Electrophysiological measures of low-level vision reveal spatial processing deficits and hemispheric asymmetry in autism spectrum disorder

Francesca Pei
Department of Psychology, Stanford University, Stanford, CA, USA
Stanford Autism Center at Packard Children’s Hospital, Department of Psychiatric, School of Medicine, Stanford University, Stanford, CA, USA

Stefano Baldassi
Department of Psychology, Stanford University, Stanford, CA, USA
Department of Neuroscience, Psychology, Pharmacology, and Child Health, University of Florence, Florence, Italy

Anthony M. Norcia
Department of Psychology, Stanford University, Stanford, CA, USA

There is accumulating evidence from electrophysiological studies that low-level visual processing is atypical in individuals with autism spectrum disorders (ASDs). Abnormalities in early stages of sensory processing are of interest because they could lead to downstream functional deficits in social or cognitive domains. Using steady-state visual evoked potentials (SSVEPs), we studied how well spatial information is transmitted over a wide range of spatial frequencies (2–30 cycles/deg), including those at the limit of visibility (visual acuity). SSVEPs were recorded over 128 channels in 16 ASD participants between 5 and 17 years old and 17 age-matched, neurotypical (NT) participants. We observed a selective reduction of the amplitude of the SSVEP second harmonic pattern reversal response between 5 and 17 cycles/deg. Responses measured at the fourth harmonic were normal at all spatial frequencies tested, as were responses at the lowest and highest spatial frequencies at the second harmonic. The reduction of second harmonic responses occurred preferentially over right occipital electrodes. Because response abnormalities are restricted to a specific response harmonic and to specific ranges of spatial frequency, we can rule out nonspecific differences between the ASD participants and the NT controls. This particular pattern of loss, combined with the observed exaggeration of the loss over the right hemisphere, suggests that a highly specific neural substrate early in the visual pathway is compromised in ASD.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment of communication skills and social interaction and by repetitive patterns of stereotyped behaviors. In addition to these core deficits, a variety of sensory abnormalities have been described in ASD patients since the discovery of the disorder. Early reports noted that the response to sensory stimuli in ASD was similar to that in deaf-blind children (Kanner, 1943; Wing, 1969). Later studies reported a high rate of sensory abnormalities, mostly on the basis of questionnaires administered to the parents (Baranek, David, Poe, Stone, & Watson, 2006; Klintwall et al., 2011). Such abnormalities have been described across all sensory domains (Marco, Hinkley, Hill, & Nagarajan, 2011). One study (Leekam, Nieto, Libby, Wing, & Gould, 2007) reported that up to 90% of individuals with ASD show tactile, auditory, or visual hypersensitivity or hyposensitivity. Because sensory symptoms and abnormal reactions to sensory stimuli are so common, they are now part of the diagnostic criteria for ASD in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000a).

The high prevalence of sensory disturbances in ASDs has led to the suggestion that at least some of the high-level deficits in social interaction and communication in ASDs could be explained in terms of downstream consequences of lower-level sensory and perceptual abnormalities (Behrmann et al., 2006; Caron, Mottron, Berthiaume, & Dawson, 2006). Abnormal visual perception in ASDs on performance-based assessment was first demonstrated as a local versus global feature-integration bias (Happe, 1996; Mottron & Belleville, 1993; Pei et al., 2009; Plaisted, O’Riordan, & Baron-Cohen, 1998; Plaisted, Swettenham, & Rees, 1999). People with ASD showed a strong bias for details and local characteristics of the task in tests such as the embedded figure test (Joliffe & Baron-Cohen, 1997; Shah & Frith, 1983) or the block design subtest of the Wechsler intelligence quotient (IQ) battery (Shah & Frith, 1983; Venter, Lord, & Schopler, 1992). These reports of superior visual performance in ASD contributed to the development of the weak central coherence hypothesis (Frith, 1989) and the enhanced perceptual functioning hypothesis (Mottron et al., 2006) of ASD. The local bias effect led researchers to focus on visual search, a task that ASD observers seem to perform with less or no influence of the number of distractors (O’Riordan & Passetti, 2006; O’Riordan, Plaisted, Driver, & Baron-Cohen, 2001), possibly due to diminished peripheral visual crowding (Baldassi et al., 2009) that in turn fits with the difficulties ASD observers experience in visual integration tasks. However, it has been argued that the deficit of global form processing in autism is far from understood because of a lack of studies using stimuli that control for the presence of low spatial frequency structure in the test material (Dakin & Frith, 2005).

Subsequent research (Milne et al., 2002, 2006; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005; Spencer et al., 2000) found elevated thresholds in ASD on coherent motion tasks in which sensitivity to motion is determined on the basis of the fraction of coherently moving dots needed by the observer to discriminate the direction of motion. Because motion direction cannot be estimated on the basis of small regions of a coherent motion display, this task is believed to tap global processing mechanisms in the extrastriate cortex (Newsome & Pare, 1988; Williams & Sekuler, 1984). Bertone, Mottron, Jelenic, and Faubert (2003) described deficits in second-order motion that were interpreted as a deficit in the perception of complex stimuli rather than as a deficit in the early detector along the magnocellular stream. However, direction discrimination thresholds are elevated for moving gratings in ASD participants and their siblings, suggesting that lower-level motion processing is, in fact, abnormal and may be a genetically mediated risk factor for ASD (Koh, Milne, & Dobkins, 2010a).

The integrity of low-level spatial mechanisms that feed higher-order visual processes has been less well studied. The spatial frequency hypothesis in ASD proposes that the detail-oriented bias in ASD reflects enhanced sensitivity to high spatial frequencies or a reduced sensitivity to low spatial frequencies (Behrmann et al., 2006; Kemner & van Engeland, 2006; Milne et al., 2002). The studies performed based on this hypothesis have used widely differing techniques to measure visual acuity and contrast sensitivity, and the results have been at least partially inconsistent (for a review see Koh et al., 2010a, b). For example, a recent study measured visual acuity, triggering a debate about the possibility of a supernormal acuity—within the range of predator birds—in ASD (Ashwin, Ashwin, Rhydderch, Howells, & Baron-Cohen, 2009). However, the methodology used in that study has been questioned and has led to several follow-up studies that did not replicate the effect (Bach & Dakin, 2009; Bolte et al., 2012; Crewther & Sutherland, 2009).

Visual acuity is just one aspect of spatial contrast sensitivity. Several behavioral studies have measured contrast sensitivity thresholds at different spatial frequencies and have found no significant difference between ASD and neurotypical (NT) age-matched controls (Behrmann et al., 2006; Bertone & Faubert, 2003; Bertone, Mottron, Jelenic, & Faubert, 2005; Koh, Milne, & Dobkins, 2010b; Pellicano et al., 2005). In contrast to these results, lower thresholds have been found in a high-risk population of 6-month-old siblings of children with ASD (McCleery, Allman, Carver, & Dobkins, 2007). Behavioral spatial acuity and contrast sensitivity measures appear to be largely unaffected in ASD, but tasks involving more integrative processing are adversely affected.

Electrophysiological recordings are particularly useful in neurodevelopmental disorders as measures of sensory processing because they do not require any task performance or language/comprehension abilities. Event-related potential (ERP) data show specific neural abnormalities in ASD that are related to low-level visual processing. ERP responses for Navon stimuli and motion stimuli have been compared by Sutherland and Crewther (2010) in people with high scores on the autism spectrum quotient (AQ), a scale that measures the prevalence of behaviors associated with ASD (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Brugha et al., 2012). The AQ is correlated with scores on the Autism Diagnostic Observation Schedule (ADOS), the current research standard for the diagnosis of ASD, but it is only weakly predictive of criterion scores for ASD. Participants with high AQ scores showed weaker initial cortical responses to low-contrast stimuli and diminished identification of the global components in the Navon task. This was interpreted as a delay in primary visual/
prestiate cortical processing of magnocellular input (Sutherland & Crewther, 2010). A follow-up study in a similar participant group also found deficits in the earliest recordable response components and larger-than-normal responses when measured over a range of contrasts (Jackson et al., 2013). The ERP in an object boundary detection paradigm was found to be abnormal in ASD, with differences emerging as early as 120 ms after stimulus presentation (Vandenbroucke, Scholte, van Engeland, Lamme, & Kemner, 2008), implying a deficit in early to midlevel cortical processing stages. Using Gabor patches of different spatial frequencies, Milne, Scope, Pascalis, Buckley, and Makeig (2009) found a general reduction in latency for the ASD group but also a more specific increase in low \( \tau \)-band power in the components located in or near the left cingulate gyrus in the participants with ASD, suggesting that different low-level strategies were used during the task by ASD versus typical participants.

ERP abnormalities have been found in the processing of suprathreshold spatial frequency gratings. ERP alterations at 6 cycles/deg (cpd) were found in the N80 component, while atypical processing of both high- and low-frequency gratings occurred later in the P100 component (Boeschoten, Kenemans, van Engeland, & Kemner, 2007). Jemel, Mimeault, Saint-Amour, Ho-sein, and Mottron (2010) recorded visual evoked potentials (VEPs) from vertical sinusoidal achromatic gratings at different spatial frequencies. The N80 component elicited by grating from 2.8 to 8 cpd was smaller at low contrast levels in ASD versus control groups. Taken together, the ERP results suggest that suprathreshold processing at very early stages of the visual pathway may be disrupted in ASD.

To further quantify the extent to which very low-level visual deficits may be present in ASD, we measured steady-state visual evoked potentials (SSVEPs) in response to a wide range of spatial frequencies using the sweep technique (Norcia & Tyler, 1985). This method has several advantages for use in populations with neurodevelopmental disorders. It can be used to estimate sensory thresholds (e.g., the limits of neuronal performance) as well as responsiveness at suprathreshold levels and, importantly, it does not require observers to engage in behavioral tasks, potentially increasing its application over a greater range of severities in clinical populations. The use of grating stimuli reduces the complexity of visual processing to the minimum level, and an analysis of the SSVEP scalp topography from high-density electroencephalography (EEG) recordings allows us to make a rough assessment as to whether the underlying generators of the response lie in the early visual cortex.

ASD participants show reductions in the VEP response recorded over the early visual cortex to a specific range of spatial frequencies (approximately 5–17 cpd), and these reductions are restricted to a specific temporal component of the VEP recording, the second harmonic. We also find a relative reduction of signal amplitude over the right hemisphere. These differences in the way spatial frequency information is processed in the autistic brain suggest that early cortical mechanisms are altered in ASD. Taken together, the patterns of deficit we observe may constitute a biomarker for ASD.

### Methods and materials

#### Participants

Sixteen children with ASD (5–17 years old; mean age = 9.2 years) participated in the study. They were recruited through the Lucile Packard Children’s Hospital at Stanford, the Interactive Autism Network at Autism Speaks, and local parents’ associations. The diagnosis of ASD was made on the basis of the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000b) since at the time of the assessment the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* had not been published. Each diagnosis was confirmed by an experienced clinician using the ADOS instrument (Lord et al., 1989). Subjects with mental retardation due to genetic and neurological pathology of other kinds were excluded from the study. Control participants were typically developing, age-matched children (n = 17; mean age = 8.6 years) with no history of serious medical, psychiatric, or neurological conditions who were recruited through local schools. Because SSVEP testing involves no instructions or tasks, is relatively unaffected by attention, and is not affected by IQ (as is a measure used in infants), we did not match the participants on cognitive level. Because SSVEP grating acuity is adult-like at age 5 (Norcia & Manny, 2003; Norcia & Tyler, 1985), we pooled the results across all ages. All participants had normal or correct-to-normal vision, as also confirmed by the results of the study. Informed consent was obtained from a parent or guardian of the child, and an assent was signed by the participant whenever possible. The Institutional Review Board at Stanford University approved the experimental protocol.

#### Experimental paradigm

Vertical, sine-wave luminance gratings were presented as gray-scale images on a contrast-linearized cathode ray tube (CRT) (Apple Inc., Cupertino, CA) 1600 × 1200 pixels and a vertical refresh rate of 72 Hz over a field size of 37° by 28° at a mean luminance of
50 cd/m². The gratings were presented at 80% contrast and were contrast reversed with a square-wave temporal profile at 7.5 Hz. The contrast reversal was precisely synchronized to the vertical refresh rate of the monitor (60 Hz). The participants sat at a viewing distance of 1.5 m and were asked to look at the center of the screen for the duration of individual trials that lasted 12.8 s. When necessary, a researcher stood behind the screen while holding a control device to stop recording when the subject was not fixating in the center of the screen. The fixation was monitored by observing the centration of the corneal reflection of the display monitor in the participants’ pupils. This measure is accurate to approximately 4°, a small fraction of the grating display area (Allen, Tyler, & Norcia, 1996).

We used a steady-state sweep VEP technique that has been used many times before to measure spatial frequency response functions both in NT infants, children, and adults and in clinical populations (Almoqbel, Leat, & Irving, 2008; Norcia & Manny, 2003). Following typical practice, the spatial frequency of the grating was swept in equal linear increments (10) over trials lasting 12 s. The spatial frequency range (2–30 cpd) was chosen based on previous studies using adults and older children as one that would span the full range between very visible and invisible, including the acuity range (Norcia & Manny, 2003; Skoczenski & Norcia, 1999). The trial began with 1 s of an unrecorded flickering 2-cpd grating in order to avoid artifacts from the transient stimulus onset. Ten trials were recorded for each subject, and all 10 trials in both groups were used for the final analysis.

**VEP recording and analysis**

The EEG data were collected using a 128-channel HydroCell Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR), bandpass filtered from 0.1 to 50 Hz and digitized at a rate of 432 Hz (Net Amps 300 TM, Electrical Geodesics). Individual electrodes were adjusted until impedances were below 60 kΩ before starting the recording.

Artifact rejection was performed off-line according to a sample-by-sample threshold procedure to remove noisy electrodes and replace them with the average of the six nearest neighboring electrodes. The EEG was then rereferenced to the common average of all the remaining electrodes. Epochs with more than 20% of the data samples exceeding 100 µV were excluded on a sensor-by-sensor basis; this is the criterion used for normal adults. Typically, these epochs included eye movements or blinks.

The 7.5-Hz pattern reversal response is an SSVEP and is traditionally analyzed in the frequency domain via Fourier analysis. The SSVEP amplitude in each 1-s epoch corresponding to the spatial frequency steps in the stimulus sweep was determined by a discrete Fourier transform (Norcia & Tyler, 1985). Within a subject, the amplitude and phase values were averaged coherently (i.e., the average considered both phase and amplitude values) over the 10 trials recorded in each participant. Thresholds in the sweep VEP method were estimated subject by subject by extrapolating amplitude versus spatial frequency function to zero amplitude.

Group-average spatial frequency response functions for the ASD and NT participants were formed by incoherently averaging (using amplitudes only) the individual subject amplitudes recorded at the second (15 Hz) and fourth (30 Hz) harmonics of the stimulus temporal frequency.

**Acuity estimation**

Grating acuity was estimated from the spatial frequency response functions by regressing the VEP amplitude versus spatial frequency function to zero amplitude using criteria described in detail in previous publications (Norcia, Clarke, & Tyler, 1985; Norcia & Tyler, 1985). Briefly, an automatic scoring algorithm searched the VEP record, starting from the highest spatial frequency bin, for sections of the record that exceeded a statistical criterion for the presence of an evoked response that was monotonically increasing with decreasing spatial frequency and whose phase was either constant or decreasing in delay. Using this search criterion, an approximately linear portion of the suprathreshold response function was selected for the regression to zero amplitude.

**Results**

As is typical of steady-state pattern-reversal responses (Regan, 1989), the recorded SSVEPs were dominated by even harmonic response components. Here reliable responses were consistently present at both the second (15 Hz) and fourth (30 Hz) harmonics. As can be seen in Figure 1, each harmonic component was distributed over electrodes centered on the occipital pole. SSVEP amplitudes were maximal at the Oz electrode in both the NT and ASD groups.

Because the focus of activity at Oz in both groups was maximal, we quantified the differences between groups as a function of spatial frequency and response harmonics at three electrodes—occipital channels O1, Oz, and O2—that are centered on the maximum. Figure 2 shows the group-average spatial frequency tuning functions at each of these channels for the
Figure 1. Topographic maps of the vector-average spectral amplitude collapsed across all spatial frequencies at the second and fourth harmonics for both NT and ASD participants.

Figure 2. Amplitude of the sweep VEPs for the second harmonic (top) and the fourth harmonic (bottom) for three locations on the scalp: O1 (left), Oz (Baca et al., 2009), and O2 (right). Electrodes are placed according to the 10-10 channels system map. Each graph shows spatial frequency tuning functions for NT (filled circles) and ASD (open squares) observers. Error bars report the standard error of the mean.
second and fourth harmonics in the top and bottom panels, respectively. The open squares plot data from the ASD group, and the filled circles plot data from the NT observers.

The second harmonic spatial frequency tuning function had a peak at \(-8\) cpd in the NT group and a second limb above \(-15\) cpd, consistent with previous results with similar stimuli (Parry, Murray, & Hadjizemonos, 1999; Strasburger, Murray, & Remky, 1993). At each electrode, second harmonic amplitudes were lower in the ASD group between 5 and 17 cpd. ASD and NT amplitudes were similar outside of this range of spatial frequencies and at all spatial frequencies at the fourth harmonic. Second harmonic response amplitude at the spatial frequency of the largest response in the NT group was 30% to 40% larger than it was in the ASD group at Oz (\(p = 0.087\)) and was more than a factor of two larger at O2 (\(p = 0.01\)). Responses at O1 were not significantly different (\(p = 0.35\)). The peak spatial frequency of the fourth harmonic function was slightly lower (5 cpd) in both groups, but there was no difference in amplitude at any of the electrodes. The locations of the peaks and the results of two-tailed \(t\)-tests for each harmonic and electrode are indicated in Figure 2 by the arrows with corresponding \(p\)-values. The top-center panel also plots the average grating acuity thresholds (the two isolated points with error along the x-axis) calculated from individual-participant vector-averaged functions, along with the standard error of the mean. Grating acuities did not differ between the ASD and NT groups (25.8 ± 1.47 cpd in the NT group and 24.6 ± 1.99 cpd in the ASD group, \(p = 0.11\), ns).

To confirm that the reported significant differences between groups were not due to a small number of individual participants in either group or unequal variance between groups and to show the power of the statistical effects, we compared the group differences on 10,000 bootstrap samples of the two groups. This allowed us to create a distribution-free, empirical sampling distribution that we used to confirm the difference we report from conventional \(t\)-tests.

Table 1 summarizes the statistical analysis performed. For each electrode and harmonic (first and second columns from left, respectively), we report the output of our two-tailed \(t\)-tests. The third column from left reports the degrees of freedom (df), which is always 31 except for the second harmonic at O2. In this specific condition the data do not fulfill the assumption of homoscedasticity and the results are corrected according to Levene’s test for equality of variances. The central column (\(t\)) reports the value of \(t\), while the column labeled \(p\) reports the \(p\)-values returned comparing the empirical data. We also performed the same comparisons on log-transformed data because this transformation equalized the variances between groups. Each of these comparisons showed \(p\)-values equal to or smaller than those reported in Table 1.

The two rightmost columns in Figure 2 report the power, measured as the proportion of significant \(t\)-test comparisons, and the median \(p\)-value. In particular, the power column clearly indicates that the difference grows steadily only in the second harmonic by moving the recording site from left to right, and the \(t\)-test is very powerful for electrode O2. At the fourth harmonic the channel showing the largest trend was significant in only about 12% of the bootstrap samples, implying no difference between groups at this harmonic.

### Discussion

SSVEP responses show that ASD has a highly specific effect on the processing of spatial information in the early visual cortex. The effect we observe is restricted to a subset of the full range of spatial frequencies tested and to the second harmonic. There are no group-level differences at any spatial frequency at the fourth harmonic. Our results are particularly clear on the specifically visual and neural nature of the difference because the selectivity of the deficits rules out nonspecific group-level differences in quality of fixation, accommodation, or motion artifacts. Each of these possible sources of group differences should affect both the second and fourth harmonics because they affect either the quality of the input or the quality of
the evoked potential recording equivalently. Similarly, variations in attention between the groups would be unlikely to explain differences between the two harmonics because they are measured simultaneously from the same data record.

Two previous behavioral studies (Behrmann et al., 2006; Koh et al., 2010b) made detailed measurements of contrast sensitivity over the range of spatial frequencies where we found second harmonic deficits (5–17 cpd). These studies found no differences in threshold sensitivity between ASD and NT controls. It is possible that the effects we observe are restricted to high levels of sensory input and may thus reflect a failure of the regulation of contrast gain rather than changes in absolute sensitivity.

What might underlie the specific loss seen at the second harmonic? A previous SSVEP spatial frequency tuning study suggested that the second harmonic of the SSVEP pattern reversal response is generated by separate channels operating at lower versus higher spatial frequencies (Strasburger et al., 1993). Our results are consistent with separate spatial processing mechanisms because the response at 2 cpd is normal but the response over the range of 8.2 to 14.4 cpd is not. However, this cannot be the whole story. First, we find another range of spatial frequencies above the limit of Strasburger et al.’s (1993) higher spatial frequency mechanism where responses are normal. This suggests the presence of a third spatial channel. Second, our channel properties are not strictly determined by their spatial frequency tuning: The fourth harmonic response component shows no effect over the entire range. Given the mass nature of the SSVEP, it is likely that multiple underlying generators contribute to the recorded signal. Our results indicate that a subset of these multiple generators is specifically affected by ASD. It will be important in future research to determine the underlying neural substrates that contribute to the second and fourth harmonics in order to pinpoint the neural basis of the ASD deficit we have observed.

Visual acuity

By recording SSVEPs over a wide range of spatial frequencies, we were also able to objectively estimate the visual acuity threshold without the task demands of psychophysical experiments. We found no difference in grating acuity in the ASD and control groups, consistent with the results of more recent behavioral studies (Bach & Dakin, 2009; Tavassoli, Latham, Dakin, & Baron-Cohen, 2011). These results further reinforce that the two groups were equally able to comply with the task demands for fixation and accommodation despite the absence of a requirement for performance of a specific behavioral task.

Hemispheric asymmetry

Another important result of the present study is the selective reduction of the SSVEP response over the right hemisphere. Right-hemisphere deficits in VEP responses have been reported in a previous study. The evoked response to photic stimulation over the right occipital cortex was depressed when measured at 11 fixed temporal frequencies (3–24 Hz) in a group of children aged 6 to 14 years with the diagnosis of autism without significant mental retardation (Lazarev, Pontes, & deAzevedo, 2009). Our findings confirm and extend this previous report of right-hemisphere alterations of the visual response in ASD. Additional evidence for right-hemisphere sensory deficits comes from a magnetoencephalography study on auditory processing (Orekhova et al., 2012). Orekhova et al. (2012) found a relationship between the severity of the sensory modulation abnormalities and the lack of normal rightward lateralization of P100 in ASD children. The right hemisphere in autistic people also fails to respond to auditory temporal novelty (Orekhova et al., 2009). Finally, broadband EEG power has an abnormal distribution suggestive of a loss in the right hemisphere when measured in boys with autism between 3 and 8 years old (Stroganova et al., 2007).

At the behavioral level, abnormal brain lateralization has also been implicated in an eye tracking study performed in a group at high risk for ASD (infant siblings of children with an ASD diagnosis). High-risk infants did not show a left visual field fixation bias like the one displayed by low-risk infants (Dundas, Gastgeb, & Strauss, 2012). Typically developing children preferentially fixate the left part of the face. Information from the left visual field is projected to the right hemisphere, which is known to be associated with face processing abilities, with notable lateralization in the right fusiform gyrus (Haxby, Hoffman, & Gobbini, 2000).

Vulnerability of one hemisphere versus another may be due to the two cerebral hemispheres having different developmental trajectories in normal development: The right hemisphere develops more quickly during typical fetal development (Geschwind & Galaburda, 1985; Hellige, 1993). Differential developmental sequences may expose the two hemispheres differentially to environmental influences or may indicate that separate genetic programs control the development of the two hemispheres. The ASD phenotype we observe could result from either of these two factors or a combination of both.

Relationship of the present findings to higher-level visual cognition

Studying the early visual system can provide information on brain circuitry as well as on the extent
to which low-level visual anomalies may influence higher-level vision and cognition. The visual world contains a wide range of spatial scales that constantly change while we are moving closer to or farther away from objects. The difficulty of processing visual targets can be predicted in typically developed subjects by using the results of spatial contrast sensitivity tests (Owsley & Sloane, 1987). This relationship may, however, break down in autism, especially at high levels of input. The method used here to identify spatial processing deficits may be useful in determining whether certain spatial frequency bands contribute to deficits on other tasks, such as ones involving local and global dimensions (Blakemore & Campbell, 1969; Brady & Oliva, 2012). Several studies in this area have suggested that the processing of local and more global aspects of both hierarchical and face stimuli is related to the processing of specific spatial frequencies (Baddock, Whitworth, Baddock, & Lovegrove, 1990; Boeschoten, Kemner, Kenemans, & van Engeland, 2005; Goffaux, Gauthier, & Rossion, 2003; Goffaux, Hault, Michel, Vuong, & Rossion, 2005; Han, Yund, & Woods, 2003; Jemel, Mottron, & Dawson, 2006; LaGasse, 1993; Ruiz-Soler & Beltran, 2006). It would be informative to compare neural measures of spatial processing such as the ones performed here with behavioral ones to determine whether one is predictive of the other, as would be the case if the local processing bias of subjects with ASD for these and other visual stimuli is related to a pervasive abnormality in spatial frequency analysis (Deruelle, Rondan, Gepner, & Tardif, 2004; Plaisted, Dobler, Bell, & Davis, 2006).

A challenge for future research is relating the suprathreshold processing deficits we have observed to behavioral responses. The SSVEP deficit we have observed is not simply a deficit at certain spatial frequencies. Some of the evoked response, that portion contained in the fourth harmonic, is not affected in ASD. Exactly what aspect of behavior would be associated with the fourth rather than the second harmonic is not completely clear at this point. What is needed is a better understanding of the nonlinear mechanisms that give rise to the SSVEP and further exploration of the full range of spatial and temporal frequencies that form the limits of spatial and temporal contrast sensitivity. Further investigation of this topic is needed in order to better understand at which point of the neural pathway the deficits we observe are generated. It will also be important to determine whether the highly selective pattern of response alterations we have observed here is specific to ASD or whether it occurs in other forms of intellectual disability. This is particularly important to establish if one wishes to use quantitative neural measures such as those presented here to guide treatment, intervention, and optimization of the stimulation used, especially given the proliferation of electronic device-based applications dedicated to a wide population of autistic users.

Conclusions

Our results add to the accumulating body of evidence suggesting that deficits at the earliest stages of sensory processing are associated with autism. Since the visual system is organized hierarchically, abnormalities in higher-level functions may be at least partially due to downstream effects of abnormalities occurring at earlier stages. Quantitative and efficient SSVEP measurements of low-level visual processing mechanisms may ultimately help us understand the overall abilities of people with ASD to interpret and make full sense of the visual world. Conversely, the specificity of the deficits we find is difficult to explain on the basis of deficits in higher-level cognitive functions such as language, task comprehension or performance issues, or IQ. Rather, our results point to what could be a very specific biological substrate that is altered in ASD.

Key points:

- Sensory processing abnormalities are common in ASD.
- The visual system can be used as an entry point to study brain activity and system regulation.
- We can use task-absent VEP tests to study very low-level visual functions that can potentially provide new biomarkers for the diagnosis of the disorder early in life.
- The spatial processing abnormalities and the brain hemispheric asymmetry that we have found may undermine high-level cognitive functions and interfere with the child’s interaction with the visual world.

Keywords: autism, vision, visual evoked potential, spatial frequency, visual perception

Acknowledgments

This work was supported by the Simons Foundation for Autism Research Initiative (SFARI) and by the Bass Society for Pediatric Scholars. We thank all the families and children who dedicated their time to help us with our research project.

Commercial relationships: none.
Corresponding author: Francesca Pei.
Email: fpei@stanford.edu.
Address: Department of Psychology, Stanford University, Stanford, CA, USA.
References


