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Lateral interactions in the visual cortex of patients with schizophrenia and bipolar disorder

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ABSTRACT

Background. Schizophrenia is associated with perceptual organization deficits and abnormal neuronal connectivity has been described in early visual areas. The purpose of this study was to investigate the functional integrity of lateral connections in early visual areas of patients with schizophrenia and type I bipolar disorder with a history of psychosis.

Method. Twenty-four out-patients with schizophrenia, 22 out-patients with bipolar disorder, and 20 healthy control subjects participated in the study. Using a computer-assisted psychophysical test, contrast thresholds were measured for centrally presented target stimuli (Gabor patches), which were surrounded by two collinear flankers. Target-to-flanker distances were 0, 1, 2, 3, 4, 6, 9 and 12λ. Psychophysical measures were contrast threshold changes at each target-to-flanker distance compared with baseline thresholds determined for isolated targets with no flankers. Clinical measures included IQ, positive, negative, and depressive symptoms.

Results. In patients with schizophrenia, flankers did not facilitate contrast detection for target stimuli at 2–6λ distances compared to controls [effect size (Cohen's *d*): 1·25–1·42]. The inhibitory effect of flankers (0 and 1λ) and contrast thresholds in the absence of flankers were spared. Patients with bipolar disorder did not differ from the controls. Medicated and non-medicated patients displayed similar performances. Positive and negative symptoms and depression did not correlate with contrast threshold values.

Conclusions. Excitatory lateral connections in early visual cortex are specifically impaired in patients with schizophrenia, which may contribute to perceptual disorders such as unclear seeing, partial or skewed sight, disrupted rectilinearity, and abnormal figure-ground segregation.

INTRODUCTION

Although several recent studies have highlighted the importance of early-stage local visual processing in schizophrenia (Butler *et al.* 2001; Braus *et al.* 2002; O'Donnell *et al.* 2002; Bedwell *et al.* 2003; Chen *et al.* 2003), much less is known about the intrinsic connectivity of visual cortical networks. A histopathological study found increased neuronal density and reduced interneuronal neuropil in the primary visual area of schizophrenia patients, which raises the possibility that connections between neurons are impaired (Selemon *et al.* 1995). In accordance with this finding, reduced levels of synaptic protein mRNAs (synaptophysin and GAP-43) (Eastwood & Harrison, 1998; Eastwood *et al.* 2000), altered gene expression profile (Mirnics *et al.* 2001), and abnormal DNA methylation of genes related to neurodevelopment and synaptic plasticity (Veldic *et al.* 2004) have been described in the occipital cortex of schizophrenia patients.

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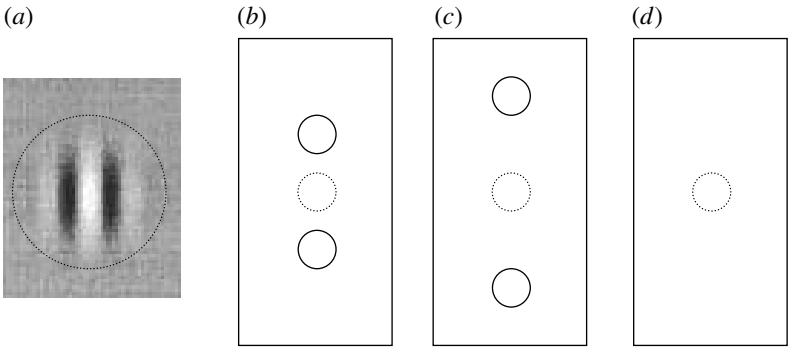


FIG. 1. (*a*) Gabor patch. The dotted line (not present during the experiment) indicates stimulus orientation and illustrates Gabor patches in panels (*b*)–(*d*). (*b*, *c*) A low-contrast central Gabor patch (dotted line) with two collinear flankers (continuous line) with different target-to-flanker distances. (*d*) An isolated central Gabor patch (dotted line) with no flankers (baseline condition).

At early cortical stages of visual processing, the retinal image is encoded by local mechanisms that are specific for elementary physical properties of stimuli such as contrast, size, orientation, and spatial frequency (DeValois & DeValois, 1990). For example, cells in primary visual area (V1) of the occipital cortex respond to small bars with such physical properties. Beyond the existence of local processing mechanisms, visual neurons have rich functional connections with each other; pyramidal cells in layers 3 and 5 have lateral interactions via bi-synaptic connections. These lateral interactions play an important role in the integration of visual information processed by local mechanisms with surrounding contextual information in order to build unified percepts. Lateral interactions between local processing units enable the visual system to integrate information over large fields of the environment (Zemon & Ratliff, 1982; Sokol *et al*. 1992; Polat & Sagi, 1993, 1994; Grose-Fifer *et al*. 1994; Kovács & Julesz, 1994; Kapadia *et al*. 1995; Adini *et al*. 1997; Polat *et al*. 1998; Stettler *et al*. 2002; Li & Gilbert, 2002).

Recently, Must *et al*. (2004) demonstrated psychophysical evidence that lateral interactions are impaired in schizophrenia. The perception of contrast (e.g. a dark bar relative to a light background) is one of the most fundamental visual functions. Contrast thresholds were measured for target stimuli (Gabor patches, Fig. 1*a*), which were surrounded by two lateral flankers with collinear or orthogonal orientations relative to the target. Healthy subjects required less contrast (lower threshold) to detect the target when collinear flankers were presented. Extensive psychophysical and physiological evidence suggests that the facilitation effect of collinear flankers is due to lateral interactions between local processing units (cells) in early visual cortex (Polat & Sagi, 1993, 1994; Kovács & Julesz, 1994; Kapadia *et al*. 1995; Adini *et al*. 1997; Polat *et al*. 1998; Li & Gilbert, 2002; Stettler *et al*. 2002). The key finding was that non-medicated and remitted schizophrenia patients showed attenuated facilitation effect compared to controls, which supports the hypothesis that lateral interactions are dysfunctional in schizophrenia (Must *et al*. 2004).

The aforementioned study raised several questions. First, the effect of flankers on the target threshold depends on target-to-flanker distances (Polat & Sagi, 1993, 1994). If the distance is small, flankers suppress the detection of the target, whereas at intermediate distances, there is a facilitation effect. At large distances, flankers have no effect on the target threshold. These phenomena may reflect different elements of the visual cortical network, consisting of excitatory and inhibitory interactions (Polat & Sagi, 1993, 1994; Kovács & Julesz, 1994; Kapadia *et al*. 1995; Adini *et al*. 1997; Polat *et al*. 1998; Li & Gilbert, 2002; Stettler *et al*. 2002). Therefore, the effect of target-to-flanker distance on target threshold should be investigated in schizophrenia. Second, the issue of diagnostic specificity must be clarified. Is the lateral interaction impairment specific for schizophrenia or is it also detectable in bipolar disorder? Third, the relationship between clinical symptoms and lateral interaction im-

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pairments has not been evaluated in detail. The purpose of this study was to investigate these issues. Our specific hypotheses were as follows: (1) patients with schizophrenia show lateral interaction impairments; (2) the deficit of lateral interactions does not correlate with clinical symptoms. The critical issue was whether our psychophysical procedure is able to discriminate patients with schizophrenia and bipolar disorder or not.

METHOD

Participants

Twenty-four patients with schizophrenia (15 male, 9 female; 12 paranoid, 6 residual, 5 undifferentiated, 1 disorganized), 22 patients with type I bipolar disorder with a history of psychosis (13 male, 9 female), and 20 healthy controls (12 male, 8 female) participated in the study. The patients were clinically stabilized, well-functioning out-patients. Fifteen patients with schizophrenia received medication [olanzapine ($n=5$), risperidone ($n=7$), amisulpride ($n=3$), citalopram ($n=5$), sertraline ($n=4$)], and 12 patients with bipolar disorder were medicated [olanzapine ($n=4$), risperidone ($n=4$), valproate ($n=5$), lithium ($n=5$), citalopram ($n=7$), sertraline ($n=1$), paroxetine ($n=2$)]. The unmedicated sample from both groups did not receive medication at least for 12 weeks. These patients refused medication because of the absence of subjective complaints but agreed to participate in a regular clinical monitoring to avoid relapse. The diagnosis was based on DSM-IV criteria (APA, 1994). All participants received the Mini-International Neuropsychiatric Interview Plus (M.I.N.I.; Sheehan *et al.* 1998). Clinical symptoms were measured by the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984*a*), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984*b*), Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960). None of the bipolar patients displayed manic episode at the time of testing [Young Mania Rating Scale (YMRS; Young *et al.* 1978) <4 points in each patient]. Four bipolar patients and one schizophrenia patient fulfilled the criteria of depressive episode. The inter-rater correlations between two assessors were high for each rating scale ($r>0{\cdot}8$). General intellectual abilities were determined with the revised Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981). History of neurological disorders, head injury, substance abuse, and electroconvulsive therapy were the general exclusion criteria. Toxicological screening for psychoactive substances was routinely performed. All participants were screened for ocular pathology and had normal or corrected-to-normal visual acuity. The study was approved by the Ethics Committee of Szeged University and after a complete description of the study, informed consent was obtained. The clinical and demographical data are shown in Table 1.

Stimuli and procedure

Stimuli were Gabor patches which are small bar-like elements defined by specific orientation and luminance distribution (Fig. 1*a*). The luminance-contrast profile of a Gabor patch is formed by the multiplication of a sinusoidal waveform with a Gaussian envelope. Gabor patches are ideal stimuli for neurons in primary visual areas, following the receptive field properties of these cells (Polat *et al.* 1998). The patches were characterized by wavelength (λ) (the reciprocal of spatial frequency) and Gaussian distribution equal to $0{\cdot}15^\circ$ of visual angle. The spatial frequency (the number cycles consisting of high and low luminance elements under 1° of visual angle) was 6·7 cycles/degree. The distances between target and high contrast (40%) flankers were 0, 1, 2, 3, 4, 6, 9 or 12λ (Michelson contrast: the difference between maximal and minimal luminance divided by their sum) (Fig. 1 *b–d*).

Stimuli were presented on a gamma-corrected Acer AL1911 monitor (resolution, 1280×1024 pixels; refresh rate, 100 Hz; VSG graphic card, version 5.02, Cambridge Research System Ltd, Rochester, UK), controlled by an IBM-compatible PC. The viewing distance was 100 cm. The mean luminance of the display was 50 cd/m^2, the mean background luminance was 5 cd/m^2 (Spectra Pritchard 1980A-CD photometer; Glen Spectra, Middlesex, UK).

Before each trial, a fixation cross (length $0{\cdot}3^\circ$ of visual angle) appeared at the center of the screen. Subjects were asked to press the space key on the computer keyboard to initiate the trial. First, a blank display of 500 ms was presented. After the 500-ms display, a brief interval

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Table 1. *Demographic and clinical data*

	Schizophrenia ($n=24$)	Bipolar disorder ($n=22$)	t	p
Age (years)	40·5 (20–67, 11·0)	36·6 (22–60, 9·9)	1·24	0·22
Gender (male/female)	15/9	13/9	—	—
Education (years)	11·4 (6–19, 3·8)	11·5 (8–19, 3·6)	−0·12	0·91
IQ (WAIS-R)	102·4 (80–126, 13·2)	108·5 (87–138, 12·0)	−1·70	0·10
Illness duration (years)	10·8 (2–27, 6·6)	12·3 (1–32, 10·2)	−0·57	0·57
Parental socioeconomic status*	3	3	—	—
SANS				
Affective flattening	12·5 (4–24, 6·0)	12·9 (5–27, 6·3)	−0·20	0·84
Alogia	5·7 (0–12, 3·5)	5·4 (0–12, 3·4)	0·29	0·78
Apathy	5·6 (1–14, 3·2)	7·5 (1–16, 4·6)	−1·56	0·11
Anhedonia	7·5 (3–17, 4·2)	8·7 (2–20, 5·2)	−0·85	0·40
Attention	4·8 (2–12, 2·2)	4·3 (1–9, 2·4)	0·77	0·45
SAPS				
Hallucinations	2·1 (0–4, 1·3)	1·5 (0–4, 1·3)	1·61	0·11
Delusions	2·2 (0–9, 2·4)	1·7 (0–5, 1·3)	0·85	0·40
Bizarre behavior	1·2 (0–4, 1·1)	0·7 (0–3, 1·0)	1·37	0·18
Thought disorder	3·1 (0–8, 1·9)	3·8 (2–7, 1·5)	−1·37	0·18
HAMD	9·7 (3–18, 3·5)	13·3 (5–24, 4·7)	−3·00	0·005

Data are mean (range, S.D.) compared with two-tailed t tests. The level of significance was $p<0·004$ (Bonferroni corrected).

The demographic parameters of the controls ($n=20$; 12 male, 8 female) were as follows: age 39·1 years (range 20–67 years, S.D. = 16·4); education 12·3 years (range 8–20 years, S.D. = 3·5); IQ 109·1 (range 90–133, S.D. = 12·7); parental socioeconomic status, 3. One-way ANOVAs revealed no significant between-group differences for age, education, and IQ ($F<2$, $p>0·1$).

HAMD, Hamilton Rating Scale for Depression; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; WAIS-R, Wechsler Adult Intelligence Scale.

* Median level according to the Hollingshead index (range 1–5).

of 90 ms appeared during which stimuli were presented. Observers were asked to indicate if they detected the target by pressing separate keys on the computer keyboard ('1' = yes, '9' = no). The next trial was not initiated without a response. Responses with reaction times exceeding 2000 ms were eliminated. The experimenter visually monitored the subjects during the whole procedure to ensure fixation. Contrast threshold was measured using the Levitt (1971) staircase method, which converges at 79% performance level. In the case of three consecutive correct responses (hits), contrast was decreased by 0·1 log unit, whereas one incorrect response (miss) resulted in an increase of 0·1 log unit in target threshold. One decrease or one increase of the contrast was considered as a reversal. One block of trials terminated after eight reversals. Contrast threshold was the average of the last seven reversals.

During each flanker block, the target-to-flanker distance was constant, whereas in controls blocks, subjects detected the isolated target in the absence of flankers. The order of flanker blocks with different target-to-flanker distances was counterbalanced across participants. Threshold changes at each target-to-flanker distance were determined relative to the detection of isolated targets (Polat & Sagi, 1993, 1994). Before testing, participants were given a practice run during which contrast threshold was measured for an isolated target. After each block, participants received a break to avoid fatigue.

Data analysis

STATISTICA 6.0 software (StatSoft Inc., Tulsa, OK, USA) was used for data analysis. Contrast threshold changes were expressed in a logarithmically transformed scale. The normality of data distribution and the equality of variance were assessed by Kolmogorov–Smirnov and Levene's tests respectively. The data did not deviate from normality or equality of variance. Analysis of variance (ANOVA) was used with contrast threshold changes as a dependent variable, experimental group as a between-subject factor, and target-to-flanker distance as a within-subject factor. Lower-bound correction was used to adjust degrees of freedom. Scheffé tests and two-tailed t tests were used for *post-hoc* comparisons. F tests were used for analysis of quadratic trend in the psychophysical data. Effects sizes also were determined (Cohen's d: differences between means divided by the pooled standard deviation) (Cohen, 1988). Pearson's

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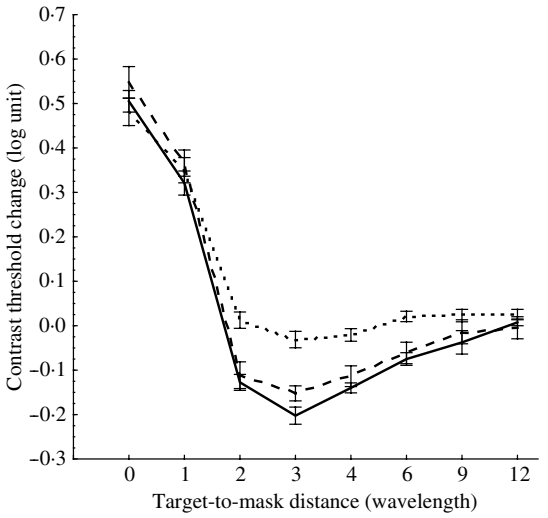


FIG. 2. Mean contrast threshold changes as a function of target-to-flanker distances (λ) in patients with schizophrenia ($n=24$; ····), bipolar disorder ($n=22$; – – –), and healthy controls ($n=20$; ——). Error bars indicate standard error of the mean.

correlation coefficients (r) were calculated between psychophysical data and scores on clinical rating scales. One-way ANOVA and t tests were used for the analysis of demographic data and clinical rating scales. The level of significance was set at $p<0{\cdot}05$. Where appropriate, Bonferroni corrections were used to avoid false-positive results due to multiple comparisons.

RESULTS

Clinical and demographical data

Table 1 demonstrates that there were no significant differences between patients with schizophrenia and bipolar disorder with the exception of HAMD scores which was higher in the bipolar group.

Psychophysics

The ANOVA conducted on contrast threshold changes during flanker presentation revealed significant main effects of group [$F(2, 63)=11{\cdot}76$, $p<0{\cdot}0001$], flanker distance [$F(1, 63)=388{\cdot}63$, $p<{\cdot}001$, $\varepsilon=0{\cdot}14$] and a two-way interaction between group and flanker distance [$F(2, 63)=3{\cdot}91$, $p<{\cdot}05$, $\varepsilon=0{\cdot}14$]. Scheffé tests revealed significant differences between controls and patients with schizophrenia ($p<0{\cdot}001$), between patients with schizophrenia and bipolar disorder ($p<0{\cdot}01$), but not between controls and patients with bipolar disorder ($p=0{\cdot}31$) (Fig. 2).

Table 2. *Comparison of psychophysical data from schizophrenia patients (Scz) ($n=24$), bipolar patients (BP) ($n=22$), and controls (Cont) ($n=20$)*

Target-to-flanker distance (λ)	t (Scz *v.* Cont)	Cohen's d (Scz *v.* Cont)	t (Scz *v.* BP)	Cohen's d (Scz *v.* BP)
0	0·59	0·23	1·42	0·45
1	−0·73	0·23	0·39	0·15
2	−5·39*	1·29	−3·58*	1·00
3	−6·37*	1·41	−4·80*	1·41
4	−6·43*	1·42	−3·47*	1·00
6	−5·26*	1·25	−3·15*	0·89
9	−2·30	0·78	−1·53	0·41
12	−1·21	0·45	−1·11	0·44

The table shows results from comparisons with two-tailed t tests.
* The level of significance was $p<0{\cdot}006$ (Bonferroni corrected: 0·05/8).

Since the normal relationship between contrast threshold changes and flanker distances can be described with a U-shaped curve (Fig. 2), we investigated whether the impairment of schizophrenia patients specifically affected this quadratic function. F tests revealed significant group (controls *versus* schizophrenia) by flanker distance interaction for a quadratic trend [$F(1, 63)=18{\cdot}11$, $p<0{\cdot}001$]. A similar effect was observed when patients with schizophrenia and bipolar disorder were compared [$F(1, 63)=15{\cdot}77$, $p<0{\cdot}001$]. Table 2 shows the t test comparisons which demonstrated that patients with schizophrenia had impaired contrast threshold changes at medium target-to-flanker distances (2–6λ) compared to controls and patients with bipolar disorder. The effect sizes were large. Fig. 2 depicts that in this flanker distance range, patients with schizophrenia did not show contrast threshold enhancements. At inhibitory short-range distances (0 and 1λ) and at large distances (>6λ), there were no significant impairments. Similarly, there were no significant differences between the experimental groups regarding averaged contrast thresholds for isolated targets in the absence of flankers [control mean, 4·9% (S.D. = 1·7); schizophrenia, 5·6% (S.D. = 2·0); bipolar, 5·8% (S.D. = 1·8); one-way ANOVA, $F<2$, $p=0{\cdot}22$].

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Effects of clinical symptoms, gender, and medication

We found no significant correlations between contrast threshold changes and SANS, SAPS, HAMD, and IQ values ($r<0{\cdot}3$). Separate ANOVAs revealed no significant differences between medicated and non-medicated patients [schizophrenia ($F<1$, $p=0{\cdot}67$); bipolar ($F<1$, $p=0{\cdot}42$)]. Male and female patients performed similarly ($F<1$, $p=0{\cdot}80$).

DISCUSSION

In accordance with our initial hypothesis, we found that patients with schizophrenia, but not patients with bipolar disorder, showed significantly less contrast threshold enhancements when the target-to-flanker distances were 2–6λ. This phenomenon did not appear to be significantly affected by clinical symptoms and medication. Our results suggest a specific dysfunction of excitatory connections in early visual areas of schizophrenia patients. The local analysis of contrast and inhibitory interactions were spared in this sample, which may suggest that connectivity is spared in short distances but fails over longer ones or that *N*-methyl-D-aspartate (NMDA) glutamate receptor-dependent excitatory processes are more affected than inhibitory processes. These findings are replications and extensions of our previous exploratory study (Must *et al.* 2004), in which we found reduced facilitation at 4λ target-flanker distance in another independent, remitted and non-medicated schizophrenia group. However, in that study only one target-flanker distance was used and no psychiatric control group was included. It is of particular interest that patients with schizophrenia and bipolar disorder did not differ markedly in demographical and clinical measures, contrary to the assumptions that bipolar disorder is less severe than schizophrenia (Tsuang & Dempsey, 1979). This may be due to the fact that both groups included clinically stabilized out-patients. This suggests that the observed perceptual dysfunction is a trait-related phenomenon and it is not a consequence of non-specific generalized deterioration. By the inclusion of a more heterogeneous and severely affected schizophrenia population, we expect a more severe impairment which may be extended to general stimulus encoding disabilities. In addition, by the inclusion of patients with more severe disorganization symptoms, an additional correlation between perceptual organization and clinical disorganization may occur, as shown by previous studies (Silverstein *et al.* 2000; Phillips & Silverstein, 2003).

Recent reviews of the literature suggest that schizophrenia and bipolar disorder have several common and overlapping features, including some aspects of clinical phenomenology, neuropsychological impairments, and a partially shared genetic background (Ketter *et al.* 2004; Tsuang *et al.* 2004). In contrast, there is some evidence that decreased interneuronal neuropil and increased neuronal density can be detected only in schizophrenia but not in bipolar disorder (Selemon & Rajkowska, 2003), suggesting disease-specific alterations in cellular connectivity. Together with previous observations using the visual backward masking task in patients (Green *et al.* 1994) and in their biological relatives (Kéri *et al.* 2001), the present report suggests that particular visual perceptual tests are able to discriminate patients with schizophrenia and bipolar disorder.

Despite the relatively small sample size, we were able to demonstrate large effect sizes, suggesting a strong and reliable phenomenon. Normal inhibition at short target-to-flanker distances and the absence of significant dysfunctions for isolated targets are against a non-specific deficit, which could be the consequence of abnormal encoding and processing of briefly presented stimuli. The patients were impaired in the range where the controls showed a robust contrast threshold decrease, which means that because of the facilitation effect of lateral flankers, target detection was easier. This finding contradicts the possibility that the results are due to task difficulty. Similarly, less reliability in the critical range of target-to-flanker distance (2–6λ) is unlikely to play a role, because true score values were similar across the whole range of distances tested (reliability coefficient, $\alpha>0{\cdot}9$) (Chapman & Chapman, 1978). Further studies should parametrically manipulate task difficulty and true-score variance in order to investigate their effect on task performance.

We used a modified staircase method with relatively large steps and a single stimulus interval (yes/no decision). In typical experiments,

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two consecutive stimulus intervals are used, and subjects are asked to decide whether the first or second interval contained the stimulus. However, this method includes a working-memory component, requiring the maintenance of the first interval. To avoid this potential confounding factor, we preferred a simple yes/no paradigm. In a smaller sample of patients [bipolar ($n=10$), schizophrenia ($n=10$)], we conducted a pilot experiment with contrast steps of 5%, two stimulus intervals, and 12 reversals for threshold measurement. As reported in the main study, the significant impairment at 2–6λ distances was observed only in schizophrenia patients. However, the experiment was too long and exhausting for the subjects, and therefore, we preferred the reported method.

Several studies reported that patients with schizophrenia are less able to organize local elements of the visual environment into whole objects (Cox & Leventhal, 1978; Place & Gilmore, 1980; Silverstein *et al*. 1996, 2000; Doniger *et al*. 2001). This failure of perceptual organization may be the consequence of abnormal lateral interactions of local processing units in early visual cortex. The physiological bases of the present psychophysical method are well characterized. For example, Kapadia *et al*. (1995) measured contrast thresholds in humans in parallel with single cell recordings from monkey V1. They found that contrast threshold for a target bar was improved 40% by a lateral flanker. Consistently with the feature specificity of V1, the effect was eliminated when the bars were separated along their axis, displaced from collinearity or their relative orientation was changed. Recordings from monkey V1 revealed that neurons showed a similar facilitation effect for a second bar outside their receptive field with a high location and orientation specificity. Therefore, human behavioral data and electrophysiological responses of V1 neurons followed the same rule. Using the method of the present study, Polat *et al*. (1998) found significant facilitation when Gabor patches with near-threshold contrasts were presented in the receptive field of cat visual neurons and were flanked by high-contrast collinear elements in the surrounding visual space. These results suggest that this is a reliable method to investigate low-level lateral interactions in early visual cortex.

However, it has been suggested that attention is necessary to achieve lateral interaction effects by modulating target-flanker interactions (Freeman *et al*. 2001, 2003). Is schizophrenia patients' deficit a mere consequence of attentional failure? First, flankers did have a significant effect on target threshold in the inhibitory range which suggests that sufficient attentional resources were allocated. Second, schizophrenia patients with spared Continuous Performance Test performances, a procedure devoted to the measurement of sustained attention and rapid visual processing, do show lateral interaction deficits (Must *et al*. 2004). Third, while patients with schizophrenia and bipolar disorder similarly scored on the attention component of the SANS, only the schizophrenia patients showed the flanker facilitation deficit. Fourth, recent data from animal studies have proven that lateral interactions are related to intrinsic connections within early visual cortex rather than to feedback projections from higher-order cortices mediating attentional effects. Stettler *et al*. (2002) determined the extent, density, and orientation specificity of V1 intrinsic connections and feedback pathways from higher-level cortical areas. They found that whereas intrinsic connections link similarly oriented domains in V1 (e.g. collinear target and flankers), feedback pathways have no such specificity. This suggests that V1 intrinsic horizontal connections provide a more likely substrate for orientation-specific perceptual effects such as facilitation of contrast detection by collinear flankers (Stettler *et al*. 2002). Fifth, recent clinical data from patients with amblyopia indicated impaired lateral interactions, an adult visual system malfunctioning due to abnormal development of the primary visual cortex during the critical period (Polat *et al*. 2004). Therefore, keeping in mind the limitations of a pure psychophysical approach, we argue that the lateral interaction deficit of schizophrenia patients may reflect the pathology of intrinsic excitatory connections in early visual areas, probably as a part of various cortical disconnection syndromes (Friston, 1998). Phillips & Silverstein (2003) emphasized that abnormal neural connections within and between cortical regions that activate synaptic channels via NMDA receptors are critical in schizophrenia and may directly contribute to perceptual disorganization phenomena.

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Abnormal neural connectivity due to disturbed synaptic development and plasticity in the occipital cortex (Selemon *et al*. 1995; Eastwood & Harrison, 1998; Eastwood *et al*. 2000; Mirnics *et al*. 2001; Veldic *et al*. 2004) may play an important role in perceptual organization failure. This may provide a direct link between the pathophysiology and experimental psychology of schizophrenia.

The exact functional consequences of impaired lateral interactions and perceptual organization dysfunctions are unknown. Silverstein *et al*. (2000) underlined the importance of perceptual organization failure in disorganized symptoms and thought disorder. Doninger *et al*. (2001) suggested that perceptual organization dysfunctions contribute to the muted world experience of patients with negative symptoms. Perceptual anomalies were dissociated from higher-level functions of repetition priming and word prompting (Doninger *et al*. 2001). Some authors proposed that perceptual disorders such as unclear seeing, partial or skewed sight, disrupted rectilinearity, and abnormal figure-ground segregation are parts of the basic symptoms of schizophrenia that are detectable before the onset of first frank psychotic symptoms (Klosterkötter *et al*. 2001). Abnormal connectivity within the visual cortex may be related to these perceptual disorders, which raises the possibility that the present method will serve as a useful tool to determine trait- or prodrome-related phenotypes of schizophrenia. In order to gain more insight into the pathophysiology of visual integration deficits, future studies should combine electrophysiological and psychophysical measures by which specific mechanisms related to short-range and long-range lateral interactions can be investigated (Zemon & Ratliff, 1982; Sokol *et al*. 1992; Grose-Fifer *et al*. 1994).

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DECLARATION OF INTEREST

None.

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