NeuroImage 55 (2011) 1219–1226

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Altered dynamic coupling of lateral occipital complex during visual perception in schizophrenia

Philippe-Olivier Harvey [a,b,*], Junghee Lee [a,b], Mark S. Cohen [a], Stephen A. Engel [c], David C. Glahn [d,e], Keith H. Nuechterlein [a,f], Jonathan K. Wynn [a,b], Michael F. Green [a,b]

[a] Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA
[b] VA Greater Los Angeles, Healthcare Center System, Los Angeles, CA, USA
[c] Department of Psychology, University of Minnesota, Minneapolis, MN, USA
[d] Olin Neuropsychiatry Research Center, Institute of Living, New Haven, CT, USA
[e] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[f] Department of Psychology, University of California, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 29 June 2010
Revised 14 December 2010
Accepted 15 December 2010
Available online 29 December 2010

Keywords:
Functional connectivity/ Dynamic coupling
Lateral occipital complex
Backward visual masking
Schizophrenia
fMRI

ABSTRACT

Introduction: There is mounting evidence that visual perception abnormalities in schizophrenia are partly explained by a dysfunction of the lateral occipital complex (LO). We previously demonstrated that schizophrenia patients had broader topography and reduced magnitude of activity of LO. However, the functional connectivity of LO with other brain regions during visual perception has not been directly investigated in schizophrenia.
Materials and methods: Eighteen patients with schizophrenia and eighteen matched controls performed a backward masking task during functional magnetic resonance imaging (fMRI). Stimulus onset asynchronies were manipulated to change the level of target visibility. To examine connectivity with LO function we conducted psychophysiological interactions (PPI) analyses using: 1) a region of interest (ROI) approach and 2) a whole brain analysis. ROIs were defined based on a contrast of trials on which a target was presented versus null trials in which no stimuli were presented.
Results: Eleven ROIs were identified. Both groups showed similar strength of coupling between LO and the 11 ROIs when visibility was not taken into account. Healthy controls showed clear changes in coupling between LO and prefrontal and parietal regions as a function of target visibility (higher coupling with more visible targets). In comparison, patients showed reduced dynamic coupling with LO in the right superior frontal gyrus (significant after correcting for multiple comparisons) and a trend for reduced coupling in the left precuneus and left inferior frontal regions. Whole brain analysis identified additional regions that showed dynamic coupling with LO in healthy controls, but not in patients.
Discussion: The increased coupling between LO and higher-level parietal and prefrontal regions during visual awareness in healthy controls likely reflects visual reentrant processing. The lack of modulation of coupling between LO and key prefrontal and parietal regions found in schizophrenia may partly reflect abnormalities in LO tuning. The altered LO coupling may contribute to visual perception abnormalities in schizophrenia.

Introduction

Schizophrenia is associated with impairment on a wide range of visual perception tasks, including object recognition, grouping, perceptual closure, face processing, and reading (Butler et al., 2008). These visual perception impairments have been reliably linked to poor functional outcome in patients, through key mediating variables (Butler and Javitt, 2005; Sergi et al., 2006). There is suggestive evidence that visual perception abnormalities in schizophrenia are partly explained by a dysfunction of the lateral occipital complex (LO) (Doniger et al., 2002; Foxe et al., 2005; Green et al., 2009; Wynn et al., 2008). LO is a mid-stage visual processing area that plays a central role in object recognition (Green et al., 2005; Grill-Spector, 2003; Grill-Spector et al., 2001; Kourtzi and Kanwisher, 2000).

LO dysfunction in schizophrenia has been explored with both EEG and neuroimaging approaches. For example, some studies examined an event-related potential, closure negativity (N_{cl}), that is associated with object recognition and distributed over the lateral occipital scalp regions. These studies demonstrated that N_{cl} differs in both magnitude

* Corresponding author. UCLA Semel Institute, West LA VA Healthcare Center, 11301, Wilshire Blvd, 210A, Room 131, Los Angeles, CA 90073-1003, USA. Fax: +1 310 268 4056.
E-mail address: poharvey@ucla.edu (P.-O. Harvey).

1053-8119/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2010.12.045

(Doniger et al., 2002) and pattern (Foxe et al., 2005) in patients with schizophrenia, providing indirect but consistent support for LO abnormalities in schizophrenia. Recent functional magnetic resonance imaging (fMRI) studies from our group explored both the topography and magnitude of LO activity in schizophrenia (Green et al., 2009; Wynn et al., 2008). One study used a visual localizer task for LO (i.e. abstract objects vs. scrambled images) and found that schizophrenia patients activated a significantly larger area in LO compared with normal controls (Wynn et al., 2008). In contrast, the groups did not differ on localizers for retinotopy, or motion detection. This widespread topography could be due to reduced specialization of the neurons within LO. Another study examined LO activation in schizophrenia using a visual backward masking paradigm. In visual masking, the visibility of a target is disrupted by a visual mask that is presented shortly before or after the target. Although both patients with schizophrenia and healthy subjects showed increased LO activation as the masking effect became weaker, patients showed relatively lower magnitude of activity in LO (Green et al., 2009). We proposed that patients' blunted LO response during visual masking may be a neural basis for abnormalities in visual processing.

While activity in visual areas like LO is necessary for object recognition, awareness of an object requires additional contributions from higher cortical areas (Crick and Koch, 1995; Haynes et al., 2005; Rees, 2007). Higher-level visual areas and parietal and prefrontal cortex are involved with conscious detection of visual stimuli (Dehaene et al., 2001; Green et al., 2005; Grill-Spector et al., 2000; Haynes et al., 2005). Other brain regions have reciprocal connections to LO that may enhance the visual representation through attentional or reentrant processes. The investigation of LO connectivity relates well to current theories of the pathophysiology and altered connectivity in schizophrenia. It has been suggested that schizophrenia is not caused by focal brain abnormalities, but results from pathological interactions among brain regions (Friston, 1998). These disconnection theories propose that that core pathology of schizophrenia is an impaired neuromodulation of synaptic plasticity, leading to abnormal functional integration of neural systems (Friston, 1998; Stephan et al., 2009). Hence, it appears likely that the visual perception abnormalities in schizophrenia do not originate solely from the LO dysfunction, but also from altered coupling between LO and other higher-level visual and attentional brain regions.

The current study extends our previous studies of LO dysfunction in schizophrenia by focusing on its functional connectivity. We examine the functional connectivity of LO using the fMRI data from our visual masking paradigm. Visual masking provides significant advantages for the investigating LO dysfunction because: (1) it allows for parametric modulation of target/object visibility, and (2) LO shows strong sensitivity to masking effects. Specifically, we tested the degree to which schizophrenia patients and normal controls showed changes in the strength of LO connectivity as a function of target visibility. The psychophysiological interaction (PPI) analytic approach is well suited to address this type of question. PPI analysis starts with a particular region of interest, in this case functionally-defined LO. It then examines connectivity with this region and whether connectivity changes with cognitive or perceptual task demands (i.e., the degree of masking of a visual target) (Friston et al., 1997). Changes in functional connectivity are also called dynamic coupling in the context of perceptual processing (Haynes et al., 2005).

We hypothesized that healthy controls would show increased coupling between LO and other higher-level brain regions with increasing intervals between target and mask (i.e., greater coupling with LO as the target becomes more visible). In contrast, we hypothesized that patients would show altered dynamic coupling with LO as a function of target visibility. We examined this hypothesis in two ways: first using a region of interest (ROI) approach, and then with a whole brain or voxel-level analysis.

Materials and methods

Participants

Eighteen patients with schizophrenia and 18 healthy controls were recruited from a larger NIMH study of early visual processing in schizophrenia (PI: MFG). Subjects had normal or corrected to normal vision. Schizophrenia patients were 18–60 years of age and recruited from outpatient clinics at the VA Greater Los Angeles Healthcare System (VAGLAHS) and through local board and care facilities. Patients were clinically stable and received the Structural Clinical Interview for DSV-IV Axis I Disorders (SCID) (First et al., 1997) to confirm diagnosis of schizophrenia. We assessed clinical symptoms using the expanded Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993) and examined the BPRS total score, as well as BPRS mean subscales for positive symptoms (thinking disturbance factor) and negative symptoms (withdrawal-retardation factor). All of the patients were medicated (1—conventional antipsychotic, 16 single second-generation, and 2—two second-generation antipsychotic medications). Exclusion criteria for patients included (1) substance abuse or dependence in the last 6 months, (2) mental retardation, (3) history of loss of consciousness>1 h, (4) identifiable neurological disorder, and (5) not sufficiently fluent in English. Normal control participants were recruited through flyers posted in the local community, newspaper advertisements, and website postings. Exclusion criteria for control participants included (1) history of schizophrenia or other psychotic disorder, bipolar disorder, recurrent depression, history of substance dependence, or any substance abuse in the last 6 months based on the SCID (First et al., 1997), (2) avoidant, paranoid, schizoid, schizotypal, or borderline personality disorders based on the SCID for Axis II disorders (First et al., 1996), (3) schizophrenia or other psychotic disorder in a first-degree relative, (4) significant neurological disorder or head injury, and (5) not sufficiently fluent in English.

SCID interviewers were trained to a minimum kappa of 0.75 for key psychotic and mood items through the Treatment Unit of the Desert Pacific Mental Illness Research, Education, and Clinical Center. Participants were evaluated for the capacity to give informed consent and provided written informed consent after all procedures were fully explained, according to procedures approved by the institutional review boards at UCLA and VAGLAHS.

Design and procedure

We examined LO connectivity with PPI according to two approaches: 1) a focused ROI approach and 2) an exploratory whole brain analysis. Both approaches required the initial identification of functional LO using a specialized LO localizer task. For the ROI approach, we focused on a set of regions that responded to targets, regardless of visibility by contrasting between trials in which a target was presented versus null trials in which no stimuli were presented. These ROIs were then subjected to PPI analyses to examine their coupling with LO. To determine whether other brain regions outside the ROIs were involved in LO connectivity, we conducted an exploratory whole-brain analysis in which we examined the entire brain for regions that showed dynamic coupling with LO as a function of target visibility.

Tasks in the scanner

All subjects completed 6 runs of the visual backward masking task followed by 3 localizer tasks (LO, retinotopic areas, and the human motion selective cortex—hMT+) in the scanner. Of these localizers, the one for LO is relevant for the current connectivity analyses. The entire scanning session lasted 60 min. The backward masking task was presented using E-prime software (Psychology Software Tools,

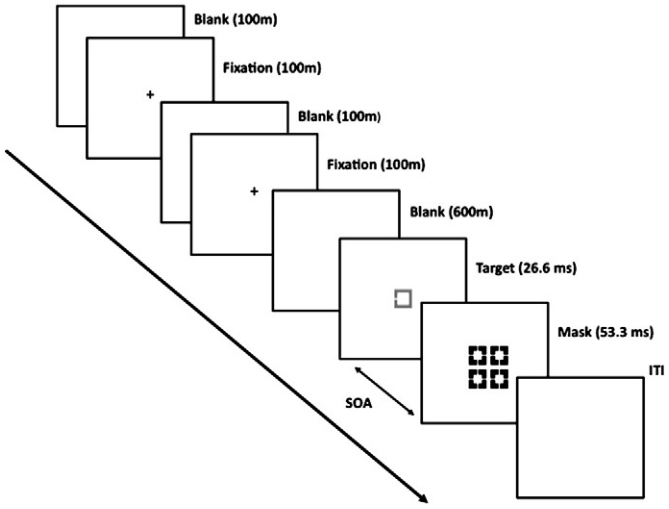

Fig. 1. Schematic diagram of a single trial in a visual backward masking task.

Pittsburgh, PA) and the localizer tasks were presented using MATLAB (The Mathworks, Natick, MA). All tasks were presented with MR-compatible LCD goggles (Resonance Technology, Northridge, CA). The experimental procedures are described elsewhere (Green et al., 2009).

For the visual backward masking task, we employed a rapid event-related design and the trials were presented in a permuted block design to maximize both hemodynamic response function (HRF) estimation and signal detection power (Deneux and Faugeras, 2006; Liu, 2004; Liu and Frank, 2004). The target was a square with a gap on 1 of 3 sides (up, down, or left) that appeared at the center of the screen. The mask was a composite square made up to 4 smaller squares, overlapping the area occupied by the target. The target subtended 5.7° and the mask 10.2° of visual angle. The beginning of each trial was signaled by two 100 ms flashes of a fixation point, followed by a 600-ms blank period (Fig. 1). Then, a target was presented for 26.6 ms, followed by a 53.3-ms mask at 1 of 4 possible stimulus onset asynchronies (SOAs): 26.6, 40, 80, 200 ms. Participants were instructed to identify the location of a gap in the target (up, bottom, or left) by pressing a corresponding button with their dominant hand. The backward masking tasks consisted of 6 runs, each with 30 5-second trials (i.e. 6 trials for each of the 4 SOAs and 6 null trials that included fixation but no stimuli for the total duration of the trial). There were very slight variations in the inter-trial interval depending on the duration of the SOA in the preceding trial.

After the visual masking task, participants performed the LO localizer (described elsewhere (Wynn et al., 2008)). Briefly, the LO localizer task consisted of alternating blocked presentations of pictures of abstract objects and scrambled pictures of objects, with each block containing 10 images presented to a total of 12.5 s (Grill-Spector and Malach, 2004; Malach et al., 1995).

fMRI data acquisition

Scanning was conducted on a 3-T scanner (Siemens Allegra, Germany) in the UCLA Ahmanson-Lovelace Brain Mapping Center. For anatomical reference, a high-resolution, echo planar, axial, T2-weighted series was obtained for each subject prior to functional scanning (repetition time = 6000 ms, echo time = 54 ms, flip angle = 90°, 30 axial slices, field of view = 20 cm). A T2*-weighted gradient-echo sequence was used to detect blood-oxygen level-dependent (BOLD) signal (repetition time = 2000 ms, echo time = 42 ms, flip angle = 80°, voxel size of 3.125 × 3.125 × 4.00 mm with a 1-mm gap), acquiring 24 slices parallel to the anterior commissure-posterior commissure plane.

fMRI initial data analysis

Data were analyzed using Statistical Parametric Mapping software SPM8 (Wellcome Department of Imaging Neuroscience, UK). For preprocessing, images were time-corrected to account for differences in sampling times for different slices, realigned to the first volume to correct for inter-scan movement, spatially normalized to the Montreal Neurological Institute (MNI) space (normalized voxel size: 2 mm × 2 mm × 2 mm) and smoothed with an 6-mm full-width half-maximum (FWHM) Gaussian kernel (Ashburner and Friston, 1997). Low-frequency temporal drifts were removed by applying a high-pass filter. Data were analyzed by the general linear model, in which individual events were modeled by a canonical HRF.

Connectivity analyses

To identify a set of brain regions that showed a significant involvement during visual backward masking task (regardless of target visibility), we ran a random-effect group analysis that included all 36 subjects (patients and controls) for all SOAs (26.6, 40, 80, and 200 ms) versus the null condition. Analyzing the data in this manner does not create a bias toward finding an effect of SOA (changes with increasing visibility) and does not bias toward finding group differences (because groups are initially combined). The statistical threshold was set at $P<0.05$, corrected for multiple comparisons. Eleven distinct clusters of activation were identified and ROIs were created from these clusters using MRIcron software (Rorden and Brett, 2000) (Table 1).

Functional LO was defined as the region with a significant activation for the contrast between the abstract objects and scrambled pictures. An individual activation map was thresholded at $p<0.005$, uncorrected, to ensure that LO activation would be observed for every

Table 1
Regions-of-interest selected for the ROI-approach.

ROI	Size	Hemisphere	MNI coordinates	Brain regions included in ROI
Inf parietal	5115	Left	x = −42, y = −30, z = 44	Inf and Sup parietal gyri (BA 7 and 40)
Lingual 1	1421	Left	x = −4, y = −80, z = −12	Lingual gyrus (BA 18), Cerebellum
Lingual 2	56	Left	x = −14, y = −78, z = 4	Lingual gyrus (BA 18)
Precuneus	52	Left	x = −22, y = −66, z = 36	Precuneus (BA 7)
Insula	356	Left	x = −44, y = 2, z = −4	Insula (BA 13)
Thalamus	303	Left	x = −16, y = −18, z = 10	Thalamus
Inf frontal	149	Left	x = −52, y = 8, z = 28	Inf frontal (BA 9)
Sup parietal	2062	Right	x = 14, y = −64, z = 64	Inf and Sup parietal gyri (BA 7 and 40)
Middle frontal	223	Right	x = 34, y = −4, z = 64	Middle frontal gyrus (BA 6)
Sup frontal	31	Right	x = 44, y = 38, z = 30	Sup frontal gyrus (BA 9)
Medial frontal	106	Right/Left	x = 0, y = −6, z = 54	Medial frontal gyrus (BA 6)

Abbreviation: ROI, Region-of-interest; BA, Brodmann's Area. The name of each ROI was determined by the localization of the peak voxel. The size of each ROI is represented by the number of voxels. MNI coordinates represent the peak voxel of each ROI. ROIs were selected from the contrast between all SOAs versus the null condition for all 36 participants.

Table 2
Demographic data, clinical data and behavioral performance on visual masking task.

	SZ patients ($N=18$)	Healthy controls ($N=18$)	Analysis
Demographic characteristics			
Age (years)	36.8 ± 10.5	42.4 ± 9.1	t = 1.70 df = 34 p = 0.10
Education (years)	13.8 ± 1.6	12.9 ± 0.8	t = -1.95 df = 34 p = 0.06
Gender (M / F)	14 / 4	13 / 5	$\chi^2 = 0.15$ df = 1 p = 0.70
BPRS[a]—total	36.6 ± 8.5		
BPRS—positive[b]	2.0 ± 0.9		
BPRS—negative[b]	1.4 ± 1.0		
Years of illness	12.5 ± 8.0		
No. of hospitalizations	6.2 ± 6.1		
Backward masking task (Accuracy, %)			
SOA1	0.33 ± 0.08	0.33 ± 0.06	
SOA2	0.38 ± 0.10	0.40 ± 0.09	
SOA3	0.70 ± 0.16	0.77 ± 0.20	
SOA4	0.94 ± 0.07	0.93 ± 0.09	

The mean performance (% accuracy) of patients and controls is shown for the four stimulus onset asynchronies (SOAs). Chance performance is 0.33.
[a] BPRS = Brief Psychiatric Rating Scale.
[b] Mean score of each BPRS subscale was calculated by dividing the total score by the number of items included in the subscale.

subject. Any activated areas outside the inferior temporal lobe and occipital lobe were removed based on previous published findings with similar activation (Malach et al., 1995; Tootell et al., 1995). Fourteen healthy controls and 13 schizophrenia patients showed bilateral functional LO activation, 3 healthy controls and 3 patients showed LO activation in the right hemisphere only, and 1 healthy control and 2 patients showed LO activation in the left hemisphere only. We included all subjects, including those showing unilateral LO activation, in the connectivity analyses. Each individual LO ROI was created using MRIcron software (Rorden and Brett, 2000).

PPI analysis

We conducted a PPI analysis to estimate dynamic coupling between LO and the rest of the brain during conditions of high versus low target visibility. Based on the performance data we combined conditions SOA1 and SOA2 (low target visibility condition) and combined conditions SOA3 and SOA4 (high target visibility condition). PPI analysis consists of a design matrix with three regressors: (1) "psychological regressor", i.e. SOAs 3–4 versus SOAs 1–2, (2) "physiological regressor", determined by the neural response in LO, and (3) interaction term of (1) and (2) (referred to as the "PPI regressor"). The PPI regressor refers to brain areas that show a greater functional connectivity with LO during high target visibility (i.e. SOAs 3–4) contrasted with low target visibility (i.e. SOAs 1–2).

The psychological regressor was determined by coding the change in target visibility (−1 for SOA1, −1 for SOA2, 1 for SOA3, 1 for SOA 4, 0 for null) convolved with the HRF. The physiological regressor was derived from individual time series for LO activation during the backward masking task by extracting the first principal component from all raw voxel time series in the LO ROI. These time series were mean-corrected and high-pass filtered to remove low-frequency signal drifts. SPM automatically deconvolved the HRF from the time series to provide a neuronal time series. The physiological regressor was then multiplied with the psychological regressor to obtain the PPI regressor. A PPI analysis was then carried out for each subject involving the creation of a design matrix with the three regressors.

For the ROI-approach, the mean contrast estimates (beta weights) of the PPI regressor were extracted from each of the 11 ROIs for each subject. A repeated measures analysis of variance (ANOVA) was then conducted, with ROI as a within-subject factor, diagnosis as a between-group factor, and functionally-defined LO size (in voxels) as a covariate. For the whole-brain analysis, individual contrast images were used to perform random effects analyses of the PPI pattern within each group (using one-sample *t*-tests). As an exploratory analysis, we also compared the two groups at the whole-brain level using a two-sample *t*-test. The statistical threshold was set at $p<0.05$, FDR-corrected at the cluster-level.

Results

Demographic and performance data

Table 2 shows demographic, clinical, and performance data for both groups. There were no significant differences in age, education, and gender. A repeated-measures ANOVA yielded a significant effect of SOA ($F_{3,102}=377.67$, $p<0.001$). Neither the main effect of group ($F_{1,34}=0.39$, $p=0.54$) nor the group × SOA interaction ($F_{3,102}=1.34$, $p=0.27$) was significant. Both schizophrenia patients and normal controls showed improved performance as SOAs increased (i.e. the masking became weaker).

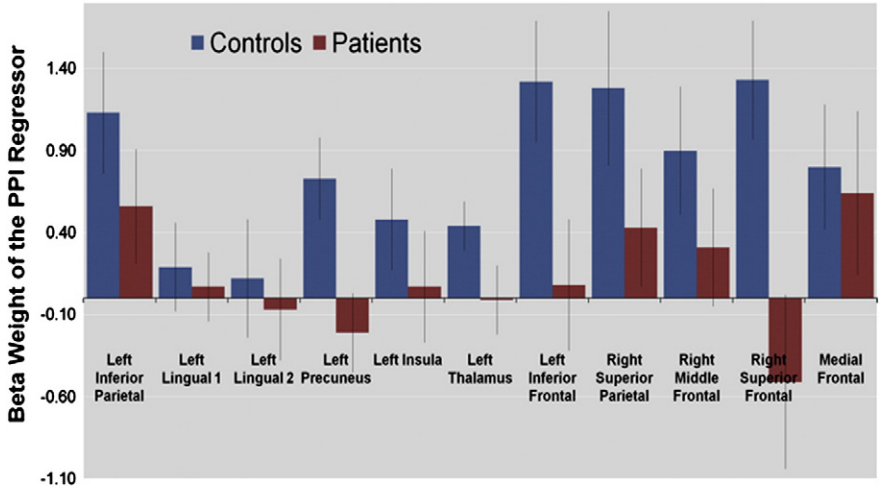

Fig. 2. Functional connectivity between LO and selected ROIs during visual masking task in healthy controls and schizophrenia patients. [a] The beta weight of the PPI regressor is an index of the change in functional connectivity between LO and ROI as a function of target visibility. Positive beta weight suggests a greater connectivity between LO and ROI during high versus low target visibility. Inversely, negative weights suggest greater connectivity between LO and ROI during low versus high target visibility. [b] Group differences were found for the left precuneus, left inferior Frontal, and right superior Frontal ROIs (all analyses $p<.05$ uncorrected for multiple comparisons). After applying a conservative Bonferroni correction for multiple comparisons, only the right superior frontal ROI remained significant ($p=.033$ following correction).

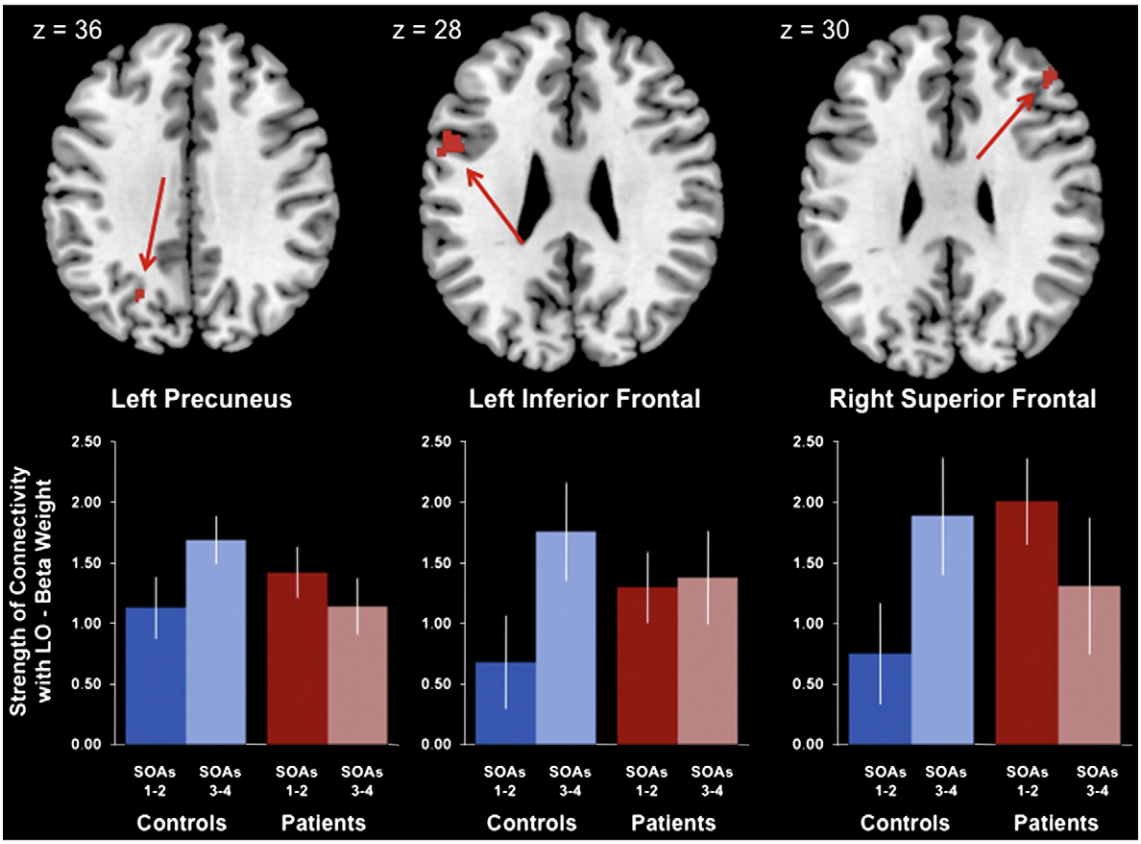

Fig. 3. Strength of connectivity (beta weight) between LO and the three significant ROIs for each group and for each target visibility condition (low target visibility = SOAs 1–2; high target visibility = SOAs 3–4).

Functional LO ROI

The mean size of the functionally-defined LO was 460 voxels (SD = 442, range 31–1720 voxels), for healthy controls and 865 voxels (SD = 578, range 59–1948 voxels) for patients. Schizophrenia patients activated a significantly larger area in LO compared with healthy controls ($t = -2.36$, df = 34, $p = 0.02$) (Wynn et al., 2008).

ROI-approach

Before examining changes in coupling with LO in patients and controls, we examined whether patients showed generally reduced coupling with LO, regardless of visibility. We did this using the physiological regressor from the PPI analysis for the ROIs. Beta weights of the physiological regressor were extracted from each of the 11 ROIs for each subject. A repeated-measures ANOVA was conducted, with ROI as a within-subject factor, diagnosis as a between-group factor, and functionally-defined LO size (in voxels) as a covariate. This analysis revealed a significant main effect of ROI ($F_{10,330} = 2.30$, $p = 0.01$), suggesting that the strength of coupling with LO varied across ROI. Neither the main effect of group ($F_{1,33} = 2.90$, $p = 0.18$) nor the group × ROI interaction ($F_{10,330} = 0.96$, $p = 0.48$) was significant. Hence, both groups showed similar strength of coupling between LO and the ROIs when the change in target visibility was not taken into account.

Next we examined changes in coupling with LO as a function of target visibility. The repeated-measures ANOVA showed a significant group × ROI interaction ($F_{10,330} = 2.38$, $p = 0.01$). The main effect of ROI was not significant ($F_{10,330} = 1.14$, $p = 0.33$), and a non-significant trend was found for the main effect of group ($F_{1,33} = 3.28$, $p = 0.08$). To better understand the significant group by ROI interaction, we conducted an exploratory multivariate ANOVA, with the 11 ROIs as dependent variables, group as the fixed factor, and functionally-defined LO size as a covariate. The analysis revealed that patients showed altered dynamic coupling with LO in left precuneus, left inferior frontal gyrus, and right superior frontal gyrus (all analyses $p < .05$ uncorrected for multiple comparisons). After applying a conservative Bonferroni correction for multiple comparisons, only the right superior frontal ROI remained significant ($p = .033$ following correction). Fig. 2 shows the connectivity results for each group and each ROI. To illustrate the nature of group differences in these three ROIs, we graphed beta weights (index of the strength of coupling with LO) separately by group and by high versus low target visibility (see Fig. 3).

Whole-brain approach

With the whole-brain approach, several brain regions in healthy controls showed changes in coupling with LO as a function of high versus low target visibility, including the left postcentral gyrus, right inferior parietal gyrus, left precentral gyrus, right inferior frontal, left precuneus, and right putamen (see supplemental Table and Figure). However, in patients no brain region yielded significant changes in coupling with LO as a function of target visibility. Finally we directly compared the groups on dynamic coupling, and found no significant differences.

Discussion

LO is a mid-stage visual processing region that is crucial for target/object awareness and recognition (Green et al., 2005; Grill-Spector, 2003; Grill-Spector et al., 2001; Kourtzi and Kanwisher, 2000). Here we examined dynamic coupling between LO and other brain regions involved in visual and attentional processing during visual masking in schizophrenia patients and matched controls. Specifically, we used

the PPI method with both ROI and whole-brain approaches to evaluate changes in the strength of coupling with LO as a function of target visibility. The ROI approach revealed group differences: patients showed altered dynamic coupling with LO as a function of target visibility in the superior frontal gyrus (significant following correction for multiple comparisons) and trends for left precuneus and left inferior frontal gyrus. Notably, we did not find generally reduced coupling with LO. The whole-brain approach showed significant changes in LO connectivity with target visibility in several parietal and frontal regions for healthy controls, but no regions for patients.

Consistent with the current findings, a separate study of healthy adults used backward masking to measure dynamic changes in coupling between brain areas as a function of visibility (Haynes et al., 2005). It reported lower visibility was associated with reduced coupling between primary visual cortex (V1) and the fusiform gyrus, and suggested that awareness of a target is associated with coupling between different levels of visual processing. Our findings in healthy controls are consistent with this interpretation because the controls showed increased coupling between LO and parietal and prefrontal regions when the target was visible. Several studies over the last decade have supported the role of prefrontal and parietal regions during visual perception (Kouider and Dehaene, 2007; Rees, 2007). Notably, the activity of these higher-level areas is not solely linked to the motor response of subjects reporting their visual experience (Rees, 2007). However, their precise functional role in visual perception still needs to be clarified. One possible explanation is that LO coupling with higher-level cortical regions reflects feedback signals to visual areas that are referred to as reentrant processing. This type of processing differs from feed-forward processing, a unidirectional processing of information from lower to higher levels in the brain. Visual masking can arise from either feed-forward or reentrant processes and recent evidence suggests that backward masking arises mainly from reentrant processes (Breitmeyer and Ogmen, 2000; Fahrenfort et al., 2007). Future studies should use additional connectivity methods that allow inferences about directionality, such as dynamic causal modeling, to confirm whether the altered coupling in schizophrenia reflects feed-forward or reentrant processing abnormalities.

Our finding of altered dynamic coupling in patients is consistent with disconnection theories that posit schizophrenia arises from dysfunctional integration of one or more large-scale distributed brain networks (Calhoun et al., 2009; Camchong et al., 2009; Friston, 1998; Stephan et al., 2009). Reduced functional connectivity has been observed in schizophrenia between the occipital, parietal and frontal areas (Henseler et al., 2010). We do not know if the altered coupling we observed is linked to disrupted anatomical connectivity in schizophrenia. This hypothesis can be directly tested by combining masking procedures with techniques such as diffusion tensor imaging that can map white matter tracts (Camchong et al., 2009; Greicius et al., 2009). The schizophrenia and control groups did not differ in overall coupling with LO, suggesting that any abnormalities in white matter fibers between LO and the key ROIs, if they exist, are likely to be subtle.

Why might schizophrenia patients show altered dynamic coupling during visual perception? The three ROIs that showed altered coupling with LO in schizophrenia have several functions. The precuneus has been implicated in episodic memory retrieval, self processing, consciousness, and visuo-spatial information processing, including preparation of spatially guided behaviors (Cavanna and Trimble, 2006). The inferior and superior frontal gyri (i.e. mainly dorsolateral prefrontal cortex / BA 9) have a role in executive functions, attention regulation, and motor planning (Alvarez and Emory, 2006; Robertson et al., 2001). The impaired coupling between LO and these three regions could be due to a problem with higher-level top down processes, or due to intrinsic abnormalities in LO. However, the current study is not able to distinguish between these two possibilities. It should be reminded that two of the ROIs, the left precuneus and left inferior frontal, did not survive a Bonferroni correction for multiple comparisons. Hence, additional studies will be required to confirm the altered coupling of these two ROIs with LO in schizophrenia patients.

For our connectivity analyses we decided to include participants with bilateral functional LO (27 participants) as well as participants with unilateral functional LO (9 participants). One might wonder whether our connectivity results would have been different if we had analyzed the left and right LO separately. Hence, we conducted post-hoc analyses for the left and right LO. Specifically, we evaluated group differences in coupling with each of the 3 ROIs that showed group differences for the main analysis. For left LO, results were fairly similar to the main analysis, with patients showing significantly altered coupling with the left precuneus ($p = 0.003$), and at trend level for the left inferior frontal ($p = 0.12$) and right superior frontal ($p = 0.06$). For the right LO, patients showed significantly altered coupling only with the right superior frontal only ($p = 0.04$). The other two ROIs were not significant (left precuneus—$p = 0.57$; left inferior frontal—$p = 0.25$). These post-hoc analyses suggest that the significant effects observed in two of the ROIs (left precuneus and left inferior frontal) were mainly due to the influence of the left LO. However, the other ROI (right superior frontal) was significant likely because of the influence of both left and right LO.

The groups did not differ in their performance during the visual masking task. At first glance, this appears to be inconsistent with performance data from many previous studies (Butler et al., 2003; Cadenhead et al., 1998; Green et al., 2003; McClure, 2001). The methods we have used in our published performance studies were optimized to show group differences. The target stimuli are small (0.24° of visual angle) and are shown at visual threshold so that all of the subjects are equated for initial sensory input. In contrast, the masking methods in the present report were optimized to elicit regional brain activity in the scanner. Stimuli were large (target = 5.7°, mask = 10.2°), dark with high contrast, and well above threshold for identification. Hence, the target in this fMRI study was about 24 times as large as in our performance laboratory studies. Although the absence of performance differences is unusual in the context of the masking literature, it provides an interpretive advantage in that performance level is not confound in considering group differences in regional brain activity and coupling. It remains possible that the lack of significant performance difference indicates that the patients in this study are atypical. As described in our previous paper (Green et al., 2009), we examine this possibility by evaluating data from a subset of patients ($n = 10$) and controls ($n = 17$) who were also examined on visual masking performance out of the scanner. The between-group effect sizes for these subjects were highly consistent with what is found in other studies. Hence, we do not consider the patient sample to be unusual in this regard.

We also made the methodological decision of using the same psychological regressor for all subjects (i.e. coding SOAs 1 and 2 as a low visibility; SOAs 3 and 4 as a high visibility). This choice was based on the mean performance data from both groups. We cross-checked this cut-off to see whether many subjects would not fit this performance pattern—we calculated for each subject the difference in performance between high and low visibility (i.e. mean accuracy for SOAs 3–4 minus SOAs 1–2). The range of difference scores for patients (0.31 to 0.56) and controls (0.31 to 0.66) indicated that, although subjects differed somewhat in their performance across SOAs, this general psychological regressor was a very good approximation of the change in target visibility for these two samples.

All patients were on antipsychotic medications at the time of the scan. The real impact of medication on our connectivity results is not easy to evaluate. It is possible that antipsychotics that block dopamine receptors have contributed to the altered coupling of LO during visual perception in schizophrenia. However, there is evidence that

antipsychotic medications tend to normalize functional connectivity in schizophrenia patients (Stephan et al., 2001). Moreover, masking deficits have been reported in unmedicated patients (Green et al., 1999). It suggests that the masking impairment in schizophrenia, and its neural correlates, are unlikely to be explained by medication.

One can speculate on the meaning of these results for previously reported findings of blunted LO response and increased LO topography in schizophrenia (Green et al., 2009; Wynn et al., 2008). The blunted response may create a situation in which coupling with LO cannot be established because it requires a certain threshold in activation that is not achieved. However, the beta weights in Fig. 3 are not consistent with this suggestion; patients showed a lack of change in coupling across visibility conditions, not a general reduction of LO connectivity. The widespread topography of LO in schizophrenia could possibly be explained by less specialization of cortex or compensatory activation within LO. It may be that neurons in LO are less specialized, so more of them respond regardless of object visibility. Such a suggestion would be consistent with an abnormality in "tuning" of LO. That is, LO in patients may be less efficient at distinguishing between visual targets and visual noise (i.e. impaired filtering of relevant vs. non-relevant information from the visual environment) leading to a general lack of modulation of coupling as a function of visibility. In fact, patients showed relatively high coupling between LO and the three ROIs during low target visibility. Possibly due to better LO tuning, healthy controls could more easily reduce coupling between LO and the higher-level areas when targets are not perceived, and increase coupling when targets are detected. Conversely, impaired LO tuning and associated reduced dynamic changes in coupling as a function of visibility might be the basis of visual processing abnormalities in schizophrenia patients.

The suggestion that altered modulation of connectivity is linked to an abnormality in LO tuning connects well to current theories of GABA function. There is compelling support for GABA abnormalities in schizophrenia, particularly interneurons that express the calcium-binding protein parvalbumin (Lewis et al., 2005). The GABA interneuron abnormalities in schizophrenia occur across the cortex, including the primary visual area (Hashimoto et al., 2008), and they lead to specific predictions for visual processing. A recent MR spectroscopy study showed a reduction in GABA concentration in visual cortex in schizophrenia (Yoon et al., 2010). A key role for GABA in the visual system is to aid the tuning of individual neurons, and the importance of GABA for tuning likely increases as one moves up the processing hierarchy from V1 to LO (Kritzer et al., 1992). Tuning in this context refers to the graded pattern of selectivity for specific visual features that is shown by neurons in visual cortex. In the monkey, when a $GABA_A$ receptor antagonist is applied to neurons in the comparable object-selective region, they lose tuning and respond to objects that do not elicit a response before or after the drug administration (Wang et al., 2000). The fact that patients maintain high coupling even when a target is not visible may reflect an abnormality in LO tuning, which in turn, could stem from GABA dysfunctions.

This study suggests that visual perception abnormalities in schizophrenia may involve an altered modulation of coupling between LO and higher-level visual and attentional brain regions. Additional neuroimaging studies with more specialized procedures will shed light on potential LO tuning abnormalities in schizophrenia, and their possible link to altered functional connectivity. One promising line of future inquiry will be to use the pattern-based decoding approaches (i.e. multi-voxel pattern analysis) and MR adaptation paradigms to further probe neural tuning in LO.

Acknowledgments

This work was supported by grant MH043292 to Dr. Green. Poorang Nori and Alisa Malin assisted in data collection. Dr. Harvey is supported by a postdoctoral fellowship from the Canadian Institutes of Health Research. For generous support of the UCLA Brain Mapping Center, we also thank the Brain Mapping Medical Research Organization, Brain Mapping Support Foundation, Pierson-Lovelace Foundation, The Ahmanson Foundation, William M. and Linda R Dietel Philanthropic Fund at the Northern Piedmont Community Foundation, Tamkin Foundation, Jennifer Jones-Simon, Capital Group Companies Charitable Foundation, Robson Family, and Northstar Fund.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2010.12.045.

References

Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol. Rev. 16, 17–42.
Ashburner, J., Friston, K., 1997. Multimodal image coregistration and partitioning—a unified framework. Neuroimage 6, 209–217.
Breitmeyer, B.G., Ogmen, H., 2000. Recent models and findings in visual backward masking: a comparison, review, and update. Percept. Psychophys. 62, 1572–1595.
Butler, P.D., DeSanti, L.A., Maddox, J., Harkavy-Friedman, J.M., Amador, X.F., Goetz, R.R., Javitt, D.C., Gorman, J.M., 2003. Visual backward-masking deficits in schizophrenia: relationship to visual pathway function and symptomatology. Schizophr. Res. 59, 199–209.
Butler, P.D., Javitt, D.C., 2005. Early-stage visual processing deficits in schizophrenia. Curr. Opin. Psychiatry 18, 151–157.
Butler, P.D., Silverstein, S.M., Dakin, S.C., 2008. Visual perception and its impairment in schizophrenia. Biol. Psychiatry 64, 40–47.
Cadenhead, K.S., Serper, Y., Braff, D.L., 1998. Transient versus sustained visual channels in the visual backward masking deficits of schizophrenia patients. Biol. Psychiatry 43, 132–138.
Calhoun, V.D., Eichele, T., Pearlson, G., 2009. Functional brain networks in schizophrenia: a review. Front. Hum. Neurosci. 3, 17.
Camchong, J., Macdonald III, A.W., Bell, C., Mueller, B.A., Lim, K.O., 2009. Altered functional and anatomical connectivity in schizophrenia. Schizophr. Bull. (Electronic publication ahead of print).
Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564–583.
Crick, F., Koch, C., 1995. Are we aware of neural activity in primary visual cortex? Nature 375, 121–123.
Dehaene, S., Naccache, L., Cohen, L., Bihan, D.L., Mangin, J.F., Poline, J.B., Riviere, D., 2001. Cerebral mechanisms of word masking and unconscious repetition priming. Nat. Neurosci. 4, 752–758.
Deneux, T., Faugeras, O., 2006. Using nonlinear models in fMRI data analysis: model selection and activation detection. Neuroimage 32, 1669–1689.
Doniger, G.M., Foxe, J.J., Murray, M.M., Higgins, B.A., Javitt, D.C., 2002. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Arch. Gen. Psychiatry 59, 1011–1020.
Fahrenfort, J.J., Scholte, H.S., Lamme, V.A., 2007. Masking disrupts reentrant processing in human visual cortex. J. Cogn. Neurosci. 19, 1488–1497.
First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W., Benjamin, L., 1996. Structured Clinical Interview for DSM-IV Axis II Personality Disorders. Biometrics Research Department, New York State Psychiatric Institute, New York.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders. Biometrics Research Department, New York State Psychiatric Institute, New York.
Foxe, J.J., Murray, M.M., Javitt, D.C., 2005. Filling-in in schizophrenia: a high-density electrical mapping and source-analysis investigation of illusory contour processing. Cereb. Cortex 15, 1914–1927.
Friston, K.J., 1998. The disconnection hypothesis. Schizophr. Res. 30, 115–125.
Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 6, 218–229.
Green, M.F., Glahn, D., Engel, S.A., Nuechterlein, K.H., Sabb, F., Strojwas, M., Cohen, M.S., 2005. Regional brain activity associated with visual backward masking. J. Cogn. Neurosci. 17, 13–23.
Green, M.F., Lee, J., Cohen, M.S., Engel, S.A., Korb, A.S., Nuechterlein, K.H., Wynn, J.K., Glahn, D.C., 2009. Functional neuroanatomy of visual masking deficits in schizophrenia. Arch. Gen. Psychiatry 66, 1295–1303.
Green, M.F., Nuechterlein, K.H., Breitmeyer, B., Mintz, J., 1999. Backward masking in unmedicated schizophrenic patients in psychotic remission: possible reflection of aberrant cortical oscillation. Am. J. Psychiatry 156, 1367–1373.
Green, M.F., Nuechterlein, K.H., Breitmeyer, B., Tsuang, J., Mintz, J., 2003. Forward and backward visual masking in schizophrenia: influence of age. Psychol. Med. 33, 887–895.
Greicius, M.D., Supekar, K., Menon, V., Dougherty, R.F., 2009. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb. Cortex 19, 72–78.
Grill-Spector, K., 2003. The neural basis of object perception. Curr. Opin. Neurobiol. 13, 159–166.

Grill-Spector, K., Kourtzi, Z., Kanwisher, N., 2001. The lateral occipital complex and its role in object recognition. Vis. Res. 41, 1409–1422.
Grill-Spector, K., Kushnir, T., Hendler, T., Malach, R., 2000. The dynamics of object-selective activation correlate with recognition performance in humans. Nat. Neurosci. 3, 837–843.
Grill-Spector, K., Malach, R., 2004. The human visual cortex. Annu. Rev. Neurosci. 27, 649–677.
Hashimoto, T., Bazmi, H.H., Mirnics, K., Wu, Q., Sampson, A.R., Lewis, D.A., 2008. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. Am. J. Psychiatry 165 (4), 479–489.
Haynes, J.D., Driver, J., Rees, G., 2005. Visibility reflects dynamic changes of effective connectivity between V1 and fusiform cortex. Neuron 46, 811–821.
Henseler, I., Falkai, P., Gruber, O., 2010. Disturbed functional connectivity within brain networks subserving domain-specific subcomponents of working memory in schizophrenia: relation to performance and clinical symptoms. J. Psychiatr. Res. 44 (6), 364–372.
Kouider, S., Dehaene, S., 2007. Levels of processing during non-conscious perception: a critical review of visual masking. Philos. Trans. R. Soc. Lond. B Biol. Sci. 362, 857–875.
Kourtzi, Z., Kanwisher, N., 2000. Cortical regions involved in perceiving object shape. J. Neurosci. 20, 3310–3318.
Kritzer, M.F., Cowey, A., Somogyi, P., 1992. Patterns of inter- and intralaminar GABAergic connections distinguish striate (V1) and extrastriate (V2, V4) visual cortices and their functionally specialized subdivisions in the rhesus monkey. J. Neurosci. 12 (11), 4545–4564.
Lewis, D.A., Hashimoto, T., Volk, D.W., 2005. Cortical inhibitory neurons and schizophrenia. Nat. Rev. Neurosci. 6 (4), 312–324.
Liu, T.T., 2004. Efficiency, power, and entropy in event-related fMRI with multiple trial types. Part II: design of experiments. Neuroimage 21, 401–413.
Liu, T.T., Frank, L.R., 2004. Efficiency, power, and entropy in event-related FMRI with multiple trial types. Part I: theory. Neuroimage 21, 387–400.
Malach, R., Reppas, J.B., Benson, R.R., Kwong, K.K., Jiang, H., Kennedy, W.A., Ledden, P.J., Brady, T.J., Rosen, B.R., Tootell, R.B., 1995. Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. Proc. Natl Acad. Sci. USA 92, 8135–8139.
McClure, R.K., 2001. The visual backward masking deficit in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 25, 301–311.
Rees, G., 2007. Neural correlates of the contents of visual awareness in humans. Philos. Trans. R. Soc. Lond. B Biol. Sci. 362, 877–886.
Robertson, E.M., Tormos, J.M., Maeda, F., Pascual-Leone, A., 2001. The role of the dorsolateral prefrontal cortex during sequence learning is specific for spatial information. Cereb. Cortex 11, 628–635.
Rorden, C., Brett, M., 2000. Stereotaxic display of brain lesions. Behav. Neurol. 12, 191–200.
Sergi, M.J., Rassovsky, Y., Nuechterlein, K.H., Green, M.F., 2006. Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. Am. J. Psychiatry 163, 448–454.
Stephan, K.E., Friston, K.J., Frith, C.D., 2009. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr. Bull. 35, 509–527.
Stephan, K.E., Magnotta, V.A., White, T., Arndt, S., Flaum, M., O'Leary, D.S., Andreasen, N. C., 2001. Effects of olanzapine on cerebellar functional connectivity in schizophrenia measured by fMRI during a simple motor task. Psychol. Med. 31, 1065–1078.
Tootell, R.B., Reppas, J.B., Kwong, K.K., Malach, R., Born, R.T., Brady, T.J., Rosen, B.R., Belliveau, J.W., 1995. Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. J. Neurosci. 15, 3215–3230.
Ventura, J., Lukoff, D., Nuechterlein, K.H., Liberman, R.P., Green, M.F., Shaner, A., 1993. Brief Psychiatric Rating Scale (BPRS) expanded version: scales, anchor points, and administration manual. Int. J. Meth. Psychiatr. Res. 3, 227–243.
Wang, Y., Fujita, I., Murayama, Y., 2000. Neuronal mechanisms of selectivity for object features revealed by blocking inhibition in inferotemporal cortex. Nat. Neurosci. 3 (8), 807–813.
Wynn, J.K., Green, M.F., Engel, S., Korb, A., Lee, J., Glahn, D., Nuechterlein, K.H., Cohen, M. S., 2008. Increased extent of object-selective cortex in schizophrenia. Psychiatry Res. 164, 97–105.
Yoon, J.H., Maddock, R.J., Rokem, A., Silver, M.A., Minzenberg, M.J., Ragland, J.D., Carter, C.S., 2010. GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. J. Neurosci. 30 (10), 3777–3781.