

Psychophysical correlates of excitatory/inhibitory imbalance during visual motion perception in adults with ASD and schizophrenia

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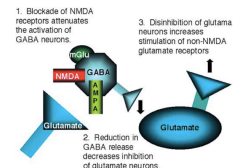
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Background

Recent evidence implicates neural excitatory (E) and inhibitory (I) imbalance as a mechanistic underpinning of autism spectrum disorder (ASD). E/I imbalance is also implicated in other disorders, such as schizophrenia (SCZ), that are associated with social and cognitive deficits. While phenotypic similarities across diagnoses suggest common mechanistic origins, no studies have tested the existence of shared markers of E/I imbalance across ASD and SCZ. According to the glutamate hypothesis of schizophrenia, reduced functioning of N-methyl-D-aspartate (NMDA) receptors on inhibitory interneurons may result in a decrease of feedback inhibition on excitatory glutamatergic pyramidal neurons, thus leading to excessive excitation within cortical circuits. Similar arguments for hyper-excitability have been made in ASD, often pointing to genetic studies implicating glutamatergic genes and the high rate of seizures in ASD. Surround suppression and gain control are two well-established neural processes affecting perception of visual motion that rely on precise E/I balance. Previous studies examining visual motion processing in ASD and SCZ have identified surround suppression and gain control abnormalities, respectively. However, none of these studies directly compared these processes across both populations.

Methods. In order to evaluate E/I balance in the context of surround suppression and gain control, visual motion perception was investigated in young adults with ASD relative to SCZ and healthy control subjects (HCS). Participants included 15 young adults with ASD, 11 with early-course SCZ, and 18 HCS, matched for demographic variables. Participants completed three visual processing tasks that involved motion discrimination of gratings that varied by size at low (Task 1) and high (Task 2) contrast, as well as gratings with fixed small size, but varied contrast levels (Task 3). Task order was counterbalanced across participants. Duration thresholds were computed for eight different sizes and contrasts. Suppression index (Tasks 1: Spatial Summation and 2: Spatial Suppression) and response gain control (Task 3) were computed by contrasting thresholds at the highest contrast level/largest size to those at the lowest contrast level/smallest size for each task. Multivariate ANOVAs were used to assess group differences in performance across sizes and contrasts within each task. One-way ANOVAs assessed differences in summation, suppression, and gain control indices. Transdiagnostic correlations with measures of sensory and social functioning were carried out to evaluate whether differences in surround suppression, gain control, or motion perception more broadly were associated with symptoms that cross traditional diagnostic boundaries.

Hypothesized Mechanism



- Adapted from: Krystal et al. (2003)
- N-Methyl-D-aspartate receptor (NMDAR) antagonists cause transient schizophrenia-like symptoms in healthy volunteers
- Hypothesized to induce a state of cortical 'disinhibition'

Sample Demographics

Characteristic	HCS (N=18)		ASD (N=15)		SCZ (N=11)		Significance
	M	S.D.	M	S.D.	M	S.D.	
Age (in years)	24.39	4.03	21.40	3.80	23.91	3.27	2.79
Sex (% male)	0.67	n/a	0.67	n/a	0.73	n/a	0.14
Handedness (% right)	51.68	49.09	73.33	42.02	42.73	57.9	1.31
IQ Verbal	121.92	16.01	116.83	14.69	112.73	24.12	0.76
IQ Non-Verbal (matrix)	117.69	12.85	111.14	19.73	4.81	19.65	1.53
WRAT-3 Reading	50.17	5.18	49.73	5.09	50.18	6.01	0.03

Table 1. Clinical Groups and Comparison Subjects Characteristics. HCS, healthy control subjects; ASD, autism spectrum disorder; SCZ, schizophrenia. WRAT-3, Wide Range Achievement Test III. M, Mean; SD, Standard Deviation. Age expressed in years; sex expressed as percentage male; handedness expressed as percentage right. Verbal and non-verbal IQ were determined using the Vocabulary and Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale-III or Wechsler Abbreviated Intelligence Scale-II.

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Experimental Paradigm



Figure 1. Participants completed three versions of the experimental task: mixed-size at high contrast (A), mixed-size at low contrast, and mixed-contrast at small size (B). Duration thresholds were computed for eight different sizes (mixed-size) and contrasts (mixed-contrast). A chin rest maintained constant participant viewing distance as drifting grating stimuli were presented on a computer monitor. For each trial (C), participants indicated perceived motion direction of the briefly presented gratings by pressing either left or right arrow keys on a keyboard. Auditory feedback accompanied correct responses. Stimulus duration was adjusted using an adaptive stimulus presentation paradigm in order to determine the duration at which participants could consistently discern the direction of stimulus motion.

Low Contrast: Spatial Summation

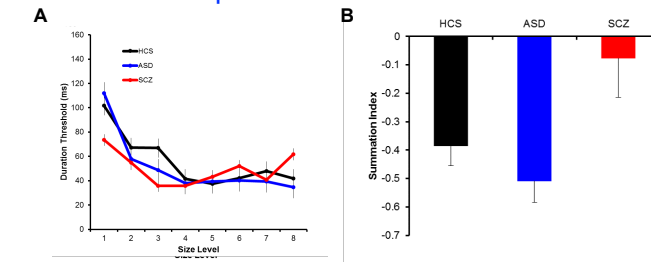


Figure 2. (A) Spatial summation with low contrast stimuli. The mixed-size at low contrast condition included eight different stimulus sizes representing equal increments from 1° to 8° in logarithmic space: 1°, 1.3°, 1.8°, 2.4°, 3.2°, 4.4°, 5.9°, and 8°. All stimuli were presented at 2.3% contrast. Participants completed a 96-trial practice block, followed by four 80-trial experimental blocks. A multivariate ANOVA with follow up one-way ANOVAs revealed no differences among groups at any stimulus size. **(B) Low contrast summation index.** Summation index was calculated by subtracting the $\log_{10}(\text{threshold})$ of the smallest stimulus from that of the largest stimulus to index the increase in performance as a function of size (i.e., spatial summation). Results revealed a significant between-groups effect, $F(2,41)=5.298$, $p=.009$. Whereas similar gains in performance with increased size at low contrast were seen in ASD and HCS ($p=.920$), individuals with SCZ showed less benefit with increased size relative to both HCS ($p=.067$) and ASD ($p=.008$).

High Contrast: Spatial Suppression

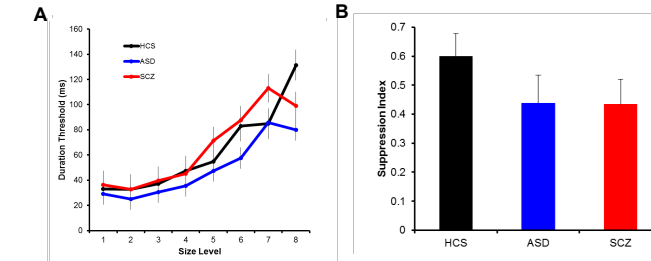


Figure 3. (A) Spatial suppression with high contrast stimuli. The mixed-size at high contrast condition included eight different size levels equivalent to those in the low contrast task: 1°, 1.3°, 1.8°, 2.4°, 3.2°, 4.4°, 5.9°, and 8°. All stimuli were presented at 99% contrast. Participants completed a 96-trial practice block, followed by four 80-trial experimental blocks. A multivariate ANOVA with follow up one-way ANOVAs were used to test between-group differences at the various sizes, but no group differences were revealed. **(B) High contrast suppression index.** Suppression index was calculated by subtracting the $\log_{10}(\text{threshold})$ of the smallest stimulus from that of the largest stimulus to index the decrease in performance as a function of size (i.e., spatial suppression). No group differences were observed in the suppression indices across groups, $F(2,41)=1.226$, $p=.304$.

Contrast Response Function

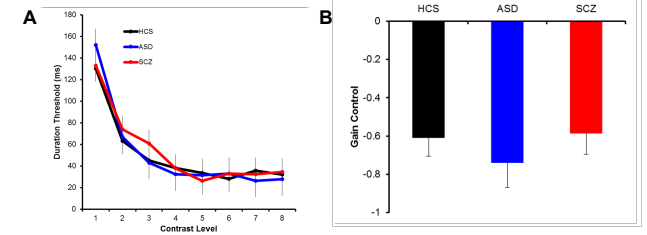


Figure 4. (A) Contrast response function at small size. The mixed-contrast at small size condition included eight contrast levels representing equal increases from 2% to 99% in logarithmic space: 2, 3.5, 6, 11, 19, 33, 57, and 99%. All stimuli were presented at the smallest size with a radius of 1°. Participants completed a 96-trial practice block followed by five 80-trial experimental blocks. A multivariate ANOVA with follow up one-way ANOVAs revealed no differences among groups at any contrast level. **(B) Gain control index.** A gain control index was calculated by subtracting the $\log_{10}(\text{threshold})$ of the lowest contrast stimulus from that of the highest contrast stimulus to index performance improvement as a function of increased contrast. No group differences were observed in gain control across groups, $F(2,41)=0.516$, $p=.601$.

SRS and SPQ Predict Motion Detection Across Groups

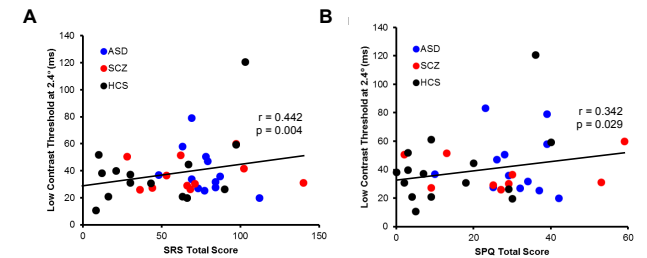


Figure 5. (A) SRS total score correlated with duration thresholds at low contrast. Across groups, a positive correlation was observed between self-report of deficits in social abilities on the Social Responsiveness Scale (SRS) and duration thresholds. The association was restricted to motion perception of low contrast stimuli across the CRF and Low Contrast tasks. **(B) SPQ total score correlated with duration thresholds at low contrast.** Likewise, across groups, those scoring high on the Schizotypal Personality Questionnaire (SPQ) had significantly higher duration thresholds when perceiving low-contrast stimuli. While motion detection abilities related significantly to clinical symptoms, no correlations were found between suppression, summation, or gain control indices and self-report of clinical traits.

Discussion

Neither deficits nor enhancements in motion perception were observed in SCZ or ASD relative to healthy control subjects, regardless of contrast or size. Contrary to previous studies, SCZ was not marked by reduced surround suppression at high contrast and no reduction in gain control was observed in ASD. However, a novel result was identified wherein SCZ participants demonstrated a reduction in summation at low contrast. This result reflects patients with early-course SCZ's failure to benefit from increasing size in the ability to perceive motion direction of low-contrast stimuli. There were no differences between healthy control subjects and ASD participants in summation at low contrast, suggesting this finding is specific to SCZ. Inconsistencies with previous findings may be a function of unique features of the population used in this study. For example, while past studies have investigated E/I imbalance during motion perception in children with ASD and older adults with chronic SCZ, the current study explored this phenomenon in an older sample (i.e., of young adults) with ASD and in individuals with SCZ early (i.e., less than three years) in their course of illness. Transdiagnostic correlations did not reveal an association between ASD and SCZ traits and indices of E/I imbalance during motion perception (i.e., suppression and gain control indices). However, higher levels of self-reported social deficits and schizotypal experiences were associated with broadly worse motion perception ability at low contrast. This finding is novel and warrants additional exploration in future studies, particularly in light of the association between schizophrenia and lack of spatial summation at play in the perception of low contrast stimuli.

Summary. Contrary to predictions, differences in surround suppression for high contrast stimuli and gain control with increasing contrast during motion discrimination were not observed in ASD or SCZ relative to controls. Moreover, an unexpected increase in suppression was observed at low contrast for SCZ participants. These data suggest that, at least in the context of low-level visual motion processing, young adults with ASD and SZ may have an E/I balance that is largely intact.