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Smaller visual arrays are harder to integrate in schizophrenia: Evidence for impaired lateral connections in early vision

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ABSTRACT

Long-range horizontal connections in early vision undergird a well-studied "collinear facilitation" effect, wherein a central low-contrast target becomes more detectable when flanked by collinear elements. Collinear facilitation is weaker in schizophrenia. Might lateral connections be responsible? To consider the possibility, we had 38 schizophrenia patients and 49 well-matched healthy controls judge the presence of a central low-contrast element flanked by collinear or orthogonal high-contrast elements. The display (target + flankers) was scaled in size to produce a lower and higher spatial frequency ("SF") condition (4 and 10 cycles/deg, respectively). Larger stimulus arrays bias processing towards feedback connections from higher-order visual areas; smaller arrays bias processing toward lateral connections. Patients had impaired facilitation relative to controls at higher but not lower SFs. Combining data from a past study on "contour integration" (in which subjects sought to detect chains of co-circular elements), we found correlated integration and facilitation performance at the higher SF and a similar effect of spatial scaling across SF, suggesting a common mechanism. In an exploratory analysis, worse contrast thresholds (without facilitation) correlated strongly with more premorbid dysfunction. In schizophrenia, inter-element filling-in worsens at smaller spatial scales potentially because of its increased reliance on impaired lateral connections in early vision.

1. Introduction

Vision is unquestionably disturbed in schizophrenia: One-quarter of patients endorse visual hallucinations, two-thirds report more subtle changes to everyday visual experience (Keane et al., 2019; Waters et al., 2014) and many also demonstrate objective impairment in perceptual organization (Keane et al., 2019; Silverstein and Keane, 2011). Can any of these abnormalities be attributed to early visual dysfunction? To address the question, we employed a collinear facilitation paradigm, wherein a central low-contrast target becomes easier to detect when surrounded by collinear high contrast elements. The effect has been documented in scores of basic vision studies and has been localized to monkey V1 (Loffler, 2008; Polat et al., 1998); Polat and Sagi, 1994). Neural models based on single-cell electrophysiology suggest that facilitation arises from a non-linear combination of thalamic-cortical feedforward input and excitatory lateral connections between orientation-tuned spatial frequency filters (Loffler, 2008; see Fig. 1A)

Collinear facilitation is reduced in schizophrenia. The reduction happens in patients who have intact attention, a 12-week medication washout period, and normal contrast sensitivity, but it does not happen in people with psychotic bipolar disorder (Kéri et al., 2005a; Must et al., 2004). The effects appear to be purely excitatory since when the flankers are very close to or touching the central target (creating inhibition), patient performance worsens in a normal fashion (Kéri et al., 2005a). Consequently, these data have been interpreted to mean that lateral excitatory connections in early vision are impaired in the disorder.

Given its potential import for understanding early visual cortical functioning, Keane et al. (2014) sought to replicate this effect. It was found that patients exhibited reduced facilitation, but only if

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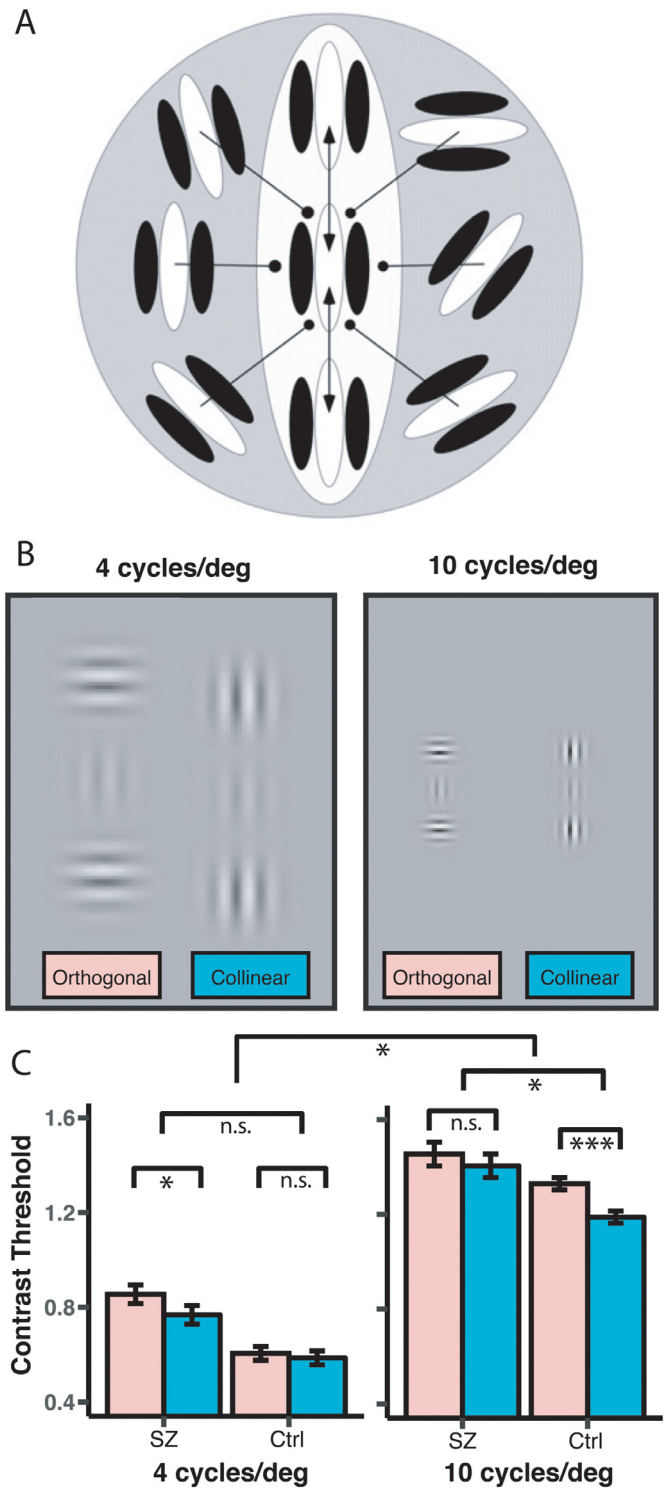

Fig. 1. (A) According to current models, cells have excitatory and inhibitory regions (white and black respectively). Intrinsic lateral connections are excitatory when relating cells in iso-orientation columns (double-sided arrows), but can be inhibitory otherwise (line segments) (Figure panel adapted from Loffler, 2008 p. 2111). (B) Stimuli. (C) Contrast thresholds (log units) are shown for each condition and subject group. Facilitation corresponds to a positive threshold difference (orthogonal – collinear). Group differences in facilitation emerged only for the scaled-down display (10 cycles/deg). Errors = 95% CI. *<0.05; ***$p<10^{-7}$.

individuals with schizoaffective disorder were removed from the analysis (prior studies also excluded schizoaffective patients) and only if the stimulus peak spatial frequency was 10 cycles per degree as compared to 4 cycles per degree (prior studies used 6.7 cycles per degree). However, this replication should be considered provisional because i) the SZ sample was small ($N = 14$), ii) high spatial frequencies were originally expected to *improve* (rather than worsen) integration deficits (Butler et al., 2005; Keane et al., 2014) and iii) the schizophrenia/schizoaffective diagnostic distinction rarely alters perceptual/cognitive performance. Here, we sought to more definitively establish the scaling effect.

An effect of scaling would be important. The visual hierarchy is tiled with orientation and spatial frequency tuned filters, and cells lower in the hierarchy capture smaller windows of space (Freeman and Simoncelli, 2011). Moreover, long-range horizontal connections are unmyelinated and conduct nerve signals too slowly (0.3 m/s) to connect elements over larger retinotopic distances; feedforward/feedback nerve conduction velocities are over an order of magnitude faster and thus likely play a more dominant role when elements are more spread out (Girard et al., 2001). Thus finding a collinear facilitation reduction for smaller, higher spatial frequency elements that are more closely spaced would strengthen the case for impaired horizontal connections in schizophrenia.

In a secondary analysis, we expanded our sample to include other psychotic disorders and examined whether facilitation varied with diagnosis or symptoms. One expectation, based on our own work and past literature, was that people with other psychotic disorders would display normal facilitation (Keane et al., 2014; Kéri et al., 2005).

Finally, we considered whether spatial-frequency specific reductions in collinear facilitation could be related to similar reductions in contour integration, wherein subjects attempt to identify chains of cocircular Gabors embedded within noisy arrays (Keane et al., 2016). Those who struggle to obtain facilitation in shrunken displays may also have trouble integrating under similar conditions.

2. Methods

2.1. Subjects

The subject sample comprised 50 healthy controls (Ctrl) and 38 participants with schizophrenia (SZ), 6 of whom recently experienced their first psychotic episode and all the rest of whom had at least one other psychotic episode (Table 1). For the second set of analyses, we additionally examined 20 participants with schizoaffective disorder (first episode = 3, later episode = 17), 5 patients with schizophreniform disorder (all first episode) and 7 patients with psychotic disorder NOS (all first episode; Table S1). These numbers do not include one other SZ individual (later-episode) or three other psychosis patients (1 first-episode/SA, 1 first-episode/Psychotic disorder NOS, 1 later-episode/SA) who did not finish the task due to computer malfunction, unwillingness to proceed, or inability to perform the task. Controls without four-year college degrees were preferentially recruited to prevent exaggerated group differences in IQ and education. For all subjects, inclusion/exclusion criteria were (1) age 18–65; (2) no electroconvulsive therapy in the past 8 weeks; (3) no neurological or pervasive developmental disorders; (4) no drug dependence in the last six months, as assessed with the Mini International Neuropsychiatric Interview 6.0 (MINI; Sheehan et al., 1998); (5) no brain injury due to accident or illness (e.g., stroke or brain tumor); (6) no amblyopia (as assessed by informal observation and self-report); (7) visual acuity of 20/32 or better (with corrective lenses, if necessary); and (8) the ability to understand English and provide written informed consent. Additional criteria for later episode patients were: having had at least two psychiatric hospitalizations and having received a DSM IV-TR diagnosis of schizophrenia or schizoaffective disorder (APA, 2000) at the time of testing (data collection occured from 08/2012 to 02/2015 and so the

Table 1
Participant characteristics.

	SZ (N = =38)		Ctrl (N = =50)		Group comp.
Variable	*Mean or Percent*	*SD*	*Mean or Percent*	*SD*	*p*
Age (yrs)	40.4	12.5	35.5	13.1	.08
Education, parental average (yrs)	12.6	3.8	13.8	2.9	.12
Education, self (yrs)	13.1	2.0	14.3	2.3	.01
FSIQ (Shipley-2)	88.0	16.5	101.3	14.6	<0.001
Gender (% Male)	71	–	56	–	.15
Handedness (% Right)	87	–	94	–	.28
Binocular Visual Acuity (logMar)	−0.01	0.09	−0.06	0.11	.02
Antipsychotic Type: typical/atypical/both (%)	24/61/12	–	–	–	–
Chlorpromazine equiv. (mg/day)	470.6	304.6	–	–	–
Functioning, current (MSIF)	3.9	1.0	–	–	–
Functioning, premorbid (PAS)	0.39	0.13	–	–	–
Illness duration (yrs)	19.1	13.5	–	–	–
Illness onset age (yrs)	20.4	6.0	–	–	–
PANSS, positive	8.9	4.7	–	–	–
PANSS, negative	12.0	4.2	–	–	–
PANSS, disorganized	6.9	2.7	–	–	–
PANSS, excitement	5.7	2.1	–	–	–
PANSS, depression	7.3	3.4	–	–	–
PANSS, total	58.5	13.1	–	–	–

Note. For the parental education average, a value from only one parent was used when the other was missing. FSIQ = Full-Scale IQ; MSIF = Multidimensional Scale of Independent Functioning; PAS = Premorbid Adjustment Scale, averaged across age period (with higher scores signifying more dysfunction); =PANSS = Positive and Negative Syndrome Scale.

use of DSM-5 was not an option.). Additional criteria for controls were: no DSM-IV-TR diagnosis of any psychotic or mood disorder, no current psychotropic- or cognition-enhancing medication, and no first-degree relative with schizophrenia or schizoaffective disorder. Additional criteria for first episode psychosis patients were: having had exactly one hospitalization for psychosis and having recently received a psychotic disorder diagnosis in most cases within one year of testing. The first episode status was confirmed by a review of medical records and a structured psychiatric interview (see below). Only one person (later-episode) admitted at the time of testing to not taking medication.

2.2. Participant information

An experienced rater (DP) and the first-author (BK) had established reliability with each other and with raters in other ongoing studies (ICC > 0.8); they administered the clinical instruments and perceptual tasks to the study participants. Psychiatric diagnosis was assessed with the Structured Clinical Interview for DSM-IV (SCID) (APA, 2000; First et al., 2002) and was supplemented with electronic medical record information when the diagnosis was unclear. Intellectual functioning of all subjects was assessed with a brief vocabulary test that correlates highly (r = 0.80) with WAIS-III full-scale IQ scores (Shipley et al., 2009, p. 65). A vocabulary subtest was preferred since verbal knowledge is putatively less dependent on illness onset and progression (Meier et al., 2014) and since it is one of the best predictors of full-scale IQ in healthy adults (Canivez and Watkins, 2010). Visual acuity was measured with a logarithmic visual acuity chart under fluorescent overhead lighting (viewing distance = 2 m, lower limit =20/10), and in-house visual acuity correction was used for individuals without appropriate glasses or contacts. Each group had an average binocular acuity of 20/20 or better (logMAR ≤ 0.0; see Table 1).

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was administered within two weeks (most typically 7 days) of the perceptual task and provided information about symptoms over the last two weeks. PANSS symptom scores were reported via a “consensus” 5-factor model (Wallwork et al., 2012). The Multidimensional Scale of Independent Functioning (MSIF) independently evaluated role position, amount of support required to perform roles, and performance in how patients performed work, education, and home tasks (in decreasing order of emphasis) within the month prior to the interview (Jaeger et al., 2003). We tested for medication effects by first converting antipsychotic dosages to chlorpromazine equivalents based on published standards (Andreasen et al., 2010) and then correlating those values with task performance.

The Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) measured sociability, peer relationship quality, scholastic performance, school adaptation, and (where appropriate) social-sexual functioning up to 1 year before illness onset: this was done for childhood (up through age 11), early adolescence (ages 12–15), late adolescence (ages 16–18), and adulthood (ages 19 and above). To gain a more precise idea as to which aspects of premorbid functioning might be disturbed, we examined each functioning domain averaged across age period and each age period averaged across functioning domain (see Analysis for further details). We excluded the PAS “general” score, as others have done, since it partly reflects functioning after illness onset (van Mastrigt and Addington, 2002). Illness onset on the PAS was defined as when one or more positive symptoms first became noticeable or concerning to the patient; illness duration was defined as the time elapsed between illness onset and task administration.

Written informed consent was obtained from all subjects after explanation of the nature and possible consequences of participation. The study followed the tenets of the Declaration of Helsinki and was approved by the Rutgers Institutional Review Board (Spatial frequency contributions to contour integration in schizophrenia; Pro2012001370). All participants received monetary compensation and were naive to the study's objectives.

2.3. Stimulus and procedure

Stimulus and procedural details of the tasks have been described elsewhere (Keane et al., 2014) but are reproduced below. In all tasks, the experimenter entered a response on behalf of the subjects to minimize the chance of group differences in key press errors (mismatching a key press with a response) and thus to minimize the influence of generalized deficit confounds

Stimuli consisted of Gabor patches, which are oriented sinusoids multiplied by a circular Gaussian:

$$G(x, y, \theta) = c \sin(2\pi f (x \sin\theta + \cos\theta)) exp\left(-\frac{x^2 + y^2}{2\sigma^2}\right)$$

where (x,y) denotes the distance in degrees from the center of the element, theta is the element's orientation (in deg), f is the peak spatial

frequency of the element, and c is the Michelson contrast. The Gabors had a sine phase (to create a balanced luminance profile), a peak spatial frequency of 4 cycles/deg, and a Gaussian envelope SD of 10.6 arcmin. The central Gabor was vertically oriented and separated from the flankers by 4 lambda (wavelength) center-to-center (Fig. 1). One half of the collinear facilitation experiment consisted of lower spatial frequency (LSF) stimuli and the other half consisted of high spatial frequency (HSF) stimuli. The two block types were counterbalanced across observers. In the LSF trials, there were three vertically aligned Gabor elements centered on a mean gray background (45 cd/m2). Stimuli in the HSF trials were similar to the LSF trials, except that the entire stimulus was scaled to 40% of the retinal size (i.e., Gabors had a peak SF of 10 c/d; see Fig. 1B). Thus, the center-to-center separation in the LSF condition was 1 deg and in the HSF condition was 0.4 deg. Similar to an earlier study (Polat, 2009), we increased the flanker contrast from 64% in the LSF block to 94% in the HSF block so that the latter would be easier to see. Flanker contrast differences within this range do not alter facilitation for lower SF stimuli.

Each trial began with a white fixation cross centered on a gray background. Upon initiating a trial, the observer saw a blank screen (400 ms), a three Gabor array (90 ms), and then another gray screen until a response was provided (present or absent). We opted to present the stimulus on every trial rather than use a two- interval forced choice since qualitatively the same results arise in the two cases (Kéri et al., 2005a), and since the former allows for a shorter experiment. A 1-up, 3-down staircase determined the threshold, the amount of contrast needed to detect the stimulus with 79.4% accuracy (Kéri et al., 2005a; 2009; 2005b; Must et al., 2004). Specifically, in the event of one incorrect response (miss), the contrast between the background and the central Gabor increased by 0.1 log units (26%) and in the event of three consecutive correct responses (hit), the contrast decreased by the same amount. A decrease or increase of contrast preceded by a contrast change in the opposite direction was labeled a "reversal", and a block of trials terminated after seven reversals. Threshold for a condition was computed as the average contrast (in log units) for all the trials following the 4th reversal. (Averaging contrasts over all trials rather than just the reversal values improves threshold estimates (Klein, 2001, p. 1449)).

In each half of the experiment, there were two blocks corresponding to whether the flankers were orthogonal or collinear to the central target. The two blocks were counterbalanced across observers and so too was the SF ordering. Collinear facilitation was measured as the orthogonal threshold minus the collinear threshold, with larger (more positive) differences reflecting greater facilitation. Subjects began each half of the experiment with 25 practice trials without flankers.

2.4. Analysis

We compared thresholds (log contrast values) with a 2 (SF: LSF or HSF) by 2 (orientation: orthogonal or collinear flankers) by 2 (group: Ctrl vs. SZ) mixed model analysis of variance (ANOVA). Collinear facilitation, if found, would manifest as a main effect of orientation; group differences in facilitation would appear as a group by orientation interaction. T-tests were two-tailed and equal variances were assumed, unless a significant Levene's test required otherwise. In the second set of analyses, we applied the same approach to compare the two diagnostic groups (SZ versus OtherPsy).

Relationships between symptoms and facilitation effects (threshold difference scores) were evaluated using Pearson's r correlations. We considered relationships between facilitation and: the five PANSS factors (disorganized, positive, negative, excited, depressed), the four SAPS scores (hallucinations, delusions, bizarre behavior, positive formal thought disorder), the four current functioning (MSIF) scores (role functioning, support functioning, performance functioning, global functioning), and the 11 premorbid functioning (PAS) scores (sociability, peer relationships, scholastic performance, adaptation to school, social-sexual functioning, childhood, early adolescent, late adolescent, adult, age of onset, and the "total" score averaged over age period). Note that these same PAS scores have been considered in earlier studies (e.g., Keane et al., 2018).

3. Results

There was a main effect of SF such that targets were less detectable (log contrast thresholds were higher) for the scaled-down (HSF) than for the large (LSF) display ($F(1,86) = 561.5$, $p < 0.001$, partial eta squared = 0.867; Fig. 1). There was an effect of group such that the patients required overall more contrast to see the targets than controls ($F(1,86) = 8.6$, $p = .004$, partial eta squared = 0.090). There was an overall large effect of flanker orientation: contrast thresholds were lower for collinear than orthogonal flankers ($F(1,86) = 25.7$, $p < 0.001$, partial eta squared = 0.230). This collinear facilitation effect was not modulated by spatial frequency ($F(1,86) = 1.79$, $p = .18$, partial eta squared = 0.020) or subject group ($F(1,86) = 0.16$, $p = .69$, partial eta squared = 0.002). However, replicating past work, there was a three-way interaction ($F(1,86) = 6.29$, $p = .01$, partial eta squared = 0.068 (Keane et al., 2014). Follow-up comparisons revealed that the flanker orientation effect in patients was similar to that of controls at 4 cycles/deg ($F(1,85) = 2.71$, $p = .10$, partial eta squared = 0.031) and significantly smaller than that of controls at 10 cycles/deg ($F(1,86) = 4.68$, $p = .046$, partial eta squared = 0.045). To put these results another way, the control group exhibited a classic collinear facilitation effect ($F(1,49) = 17.0$, $p < .001$, partial eta squared = 0.258) that strengthened with higher SF ($F(1,49) = 19.8$, $p < .001$, partial eta squared = 0.288), consistent with prior studies (Polat, 2009); while the schizophrenia group demonstrated collinear facilitation ($F(1,37) = 9.84$, $p = .003$, partial eta squared = 0.210) that did not change significantly across SF ($F(1,37) = 0.343$, $p = .562$, partial eta squared = 0.009).

Medication effects cannot explain our findings. CPZ equivalent dosages did not correlate with the magnitude of facilitation in patients at either SF (both $p > .3$). When CPZ values were added as a covariate (using an ANCOVA), medication did not interact with any other variable (all $p > .4$). Using one-way ANOVAs and interaction scores, we found that, at each SF, facilitation effects did not depend on whether subjects were on typical, atypical, or both types of antipsychotic medications.

Although patients had 20/32 vision or better and an average visual acuity of slightly better than 20/20 (logMAR = −0.008), they still had worse visual acuity than controls (Ctrl logMAR = −0.061; $p = .02$). However, VA was of doubtful significance since it did not correlate with collinear facilitation in either controls or patients for either SF (all $p > .1$).

Previous studies reported collinear facilitation effects with schizophrenia patients performing near normal in the orthogonal condition (e.g., Must et al., 2004). This was done by requiring patients to perform normally on an attentionally demanding task (e.g., a CPT task or Vernier discrimination task) (Kéri et al., 2009; Must et al., 2004). To remain faithful to these earlier studies, we re-ran the same analysis as before while including only patients who had high SF thresholds within 1.5 SD of the control mean on the orthogonal condition (Keane et al., 2019; Kéri et al., 2009; Must et al., 2004). An advantage to using this restricted sample (28 SZs) is that the two subject groups had not only similar high SF orthogonal thresholds ($p = .55$), but also similar low SF orthogonal thresholds ($p = .10$) and visual acuity ($p = .37$). The ANOVA results remained qualitatively the same, with a significant three-way interaction ($F(1,76) = 5.4$, $p = .02$, partial eta squared = 0.07), and a specific two way interaction (group x orientation) at the high SF $F(1,76) = 4.5$, $p = .037$).

One schizophrenia subject was an outlier (> 3 SD) from the group mean for the HSF interaction and the three-way interaction scores, and thus appeared to unduly drive the effects stated above. If a non-parametric t-tests were applied to the interaction scores, the three-way

interaction would remain significant (Mann–Whitney $U = 670$, $p = .02$), but the two-way interaction would only reach the trend level (Mann-Whitney $U = 744.5$, $p = .08$). The HSF facilitation reduction should still be considered credible, we believe, since the direction (and significance) has been established in at least five different studies (Kelemen et al., 2013; Kéri et al., 2009; 2005b; 2005a; Must et al., 2004).

3.1. Facilitation effects including other psychotic disorders

In an earlier paper, we had tentatively reported a facilitation difference between schizophrenia and schizoaffective disorder (Keane et al., 2014). To consider whether facilitation reductions were schizophrenia-specific, we expanded our sample and compared psychosis patients with and without schizophrenia. We found a marginal three-way interaction ($F(1,68) = 3.86$, $p = .053$, partial eta squared = 0.054) in the expected direction, but no other group differences ($ps > 0.18$). When comparing non-schizophrenia psychosis patients to controls, there were no interactions with group (all $p > .4$), including the critical three-way interaction ($F(1,80) = 0.02$, $p = .9$), although the psychosis group had marginally higher thresholds overall ($F(1,80) = 3.3$, $p = .08$). This is broadly consistent with past work showing normal facilitation in other forms of psychosis (Kéri et al., 2005a)

In the expanded sample, we also compared people with first versus later episode psychosis. Applying the same ANOVA as before, there were no significant effects (all $p > .2$), with an interesting exception that the first-episode patients had overall lower thresholds (that is, better detection, $F(1,68) = 11.3$, $p = .001$, partial eta squared = 0.142). These results are consistent with past studies showing that contrast sensitivity is normal in medicated first episode patients and worse in medicated or unmedicated chronic patients (Butler et al., 2005; Kelemen et al., 2013)

3.2. Clinical correlations

For schizophrenia patients, we found that, at the lower SF, poorer collinear facilitation was associated with increased cognitive disorganization (PANSS; $r = -0.37$, $p = .03$). The disorganization effect was presaged by our earlier study with a smaller sample (Keane et al., 2014), and thus should be considered real (albeit modest). No other effect survived correction for multiple comparisons.

An effect impressive in its consistency and magnitude but not directly related to our original research aims was that higher "orthogonal" thresholds in SZ patients (averaged across SF) were related to worse overall premorbid adjustment (Fig. 2; $r = 0.59$, $p = .0004$). The particular age periods that were important were childhood ($r = 0.66$, $p = .00004$) and early adolescence ($r = 0.61$, $p = .0003$). The particular functioning domains that reached significance were adaptation to school ($r = 0.53$, $p = .002$), peer relationships ($r = 0.53$, $p = .002$), and sociability ($r = 0.51$, $p = .003$; Supplementary Figure S1). Note that acuity did not correlate with the PAS scores (all $p > .18$, uncorrected) and so cannot explain the contrast threshold effects.

3.3. Relating collinear facilitation to contour integration

The spatial scaling effect resembles that found in contour integration studies: when subjects sought to identify a sparsely sampled circular target embedded in varying amounts of randomly oriented "noise" elements, schizophrenia patients integrated worse than controls, but mainly for scaled-down (high spatial frequency) displays (Keane et al., 2016). Threshold in that study corresponded to the number of noise contour elements that subjects could tolerate while achieving threshold accuracy (higher threshold = better performance; Fig. 3). To consider the relation between the two tasks, we compared the contour integration thresholds and the facilitation effects (threshold differences) for 37 patients and 49 controls for the high SF condition (scaled-down in size); we also compared the amount by which contour integration and collinear facilitation performance changed across spatial scales. Note that because the correlations were modest in magnitude, we were not able to detect significant effects only within schizophrenia patients or only within controls. However, across all subjects, we found a correlation at the high SF ($r = 0.24$, $p = .02$) indicating that—at smaller spatial scales—subjects who had more trouble detecting chains of contour elements also had more trouble obtaining facilitation. We also found a correlation for the performance *change* across SF ($r = 0.26$, $p = .01$), indicating that the more that spatial scaling affected a subject in one task, the more it would do so in the other. These two effects remained qualitatively the same if the outlier from the facilitation task were removed (as in Fig. 3) or if a non-parametric test were used. To ensure that the results could not be ascribed to decreased stimulus visibility in the high SF condition, we reran the same analyses only for subjects with at least 20/20 binocular vision (27 SZ, 43 controls). Interestingly, the effects grew numerically stronger for the high SF ($r = 0.4$, $p = .0004$) and for the performance change across SF ($r = 0.30$, $p = .01$), possibly because poor visual acuity added more noise to the threshold estimates.

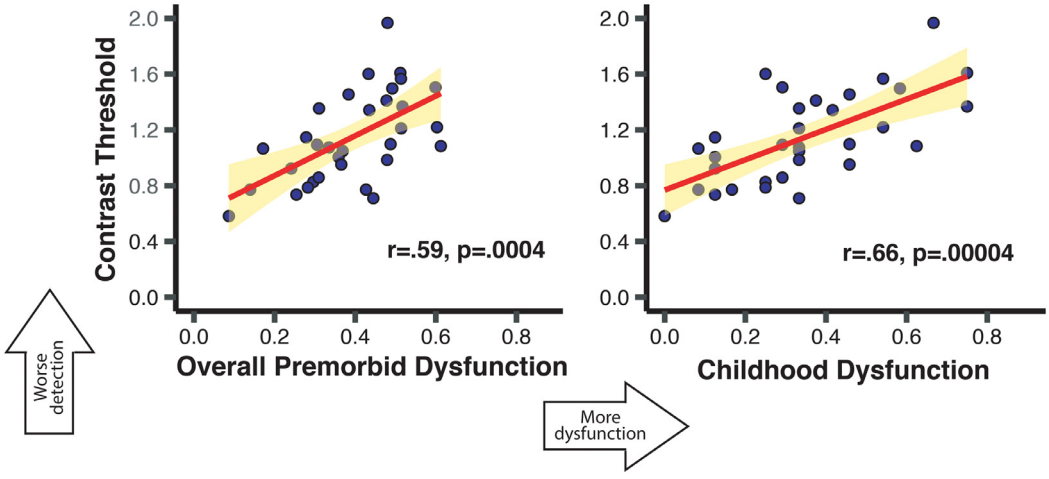

Fig 2. *Scatterplots relating premorbid functioning to contrast thresholds (log units) averaged across spatial frequency*. Higher values along the abscissa and ordinate denote worse functioning and contrast detection, respectively. Childhood dysfunction yielded the largest and arguably most surprising effect of the Premorbid Adjustment Scale subscores. Yellow bands show the 95% confidence intervals for the fitted regression lines.

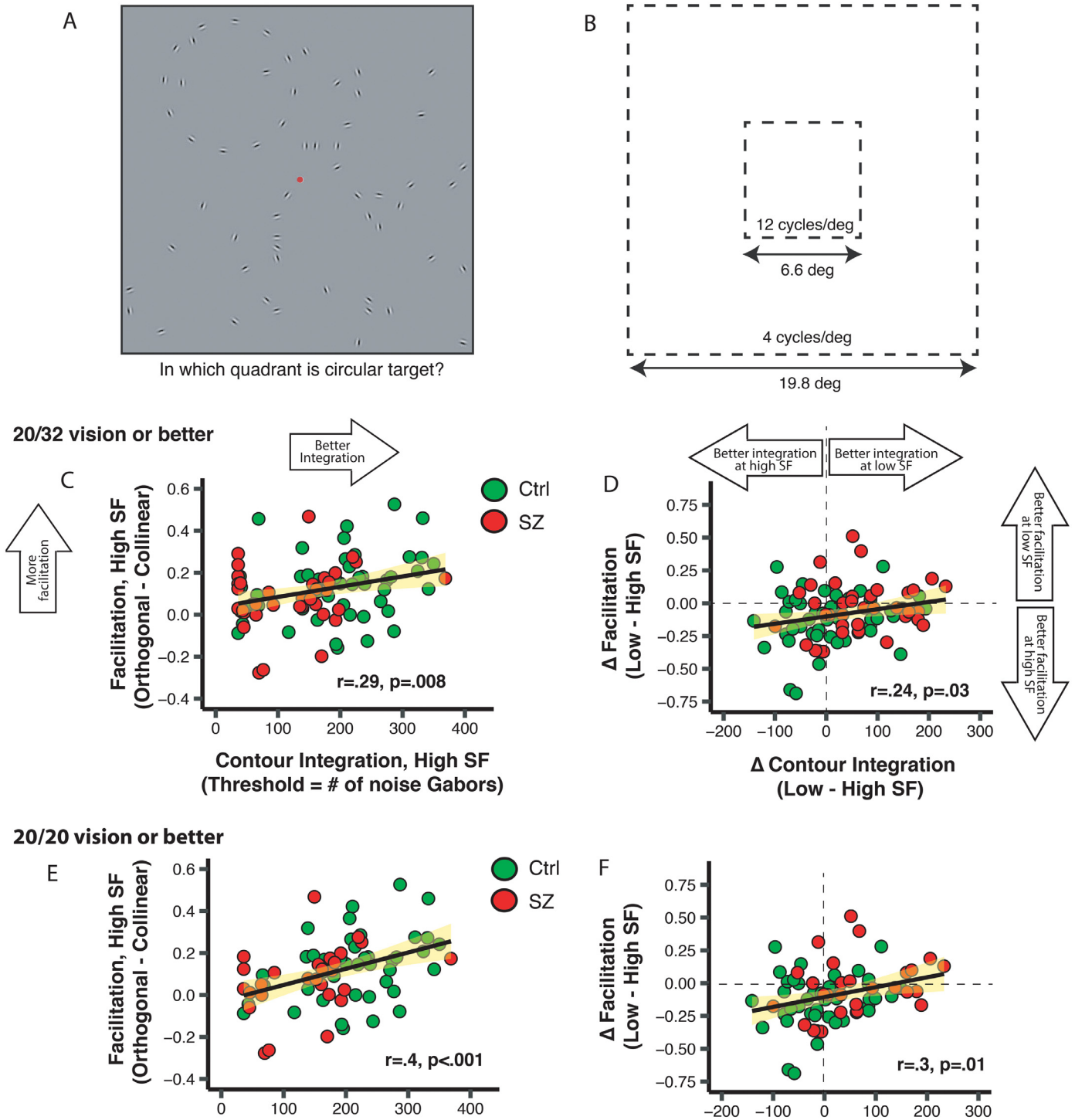

Fig. 3. *Contour integration versus collinear facilitation*. (A) In a contour integration task, subjects indicated which of four quadrants contained a co-circular chain of elements. Difficulty depended on the number of noise elements that accompanied the circular target. Threshold corresponded to the number of noise elements that were needed to generate threshold accuracy (higher threshold = better integration). (B) The entire contour integration display was scaled in size to produce two SF conditions (4 and 12 cycles/deg). (C) Across subjects, for the higher SF, better contour integration correlated with better facilitation. (D) The more that spatial scaling altered facilitation, the more it would do so for contour integration. (E,F) Inter-task effects strengthened when all subjects had at least 20/20 vision. Yellow bands show the 95% confidence intervals for the fitted regression lines.

4. Discussion

By employing a relatively simple, but well-explored visual psychophysical paradigm and by spatially scaling the stimuli to create two otherwise identical conditions, we have shown that people with schizophrenia were less able to integrate scaled-down visual displays. The effect could not be explained in terms of poor contrast sensitivity, visual acuity impairments, or medication use. The effect was marginally less pronounced among people with other psychotic disorders, suggesting a diagnosis-specific effect. Reduced facilitation was not related to first-episode status or illness duration. Upon including data from a prior contour integration study, we found that high SF collinear facilitation

and contour integration performance were significantly correlated, and that the more that spatial scaling impacted facilitation, the more it would do so for contour integration, suggesting a common mechanism. In exploratory analyses, reduced contrast sensitivity (without facilitation) was strongly associated with worse premorbid functioning.

The specificity of patient deficits to small, higher spatial frequency stimuli suggest that there may be dysfunction with long-range horizontal excitatory connections in early visual cortex. Such connections play a critical role in collinear facilitation and contour integration (Liang et al., 2017; Polat et al., 1998). Moreover, cells earlier in the visual hierarchy have smaller receptive fields and are more responsive to smaller contour elements with higher spatial frequencies (Freeman and Simoncelli, 2011). Finally, lateral connections typically stretch across only small patches of cortex and are unmyelinated, having conduction velocities one-tenth as fast as feedback connections (Girard et al., 2001; Loffler, 2008). Lateral connections will therefore be less relevant for connecting briefly-flashed, distantly-spaced elements presented at only 4 cycles/degree.

Spatial scaling altered integration in a similar way for collinear facilitation and contour integration. Note that the range of the spatial frequencies was different between the two tasks (4–10 versus 4–12 cycles/deg) and the Gaussian envelope SD was smaller in the contour integration study (7.3 versus 10.6 arcmin; see below). Moreover, inter-experiment correlations in general tend to be weak, even when the task stimulus and procedure are nearly identical (Grzeczkowski et al., 2017). The detection of a relationship between these two tasks, despite non-trivial procedural and stimulus differences, suggests that impaired lateral connections may underlie the spatial scaling effect in each case.

Although we replicated our earlier finding at the HSF, the effect size was smaller than previously reported (e.g., $d = 1.13$ in Must et al. (2004) versus $d = 0.44$ in our high SF condition). Aside from possible sampling differences, the variation could have also arisen from differences in the Gabor function itself, with $2\sigma^2$ rather than σ^2 defining the width of the Gaussian envelope. Wider Gabors are easier to see and thus are less likely to generate ceiling effects (e.g., certain subjects may need 100% target contrast to see a Gabor whose envelope is too restrictive). Likewise, wider Gabors allowed us to include subjects with slightly impaired visual acuity (e.g., 20/32; earlier studies had used a cut-off of 20/25). Yet wider Gabors also bias the stimulus toward cells that have larger receptive fields and that operate higher within the cortical hierarchy. Group differences may be more apparent with a narrower Gabor Gaussian envelope.

Why did controls fail to exhibit facilitation at 4 cycles/degree? For unpracticed psychophysical observers, collinear facilitation occurs only for higher spatial frequencies (>1.5 cycles/deg; Polat, 2009). Furthermore, facilitation weakens for larger Gaussian envelopes (Woods et al., 2002). Therefore, our controls demonstrated little facilitation in this condition plausibly because the spatial frequency was lower, the Gaussian envelope was larger (using $2\sigma^2$ rather than σ^2, as noted), and the observers were unpracticed.

We found an unexpectedly strong correlation between contrast sensitivity (without facilitation) and premorbid functioning. The exact reason why there should be such a relation is unknown but poor premorbid functioning is associated with an earlier and more insidious onset, poorer long-term outcome, cognitive impairment, enlarged ventricles, and certain visual organizational deficits, suggesting that lowered contrast sensitivity may also characterize this patient subtype (Cannon-Spoor et al., 1982; Saracco-Alvarez et al., 2009; Silverstein, 2016).

A limitation is that we did not control for eye movements. However, the potential confound is minimal since the task already requires keeping the eyes within a small spatial window to achieve normal performance (this was clearest when our analyses required near-normal detection in the orthogonal condition, noted above). Another limitation is that although medication effects were not discovered, they cannot be ruled out completely. Additionally, the number of first episode schizophrenia patients was small, making it difficult to ascertain illness duration effects within this subgroup. Finally, our results, being behavioral in nature, must be confirmed with direct anatomical and physiological observation (e.g., post-mortem studies on the axons spanning pyramidal cells in striate cortex, pharmacological animal models of schizophrenia). Nevertheless, by invoking a well-established psychophysical paradigm, we have provided evidence that dysfunctional horizontal connections in early vision may be responsible for certain varieties of integration deficits in schizophrenia.

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None.

Declaration of Competing Interest

There are no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112636.

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