Neuropsychopharmacology (2013) 38, 2607–2612

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Altered Contextual Modulation of Primary Visual Cortex Responses in Schizophrenia

Kiley Seymour*[,1,2], Timo Stein[1,3,4], Lia Lira Olivier Sanders[1,3], Matthias Guggenmos[1,5], Ines Theophil[1] and Philipp Sterzer[1,3,5]

[1]Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Department of Cognitive Science, Centre of Excellence in Cognition and its Disorders, Macquarie University, Sydney, NSW, Australia; [3]Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, Germany; [4]Center for Mind/Brain Sciences, CIMeC, University of Trento, Trento, Italy; [5]Bernstein Center for Computational Neuroscience, Berlin, Germany

Schizophrenia is typically associated with higher-level cognitive symptoms, such as disorganized thoughts, delusions, and hallucinations. However, deficits in visual processing have been consistently reported with the illness. Here, we provide strong neurophysiological evidence for a marked perturbation at the earliest level of cortical visual processing in patients with paranoid schizophrenia. Using functional magnetic resonance imaging (fMRI) and adapting a well-established approach from electrophysiology, we found that orientation-specific contextual modulation of cortical responses in human primary visual cortex (V1)—a hallmark of early neural encoding of visual stimuli—is dramatically reduced in patients with schizophrenia. This indicates that contextual processing in schizophrenia is altered at the earliest stages of visual cortical processing and supports current theories that emphasize the role of abnormalities in perceptual synthesis (eg, false inference) in schizophrenia.
Neuropsychopharmacology (2013) **38,** 2607–2612; doi:10.1038/npp.2013.168; published online 7 August 2013

Keywords: schizophrenia; context; visual perception; fMRI; primary visual cortex; surround suppression; inhibition

INTRODUCTION

Schizophrenia is an illness that is commonly linked to high-level cognitive dysfunction, typically manifesting itself in disorganized thoughts, delusions, and hallucinations. However, recent models of schizophrenia suggest that these higher-level cognitive symptoms might reflect a more pervasive deficit, starting with alterations at the earliest stages of perceptual processing (Fletcher and Frith, 2009; Phillips and Silverstein, 2003).

It has also recently been argued that our understanding of schizophrenia may greatly benefit from the employment of the rigorous methodological approaches used in the field of vision science (Silverstein and Keane, 2011). The visual system, and in particular the primary visual cortex (V1), has been the most extensively studied brain system to date and has thus played a central role in our understanding of brain function in general. For instance, because V1 has a strict retinotopic organization and V1 neurons respond selectively to specific low-level stimulus features, such as line orientation, researchers can use V1 as a model to examine cortical coding principles with great experimental precision. In this experiment, we exploited a well-established property of processing in V1—contextual modulation of neuronal responses to visual stimuli—to probe the integrity of early visual cortical mechanisms in schizophrenia. Contextual modulation is the modulation of responses to stimuli placed within a neuron's receptive field by stimuli presented in adjacent regions outside the classical receptive field (Blakemore and Tobin, 1972). As a number of recent behavioral experiments have suggested a weakening of contextual processing in schizophrenia (Dakin *et al*, 2005; Fogelson *et al*, 2011; Must *et al*, 2004; Tadin *et al*, 2006; Uhlhaas *et al*, 2006; Yoon *et al*, 2009), we investigated the neural mechanisms of contextual modulation at the earliest level of visual cortical processing—retinotopically defined V1—in patients with the illness.

MATERIALS AND METHODS

Participants

Our functional magnetic resonance imaging (fMRI) study consisted of 18 participants with paranoid schizophrenia and 18 healthy controls matched on age, gender, and years of education (for demographic and clinical characteristics, see Table 1). All patients were clinically stable and recruited as outpatients. Diagnosis was made by experienced psychiatrists using a structured clinical interview for DSM-IV Axis I disorders (SCID I) and the Positive and

*Correspondence: Dr K Seymour, Department of Cognitive Science, Centre of Excellence in Cognition and its Disorders, Macquarie University, Balaclava Road, North Ryde, Sydney, NSW 2109, Australia, Tel: +61 2 9850 6059, E-mail: kileyseymour@gmail.com
Received 5 May 2013; revised 15 June 2013; accepted 24 June 2013; accepted article preview online 11 July 2013

Table 1 Subject Demographic and Patient Clinical Characteristics

	Patients ($n = 18$)		Controls ($n = 18$)		t value
	Mean	SD	Mean	SD	
Gender (% of male subjects)	53.80		53.80		
Age (years)	33.27	5.57	33.72	6.35	0.00 ns
Education (years)	15.79	4.19	15.39	3.73	0.40 ns
Illness duration (years)	9.00	6.88	—	—	—
CPZ equivalent (mg/day)	282	256.65	—	—	—
PANSS					
Positive symptom	11.90	4.62	—	—	—
Negative symptoms	13.90	5.17	—	—	—
General symptoms	24.80	7.89	—	—	—

Abbreviation: ns, not significant.

Negative Syndrome Scale (Kay *et al*, 1987). All but one patient were on stable doses of antipsychotic medication at the time of testing. Exclusion criteria for both groups were benzodiazepine-intake within 15 h prior to the experiment, illicit substance use up to 10 days before the experiment, and neurological co-morbid diagnoses. Prior to scanning, participants were given an opportunity to familiarize themselves with the stimuli and task. All participants had normal or corrected-to-normal vision and gave written informed consent before participation in the study, which was approved by an accredited Medical Ethics Review Committee.

Measuring Orientation-Specific Surround Suppression.

We adapted a standard approach from electrophysiology for investigating contextual modulation in V1. Using fMRI, we followed a similar methodology and stimulus design used by Zenger-Landolt and Heeger (2003) to measure suppression of the blood oxygenation level-dependent (BOLD) response associated with viewing a center (annulus) grating embedded within one of two contextual surround gratings, oriented either orthogonal or parallel to the center grating's orientation (Figure 1). This specific stimulus configuration (ie, using an annulus rather than a central disc grating) was chosen to allow for the best dissociations of visual regions corresponding to the 'center' grating from regions representing the 'surround' grating within separately mapped retinotopic areas (V1, V2 and V3). It has been well established that, especially in area V1, neurons tuned to the orientation of the contextual surround grating suppress the responses of neurons tuned to the orientation of the center grating (Blakemore and Tobin, 1972; Schwartz *et al*, 2007; Zenger-Landolt and Heeger, 2003). Moreover, an important feature of this surround suppression is its orientation specificity, with suppression being strongest when the orientations of the center grating and the contextual surround are parallel (Blakemore and Tobin, 1972; Schwartz *et al*, 2007).

Stimuli and Design of the Main Experiment

We used an optimized block design in which a grating (a sinusoidal pattern; 1.1 cycle/deg, reversing in phase at 4 Hz) was continuously displayed within the annular 'center' region while a grating in the 'surround' regions appeared and disappeared with a square-wave temporal profile lasting 20 s per cycle (ie, 10 s 'off' and then 10 s 'on', as in Figure 1). This temporal structure was selected in order to best maximize surround suppression of the BOLD response (Haynes *et al*, 2003; McDonald *et al*, 2009; Williams *et al*, 2003; Zenger-Landolt and Heeger, 2003). The annulus region extended from 1.8 to 4.0° eccentricity and the 'surround' region, which included the areas both inside and outside of the annulus, extended to 12.0° eccentricity. Two different center-surround configurations were used: a 'parallel surround' condition where the annulus center grating and the surround grating were presented at the same orientation, and an 'orthogonal surround' condition where the annulus center grating and the surround grating were presented with an angular difference of 90°. Each run comprised four on–off center-surround cycles for each condition, presented in an alternating sequence over the run. The order of these conditions was counterbalanced across runs and subjects. Blank fixation periods (10 s) were also displayed at the beginning, middle, and end of each run, resulting in a run duration of 3 : 17 min.

To avoid any orientation processing biases whereby greater BOLD responses are elicited for horizontal and vertical orientations compared with diagonal orientations (Engel and Furmanski, 2001), we presented each condition at four different stimulus orientations (0, 45, 90 and 135°) such that every discrete stimulus orientation occurred once over the course of each run. Hence, the parallel and orthogonal blocks differed only in the relative orientation of center and surround and not in the distribution of absolute orientations. Blocks were also ordered in a balanced design over the entire scan session so that each block type occurred an equal number of times before every other block type.

To control for attentional set and to ensure that participants were not moving their eyes during the experiment, we used an incidental task, where a fixation point (0.25° in diameter) was present throughout all runs and participants were asked to fixate and respond with a button press when its color changed from white to red. These changes occurred at 9–10 random time intervals distributed across each 20-s block.

Participants were scanned for a total of 10 fMRI runs. Five runs were devoted to measuring suppression of the BOLD response associated with parallel and orthogonal surrounds. Two independent localizer runs, carried out after the first three experimental runs, were employed to isolate the cortical representation of the annulus from the surround representation, and a further three runs were conducted to perform standard phase-encoded retinotopic mapping (Sereno *et al*, 1995).

We also measured eye movements from the majority of participants (14 from the patient group and 12 from the control group) in a separate session outside of the scanner following the fMRI experiment. Subjects viewed an identical stimulus to that used in the fMRI experiment and were engaged in the same fixation task. Eye movements that exceeded 0.5° eccentricity from the fixation point were recorded using a video-based eye tracker (sampling rate: 250 Hz, spatial resolution: 0.05°, Cambridge Research Systems, UK).

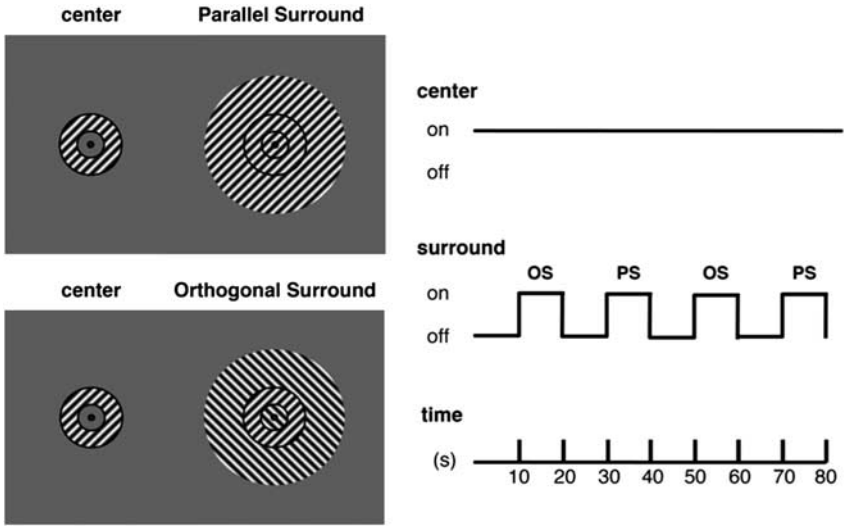

Figure 1 Example stimuli. Two center-surround conditions were used: a 'parallel surround' (PS) and an 'orthogonal surround' (OS). The central annulus region was considered the 'center' in this stimulus configuration. This stimulus design allowed for maximum blood oxygenation level-dependent (BOLD) suppression and optimal discrimination of visual regions corresponding to the 'center' and 'surround' parts of the stimulus within retinotopic cortex.

fMRI Data Acquisition

Functional images were acquired in a 3 Tesla Siemens (Erlangen, Germany) Trio scanner using a gradient echo planar imaging (EPI) sequence and a twelve-channel head coil. We collected 33 slices positioned at an orientation parallel to the calcarine sulcus using a descending sequence with the following parameters: repetition time (TR) 2.5 s; echo time (TE) 30 ms, flip angle: 81°, slice thickness 3 mm, interslice gap 0.3 mm, voxel size $3 \times 3 \times 3$ mm. For each subject, a high-resolution (1 mm isotropic) T1-weighted MPRAGE image was acquired for surface reconstruction and was used as an anatomical reference. Functional data were co-registered to the raw anatomical scan and not transformed to any standard coordinate system. We corrected for head motion and made a mean intensity adjustment (global scaling), but no spatial smoothing was applied to the functional data.

Areas V1, V2, and V3 of the visual cortex were delineated manually on the basis of field sign alternations (Slotnick and Yantis, 2003) that were projected on inflated cortical maps created in Freesurfer (Dale *et al*, 1999; Fischl *et al*, 1999).

We restricted our analysis for examining contextual suppression of the BOLD response to those voxels within retinotopic cortex that responded exclusively to the center annulus grating (ie, surviving a threshold of $p<0.05$, uncorrected, in an SPM contrast between activation associated with a 'central annulus alone' condition and activation associated with a 'surround alone' condition—collected during separate independent localizer runs). Our regions of interest (ROIs) were then created by intersecting this localiser mask with the separate retinotopic areas. For each subject, signal time courses for every voxel were estimated using a general linear model (GLM) as implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). We modeled separate regressors for the baseline condition, the parallel surround condition, and the orthogonal surround condition, all convolved with the canonical haemodynamic response function. Following this, using the Matlab-based REX toolbox (http://web.mit.edu/swg/software.htm), signal time courses were extracted from each ROI and a voxel-weighted average was computed such that voxels that gave the strongest 'central annulus alone' response during the independent localizer runs were given the highest weighting. Specifically, voxels within the ROI that exhibited the highest *t*-values in the SPM contrast between 'central annulus alone' and 'surround alone' were taken as the weights to be used for computing a weighted average across all voxels within the ROI. *t*-values were normalized to sum to 1 and a weighted sum was computed.

Data were then normalized to a percent signal change, which was referenced to the local mean signal elicited during fixation periods. BOLD suppression was calculated for the two surround conditions by subtracting the mean signal measured during the baseline condition. For each ROI, orientation-specific contextual suppression was evaluated in a repeated-measure ANOVA using the factors group and orientation.

RESULTS

In healthy participants, we found suppression of BOLD responses in V1 to be significantly stronger when the contextual surround grating was oriented parallel in comparison to when it was oriented orthogonal ($t(17) = -2.83$ $p = 0.012$; see Figure 2), consistent with previous findings of orientation-specific contextual suppression (Blakemore and Tobin, 1972; Haynes *et al*, 2003; McDonald *et al*, 2009; Williams *et al*, 2003). This was also the case in V2 ($t(17) = -2.86$, $p = 0.011$) and V3 ($t(17) = -3.06$, $p = 0.009$). In contrast, the data from schizophrenic patients revealed a marked alteration of orientation-specific contextual suppression, with the surround grating's orientation exerting no significant influence on the magnitude of BOLD suppression in V1, V2, or V3 (all $t<1$). This difference in orientation-specific contextual suppression

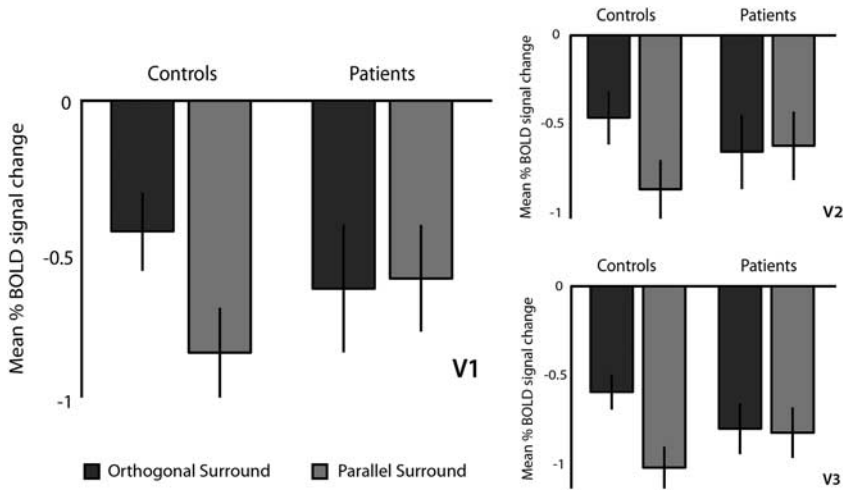

Figure 2 Mean percent signal change of the blood oxygenation level-dependent (BOLD) response in V1, V2, and V3 following the presentation of oriented contextual surrounds. Negative values indicate suppression of the BOLD response relative to a 'center alone' baseline condition (the surround 'off' period). Error bars represent SEM.

between controls and patients was reflected in a significant group-by-orientation interaction for V1 ($F(1, 34) = 4.87$ $p = 0.034$), V2 ($F(1, 34) = 4.70$, $p = 0.037$), and V3 ($F(1, 34) = 6.11$, $p = 0.018$).

Importantly, the group difference in orientation specificity between patients and controls was not due to overall weakened suppression in patients, as there was no significant main effect of group in any visual region ($F < 1$), nor could baseline differences in the absence of a contextual surround explain the results, as BOLD responses to the annulus grating alone did not significantly differ between patients and controls ($t < 1$), in addition, there were no significant differences in the size of retinotopically defined ROIs between the two groups ($t < 1$). Furthermore, the lack of orientation-specific contextual suppression in schizophrenic patients is unlikely to be an effect of pharmacological treatment, as a correlation of orientation selectivity (ie, the difference between suppression in the orthogonal and parallel condition) with chlorpromazine equivalents of patients' antipsychotic medication uncovered no significant relationship in any area examined (V1: $R = -0.21$, $p = 0.463$, V2: $R = -0.04$, $p = 0.882$, V3: $R = 0.02$, $p = 0.964$). Furthermore, our results are unlikely to reflect differences in focal attention (Barch *et al*, 2009), as accuracy in performing a fixation task concurrently during the experiment did not differ between groups (mean performance: patients: 81.3% ± 4.8 SD correct, controls: 84.4% ± 5.0 SD, $t(17) = 1.65$, $p = 0.113$), nor did a correlation between the total number of deviant eye movements (recorded in a separate eye-tracking control session) and the magnitude of orientation selectivity reveal a significant relationship for controls ($R = 0.082$, $p = 0.771$) or patients ($R = -0.01$, $p = 0.944$).

Correlations of orientation selectivity with overall PANNS scores failed to show any relationship between illness severity and orientation-specific contextual modulation (positive scores: $R = 0.42$, $p = 0.179$; negative scores: $R = -0.49$, $p = 0.104$; general scores: $R = -0.08$, $p = 0.799$; total score: $R = -0.00$, $p = 0.988$). Moreover, no relationship was found between orientation selectivity and the subjects' daily nicotine intake (controls; $R = -0.31$, $p = 0.38$, patients; $R = -0.14$, $p = 0.65$).

DISCUSSION

These results are the first demonstration of altered contextual neural processing in primary visual cortex of patients with schizophrenia. Although failures to use contextually appropriate information have long been suggested a key feature of the illness (Chambon *et al*, 2008; Cohen and Servan-Schreiber, 1992; Hemsley, 2005; Phillips and Silverstein, 2003; Silverstein and Schenkel, 1997), our data now provide evidence at the neural level that contextual influences on visual information processing in schizophrenia are altered at the earliest stages of the visual cortex.

Specifically, the absence of orientation-specific contextual modulation suggests a disruption of inhibitory neural signals in V1, which is in line with the large body of evidence supporting GABAergic dysfunction in schizophrenia (Benes, 2000; Lewis *et al*, 2005; Nakazawa *et al*, 2012; Yoon *et al*, 2010), as well as NMDA receptor-mediated hypofunction (Corlett *et al*, 2009; Kehrer *et al*, 2008; Phillips and Silverstein, 2003). Such disruptions may affect local inhibitory mechanisms within V1 (Blakemore and Tobin, 1972) or feedback connections from higher areas (Hupe *et al*, 1998; Zipser *et al*, 1996), both of which generate extra-classical receptive field effects in V1, boosting the gain of sensory signals (Angelucci and Bullier, 2003). Moreover, suppression of V1 BOLD responses, as measured in our study, is a classical demonstration of efficient hierarchical encoding of visual information (Rao and Ballard, 1998), whereby the contextual surround provides a statistical prediction of the central signal, and the prediction error (ie, the difference between the prediction and the actual signal) is transmitted to the next stage of processing. Thus, our findings of altered contextual modulation in patients with schizophrenia support current theoretical models that link the positive symptoms of the illness to a disruption in predictive coding (Corlett *et al*, 2009; Fletcher and Frith, 2009; (Silverstein and Schenkel, 1997). Our next challenge will be to disentangle the roles of feedback and local mechanisms in this alteration, for example, by using

experimental designs that preclude local lateral inhibition in V1 (eg, Harrison *et al*, 2007).

Although our analysis did not reveal a direct relationship between psychopathology and orientation-specific suppression in early visual cortex, it should be noted that in order to obtain valid fMRI measurements, we only included outpatients who were diagnosed with paranoid schizophrenia on the basis of previous psychotic episodes but were clinically stable at the time of testing. This is reflected by an average total PANSS score of ~ 50 in our patient sample, which corresponds to only mild clinical impairment (Lawrie *et al*, 2002). The group difference in orientation-specific suppression is therefore unlikely to be related to the current psychopathology of our patients but might rather represent a trait marker for the illness. However, examining patients exhibiting higher levels of delusional thought might reveal a link between symptom severity and the magnitude of orientation-selective suppression. In any case, given that addressing visual function is a more tractable means of examining the integrity of brain mechanisms in schizophrenia, this approach may provide a more precise assessment of neurological impairment in schizophrenic patients (Silverstein and Keane, 2011).

Finally, surround suppression of neural responses is a mechanism ubiquitous to sensory systems, serving to regulate the gain of perceived stimulus contrast and facilitate figure-ground segmentation (Albright and Stoner, 2002; Carandini and Heeger, 2012; Tsubomi *et al*, 2012; Zenger-Landolt and Heeger, 2003). Thus, these data lend support for the vast number of low-level perceptual abnormalities documented in the literature (Butler *et al*, 2008; Butler *et al*, 2005; Dakin *et al*, 2005; Javitt, 2009; Silverstein and Keane, 2011; Uhlhaas and Mishara, 2007; Yoon *et al*, 2010). Furthermore, as nicotine has been shown to mediate gain control mechanisms within V1 and improve the detection of visual stimuli (Disney *et al*, 2007), these findings may account for the increased nicotine intake commonly observed in patients with schizophrenia (Kumari and Postma, 2005). Nonetheless, future research is needed to ascertain whether perturbations of early sensory neural mechanisms, as observed in this study, reflect a discrete problem at lower levels, akin to the earlier reports of a sensory gating deficit in schizophrenia (Braff *et al*, 1978; Freedman *et al*, 1987), or whether the problem is a widespread and pervasive alteration of context-dependent neural processing occurring at all levels of the hierarchy (Corlett *et al*, 2009; Fletcher and Frith, 2009; Silverstein and Schenkel, 1997).

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This research was supported by a grant awarded to KS from the Alexander von Humboldt Foundation. We thank Mark Schira, Colin Clifford and John-Dylan Haynes for their helpful comments.

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