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ORIGINAL PAPER

Neural Basis of Visual Attentional Orienting in Childhood Autism Spectrum Disorders

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Abstract We examined spontaneous attention orienting to visual salience in stimuli without social significance using a modified Dot-Probe task during functional magnetic resonance imaging in high-functioning preadolescent children with Autism Spectrum Disorder (ASD) and age- and IQ-matched control children. While the magnitude of attentional bias (faster response to probes in the location of solid color patch) to visually salient stimuli was similar in the groups, activation differences in frontal and temporoparietal regions suggested hyper-sensitivity to visual salience or to sameness in ASD children. Further, activation in a subset of those regions was associated with symptoms of restricted and repetitive behavior. Thus, atypicalities in response to visual properties of stimuli may drive attentional orienting problems associated with ASD.

Keywords Autism spectrum disorder · Attention orienting · Visual salience · fMRI · Restricted and repetitive behavior

Introduction

Atypical orienting of attention has been posited to contribute to social dysfunction in Autism Spectrum Disorders (ASD). Children and adults with ASD show reduced orienting of attention to emotional faces, eye gaze, and gestures (Dalton et al. 2005; Dawson et al. 1998; Kliemann et al. 2012). Further, studies of eye-movements while viewing complex scenes show fewer fixations on faces in individuals with ASD (Klin et al. 2002; Pierce et al. 2011). In the brain, individuals with ASD show abnormally higher involvement of the amygdala, a central region in emotional processing, during attention to eye gaze (Dalton et al. 2005; Kliemann et al. 2012) and emotional faces (Monk et al. 2010). Together, these findings establish that ASD is characterized by atypical attentional processing of social information.

Abnormal ascription of salience to social stimuli may contribute to decreased attentional orienting to social information in ASD, leading to social interaction difficulties (Dawson et al. 1998). Current views of attentional orienting consider two guiding sources, visual salience and top-down information such as the meaning of the stimulus and prior experience with it (Desimone and Duncan 1995; Itti and Koch 2001), including previous associations with reward (Awh et al. 2012). Visual salience refers to bottom-up stimulus attributes encoded by the visual system as evaluated across a number of individual visual channels, such as intensity, contrast, color opponency, and orientation, and is pertinent early in visual processing when higher saliency biases visual attention orienting. Visual attention orienting

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to salient information is an important determinant of what information is subsequently processed in perception and memory. Thus, if ascription of salience to social information is atypical in ASD, its downstream effects on perception and memory are likely to result in social interaction difficulties. Indeed, recent evidence in individuals with ASD supports this possibility. In a study using eye-fixations as an index of attention orienting during complex naturalistic scenes, individuals with ASD fixated on social stimuli (faces, person) as much as controls, but differed qualitatively in visual attention orienting: adolescents with ASD were delayed in fixating on salient features (heads) (Freeth et al. 2011) and children with ASD relied on bottom-up visual saliency when orienting to social stimuli to a greater extent than controls, which predicted social and communicative symptoms (Amso et al. 2014). These findings support the view that atypical early-maturing visual attention processes contribute to social dysfunction in ASD.

However, identifying a definitive role of atypical visual attention processes in ASD requires ruling out the potential impact of top-down information, such as the meaningfulness of the social stimuli, in driving that atypicality. Thus, it is important to investigate attention orienting to visual salience in ASD in the absence of top-down meaning to isolate purely bottom-up visual salience differences in ASD. This is particularly important when considering another set of core ASD symptoms: restricted and repetitive patterns of behavior, interests, or activities (RRBI) also associated with abnormal sensory responses (American Psychiatric Association 2013). Children and adolescents with ASD who completed the Attention Network Task have showed impaired orienting relative to controls, despite no differences in alerting or executive control (Keehn et al. 2010). However, support for the notion that bottom-up visual processing per se (without manipulation of saliency or attention) is atypical in ASD comes from visual search studies showing greater stimulus discriminability (Joseph et al. 2009), likely associated with greater focused attention to stimulus features gauged by pupillometry (Blaser et al. 2014) and larger receptive fields in extrastriate cortex (Schwarzkopf et al. 2014), both of which correlated positively with ASD symptoms (Joseph et al. 2009; Schwarzkopf et al. 2014). Such bottom-up visual processing enhancement may lead to an over-reliance on visual saliency in attention orienting in ASD. How such enhancement may lead to the development of ASD symptoms has been speculated upon; increased attention to visual salience may decrease attention to social stimuli early in life, leading to diminished abilities to learn social constructs (Amso et al. 2014; Joseph et al. 2009). In addition, increased attention to visual salience may lead to a more general predisposition to focused attention in ASD, which may contribute to RRBI (Blaser et al. 2014).

The current study examined neural correlates of attention orienting to visually salient non-social stimuli in 8–13 year-old children with ASD and age- and IQ-matched control children, using a "non-social" version of the dot-probe paradigm most often used to examine emotional bias attention orienting (Mogg and Bradley 1999). We modified the task using brief presentation of a pair of color patches, one with a colorful pattern and the other monochromatic/solid as cue stimuli (in lieu of a fearful- and neutral-emotion face) followed immediately by a detection probe (e.g., star), appearing at the same location of either of the two patches. Faster detection times to probes appearing on the same side as the salient stimuli (e.g., fearful face in the original task) relative to the neutral one, indicates attention bias towards the salient stimuli. A control condition reflecting non-biased attention comprised trials with identical stimuli, two solid patches in our version (termed neutral trials). Computation of salience values based on winner-take-all linear summation across visual channels [using the Saliency Toolbox (Walther and Koch 2006), see methods below] indicated that visual salience was higher for the solid color patches, and therefore, behaviorally, attention ought to be biased towards the solid more than patterned patches. However, to the extent that there are qualitative differences in ascription of salience to visual stimuli, biases would be evident in children's reaction times, allowing objective assessment of which stimulus (patterned or solid) drew attention involuntarily.

In the brain, we expected greater activation during biased-attention trials, which have both types of stimuli (termed biased trials) relative to neutral trials, which have only solid stimuli. In particular, we expected increased activation in regions comprising the dorsal and ventral attention networks—including the intraparietal sulcus, temporoparietal junction, frontal eye fields, and ventrolateral frontal gyrus—which have been respectively associated with preparatory and stimulus-driven orienting of spatial attention (Corbetta et al. 2008; Posner and Petersen 1990). Further, for regions showing differences between the groups, we examined whether activation predicted ASD symptom severity. Based on previous findings in which atypical visual attention was associated with symptoms of RRBI in individuals with ASD (Blaser et al. 2014), we hypothesized that regions differing in children with ASD will be associated with RRBI symptom severity. However, given the paucity of past work in attentional bias to non-social visual salience, we had no basis to formulate specific predictions regarding the nature and loci of group differences in behavior or activation, respectively. A strength of the dot-probe paradigm is that it provides an objective behavioral index of attention orienting (difference in response time when probe is on the same side as the salient cue relative to the opposite side), providing a basis for interpretation of the activation differences. Further, if both groups show evidence of bias and its

magnitude does not differ between groups, differences in brain activity cannot be driven by performance differences and can be interpreted as showing a qualitatively different neural mechanism underlying attention orienting.

Materials and Methods

Subjects

Twenty-three children with a diagnosis of ASD and 35 typically developing children (Table 1) participated in the study after complying with consenting guidelines of the Georgetown University and Children's National Health System (CNHS) Institutional Review Boards. Five additional children with ASD and 3 control children who completed the study were dropped from analysis due to excessive motion (see imaging analysis). Control children were recruited from the Washington DC area community through advertisements at public venues and pediatrician offices. Children with ASD were recruited through the Center for Autism Spectrum Disorders at CNHS.

ASD case classification followed diagnosis based on the DSM-IV-TR criteria by an expert diagnostician (APA 2013) and was confirmed with the Autism Diagnostic Interview—Revised (ADI-R) (Lord et al. 1994) and the Autism Diagnostic Observation Schedule—Generic (ADOS-G) (Lord et al. 2000) following the criteria established by the NICHD/NIDCD Collaborative Programs for Excellence in Autism (Lainhart et al. 2006).

Exclusion criteria included: (1) Full-Scale IQ below 80 as measured by the Wechsler Intelligence Scale for Children (WISC-IV) or Wechsler Abbreviated Scale of Intelligence (WASI) (Weschler 1999); (2) Other neurological diagnosis (e.g., epilepsy) based on parent report; (3) Psychiatric diagnosis based on Child and Adolescent Symptom Inventory −4R (Lavigne et al. 2009) for control children; and (4) Contraindications for MRI such as metallic implants or pregnancy. For subjects assessed with the WISC-IV, we used the General Ability Index (GAI) as a measure of Full Scale IQ (Weiss et al. 1999). Participants with WASI scores had subtest scores converted into WISC-IV Index scores (Tellegen and Briggs 1967). To facilitate the correlation of imaging and diagnostic measures, ADOS raw scores for ASD subjects were standardized into Social Affect Severity (SAS) scores and Restricted and Repetitive Behavioral Severity (RRBS) scores (Hus et al. 2014). Standardized ADOS scores could not be completed for one child due to missing item-level scores, and for one additional child who was tested using the Module 4 ADOS, for which no method of standardization has been calibrated. Five children in the ASD group were on stimulants that were withheld for at least 24 h before scanning; in addition one child with ASD was on non-stimulant and anti-anxiety medications that could not be withdrawn. All remaining children were not medicated.

Table 1 Demographic characteristics

	CON	ASD	Statistic	P value
N	35	23		
Gender	17M	17M	$Chi^2(1) = 2.704$	0.100
Age	10.74 (1.82)	11.36 (1.65)	$t(56) = 1.303$	0.198
IQ	121.97 (10.63)	114.9 (16.30)	$t(56) = 2.001$	0.05
ADOS overall severity		6.61 (2.28)		
ADOS social affect severity		7.67 (1.56)		
ADOS restricted & repetitive behaviors (raw)		6.52 (2.69)		
ADI verbal (raw)		16.48 (4.43)		
ADI RRBI (raw)		4.43 (1.54)		
ADI social interaction (raw)		19.39 (7.32)		

Data in chart reflects only children included in fMRI/behavioral analysis

Task Procedure

Stimuli were created in Photoshop (Adobe Systems Inc, CA), presented in E-prime (Psychological Software Tools, Inc, PA), and viewed via a magnet-compatible projector through a mirror mounted on the head coil. Head movement was minimized with padding between the head and coil. Body movement was minimized by providing ASD and control children an option of an MRI-compatible weighted blanket along the length of their torso and legs.

Subjects performed two functional runs of a "non-social" dot-probe task, each lasting 353 s. Trials consisted of a central fixation cross presented for 500 ms, followed by a cue trial comprising two square visual patches on the left and right sides of the screen shown simultaneously for 500 ms, followed immediately by the probe, a white star that appeared either on the left or right sides in the location of one of the two squares, for 200 ms (Fig. 1), followed by a blank screen for 1300 ms. Subjects were instructed to focus on the central fixation cross when visible, and then indicate which side of the screen the star appeared via a button press with left or right thumb buttons. Subjects were reminded of these instructions at the beginning of each fMRI run. Two types of cue trials were included: (1) 18 trials in which the two patches were of an identical solid color (termed

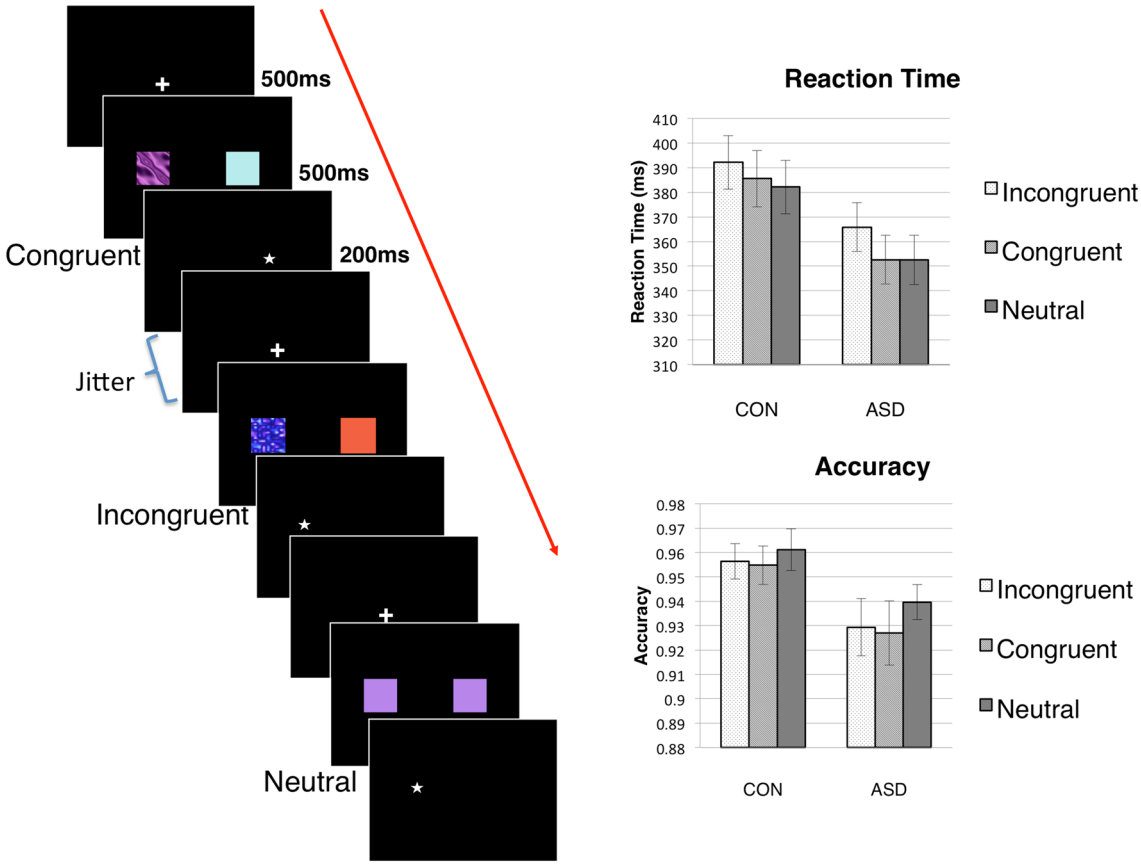

Fig. 1 Example task stimuli comprising Congruent, Incongruent, and Neutral trials. *Color* patches are simultaneously shown for 500 ms, followed by target (*star*) in place of left or right patch for 200 ms. Attentional bias towards solid-color or pattern patch computed as RT differences between response to congruent and incongruent targets. *Error bars* show SEM. (Color figure online)

Neutral); (2) 72 trials in which the two patches differed such that one was a solid color and the other a colorful wall paper pattern (termed Biased). The left/right placement of the two types of visual patches and the star-probe was counterbalanced such that the star-probe was on the same side as the color patch for 36 trials and on the same side as the patterned patch for the remaining 36 trials, and in each case 18 trials had a left-sided response and 18 trials had a right-sided response. Trials were separated by a jittered inter-trial interval between 0 and 7500 ms and presented in a pseudo-randomized order optimized for event-related design using optseq2 (https://surfer.nmr.mgh.harvard.edu/optseq/).

Measurement of Visual Salience in Stimuli

To quantify the salience of the patches, all stimuli were analyzed using the Saliency Toolbox (Walther and Koch 2006). Each image of a presented pair of patches was downsampled into a 33×45 grid, where each cell was evaluated for intensity, orientations, and color, which were then combined to create an overall saliency map, and a winner-take-all map showing the most salient area in the image (Supplementary Fig. 1). For every image, the average salience value for each full color patch was calculated, and values for patterned and solid-color patches were entered into a between-sample t-test. Salience values for solid-color patches were significantly greater than for patterned patches, $t(286) = 3.96$, $p < 0.001$. Given this, we predicted that attention would be biased towards the solid color patches. As stimuli were not designed to vary salience parameters by only one channel at a time (luminance, color, etc), it was not possible in this study to determine whether one channel of visual salience in particular drove group differences.

Imaging Analysis

Imaging acquisition parameters and preprocessing steps, including motion correction, can be found in supplementary materials.

fMRI responses were modeled by a canonical hemodynamic response function convolved with onset vectors for trials in which subjects accurately identified the target location within 200 and 800 ms following the appearance of the target, a criterion that has previously been used for

the dot-probe task (Monk et al. 2006). After implementing these criteria, groups did not differ on the total number of Biased ($t(56)=0.49$, $p=0.62$; ASD M:124.5, SD: 24.72; CON M:127.89, SD: 25.39) or Neutral trials modeled ($t(56)=0.422$, $p=0.67$; ASD M:31.48, SD: 6.04; CON Neutral M: 32.20, SD: 6.57), nor on the ratio of Biased to Neutral trials ($t(56)=0.531$, $p=0.60$). For each subject, condition regressors included in the model were Neutral, Biased, and Fixation/null trials; left and right response trials were not modeled separately. Three second-level analyses were performed with the contrast of interest, Biased vs. Neutral trials. First, to determine regions that were more activated during biased attention to either the solid or patterned color patch, one-sample *t* tests were performed separately for each group. Confirmatory tests ensured that results were not driven by unequal numbers of Biased and Neutral trials (described in Supplementary Materials). Second, to determine regions where activation during biased attention differed between groups, a two-sample *t* test was performed comparing ASD and control groups. Significant regions for imaging analyses were identified at a threshold of $p<0.005$, with a cluster threshold of 50 voxels; a significance level of $p<0.05$ corrected for multiple comparisons based on whole-brain Monte Carlo simulation of random noise distribution, calculated using the 3dClustSim cluster analysis module of AFNI (Forman et al. 1995). Third, to determine whether activation predicted individual differences in ASD symptoms, regions of interest (ROIs) were created from clusters showing significant group differences in the above analysis. Values for the Biased vs. Neutral contrast were averaged across voxels of each ROI for every subject with ASD. Pearson's r correlations were then computed between the contrast value for each ROI and standardized ADOS scores of SAS and RRBS with $p<0.025$ as the Bonferroni-corrected threshold for significance (0.05/2).

Behavioral Analyses

For each subject, correct left and right responses were combined to compute accuracy and mean reaction time (RT) for Biased and Neutral trials (Fig. 1). For Biased trials, Mean RT was calculated separately for trials in which the probe appeared on the side of the solid-color patch and trials in which the probe appeared on the side of the patterned color patch, and a difference between the two averages was calculated for each subject. A faster RT for one trial type over the other indicated a subject's attentional bias, or preferential attention, towards solid or patterned patches. Based on the finding of greater attentional bias towards solid-color than patterned color patches, in subsequent analyses, we labeled trials with the probe on the side of a solid-color patch as "congruent trials", and trials with the probe on the side of a patterned patch as "incongruent trials". To examine whether attentional bias was statistically significant and differed by group, and whether Biased trials differed from Neutral trials, we conducted a Group (ASD, Control) X Trial-type (neutral, congruent, incongruent) analyses of variance (ANOVAs) on mean RT. Further, to determine whether the number of children showing attentional bias to the solid patches (mean RT incongruent—congruent >0) differed between the groups, a Chi square test was conducted on the difference score.

Results

Behavior

Figure 1 depicts RT and accuracy performance for Neutral, Incongruent and Congruent trials for each group. For analysis of RT, a 2 (Group: Control, ASD) x 3 (Trial-type: Neutral, Incongruent, Congruent) ANOVA found no significant Group X Trial-type interaction ($F(2, 56)=1.27$, $p=0.285$, $\eta^2=0.022$). The main effect of trial type was significant ($F(2, 56)=18.15$, $p<0.001$, $\eta^2=0.380$), with congruent trials significantly faster than incongruent trials ($t(57)=4.48$, $p<0.001$, $d=0.152$, 95% CI: 7.12–15.49), and neutral trials also significantly faster than incongruent trials ($t(57)=5.41$, $p<0.001$, $d=0.034$, 95% CI: 5.11–13.38). The main effect of group was marginally significant ($F(2, 56)=3.54$, $p=0.065$, $\eta^2=0.059$), with subjects with ASD showing a trend towards faster RT than control subjects. For analysis of accuracy, an identical ANOVA found no significant Group X Trial-type interaction ($F(2, 56)=0.145$, $p=0.865$, $\eta^2=0.003$). The main effect of trial type was not significant ($F(2, 56)=01.23$, $p=0.296$, $\eta^2=0.022$), but a main effect of group was significant ($F(2, 56)=5.398$, $p=0.024$, $\eta^2=0.088$), with ASD showing lower overall accuracy [ASD: Neut: M=0.94 (0.03), Bias: M=0.93 (0.06); CON: Neut: M=0.96 (0.05), Bias: M=0.96 (0.04)]. These results suggest that children with ASD may have prioritized speed over accuracy to a slightly greater degree than control subjects.

Attentional bias towards the solid-color patches was more frequent among both groups, with 21 subjects with ASD biased towards solid-color patches and two subjects biased towards pattern patches, and 23 control subjects biased towards solid-color patches and 12 subjects biased towards pattern patches. Differences in these distributions approached significance between the groups, ($X^2(1, N=58)=3.664$, $p=0.056$), with solid-color bias seen in approximately 66% of controls and approximately 91% of subjects with ASD. To ensure that group differences in bias did not influence imaging analysis, we performed between-group comparisons with both whole groups, as well as only including individuals showing a bias towards solid-color patches. Attentional bias did not differ by gender ($X^2(1, N=58)=0.000$, $p=1$), so gender was not included in subsequent analyses.

Imaging

For each group, a one-sample *t* test evaluated differences in activation between Biased and Neutral trials. In control children, activation was greater in Biased than Neutral trials in three clusters, a large one including right precentral and postcentral gyri and two smaller clusters, one in the bilateral calcarine and left lingual gyrus and another in left postcentral gyrus. No regions showed greater activation in control children for Neutral trials than for Biased trials (Supplementary Table 1, Fig. 2). In children with ASD, while no regions showed greater activation for Biased trials than for Neutral trials, three clusters in the right hemisphere showed greater activation for Neutral than for Biased trials. Specifically, the largest cluster included parts of anterior lateral inferior frontal gyrus and lateral inferior orbitofrontal cortex (OFC), extending medially to the right ventromedial prefrontal cortex (vmPFC) and pregenual anterior cingulate (pACC). The other clusters included regions in the right cerebellum, and the right temporoparietal region, including the right angular gyrus (Supplementary Table 1, Fig. 2). A follow-up analysis confirmed that this pattern held when number of Biased and Neutral trials is held equal (Supplementary Table 2).

Group comparison revealed that five clusters differed between groups such that in control children, they were more activated during Biased relative to Neutral trials whereas in children with ASD they were more activated during Neutral relative to Biased trials. These included two clusters along the left central sulcus, a dorsal cluster that included precentral and postcentral gyri, and a ventral cluster including postcentral gyrus and left frontal operculum. Three additional clusters included a cluster comprised of posterior cingulate (PCC) and precuneus, a cluster including right angular gyrus and posterior rolandic operculum, and right OFC (Table 2; Fig. 3). This pattern of group differences was also confirmed in the comparison of the subset of ASD (N = 21) and control (N = 23) children showing attentional bias towards the solid patches (see Supplementary Materials). Thus, observed activation differences between groups did not result from group differences in heterogeneity in attentional orienting performance within groups. Additionally, the similarity with the full group results suggests that they were not driven by sample-size differences.

ADOS RRBS scores were negatively correlated with contrast values of the left pre- and postcentral gyrus ($r = -.579$, $p = 0.006$), PCC and precuneus ($r = -.654$, $p = 0.001$) at the Bonferroni corrected threshold, indicating that greater activation of the region in the Neutral trials relative to the Biased trials was associated with more severe symptoms (Fig. 3). A negative correlation of right OFC activation with the ADOS RRBS scores approached significance at the Bonferroni corrected threshold ($r = -.484$, $p = 0.026$).

Table 2 Regions showing greater activation in control (CON) than ASD children for the biased vs. neutral trial contrast

Contrast	Region	BA	X	Y	Z	Z-value	Voxels
Con vs. ASD							
	L precentral gyrus	6	−57	−1	43	3.60	91
	L postcentral gyrus	4	−51	−4	16	3.46	74
	R Inf orbitofrontal gyrus	47	36	38	−2	3.35	51
	L post cingulate gyrus	29	−6	−40	13	3.31	107
	R rolandic operculum	13	39	−37	19	3.09	79

Regions showing group differences for the biased vs. neutral trials contrast. Control children showed greater activation in these regions for biased relative to neutral trials whereas ASD children showed greater activation in these regions for neutral relative to biased trials

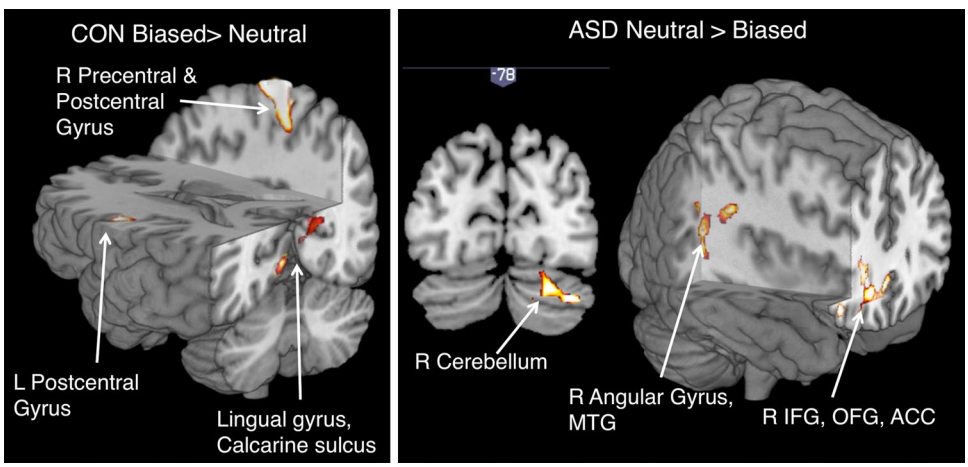

Fig. 2 Regions showing within-group differences in activity between Biased and Neutral trials. Control children showed greater activation for Biased than Neutral, and no greater activation for Neutral than Biased. ASD showed greater activation for Neutral than Biased trials, and no greater activation for Biased than Neutral

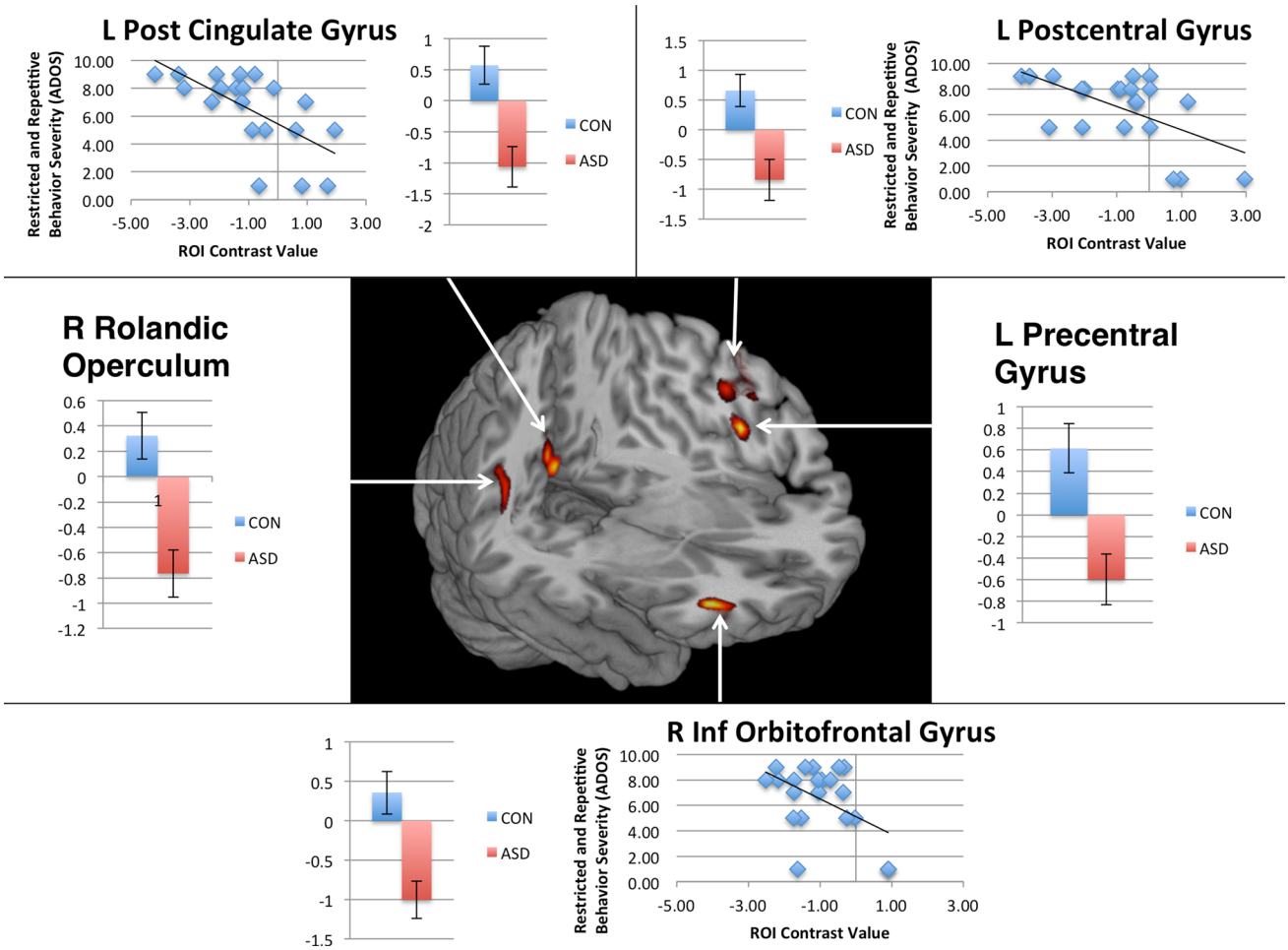

Fig. 3 Regions showing group differences in Biased > Neutral contrast. *Bar* graphs show average group beta weights for significant clusters, positive values indicate greater activation for Biased than Neutral trials, negative values indicate greater activation for Neutral than Biased. *Cluster plots* show significant correlations between contrast values and ADOS RRBS scores in ASD subjects for left postcentral gyrus, PCC and precuneus, and right OFC

Discussion

We found that attention orienting to salient visual non-social stimuli was behaviorally similar in children with ASD to that of controls but differed in the extent of engagement of multiple regions implicated in orienting of visuospatial attention, including the precuneus, PCC, right temporoparietal, left pre- and postcentral gyri, left inferior frontal operculum, and right lateral OFC. Specifically, control children engaged those regions during biased attention orienting to the solid-color patches, children with ASD engaged them to a greater extent during the neutral condition, which included only solid-color patches and no selective orienting of attention. Furthermore, greater activation in the OFC, postcentral gyrus, and PCC in children with ASD during the neutral condition was associated with more RRBS symptoms measured by the ADOS. Together, these findings suggest hyperresponsivity of dorsal and ventral attention network regions (that nominally drive spontaneous attention orienting measured by the dot-probe paradigm) in children with ASD to visually salient stimuli or to sameness of stimuli without social or affective content.

Behaviorally, attention orienting was similar between groups, but with some notable differences. As predicted by computational salience values, both ASD and control children oriented attention to the solid-color patches to the same magnitude, establishing that attentional orienting to visually salient information is intact in children with ASD. At the individual level, almost all children with ASD and the majority of control children exhibited this attention bias. Despite this behavioral similarity, however, children with ASD tended to respond overall more quickly than controls, on all types of trials, albeit not reaching statistical significance. Faster response in children with ASD has also been observed with the emotional dot-probe task (Monk et al. 2010). Further, as evident in Fig. 1, congruent trials (that do

not require attention shifts for probe detection) were as fast as neutral trials in children with ASD, whereas in control children the pattern of response time was more graded with neutral trials being the fastest. Perhaps a choice response (rather than detection) may have served to prevent the apparent floor effects, slowing response times and providing more opportunity for observing individual differences in the magnitude of attention bias among children within each group.

The most surprising finding of the present study was that regions involved in processing attention and salience were engaged by qualitatively different stimuli in the two groups. While these regions were activated by biased trials (i.e., stimuli pair with one solid and one patterned patch) in controls, they were activated by neutral trials (i.e., stimuli pair with two solid patches) in ASD children. Specifically, these were regions implicated in the orienting of visual attention, including the left pre- and postcentral gyri, left inferior frontal operculum, right lateral OFC, PCC and precuneus, and right angular gyrus. The PCC responds to the physical salience of visual stimuli, including salient patterns (Vogt et al. 1992), while the precuneus has been implicated in shifting spatial attention, including in anticipation of motor responses to spatial information (Cavanna and Trimble 2006). The right angular gyrus and surrounding temporo-parietal regions have been implicated in attentional orienting (Taylor et al. 2011), and are particularly active when orienting towards stimuli with high salience or relevance (Indovina and Macaluso 2007). The right lateral OFC is part of the ventral attention network, and is thought to evaluate the relevance of novel stimuli that had not been the focus of attention (Corbetta and Shulman 2002). Greater activity of these regions in Biased than Neutral trials, which involve orienting of attention to differences in visual salience, would be consistent with these previous findings and was seen in control children. However, the finding of greater activation of these regions in ASD to Neutral than Biased trials, in which the stimuli pairs were identical, was unexpected, particularly as behavior in the two groups—attention bias towards solid patches—was similar.

There are two potential interpretations of the observed activation results in children with ASD: Attention-orienting neural circuitry is driven by hyper-responsivity to salience (exemplified by higher activation for greater quantity of salience) or it is driven by preference for sameness. Considering the first interpretation, greater activation of attention orienting regions in response to neutral trials, which included two instances of the visually salient stimulus (solid patches) than only one on the biased trials, suggest that in children with ASD these regions respond proportionally to the presence of visual salience. In contrast, control children may habituate to salience, attenuating their response to the neutral trials but augmenting it when salience is selectively encoded in the context of a less salient stimuli. The increased response or lack of habituation in children with ASD may reflect hyper-responsivity of bottom-up processing of salient visual stimuli in children with ASD, a hypothesis supported by findings of exaggerated bottom-up influence in attentional orienting in individuals with ASD when viewing naturalistic scenes (Amso et al. 2014; Freeth et al. 2011). It is possible that this increase may be attributable to differences in the visual receptive fields in ASD, which were noted recently by increased perifoveal population receptive fields (pRF) in extrastriate cortex, indicating either hyper-excitability of the visual cortex and/or poor peripheral spatial attention in individuals with ASD (Schwarzkopf et al. 2014). These pRF measures also correlated with a measure of autism symptom severity (Autism-Spectrum Quotient), suggesting that abnormalities in cortical function associated with spatial attention may relate to ASD symptoms. It has been suggested that neural differences leading to increased attention to visual salience in ASD may also contribute to abnormally focused attention, which may contribute to RRBI (Blaser et al. 2014; Joseph et al. 2009). Indeed, activity in three of the five regions showing group differences, correlated with RRBS in the present study. These regions—the left pre- and postcentral gyrus, PCC and precuneus, and right lateral OFC—are involved in recognizing and orienting attention to salient stimuli.

An alternate interpretation is also tenable—greater activation of visual attention regions during neutral trials may reflect a preference for sameness, which is an integral part of ASD symptomatology. Increased sensitivity to visual symmetry has been reported in individuals with ASD, with a lower detection threshold for symmetrical stimuli amid visual noise (Perreault et al. 2011), as well as an ability to detect asymmetry at lower difference thresholds (Kéïta et al. 2011). The observed correlation between neural activity and RBBS may support this view, as manifestations of repetitive behaviors often include an insistence on sameness, including a strong need for symmetry (Fischer-Terworth and Probst 2009). The current experimental design cannot adjudicate between the two interpretations, as both hyper-response to salience and preference for sameness would predict more activation in response to trials with two salient stimuli. Inclusion of a second neutral trial condition including two patterned patches would have adjudicated between the two interpretations as a preference for sameness ought to be manifested regardless of the salience of the stimuli, whereas hyper-responsivity to visual salience ought to be observed selectively for the solid-patch neutral trials and not for the patterned-patch neutral trials. In addition to including patterned neutral trials, future studies should also manipulate particular channels of visual saliency, such as intensity or contrast, to examine which contribute more strongly to atypical attentional orienting in ASD.

In conclusion, the present findings suggest that atypical neural response to salient stimuli in individuals with ASD extends to information without social or affective value. This finding raises the possibility that attentional orienting deficits that have been well documented in ASD when using social stimuli may be rooted, at a more fundamental level, in atypical responsivity to visual salience and associated early visual attentional processes. The failure to orient attention toward what is typically considered important in a given situation is a fundamental problem in ASD that impairs learning and the development of social skills (Klin et al. 2003). Insight into bottom up processes (whether sameness or properties visual salience) that can be leveraged to enhance orientation of attention to important information can guide future intervention strategies.

Author Contributions EM, LK, and CV designed the study and wrote the manuscript. EM and MN collected data. LK and JS clinically characterized children with ASD. WG designed the study and recruited participants. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

Conflict of Interest Eric R. Murphy, Megan Norr, John F. Strang, Lauren Kenworthy, William D. Gaillard, Chandan J. Vaidya declares that they has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders V (Fifth)*. Arlington, VA: American Psychiatric Publishing.

Amso, D., Haas, S., Tenenbaum, E., Markant, J., & Sheinkopf, S. J. (2014). Bottom-up attention orienting in young children with autism. *Journal of Autism and Developmental Disorders, 44*(3), 664–673. doi:10.1007/s10803-013-1925-5.

Awh, E., Belopolsky, A. V., & Theeuwes, J. (2012). Top-down versus bottom-up attentional control: A failed theoretical dichotomy. *Trends in Cognitive Sciences, 16*(8), 437–443. doi:10.1016/j.tics.2012.06.010.

Blaser, E., Eglington, L., Carter, A. S., & Kaldy, Z. (2014). Pupillometry reveals a mechanism for the autism spectrum disorder (asd) advantage in visual tasks. *Scientific Reports, 4*. doi:10.1038/srep04301.

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain: A Journal of Neurology, 129*(3), 564–583. doi:10.1093/brain/awl004.

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: From environment to theory of mind. *Neuron, 58*(3), 306–324. doi:10.1016/j.neuron.2008.04.017.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*(3), 201–215. doi:10.1038/nrn755.

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., … Davidson, R. J.. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience, 8*(4), 519–526. doi:10.1038/nn1421.

Dawson, G., Meltzoff, A. N., Osterling, J., Rinaldi, J., & Brown, E. (1998). Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders, 28*(6), 479–485.

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience, 18*(1), 193–222. doi:10.1146/annurev.ne.18.030195.001205.

Fischer-Terworth, C., & Probst, P. (2009). Obsessive–compulsive phenomena and symptoms in Asperger's disorder and high-functioning autism: An evaluative literature review. *Life Span and Disability, 12*(1), 5–27.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fmri): Use of a cluster-size threshold. *Magnetic Resonance in Medicine, 33*(5), 636–647. doi:10.1002/mrm.1910330508.

Freeth, M., Foulsham, T., & Chapman, P. (2011). The influence of visual saliency on fixation patterns in individuals with Autism Spectrum Disorders. *Neuropsychologia, 49*(1), 156–160. doi:10.1016/j.neuropsychologia.2010.11.012.

Hus, V., Gotham, K., & Lord, C. (2014). Standardizing ADOS domain scores: Separating severity of social affect and restricted and repetitive behaviors. *Journal of Autism and Developmental Disorders, 44*(10), 2400–2412. doi:10.1007/s10803-012-1719-1.

Indovina, I., & Macaluso, E. (2007). Dissociation of stimulus relevance and saliency factors during shifts of visuospatial attention. *Cerebral Cortex, 17*(7), 1701–1711. doi:10.1093/cercor/bhl081.

Itti, L., & Koch, C. (2001). Computational modelling of visual attention. *Nature Reviews Neuroscience, 2*(3), 194–203. doi:10.1038/35058500.

Joseph, R. M., Keehn, B., Connolly, C., Wolfe, J. M., & Horowitz, T. S. (2009). Why is visual search superior in autism spectrum disorder?. *Developmental Science, 12*(6), 1083–1096. doi:10.1111/j.1467-7687.2009.00855.x.

Keehn, B., Lincoln, A. J., Müller, R.-A., & Townsend, J. (2010). Attentional networks in children and adolescents with autism spectrum disorder. *Journal of Child Psychology and Psychiatry, 51*(11), 1251–1259. doi:10.1111/j.1469-7610.2010.02257.x.

Kéïta, L., Mottron, L., Dawson, M., & Bertone, A. (2011). Atypical lateral connectivity: A Neural basis for altered visuospatial processing in autism. *Biological Psychiatry, 70*(9), 806–811. doi:10.1016/j.biopsych.2011.07.031.

Kliemann, D., Dziobek, I., Hatri, A., Baudewig, J., & Heekeren, H. R. (2012). The role of the amygdala in atypical gaze on emotional faces in autism spectrum disorders. *The Journal of Neuroscience, 32*(28), 9469–9476. doi:10.1523/JNEUROSCI.5294-11.2012.

Klin, A., Jones, W., Schultz, R., & Volkmar, F. (2003). The enactive mind, or from actions to cognition: Lessons from autism. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 358*(1430), 345–360. doi:10.1098/rstb.2002.1202.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry, 59*(9), 809–816. doi:10.1001/archpsyc.59.9.809.

Lainhart, J. E., Bigler, E. D., Bocian, M., Coon, H., Dinh, E., Dawson, G., … Volkmar, F. (2006). Head circumference and height in autism: A study by the collaborative program of excellence in autism. *American Journal of Medical Genetics Part A, 140 A*(21), 2257–2274. doi:10.1002/ajmg.a.31465.

Lavigne, J. V., Cromley, T., Sprafkin, J., & Gadow, K. D. (2009). The child and adolescent symptom inventory-progress monitor: A brief diagnostic and statistical manual of mental disorders, 4th edition-referenced parent-report scale for children and adolescents. *Journal of Child and Adolescent Psychopharmacology, 19*(3), 241–252. doi:10.1089/cap.2008.052.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H. Jr., Leventhal, B. L., DiLavore, P. C., … Rutter, M. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders, 30*(3), 205–223.

Lord, C., Rutter, M., & Couteur, A. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24*(5), 659–685. doi:10.1007/BF02172145.

Mogg, K., & Bradley, B. P. (1999). Orienting of attention to threatening facial expressions presented under conditions of restricted awareness. *Cognition & Emotion, 13*(6), 713–740. doi:10.1080/026999399379050.

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., … Pine, D. S. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *The American Journal of Psychiatry, 163*(6), 1091–1097. doi:10.1176/appi.ajp.163.6.1091.

Monk, C. S., Weng, S.-J., Wiggins, J. L., Kurapati, N., Louro, H. M. C., Carrasco, M., … Lord, C. (2010). Neural circuitry of emotional face processing in autism spectrum disorders. *Journal of Psychiatry and Neuroscience, 35*(2), 105–114. doi:10.1503/jpn.090085.

Perreault, A., Gurnsey, R., Dawson, M., Mottron, L., & Bertone, A. (2011). Increased sensitivity to mirror symmetry in autism. *PLOS ONE, 6*(4), e19519. doi:10.1371/journal.pone.0019519.

Pierce, K., Conant, D., Hazin, R., Stoner, R., & Desmond, J. (2011). Preference for geometric patterns early in life as a risk factor for autism. *Archives of General Psychiatry, 68*(1), 101–109. doi:10.1001/archgenpsychiatry.2010.113.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13*, 25–42. doi:10.1146/annurev.ne.13.030190.000325.

Schwarzkopf, D. S., Anderson, E. J., de Haas, B., White, S. J., & Rees, G. (2014). Larger extrastriate population receptive fields in autism spectrum disorders. *The Journal of Neuroscience, 34*(7), 2713–2724. doi:10.1523/JNEUROSCI.4416-13.2014.

Taylor, P. C. J., Muggleton, N. G., Kalla, R., Walsh, V., & Eimer, M. (2011). TMS of the right angular gyrus modulates priming of pop-out in visual search: Combined TMS-ERP evidence. *Journal of Neurophysiology, 106*(6), 3001–3009. doi:10.1152/jn.00121.2011.

Tellegen, A., & Briggs, P. (1967). Old wine in new skins: grouping wechsler subtests into new scaLES. *Journal of Consulting Psychology, 31*(5), 499–506. doi:10.1037/h0024963.

Vogt, B. A., Finch, D. M., & Olson, C. R. (1992). Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions. *Cerebral Cortex, 2*(6), 435–443. doi:10.1093/cercor/2.6.435-a.

Walther, D., & Koch, C. (2006). Modeling attention to salient proto-objects. *Neural Networks, 19*(9), 1395–1407. doi:10.1016/j.neunet.2006.10.001.

Wechsler, D. (1999). Manual for the Wechsler abbreviated intelligence scale (WASI). San Antonio, TX: The Psychological Corporation.

Weiss, L. G., Saklofske, D. H., Prifitera, A., Chen, H.-Y., & Hildebrand, D. (1999). The calculation of the WISC-Ill general ability index using Canadian Norms. *Canadian Journal of School Psychology, 14*(2), 1–10. doi:10.1177/082957359901400202.