced social preference persisted over time as both early fixations (average of fixations 2–5) and late fixations (average of fixations 6–10) showed a difference compared to general controls (Early: ASD: 2.66 ± 1.90 , general control: 10.66 ± 1.55 ; $t(14)=-3.26$, $p=0.0057$, $g=-1.54$; Late: ASD: 8.63 ± 3.11 , general control: 23.50 ± 3.19 ; $t(14)=-3.34$, $p=0.0049$, $g=-1.58$), although fixation-by-fixation comparisons across subject groups (one-way ANOVA) and with general controls did not reveal reliable differences when corrected for multiple comparisons (all statistical comparisons are listed in Supplemental Table 4). Comparing people with ASD and amygdala lesion patients, we observed differences only for early fixations (ASD: 2.66 ± 1.90 , amygdala: 10.55 ± 2.05 ; $t=2.32$, $p=0.045$, $g=1.44$; also difference at the 2nd and 4th fixations). However, we observed no difference in social preference between amygdala lesion patients and general controls (two-tailed t -test; $p>0.05$ for all fixations and averages; see statistics in Supplemental Table 4). Furthermore, we observed no difference between general controls and NUS controls ($p>0.05$ for all fixations and averages). Our results suggest a possibly mildly reduced bias for social preference in ASD.

However, this was not borne out in Experiment 2 (Fig. 4B). When low-level saliency between social and non-social items was equalized, people with ASD showed entirely normal general social preference as compared to ASD controls (one-way ANOVA across three subject groups: $p>0.05$ for all fixations and averages; two-tailed t -test compared to ASD controls: $p>0.05$ for all fixations and averages; see Supplemental Table 4).

Notably, general social preference did not differ between Experiment 1 and Experiment 2 for people with ASD (overall: Experiment 1: 5.97 ± 2.31 , Experiment 2: 8.07 ± 2.59 , unpaired two-tailed t -test: $t(19)=-0.55$, $p=0.59$, $g=-0.24$; Early: Experiment 1: 2.66 ± 1.90 , Experiment 2: 5.98 ± 2.01 , $t(19)=-1.12$, $p=0.28$, $g=-0.48$; Late: Experiment 1: 8.23 ± 3.11 , Experiment 2: 9.74 ± 3.44 , $t(19)=-0.22$, $p=0.83$, $g=-0.096$) or NUS controls (overall:

Experiment 1: 14.06 ± 1.96 , Experiment 2: 13.69 ± 2.36 , paired two-tailed t -test: $t(10)=0.12$, $p=0.91$, $g=0.049$; Early: Experiment 1: 9.79 ± 1.13 , Experiment 2: 9.80 ± 2.13 , $t(10)=-0.0067$, $p=0.99$, $g=-0.0022$; Late: Experiment 1: 17.47 ± 3.55 , Experiment 2: 16.80 ± 3.40 , $t(10)=0.13$, $p=0.90$, $g=0.055$). Furthermore, fixation-by-fixation comparison between Experiment 1 and Experiment 2 confirmed no difference for people with ASD (unpaired two-tailed t -test: $ps > 0.05$) or NUS controls (paired two-tailed t -test: $ps > 0.05$), indicating that the mild difference observed in Experiment 1 might be mostly driven by higher social preference in general controls.

Similarly, in Experiment 3 (Fig. 4C) in which low-level saliency between social and non-social items was also equalized, people with ASD showed normal general social preference to our stimuli as compared to ASD controls (one-way ANOVA across four subject groups: $p > 0.05$ for all fixations and averages; two-tailed t -test compared to ASD controls: $p > 0.05$ for all fixations and averages; see Supplemental Table 4). Amygdala lesion patients also had normal social preference compared to ASD controls ($p > 0.05$ for all fixations and averages) and similar social preference compared to people with ASD ($p > 0.05$ for all fixations and averages), suggesting that neither people with ASD nor amygdala lesion patients have global deficits in social preference. The fine-detailed fixation-by-fixation analysis again confirmed the global interactive patterns shown at the beginning of this section.

3.4. Reduced orientation towards target-relevant items in visual search

The above analysis has shown that people with ASD do not have globally reduced social preferences, once low-level saliency is equalized. But how might social attention interact with task demands during visual search? We next analyzed target-relevant effects to answer this question.

All subjects oriented to social items rapidly and kept on searching within social items if the target was social (Fig. 5 upper row). Pronounced differences in the proportion of fixations onto social and non-social items were evident as early as the 2nd fixation and lasted until the 10th fixation. Symmetrically, when searching for a non-social target (Fig. 5 lower row), subjects oriented to non-social items and kept on searching within non-social items.

We defined a target-relevant effect as the difference in the percentage of fixations on target-congruent items and the percentage of fixations on target-incongruent items. All subjects showed rapid and sustained target-relevant effects, for both social targets and non-social targets (Fig. 6). In Experiment 1, we found disproportionate target-relevant effects between social and non-social stimuli across fixations (two-way mixed ANOVA (target type \times subject group); main effect of target type; average of fixations 2–10: social: 37.84 ± 2.31 , non-social: 24.69 ± 1.72 ; $F(1,26)=55.4$, $p=6.63 \times 10^{-8}$, $\eta^2=0.26$; see Supplemental Table 5 for statistics), showing stronger attention towards social items than non-social items when searching for their respective targets. Both early (average of fixations 2–5: social: 33.54 ± 2.39 , non-social: 21.97 ± 1.88 ; $F(1,26)=43.9$, $p=4.97 \times 10^{-7}$, $\eta^2=0.20$) and late fixations (average of fixations 6–10: social: 41.53 ± 2.58 , non-social: 27.27 ± 2.52 ; $F(1,26)=26.3$, $p=2.38 \times 10^{-5}$, $\eta^2=0.21$) showed stronger social target-relevant effects, which persisted through fixation 7. Importantly, here we also found pronounced target-relevant effects that differed between subject groups (main effect of subject group; average of

fixations 2–10 collapsing social and non-social targets: ASD: 22.20 ± 3.30 , amygdala: 28.81 ± 1.02 , general control: 35.64 ± 3.05 , NUS control: 35.34 ± 2.53 ; $F(3,26) = 4.76$, $p = 8.94 \times 10^{-3}$, $\eta^2 = 0.21$), especially during early fixations (average of fixations 2–5: ASD: 16.78 ± 3.54 , amygdala: 26.38 ± 1.35 , general control: 31.47 ± 2.62 , NUS control: 33.41 ± 2.58 ; $F(3,26) = 6.79$, $p = 1.57 \times 10^{-3}$, $\eta^2 = 0.28$), with people with ASD showing reduced target-relevant effects. The reduced target-relevant effect in people with ASD persisted from the 2nd fixation to the 5th fixation, showing that they did not look at relevant targets as rapidly as controls during the initial fixations of their search. However, there was no difference between people with ASD and controls for later fixations (average of fixations 6–10: ASD: 26.54 ± 3.56 , amygdala: 30.76 ± 2.14 , general control: 40.11 ± 5.39 , NUS control: 36.96 ± 2.81 ; $F(3,26) = 2.38$, $p = 0.093$, $\eta^2 = 0.12$; also see Supplemental Table 5 for fixation-by-fixation analysis), showing that people with ASD could catch up at later points in time. Although the impaired target-relevant effect in ASD was qualitatively more pronounced for searching social targets than non-social targets (cf. Fig. 6; social–non-social for average of fixations 2–10: ASD: 6.88 ± 4.08 , amygdala: 18.57 ± 7.42 , general control: 17.85 ± 2.85 , NUS control: 12.80 ± 2.55), there was no significant interaction between target type and subject group ($F(3,26) = 2.07$, $p = 0.13$, $\eta^2 = 0.030$; also see Supplemental Table 5 for fixation-by-fixation analysis).

We further compared people with ASD to general controls and found that people with ASD had reduced target-relevant effects and the impairment in people with ASD mainly came from the initial fixations of their search (see Supplemental Results for statistics). When analyzing target-relevant effects separately for social targets (Fig. 6A) and non-social targets (Fig. 6B), fixation-by-fixation analysis revealed that the target-relevant effect was reduced in people with ASD for social targets at early fixations (one-way ANOVA across subject groups, $p < 0.05$ for fixations 2–4) but not for non-social targets ($p > 0.05$ for all fixations), further demonstrating a more severe impairment of people with ASD in social attention. Strikingly, there was no significant difference between people with ASD and controls at later fixations, showing that people with ASD could catch up gradually. Similar results were derived when comparing people with ASD to NUS controls, where we found a significant interaction between subject group and target type, again with the impairment in people with ASD most pronounced for social targets (Supplemental Table 5). However, we observed no difference between amygdala lesion patients and general controls, nor between general controls and NUS controls (see Supplemental Results for details).

The above results were robust to several factors. First, when controlling for the overall fewer numbers of fixations made by people with ASD on array items (Fig. 5 and Supplemental Fig. 3A and B), we obtained the same pattern of findings with normalized fixation percentages (Supplemental Fig. 3C and D). Likewise, our results were robust to the particular size of the ROI that defined each item (we tried several different sizes, all producing qualitatively the same results). Finally, our analysis was based on target-present trials only; again, the target-relevant effects above all held when we analyzed target-absent catch trials only.

In conclusion, we found that people with ASD did not orient towards target-relevant items as rapidly as controls, an abnormality that was present for all stimuli but most pronounced

for social stimuli, and furthermore, that this impairment was not evident in patients with amygdala lesions.

3.5. The attentional deficit in ASD cannot be explained by low-level visual properties of the stimuli

In Experiment 1, we observed reduced rapid orientation towards target-relevant items in people with ASD, especially for social targets. To check whether this might be due to low-level saliency differences, we conducted Experiment 2 in which low-level properties of social and non-social items were equalized within each search array (Supplemental Fig. 2A–C).

Target-relevant effects were replicated in Experiment 2. All subjects showed rapid and sustained target-relevant effects, for both social targets (Supplemental Fig. 4 upper row) and non-social targets (Supplemental Fig. 4 lower row). Even with equal low-level saliency, social targets still featured greater target-relevant effects (two-way mixed ANOVA (target type \times subject group); main effect of target type; average of fixations 2–10: social: 37.19 ± 2.62 , non-social: 26.18 ± 1.64 ; $F(1,29)=31.3$, $p=4.91 \times 10^{-6}$, $\eta^2=0.17$; see Supplemental Table 5 for statistics) and for both early fixations (social: 34.45 ± 2.47 , non-social: 22.10 ± 1.56 ; $F(1,29)=39.2$, $p=7.88 \times 10^{-7}$, $\eta^2=0.22$) and late fixations (social: 39.43 ± 2.94 , non-social: 29.49 ± 2.22 ; $F(1,29)=15.0$, $p=5.74 \times 10^{-4}$, $\eta^2=0.10$), showing persistent stronger attention towards social items than non-social items. Consistent with Experiment 1, the stronger social attention persisted through the 8th fixation. Still, people with ASD had reduced overall target-relevant effects (main effect of subject group; average of fixations 2–10 collapsing social and non-social targets: ASD: 25.07 ± 3.55 , ASD control: 32.82 ± 1.51 , NUS control: 38.68 ± 2.36 ; $F(2,29)=6.00$, $p=6.62 \times 10^{-3}$, $\eta^2=0.20$) and for both early fixations (ASD: 21.76 ± 3.14 , ASD control: 30.03 ± 2.09 , NUS control: 34.71 ± 2.07 ; $F(2,29)=6.63$, $p=4.26 \times 10^{-3}$, $\eta^2=0.19$) and late fixations (ASD: 27.71 ± 4.01 , ASD control: 35.05 ± 2.06 , NUS control: 42.00 ± 3.26 ; $F(2,29)=4.52$, $p=0.020$, $\eta^2=0.16$). Comparing people with ASD to ASD controls alone revealed a marginally significant reduction of overall target-relevant effect during early fixations (ASD: 21.76 ± 3.14 , ASD control: 30.03 ± 2.09 ; $F(1,19)=3.61$, $p=0.073$, $\eta^2=0.10$; see Supplemental Table 5). Comparing people with ASD to NUS controls showed similar results and revealed significantly reduced overall target-relevant effects for all fixations, early fixations and late fixations (Supplemental Table 5). Separate analysis within social targets (Fig. 6C) and non-social targets (Fig. 6D) showed that the deficit mainly came from social targets (see Supplemental Table 5), replicating Experiment 1.

Notably, no difference was found between Experiment 1 and Experiment 2 at all fixations (excluding the very first fixation) for people with ASD (unpaired two-tailed t -test: $p>0.05$) or NUS controls (paired two-tailed t -test: $p>0.05$), for both social targets and non-social targets.

In conclusion, Experiment 2 replicated the findings of Experiment 1 and thus corroborated our claim of reduced rapid orientation to target-relevant items, especially when these were social, in people with ASD. Importantly, Experiment 2 demonstrated that the findings in Experiment 1 were not due to low-level visual properties of the stimuli.

3.6. The attentional deficit in ASD is more severe with high task demands

Experiments 1 and 2 show that people with ASD, but not with amygdala lesions, have reduced attention to target-relevant items. Do these effects depend on cognitive load? To test this hypothesis, we further designed simpler arrays with fewer items to make the search easier. We still equalized low-level saliency, distance to center and item size for these simpler search arrays.

As in Experiments 1 and 2, all subjects oriented to social items rapidly and kept on searching within social items if the target was social (Supplemental Fig. 5 upper row) and oriented to non-social items if the target was non-social (Supplemental Fig. 5 lower row), showing rapid and sustained target-relevant effects for both social targets and non-social targets. In contrast to Experiments 1 and 2, with fewer items in the search array, the difference between social target-relevant effects and non-social target-relevant effects became very small (social–non-social, Experiment 1: 13.15 ± 1.82 , Experiment 2: 11.01 ± 1.94 , Experiment 3: 6.30 ± 2.42 ; two-way mixed ANOVA (target type \times subject group); main effect of target type; average of fixations 2–10: $F(1,31)=6.50$, $p=0.016$, $\eta^2=0.043$), and no difference was found at the single fixation level (see Supplemental Table 5 for statistics). The deficit of target-relevant orientation in people with ASD also became very small (main effect of subject group; average of fixations 2–10: ASD: 35.55 ± 3.32 , amygdala: 39.38 ± 6.88 , NUS control: 50.75 ± 4.21 , ASD control: 46.53 ± 2.94 ; $F(3,31)=3.54$, $p=0.026$, $\eta^2=0.19$; only the 2nd fixation showed a difference) and there was no interaction.

Comparing people with ASD and ASD controls also revealed a small but significant difference in target-relevant effects (average of fixations 2–10: ASD: 35.55 ± 3.32 , ASD control: 46.53 ± 2.94 ; $F(1,19)=5.15$, $p=0.035$, $\eta^2=0.14$), and there was no fixation-by-fixation difference (Supplemental Table 5). Further, consistent with Experiments 1 and 2, we found no difference in target-relevant effects between amygdala patients and ASD controls, or between amygdala patients and NUS controls, for the average of all fixations, nor at each fixation ($p>0.05$ for all fixations; Supplemental Table 5). Amygdala lesion patients had similar target-relevant effects as people with ASD at all fixations (Supplemental Table 5). Lastly, separate analysis within social targets (Fig. 6E) and non-social targets (Fig. 6F) confirmed the above results (see Supplemental Results for details). In conclusion, we were able to find impaired attention to target-relevant stimuli in ASD only for the larger search array, but not for the smaller search array of Experiment 3. Likely explanation for the lack of an effect in Experiment 3 is reduced cognitive load.

4. Discussion

In this study we found that people with ASD had reduced attention to target-relevant items in visual search. Bilateral lesions of the amygdala did not result in a similar deficit. The impairment seemed most pronounced for social targets, although there was a deficit for non-social targets as well. The effect was not attributable to low-level properties of the stimuli. With arrays containing a reduced number of items, we found a much weaker deficit. Overall, we revealed a search-dependent attentional deficit in people with ASD that was dependent on task demands.

Visual search involves several subprocesses, including distinguishing between targets and distracters, orienting attention to the target category, restricting attention to and searching among items sharing the same feature as the target, and finally comparing between the target and distracters from the target category which in turn involves memory and conscious recognition. In this study, we conducted detailed eye movement analyses to elucidate the mechanisms underlying visual search. We found that initial orientation towards the target played the key role to explain the more rapid detection of non-social targets, although individual social items featured shorter fixation duration and hence more efficient information processing. Conscious detectability could not explain the detection advantages of non-social targets, nor the latency from target being fixated to target being detected. The detection advantage of non-social targets was due to non-social items being more distinct from one another, as evidenced by both the RT and the total number of fixations. Similarly, control subjects performed the search more efficiently than people with ASD and amygdala lesion patients, which again was best explained by the attentional mechanism of initial orientation. Together with the reduced target-relevant effects in people with ASD, it seems that people with ASD were mostly influenced by orienting to targets and restricting attention to items within the target category.

The impairment in social attention observed in people with ASD could be caused by either impaired attention to social items or a greater saliency representation of non-social items that attracted their attention away from target-relevant social items. However, as the attentional deficit was also evident with non-social targets (though less impaired), the attentional deficit could not be simply attributed to the higher saliency of non-social items, because otherwise people with ASD would have an even stronger task-relevant effect with non-social targets. Therefore, the reduced social attention observed in people with ASD is compatible with a deficit in top-down attentional control and may result in part from different strategies used in visual search.

As can be seen in Fig. 6, there was an effect of cognitive load on all participant groups, as one would expect. However, the effect was disproportionate in the case of the ASD group. Our interpretation of this is that the effect of cognitive load interacts with our main effect of interest—an ability to attend to socially salient stimuli. Given our ASD participants were all high-functioning, they were able to fully compensate on the task with the smaller search array. Given they were impaired in social attention, this deficit got unmasked with the larger and more difficult search array. Given that subject groups were in fact well matched for IQ, it was unlikely that mere cognitive load per se could be responsible for the impairments we found. In future studies it would be important to establish this further, for instance by increasing cognitive load with a separate (dual) task (for instance, an unrelated and non-social continuous performance task of some kind): under such dual-task conditions, even performance on the smaller search array should suffer; or, equivalently, performance on the additional task may be compromised. Either outcome would show that people with ASD, when high-functioning, require additional cognitive resources in order to perform in the normal range on visual search for social stimuli.

With respect to points of contact with the related literature in autism research, we take up the following issues in more detail below: relation to studies of visual search in autism, and the connection with the amygdala.

4.1. Visual search in autism

In a typical visual search task, an observer looks for a target item among an array of distractor items and responds by indicating whether a target is present or absent. In “classic guidance”, attention is guided towards likely targets by a limited set of stimulus attributes such as color and size (Wolfe & Horowitz, 2004; Wolfe, 2012). While most studies of visual search in autism focused on low-level features and inanimate stimuli (e.g., letters and shapes) (Kemner et al., 2008; Manjaly et al., 2007; Plaisted et al., 1998; O’Riordan & Plaisted, 2001; O’Riordan et al., 2001; O’Riordan, 2004), far fewer studies have examined complex images and social stimuli. Some studies employed visual search to investigate recognition abilities of facial expressions in children with ASD and found that faces with certain emotions are detected faster than others (Farran, Branson, & King, 2011; Rosset et al., 2011). However, when compared with age-matched controls, no significant differences were found anymore.

Semantic-level features like faces can be considerably more potent than low-level cues to attract gaze in complex stimuli (Cerf, Frady, & Koch, 2009; Judd, Ehinger, Durand, & Torralba, 2009; Xu, Jiang, Wang, Kankanhalli, & Zhao, 2014; Zhao & Koch, 2011, 2012). In this study, we not only included social stimuli, but instead of isolated facial emotions used natural social (faces and people with various emotions and poses) and non-social (e.g., furniture, toys and food) pictures. In Experiments 2 and 3, we equalized the low-level saliency, item size and location of items, thus helping to isolate effect to the semantic level. Our results suggest that reduced target-congruent attention in people with ASD is mostly restricted to the social domain and the semantic level. It is also important to note that unlike simple feature search tasks, our particular visual search protocol relied mainly on top-down attentional control and our results reflected differences in the top-down strategies and/or individual capacity differences in top-down attentional control.

Taken together, our findings and the prior literature then suggest that there may be two types of effects that distinguish visual search in people with ASD. One effect is that search is more efficient when it is based on low-level features and does not involve social content. A second effect is that search is less efficient when it is based on semantic-level features, and perhaps in particular when it involves social content. Respectively, these two putative effects bear some similarity to the two core aspects of the ASD diagnosis: augmented interests and focus on certain non-social patterns of stimuli and/or behavior; and diminished interest and focus on social communicative aspects.

4.2. The amygdala and saliency

Earlier views of the amygdala emphasized a fear-related function (Adolphs et al., 1994; Bechara et al., 1995; LeDoux, 1993; Morris et al., 1996). Recently, however, the amygdala has been proposed to respond to a broader spectrum of social attributes such as facial emotions in general (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006) and regulating a

person's personal space (Kennedy, Glascher, Tyszka, & Adolphs, 2009). Electrophysiological recordings in monkeys (Leonard, Rolls, Wilson, & Baylis, 1985; Rolls, 1984) and humans (Kreiman, Koch, & Fried, 2000; Rutishauser et al., 2011) have found single neurons that respond not only to faces, but also to face identities, facial expressions and gaze directions (Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007; Hoffman, Gothard, Schmid, & Logothetis, 2007). A recent study has shown that single neurons in the human amygdala encode subjectively perceived emotion rather than stimulus identities (Wang et al., 2014b). Further, the amygdala processes more abstract attributes such as stimulus unpredictability (Herry et al., 2007). Amygdala lesions result in an absence or reduction of fixations on novel objects observed in monkeys (Bagshaw, Mackworth, & Pribram, 1972). It has also been shown that the amygdala mediates emotion-enhanced vividness (Todd, Talmi, Schmitz, Susskind, & Anderson, 2012) and responds more to animate entities compared to inanimate ones (Mormann et al., 2011; Yang, Bellgowan, & Martin, 2012). Overall, the amygdala might act as a detector of perceptual saliency and biological relevance (Adolphs, 2008; Sander et al., 2005)—a reasonable substrate also for the altered preferences evident in people with ASD.

Our search arrays contained people and faces with various identities, expressions and gaze directions, but our data did not find any impairments in the three amygdala patients in deploying attention to target-relevant items, either for social or non-social targets. While our findings show that the amygdala cannot be essential in our task, we acknowledge that we are limited by statistical power given our small subject sample. It is also worth noting that compensatory circuits may account for the intact social attention in amygdala lesion patients (Becker et al., 2012) and a recent finding has also shown that amygdala lesion patients have intact preferred attention towards animals (Wang et al., 2014a), even though these findings would not be expected on the basis of neuronal responses observed in the amygdala to animals (Mormann et al., 2011). Our finding is also consistent with preserved attentional capture by emotional stimuli and intact emotion-guided visual search in patients with acute amygdala lesions due to neurosurgical resection (Piech et al., 2010, 2011). Taken together, there are now numerous examples of a discrepancy between engagement of the amygdala (e.g., in functional neuroimaging studies) in tasks for which there is no obvious corresponding behavioral impairment when the amygdala is lesioned. This of course poses some challenges also for how to view the possible role of the amygdala in ASD, a final topic to which we turn next.

4.3. Amygdala theory of autism

The abnormal facial scanning patterns generally reported in people with ASD (Adolphs, Sears, & Piven, 2001; Klin et al., 2002; Kliemann et al., 2010; Pelphrey et al., 2002; Neumann et al., 2006; Spezio et al., 2007a, 2007b) may plausibly be related to amygdala dysfunction (Baron-Cohen et al., 2000). This hypothesis is supported by rather similar patterns of deficits seen in patients with amygdala damage, who fail to fixate on the eyes in faces (Adolphs et al., 2005), single neuron recordings in the human amygdala showing weaker response to eyes in people with ASD (Rutishauser et al., 2013), as well as neuroimaging studies showing that amygdala activation is specifically enhanced for fearful faces when saccading from the mouth to the eye regions (Gamer & Büchel, 2009). This

amygdala-mediated orientation towards eyes seen in blood–oxygen-level dependent (BOLD)-fMRI is dysfunctional in ASD (Kliemann et al., 2012). Activation in the amygdala has also been reported to be correlated with the time spent fixating the eyes in ASD (Dalton et al., 2005). The idea of amygdala abnormalities in autism is supported by a substantial literature showing structural abnormalities (Amaral et al., 2008; Bauman & Kemper, 1985; Ecker et al., 2012; Schumann et al., 2004; Schumann & Amaral, 2006) and atypical activation (Gotts et al., 2012; Philip et al., 2012) in the amygdala in ASD.

While actual amygdala lesions did not result in search-related attentional deficits in our tasks, it is important to keep in mind that people with ASD of course do not have amygdala lesions. It is thus still conceivable that more subtle malfunction (including hyperactivation) of the amygdala contributes to ASD, even though a bona fide lesion of the amygdala has no effect that bears similarity to ASD (see also Paul, Corsello, Tranel, and Adolphs (2010)). Finally, autism spectrum disorders are well known to be highly heterogeneous at the biological and behavioral levels, and it is likely that there will be no single genetic or cognitive cause for the diverse symptoms defining autism (Happé, Ronald, & Plomin, 2006). No unanimously endorsed hypothesis for a primary deficit has emerged that can plausibly account for the full triad of social, communicative and rigid/repetitive difficulties (Happé, 2003). Nonetheless, our present findings argue for at least one further feature at the cognitive level that can be used to describe ASD: an inability to use semantic-level task demands, especially with high cognitive load and especially for social stimuli, in order to efficiently guide attention selection during visual search. As we noted at the beginning of our *Discussion*, it will be important to extend these studies to additional measures in the future, notably including neuroimaging studies of people with ASD during visual search.

4.4. Future directions

Our findings suggest some clear future directions. There are in our view three core extensions of our study that would be important to undertake, aside from sheer replication. The first is replication together with generalization: that is, replicate our finding in a sample of people with ASD who are younger, and/or lower functioning, and/or have more substantial comorbidity. This direction would be perhaps the most important from a clinical perspective. The second extension would be to broaden the difficulty of the search task. It is worth noting that (a) we only observed clear deficits in the ASD group for our larger search array (24 items; Experiments 1 and 2), but not for the smaller array (12 items; Experiment 3); and (b) all groups were close to ceiling in overall performance accuracy. Would one find a much larger deficit if more severe time constraints were imposed, or if arrays larger than 24 items were used? This might substantially increase the sensitivity of the task to detect abnormalities in ASD. The third extension of our study would be to probe in more detail the neural substrates of the effect, thus shedding light on the neurological basis of impaired social attention in ASD. The fact that we found no impairment in patients with amygdala lesions suggests that the amygdala is not essential here, but this of course does not rule out the possibility that the amygdala nonetheless plays a role in brains without amygdala lesions, including people with ASD. Translating our task into an fMRI study would thus be an informative future direction.

4.5. Conclusion

While a sizable literature in ASD has investigated search for simple, non-social objects (shapes, letters, etc.) and only manipulated low-level attributes of the stimuli, far fewer studies have examined visual search with social stimuli. In this study, we used a visual search protocol with well-validated social stimuli. We observed reliable attentional deficits in people with ASD, especially social attention. Our findings were further corroborated by (1) a replication in an independent sample of ASD subjects, (2) a control experiment that equated the stimuli in the search array for low-level visual properties and ruled out the potential influence from low-level features, (3) a direct comparison with amygdala lesion patients who showed normal target-relevant effects, and (4) manipulation of task demand that revealed the dependence of the attentional deficit on cognitive load. We also showed that general social preference did not differ between people with ASD and controls when controlling for low-level saliency, and our detailed eye movement analyses elucidated the mechanisms underlying visual search. Taken together, our study has tested a key hypothesized function of the amygdala in autism, and argued for at least one further well-characterized deficit of social attention in people with ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2014.09.002>.

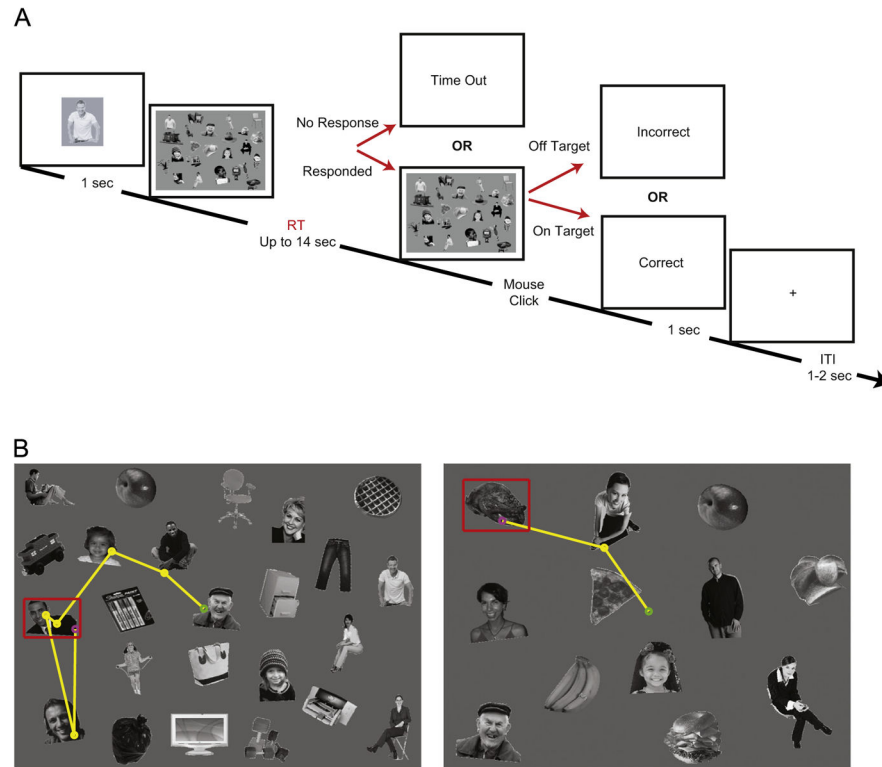


Fig. 1. Task and sample stimuli. (A) Task structure. A target is presented for 1 s followed by the search array. Subjects have a maximum of 14 s to respond by pressing the space bar to indicate that the target is present, or the letter ‘N’ to indicate that the target is absent. Following target detection, subjects provide a mouse click on target. A feedback message of ‘Correct’, ‘Incorrect’ or ‘Time Out’ is displayed for 1 s before an ITI of 1–2 s. (B) Sample visual search arrays with fixations. Left: standard array used in Experiment 2. Right: simple array used in Experiment 3. Each circle represents a fixation. Green circle: start fixation. Magenta circle: end fixation. Yellow line: eye movement (saccade). Red box: target. Items in the search arrays are cropped and modified from Sasson et al. (2008). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

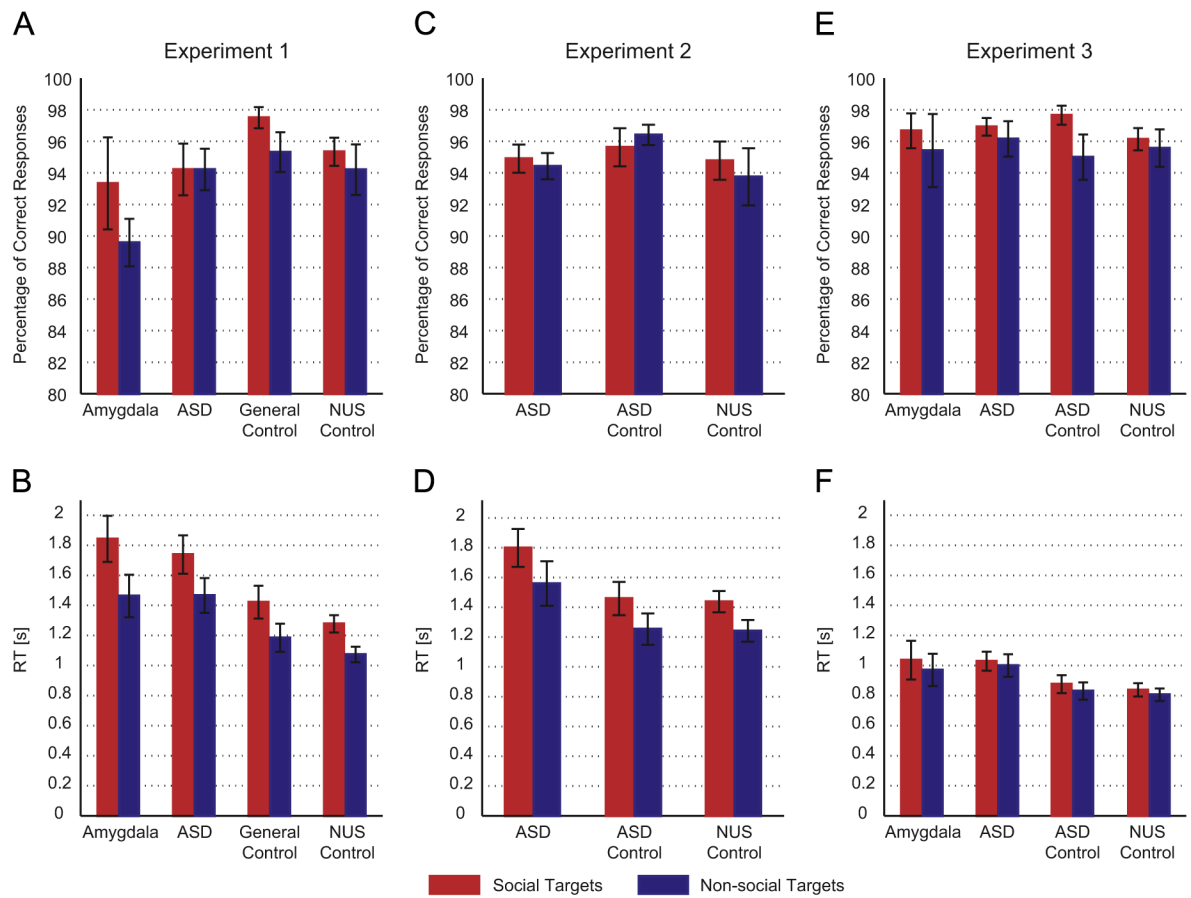
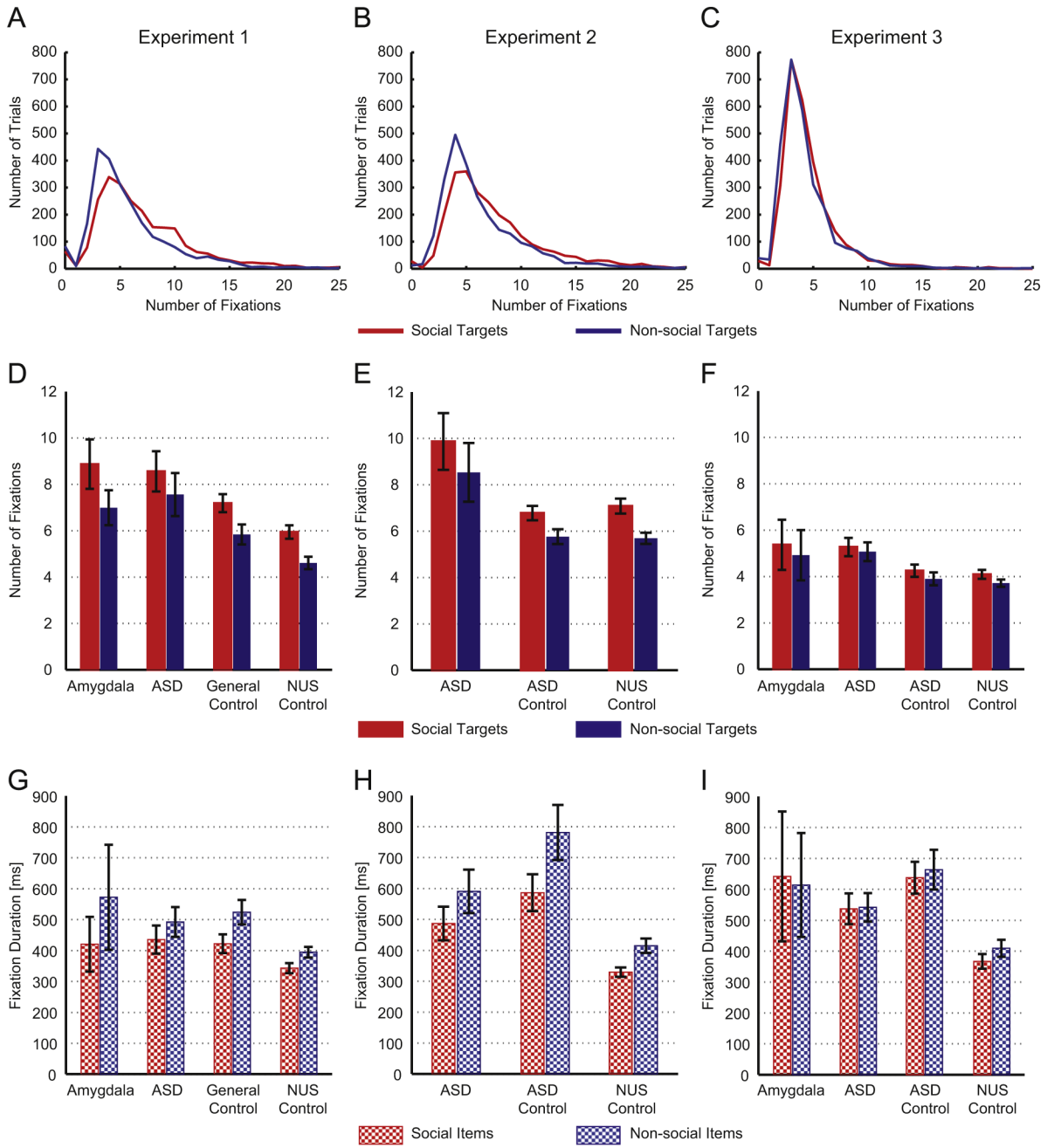


Fig. 2. Behavioral performance for (A, B) Experiment 1, (C, D) Experiment 2, and (E, F) Experiment 3. (A, C, and E) Percentage of correct response. (B, D, and F) Reaction time (RT). Error bars denote one SEM of the mean. All trials analyzed in this figure are target-present trials.



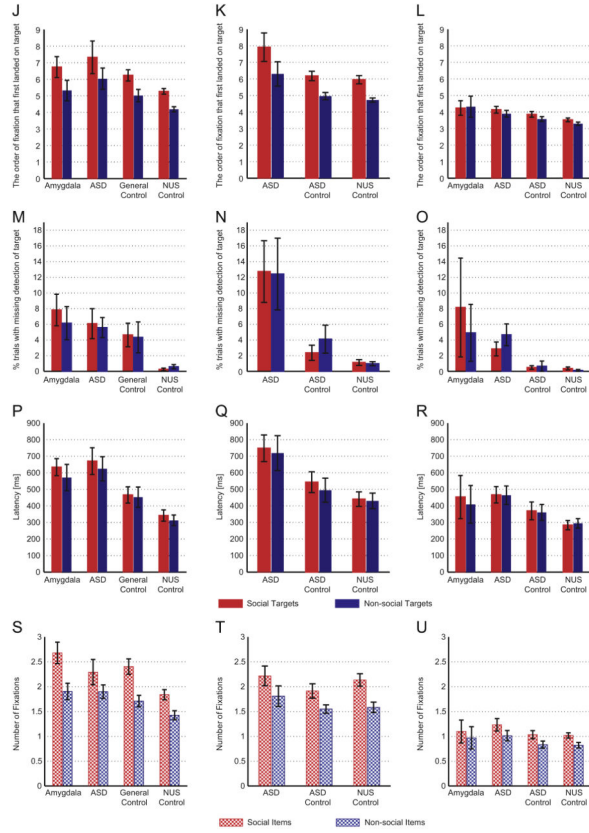


Fig. 3. Quantification of fixation properties. All trials analyzed in this figure are target-present trials. (A–C) Distribution of the total number of fixations for social and non-social targets. (D–F) Average number of fixations for each condition. (G–I) Average fixation duration on array item. (J–L) The serial order of fixation that first landed on target. (M–O) Percentage of trials with missing detection of target despite direct fixation on the target. (P–R) Latency from first fixation onto target to detection of target. (S–U) Average number of fixations on social and non-social items. (A, D, G, J, M, P, and S) Experiment 1. (B, E, H, K, N, Q, and T) Experiment 2. (C, F, I, L, O, R, and U) Experiment 3. Error bars denote one SEM across subjects.

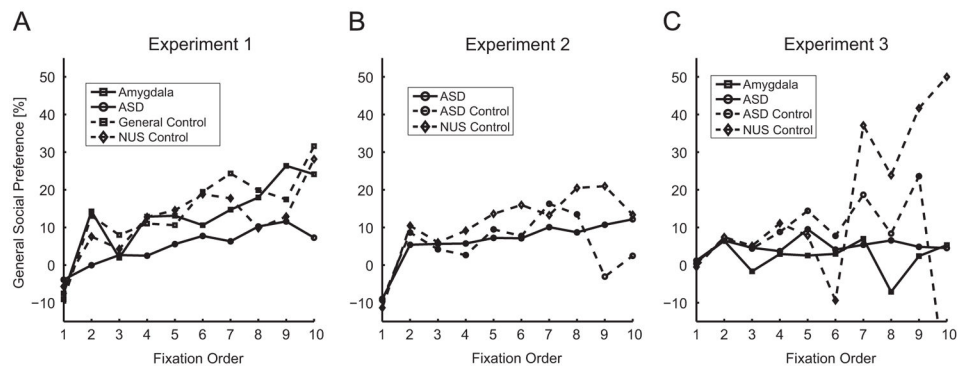


Fig. 4. General social preference. (A) Experiment 1. (B) Experiment 2. (C) Experiment 3. We calculated social preference as the average number of fixations (irrespective of task condition) across all trials that fell onto social stimuli, minus the average number of fixations that fell onto non-social stimuli, expressed as a percentage.

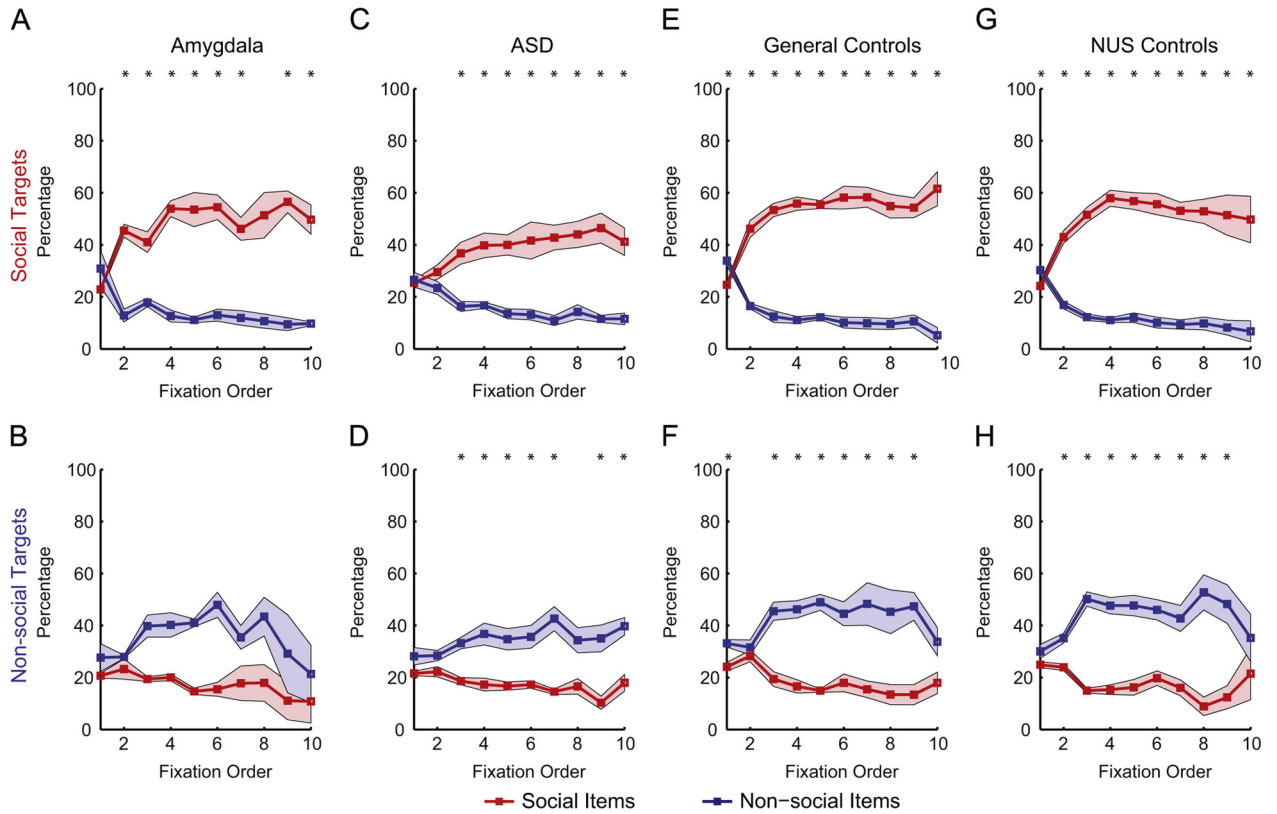


Fig. 5.

Social and non-social target effects. In Experiment 1, all subjects looked at target-congruent items in a fast and sustained manner. (A, B) Amygdala patients. (C, D) People with ASD. (E, F) General controls. (G, H) NUS controls. Red: social items. Blue: non-social items. Upper row (A, C, E, and G): when searching for social targets. Lower row (B, D, F, and H): when searching for non-social targets. Asterisk indicates significant difference between target-congruent items and target-incongruent items (two-tailed paired t -test: $p < 0.05$). Shaded area denotes \pm SEM over the group of subjects. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

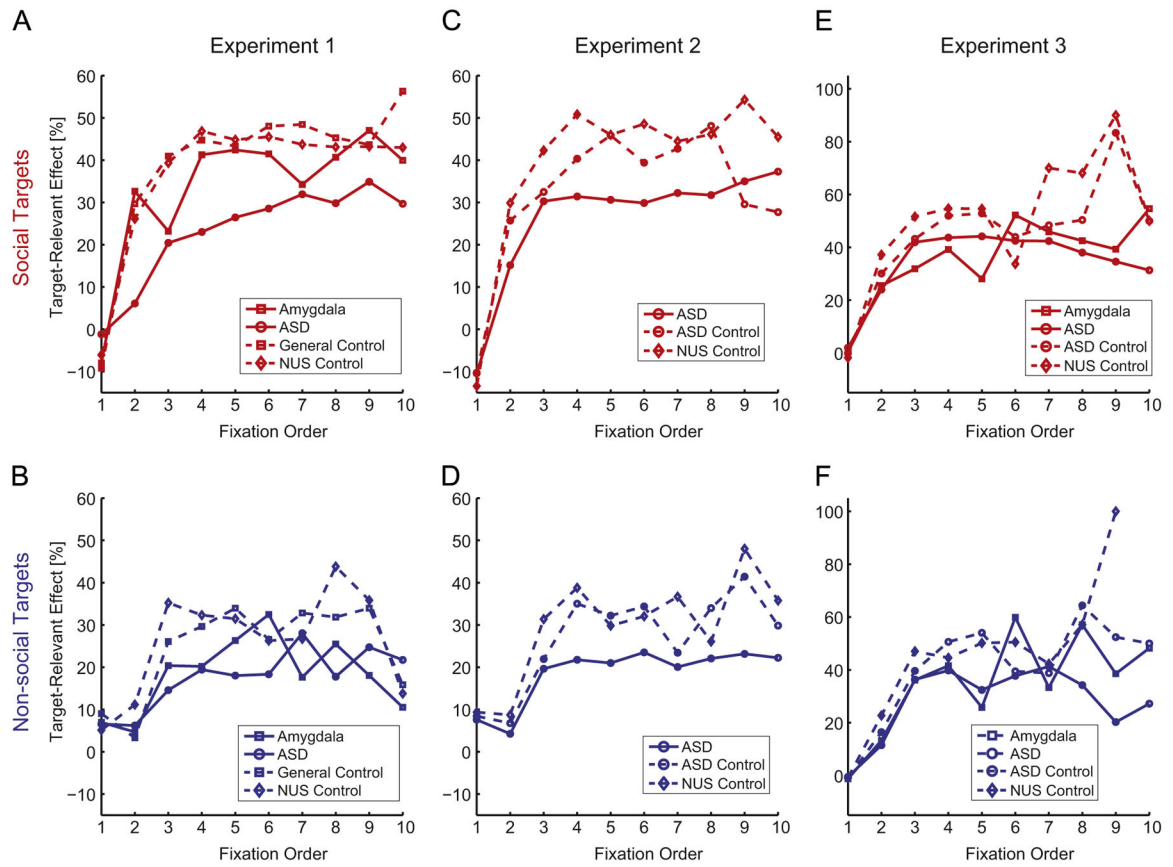


Fig. 6.

Target-relevant effects. (A, B) Experiment 1. (C, D) Experiment 2. (E, F) Experiment 3.

People with ASD have reduced attention towards social items when searching for social targets (A, C), an impairment that is less severe when searching for non-social targets (B, D) and with simpler search arrays (E, F).