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Normal binocular rivalry in autism: Implications for the excitation/inhibition imbalance hypothesis

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ABSTRACT

Autism is characterized by disruption in multiple dimensions of perception, emotion, language and social cognition. Many hypotheses for the underlying neurophysiological basis have been proposed. Among these is the excitation/inhibition (*E*/*I*) imbalance hypothesis, which states that levels of cortical excitation and inhibition are disrupted in autism. We tested this theory in the visual system, because vision is one of the better understood systems in neuroscience, and because the *E*/*I* imbalance theory has been proposed to explain hypersensitivity to sensory stimuli in autism. We conducted two experiments on binocular rivalry, a well-studied psychophysical phenomenon that depends critically on excitation and inhibition levels in cortex. Using a computational model, we made specific predictions about how imbalances in excitation and inhibition levels would affect perception during two aspects of binocular rivalry: mixed perception (Experiment 1) and traveling waves (Experiment 2). We found no significant differences in either of these phenomena between high-functioning adults with autism and controls, and no evidence for a relationship between these measurements and the severity of autism. These results do not conclusively rule out an excitation/inhibition imbalance in the visual system of those with autism, but they suggest that such an imbalance, if it exists, is likely to be small in magnitude.

1. Introduction

Autism is characterized by disruption in multiple dimensions of perception, emotion, language and cognition (Baron-Cohen, Tager-Flusberg, & Cohen, 2000; Happe & Frith, 2006; Minshew, Goldstein, & Siegel, 1997; Moldin & Rubenstein, 2006; Simmons et al., 2009; Williams, Goldstein, & Minshew, 2006). Many hypotheses for the underlying neurophysiological basis have been proposed. Among these is the excitation/inhibition (*E*/*I*) imbalance hypothesis, which states that levels of cortical excitation and inhibition are disrupted in autism, and that this disruption might extend throughout all cortical systems (Jamain et al., 2008; Markram, Rinaldi, & Markram, 2007; Rubenstein & Merzenich, 2003; Vattikuti & Chow, 2010). According to one version of this hypothesis, the *E*/*I* ratio in cortex is unusually high, either because of increased glutamatergic (excitatory) signaling or because of decreased GABAergic (inhibitory) signaling. Although the theory is based mostly on animal models, the proposed *E*/*I* imbalance is consistent with some perceptual processing abnormalities in humans with autism. In particular, an *E*/*I* imbalance might explain hypersensitivity to sensory stimuli, including aversion to loud noises, tactile stimulation, and bright lights (Asperger, 1991; Baron-Cohen et al., 2009; Dakin & Frith, 2005; Gomot et al., 2002; Jones, Quigney, & Huws, 2003; Kanner, 1943; Kern et al., 2006; Leekam et al., 2007; Simmons et al., 2009; Tomchek & Dunn, 2007). The *E*/*I* imbalance hypothesis is also consistent with the observation that rates of epilepsy are higher in the autism population than in the general population (Levisohn, 2007; Rossi et al., 1995; Tuchman & Rapin, 2002). It has therefore been proposed that the excitation/inhibition (*E*/*I*) imbalance may be present not only in sensory systems, but also in social, emotional, and language systems in the brain (Rubenstein & Merzenich, 2003). The *E*/*I* imbalance hypothesis, while potentially groundbreaking, has for the most part remained relatively vague. In fact, much of the evidence from animal models is contradictory, with some studies suggesting that the *E*/*I* ratio in autism may be too high, and others suggesting that it may be too low (see Section 4).

To test the *E*/*I* imbalance hypothesis in humans, we performed psychophysical tests on the visual system. We chose to study the visual system for two reasons. First, visual system alterations such as sensitivity to bright light and impaired face recognition have been observed in autism (Behrmann, Thomas, & Humphreys,

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2006), although there is some evidence that impaired face processing may be limited to unfamiliar faces (Simmons et al., 2009). Second, the visual system is one of the better understood systems in human neuroscience, and a rich history of precise computational models makes it well suited for linking behavior to underlying neural circuitry. Thus, even though the visual problems in autism may be considered secondary in importance to the social problems, vision might be one of the most tractable systems for understanding the disorder.

Our psychophysical tests of the *E*/*I* hypothesis relied on binocular rivalry, a particularly well-studied visual phenomenon that depends critically on excitation and inhibition levels (Alais & Blake, 2005; Lehky, 1988; Levelt, 1965; Wheatstone, 1838). During binocular rivalry, the two eyes are presented with incompatible patterns that compete for perceptual dominance. The dynamics of the perceptual changes can be used to make inferences about underlying neural dynamics (Alais & Blake, 2005; Brascamp et al., 2006; Lee, Blake, & Heeger, 2005, 2007; Tong et al., 1998; Wilson, Blake, & Lee, 2001). We conducted two experiments to examine two complementary aspects of binocular rivalry in individuals with and without autism. In both cases, we used a computational model to specify the link between psychophysical data and underlying levels of neural excitation and inhibition (Wilson, Blake, & Lee, 2001).

In the first experiment, we examined "mixed perception" during presentation of traditional rival stimuli. Typically, when the two eyes are presented with incompatible images (Fig. 1), perception alternates between the two eyes. However, a mixture of the two images may be perceived for a substantial fraction of the time. Using model simulations, we determined that low levels of either cortical inhibition or cortical excitation would cause an increase in mixed perception.

In the second experiment, we measured "traveling wave" speed. When observers are shown spatially extended rival stimuli, they typically report seeing waves in which the dominance of one pattern emerges locally and then expands to overtake the other pattern. Model simulations show that low levels of inhibition or high levels of excitation would cause an increase in the speed of traveling waves.

The two experiments are complementary tests of the *E*/*I* imbalance hypothesis, and allow us to distinguish atypical levels of excitation from atypical levels of inhibition. A high *E*/*I* ratio would be evident in high traveling wave speeds. A high level of both excitation and inhibition would be evident in a low amount of mixed perception and slow traveling wave speeds. Normal excitation and inhibition levels would be evident in a normal amount of mixed perception and normal wave speeds.

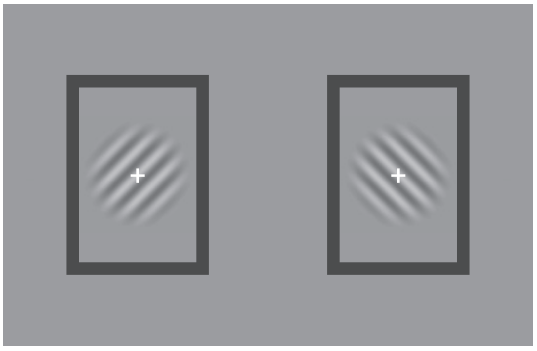

Fig. 1. Experiment 1 stimulus. Subjects wore prism goggles so that the left grating was presented to the left eye and the right grating was presented to the right eye at corresponding locations in the two eyes. At any given time, subjects perceived either the grating tilted clockwise of vertical, counterclockwise of vertical, or a mixture of the two (typically perceived as a plaid).

2. Methods and materials

2.1. Experiment 1: Mixed percepts

2.1.1. Subjects

Nineteen high-functioning adults with autism (IQ > 80) and 20 controls participated in Experiment 1. The age distributions, gender distributions, and average IQs were very similar across the two groups (Table 1). In an additional analysis, we also examined the results only for those adults with autism for whom close one-to-one control matches could be selected, where the gender was matched, the mean age difference was 4 (SD = 3), and the mean IQ difference was 8 (SD = 3).

All subjects provided written informed consent and were paid for their participation in the study. The University Committee on Activities Involving Human Subjects at New York University and the Institutional Review Boards at Carnegie Mellon University and the University of Pittsburgh approved the experimental procedures.

The diagnosis of autism was established using the Autism Diagnostic Interview Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994), the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000), and expert clinical opinion. The individuals with autism, recruited from autism conferences and parent support groups, and the clinical community, were medically healthy and had no identifiable genetic, metabolic, or infectious etiology for their disorder. Participants were also free of seizures, attention deficit disorder, and depression. Full scale IQ was determined for all participants using the Wechsler Abbreviated Scale of Intelligence.

2.1.2. Design

Stimuli were presented on a calibrated CRT display positioned 57 cm from the subject's head. In both experiments, subjects viewed a split screen with the left half of the CRT being presented to the left eye and the right half of the screen to the right eye. Subjects wore base-out prism glasses while they viewed stimuli positioned 4° from the left and the right of the center of the screen. A black septum blocked contralateral stimuli from reaching the eyes (i.e., so that the left half of the screen was not visible to the right eye and vice versa).

Subjects were shown a pair of sinusoidal grating patches oriented at 45° clockwise of vertical in one eye and another grating oriented at 45° counterclockwise of vertical in the other eye (Fig. 1). Gratings were 1° in diameter and fell off with a quarter cycle of a cosine function (.3°). Gratings were sinusoidally modulated in luminance at 6.5 cycles/deg. Orientation was counterbalanced with eye laterality across ten 40 s blocks. Preliminary tests were conducted to correct for differences in contrast sensitivity between the eyes (Supplemental Information).

While the stimuli on the screen remained fixed throughout each block, the subjects perceived one of the following at any given mo-

Table 1
Experiment 1 demographics for all subjects (top) and only those subjects who had a close one-to-one demographic match (bottom). We report results from all subjects (because of the high statistical power) and from only those subjects who had a close demographic match (because of the tighter experimental control) and obtained the same results either way. Standard deviations are in parentheses. We did not measure IQ for 7 of the control subjects.

	N	Females	Age	FSIQ	ADOS
All subjects					
Autism	19	2	24 (7)	110 (17)	14 (3)
Control	20	2	25 (5)	113 (7) (*n* = 13)	N/A
Matched pairs					
Autism	11	1	25(6)	115 (15)	14 (3)
Control	11	1	25(4)	114 (7)	N/A

ment: (1) A dominant grating oriented at 45° clockwise of vertical. (2) A dominant grating oriented at 45° counterclockwise of vertical. (3) A mixed percept, typically appearing as a plaid. Subjects reported their percepts by continuously pressing one of three buttons. Subjects were asked to consider an orientation as "dominant" if it appeared to comprise 90% or more of their percept. This instruction was given to minimize intersubject differences in what was considered a dominant or mixed percept.

We computed the prevalence of mixed percepts as the overall percentage of time subjects reported mixed percepts. As a secondary measure, we computed for each subject the median duration of mixed percept periods (see Supplemental Information). We used *t*-tests to make comparisons between groups because the distributions used in all tests did not significantly differ from normality (Kolmogorov–Smirnov test, all p's > 0.20).

It was critical to the design that subjects affirmatively pressed a button to report mixed percepts. Many binocular rivalry experiments not focused on mixed percepts allow subjects to report them by withholding a button press. We used this standard design in a preliminary pilot experiment and found that adults with autism withheld button presses significantly more than control subjects. However, it was unclear whether this effect indicated a difference in perception between groups, or a difference in decision processes. The present design isolates perceptual effects by requiring affirmative button presses for mixed percepts.

2.2. Experiment 2: Traveling waves

2.2.1. Subjects

Fourteen high-functioning adults with autism (IQ > 80) and 15 controls were included in Experiment 2. An additional 6 adults with autism and 6 control subjects were excluded because they did not report seeing waves or because they had unrealistic wave speeds (values that were negative or >9°/ms). The age distributions, gender distributions, and average IQs of the included subjects were very similar across the two groups (Table 2). In an additional analysis, we also examined the results only for those adults with autism for whom close one-to-one control matches could be selected, where the gender was matched, the mean age difference was 3 (SD = 3), and the mean IQ difference was 5 (SD = 4).

Some of the subjects who participated in Experiment 2 also participated in Experiment 1. In almost all of these cases, subjects performed one run of Experiment 2 before participating in Experiment 1. If time permitted, subjects performed a second run of Experiment 2. Of those who completed the first run of Experiment 2, all but one adult with autism and two control subjects also completed the second run.

2.2.2. Design

On each trial, subjects viewed a high contrast green ring with spiral bands in one eye, and a low contrast red ring with radial bands in the other eye (Fig. 2A). The inner edge of each ring was 1.2° from fixation, and the outer edge was 1.8°. To make the green stimulus dominate initially, we presented it with higher contrast, and we also used a variant of the flash suppression technique, in which the red stimulus was briefly shown for 24 ms, and then followed by both stimuli. (The brief period in which only the red stimulus was present is not shown in Fig. 2.) After 360 ms of both stimuli on the screen, there was a brief 71 ms increase in the contrast of a small region (Gaussian window, $\sigma = 30°$ polar angle) at the top of the suppressed red stimulus (Fig. 2B). After this brief contrast increment, the two stimuli returned to their original contrast for 2670 ms. The brief contrast increment typically triggered the perception of a traveling wave, in which the previously suppressed red stimulus was perceived to overtake the green stimulus (Fig. 2C). On each trial, white marker lines were placed at some location along the ring (65°, 90°, 115°, or 140° polar angle from the top, on either the left or right side). Subjects pressed a button as soon as they perceived the red traveling wave to cross the white marker lines. Subjects were instructed to withhold button presses if the wave dissipated before reaching the marker, or if any region of the path toward the marker was already red before the wave arrived. In the autism group, button presses were withheld in 31% of trials (SD across subjects = 21%). In the control group, they were withheld in 32% of trials (SD across subjects = 16%).

The trials within each run were organized into 16 blocks of 8 trials each, with a fixed marker location for each block. Within each block, the red stimulus was presented 4 times to the left eye and 4 times to the right eye. The green spirals were oriented clockwise in 4 trials and counter-clockwise in 4 trials, counterbalanced with eye laterality.

For each subject and each marker distance, we excluded response latencies that were <200 ms, as well as outliers that were more than 2 standard deviations from the mean. In the autism group an average of 63 trials per subject were included in the analysis (SD = 25). In the control group, an average of 60 trials per subject were included (SD = 20). The differences in the number of trials between subjects arose because of intersubject differences in the number of runs (see Section 2.1.1), button-withheld trials (see above), and outliers. For each subject, we determined wave speed by computing the best fit regression line for response latency as a function of marker distance, and taking the inverse of the slope. This measure is not affected by baseline differences in reaction times between groups, which will only affect the intercept of the regression line, not the slope. We used *t*-tests to make comparisons between groups because the distribution of speeds in each group did not significantly differ from normality (Kolmogorov–Smirnov test, all p's > 0.20).

Before the main experiment, we conducted preliminary psychophysical tests so that the difference in contrasts between the two stimuli would be just high enough that the green stimulus would typically dominate at first, but low enough that the red stimulus could still overtake it when it was triggered (see Supplemental Information).

2.3. Model predictions

To understand the effects of excitation and inhibition on binocular rivalry, we systematically adjusted the excitatory and inhibitory connection strengths of a computational model (Kang et al., 2010; Wilson, Blake, & Lee, 2001), while measuring simulated mixed perception and traveling wave speed. The model contained two populations of simplified firing rate neurons, each selective for one of two stimuli (Fig. 3A). Within a population, each neuron corresponded to a spatial location in the visual field, and mutually excited neighboring neurons with the same orientation preference while inhibiting neurons in the other population with the orthogonal orientation preference. Intuitively, a population of neurons in

Table 2
Experiment 2 demographics for all subjects (top) and for only those subjects who had a close one-to-one demographic match (bottom). Standard deviations are in parentheses. We did not measure IQ for 5 of the control subjects.

	N	Females	Age	FSIQ	ADOS
All subjects					
Autism	14	2	26 (7)	109 (17)	14 (2)
Control	15	2	23 (3)	112 (9) (n = 10)	N/A
Matched subjects					
Autism	7	0	25 (5)	113 (14)	14 (2)
Control	7	0	24 (4)	114 (8)	N/A

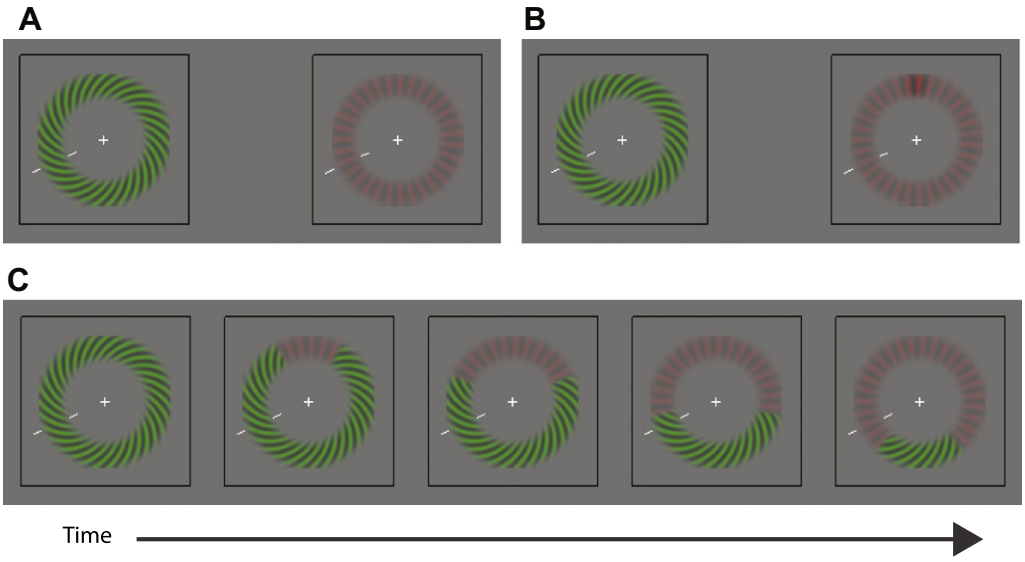

Fig. 2. Experiment 2 stimuli. (A) Green spiral grating, shown here to the left eye. Red radial grating, shown to the right eye. The green spiral percept was initially dominant on most trials. (B). Brief contrast increment at the top of the right eye stimulus triggered a perceptual traveling wave. (C) Example of traveling waves percept following the contrast increment. The traveling wave was perceived even though the stimulus was physically unchanging. Subjects pressed a button when the wave crossed the tick mark (bottom left in this example). The tick mark was at different locations on different trials to estimate wave speed.

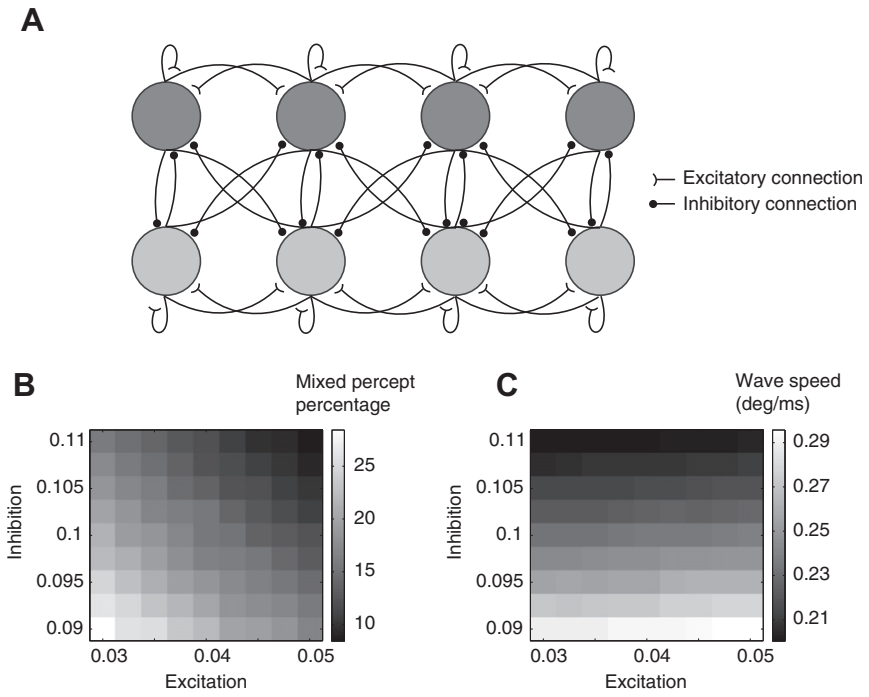

Fig. 3. Model and model predictions. (A) Schematic of computational model. Dark gray neurons respond to one stimulus orientation and light gray neurons respond to the orthogonal orientation. While this schematic shows an 8-neuron model for simplicity, mixed perception was simulated with a 20-neuron model, and traveling waves were simulated with a 400-neuron model. (B) Effects of excitatory and inhibitory weight strengths on model mixed perception. Lighter shading indicates a higher percentage of time in a mixed percept state. (C) Effects of excitatory and inhibitory weight strengths on traveling wave speed. Lighter shading indicates faster waves. Wave speed is scaled to typical values in units of deg/ms.

the model maintained dominance of one of the two percepts by inhibiting the other population. Alternations in dominance occurred because of endogenous noise and because of adaptation in the dominant population (Wilson, Blake, & Lee, 2001). The model is described in more detail elsewhere (Kang et al., 2010).

The model was not intended to describe the precise biophysical details of visual cortex, nor was it intended to make precise quantitative predictions about behavior. Rather, we used it as a guide for understanding how excitation and inhibition levels were qualitatively related to binocular rivalry behavior. The model is agnostic on the question of whether rivalry occurs mostly at early stages, late stages, or at multiple stages of visual cortex (Blake & Logothetis, 2002). Unless mentioned otherwise below, the parameters we used in the model were identical to those used previously (Kang et al., 2010).

2.3.1. Mixed perception simulations

To simulate mixed perception (Experiment 1), we used a network with twenty neurons, with ten for each percept. Each neuron

provided excitatory connections onto nearby neurons corresponding to the same percept, and inhibitory connections onto nearby neurons corresponding to the opposite percept (Fig. 3A). To avoid edge artifacts and for consistency with the model in Experiment 2, the network was organized as a ring, such that the last neurons in the chain connected back to the first neurons in the chain. Stimulus input (30% contrast) was provided to both populations to simulate the dichoptic grating stimuli in Experiment 1. Low-pass filtered noise was added to each neuron's input, a feature not present in the original model (Kang et al., 2010), but necessary to simulate the stochastic nature of mixed perception. The noise was independent for each neuron and was generated by convolving Gaussian white noise with a 200 ms Gaussian kernel.

Model perception at each time point was determined by a percept index:

$$P(t) = \frac{A(t) - B(t)}{A(t) + B(t)}$$

where $A(t)$ and $B(t)$ were the time-courses of simulated responses to the two percepts, averaging across the 10 neurons corresponding to each of the two percepts. The index is bounded by -1 and 1, which represent complete dominance of B and A, respectively. Mixed perception was defined as the percentage of all time points during which the value of P was between $-1/3$ and 1/3.

We ran model simulations for 9 different values of excitatory weight strengths and 9 different values of inhibitory weight strengths. The range of values for these parameters was centered around those used in Kang et al. (2010). To obtain reliable estimates, we repeated 10 iterations of 250,000 ms of model time for each of the 81 possible parameter combinations, and averaged the mixed percept percentages across iterations.

We found that increasing both the excitatory weights and the inhibitory weights reduced the amount of mixed perception (Fig. 3B). Intuitively, strong excitatory weights allow the dominant neuron to maintain its dominance for longer since it can effectively excite itself. Strong inhibitory weights allow the dominant neuron to more effectively suppress the other neuron.

2.3.2. Traveling wave simulations

To precisely estimate model traveling wave speeds (Experiment 2), we used a larger network of 400 neurons, with 200 for each population. To avoid edge effects and to simulate the annulus in Experiment 2, the network was organized as a ring, such that the last neurons in the chain connected back to the first neurons in the chain. We again ran model simulations for 9 different values of excitatory weight strengths and 9 different values of inhibitory weight strengths. The green stimulus was made initially dominant, and then a wave of the red stimulus was triggered by a brief contrast increment at the top of the red stimulus. The procedures for implementing and measuring this process in the model are described in Supplemental Information.

We found that increases in excitation strength and decreases in inhibition strength both increased the speed of traveling waves (Fig. 3C). With strong excitation, the dominant neurons at the front of the wave were able to more effectively excite nearby (but currently suppressed) neurons with the same stimulus preference. With weak inhibition, the suppressed neurons beyond the wave were only weakly suppressed, and were therefore more readily excited by the approaching wave.

3. Results

3.1. Experiment 1

In the autism group, subjects perceived mixed percepts 31% of the time (SD = 16). In the control group, subjects perceived mixed percepts 27% of the time (SD = 13). This difference was not significant ($t(37) = .74$, $p = .46$, $\eta = .01$) (Fig. 4A). When restricting the analysis only to subjects with close one-to-one matches, subjects in the autism group perceived mixed percepts 33% of the time (SD = 15), and subjects in the control group perceived them 23% of the time (SD = 14). This difference was not significant, but exhibited a trend toward more mixed percepts in the autism group ($t(22) = 1.76$, $p = .09$, $\eta = .12$). Among adults with autism, there was no evidence for a correlation between mixed percept percentage and ADOS total score ($r = .12$, $p = .63$). Collapsing across all subjects from both groups, there was no significant relationship between IQ and mixed percept time ($r = .14$, $p = .44$).

In addition to the overall percentage of time subjects experienced mixed percepts, we also computed the median duration of individual percept periods for each subject. The pattern of results for the median duration analysis was similar to those obtained for the mixed percept percentage analysis, and no significant difference was observed between populations (see Supplemental Information).

3.2. Experiment 2

The average wave speed for the autism group was 0.22 deg/ms (SD = .13), and the average for the control group was .29 deg/ms (SD = .12). There was no significant difference between groups ($t(27) = 1.6$, $p = .12$, $\eta = .09$) (Fig. 4B and C). When restricting the analysis only to matched subjects, the average wave speed for the autism group was 0.25 deg/ms (SD = .17), and the average for the control group was 0.25 deg/ms (SD = .10). There was no significant difference between groups ($t(12) = 0.05$, $p = .96$, $\eta = 0$). Among adults with autism, there was no significant correlation between wave speed and ADOS total score ($r = .04$, $p = .90$). Collapsing across all adults with autism and controls, there was a trend for a relationship between IQ and wave speed ($r = .36$, $p = .10$).

3.3. Combining Experiments 1 and 2

Even though there were no differences between groups when the results of Experiments 1 and 2 were considered individually, it was possible that differences might emerge when the results from both experiments were combined. Using data from the 11 adults with autism and 10 control subjects who participated in both experiments, we trained a two-dimensional linear discriminant classifier to distinguish between groups based on the results of both experiments together (see Supplemental Information). The classifier did not significantly distinguish between groups either when provided with mixed percept percentages and wave speeds (d-prime = .37, $p = .28$, permutation test) or when provided with median mixed percept durations and wave speeds (d-prime = .37, $p = .28$).

4. Discussion

We used binocular rivalry and a computational model to test the hypothesis that an imbalance in the excitation/inhibition (E/I) ratio underlies autism. We did not find clear evidence for abnormal perception in autism during binocular rivalry, although there was a slight trend towards faster traveling waves and more mixed percepts. These results suggest that an E/I imbalance in the visual system of individuals with autism, if it exists, is likely to be small in magnitude.

Our results do not imply that there are no disruptions in excitatory or inhibitory synapses in autism. First, there are a variety of ways in which the developing brain can compensate for synaptic disruptions to maintain a normal overall E/I balance. For example,

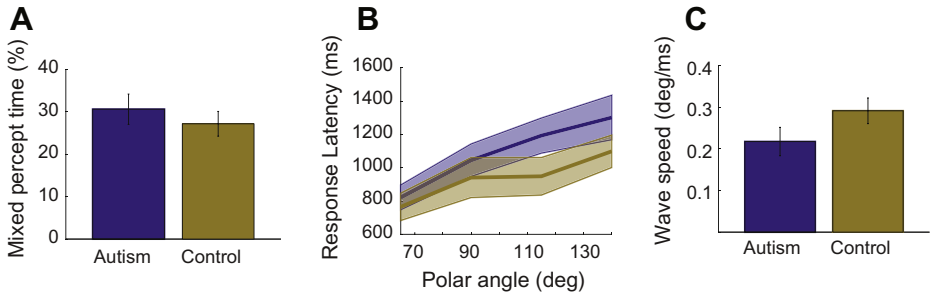

Fig. 4. (A) *Experiment 1*: Percentage of the time subjects perceived a mixture of the two stimuli. Error bars represent the standard error of the mean. (B) *Experiment 2*: Subject response latency as a function of tick mark position. Blue, autism group. Brown, control group. Shaded regions represent standard error of the mean. Wave speed was estimated by computing the inverse slope of this function. (C) *Experiment 2*: Wave speed, averaged across subjects. Error bars, standard error of the mean.

low levels of GABA receptor expression (Fatemi et al., 2009) could potentially be counterbalanced by more GABA being released from presynaptic terminals or by more inhibitory synapses. These compensatory mechanisms might have network consequences that are different from an overall average imbalance in excitation and inhibition. For example, it is conceivable that such compensation, through the course of development, might result in the unreliable and noisy neural responses observed in autism (Dinstein et al., 2010, 2012; Hasson et al., 2009; Rubenstein & Merzenich, 2003) without affecting the overall *E*/*I* balance. Second, it is conceivable that noisy neural responses in autism may themselves disrupt binocular rivalry in a way that is counteracted by a real *E*/*I* imbalance. Third, it is possible that *E*/*I* disruptions in autism are less apparent in the high-functioning population used in our study than they are in the general autistic population. We restricted our experiment to high-functioning participants because the instructions for binocular rivalry experiments can be difficult to understand, particularly for the traveling waves experiment. Fourth, even though all subjects in Experiment 1 were instructed to use a "90%" cutoff to separate dominant percepts from mixed percepts, it is possible that uncontrolled intersubject differences in criterion could mask real differences between the populations. Fifth, it is possible that the computational model we used is incorrect. However, all models of binocular rivalry depend critically on excitation and inhibition levels. Consequently, it is unlikely that typical binocular rivalry perception could occur with disrupted excitation/inhibition levels. Sixth, it is possible that our experiment was underpowered, and that more trials or more subjects could reveal a significant difference. However, such a difference would still only reflect a small effect size, with substantial overlap between populations.

4.1. Mixed evidence for an excitation/inhibition imbalance

The existing evidence in support of the excitation/inhibition imbalance hypothesis is mixed. Psychophysical evidence from oculomotor saccade tasks suggests an increase in the *E*/*I* ratio in autism (Vattikuti & Chow, 2010). Tissue samples from postmortem autistic brains show low levels of GABA receptor expression in parietal cortex, consistent with the increased *E*/*I* hypothesis, but mixed results in frontal cortex, where some GABA receptor subunits are overexpressed and others are underexpressed (Fatemi et al., 2009). A number of genetic association studies have linked mutations in genes associated with excitatory and inhibitory synapses to autism or other disorders with autism-like properties (Buxbaum et al., 2002; Jamain et al., 2002; Shao et al., 2003). However, genetic association studies do not typically indicate whether the mutation increases or decreases the efficacy of synaptic transmission. Results from animal models are also mixed (Chao et al., 2010; Tabuchi et al., 2007). It is therefore possible that the *E*/*I* hypothesis is wrong, and that the best explanations for the neural basis of autism could be found among other hypotheses, including those related to enhanced processing of local features (Happe & Frith, 2006), noisy neural responses (Dinstein et al., 2012; Hasson et al., 2009; Milne, 2011; Rubenstein & Merzenich, 2003; Simmons et al., 2009), theory of mind (Baron-Cohen, Tager-Flusberg, & Cohen, 2000), emotion processing (Moldin & Rubenstein, 2006), executive control (Hill, 2004), or a disparate group of cognitive factors with no unifying theme (Happé, Ronald, & Plomin, 2006).

4.2. Intersubject variability in autism

Many previous reports have found higher intersubject variability in autism groups than in controls groups (Simmons et al., 2009). Because of this high intersubject variability, some studies have used large sample sizes. However, smaller sample size was appropriate in our study for at least two reasons. First, there was no evidence for high intersubject variability in our results; the confidence intervals (error bars) on the measurements for the autism group were not larger than those for the control group (Fig. 4). This enables us to conclude that for high–functioning adults with autism, any difference between groups in the *E*/*I* ratio, if it exists at all, is small. Second, a study with a much larger sample size that rejected the null hypothesis would not change this conclusion.

4.3. Visual processing advantages in autism

Some studies have shown some evidence for a visual processing advantage, particularly for local features (Happe & Frith, 2006; O'Riordan et al., 2001; Perreault et al., 2011; Plaisted, O'Riordan, & Baron-Cohen, 1998; Shah & Frith, 1993). While our experiments tested the visual system, they measured subjective perception on a task in which there were no right or wrong answers, and thus do not directly address the issue of a putative visual processing advantage in autism. However, if such an advantage does exist, it most likely is not caused by an atypical balance in excitation and inhibition.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.visres.2012.11.002.

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