Regional Brain Activity During Early Visual Perception in Unaffected Siblings of Schizophrenia Patients


Background: Visual masking paradigms assess the early part of visual information processing, which may reflect vulnerability measures for schizophrenia. We examined the neural substrates of visual backward performance in unaffected sibling of schizophrenia patients using functional magnetic resonance imaging (fMRI).

Methods: Twenty-one unaffected siblings of schizophrenia patients and 19 healthy controls performed a backward masking task and three functional localizer tasks to identify three visual processing regions of interest (ROI): lateral occipital complex (LO), the motion-sensitive area, and retinotopic areas. In the masking task, we systematically manipulated stimulus onset asynchrony (SOAs). We analyzed fMRI data in two complementary ways: 1) an ROI approach for three visual areas, and 2) a whole-brain analysis.

Results: The groups did not differ in behavioral performance. For ROI analysis, both groups increased activation as SOAs increased in LO. Groups did not differ in activation levels of the three ROIs. For whole-brain analysis, controls increased activation as a function of SOAs, compared with siblings in several regions (i.e., anterior cingulate cortex, posterior cingulate cortex, inferior prefrontal cortex, inferior parietal lobule).

Conclusions: The study found: 1) area LO showed sensitivity to the masking effect in both groups; 2) siblings did not differ from controls in activation of LO; and 3) groups differed significantly in several brain regions outside visual processing areas that have been related to attentional or re-entrant processes. These findings suggest that LO dysfunction may be a disease indicator rather than a risk indicator for schizophrenia.

Key Words: Backward masking, early visual perception, lateral occipital complex, schizophrenia, unaffected siblings

In a visual masking paradigm, the ability to identify a visual target is disrupted when a mask occurs briefly before or after the target (1,2). If the mask follows the target, it is called “backward masking.” In general, schizophrenia patients have more difficulty, compared with control subjects, in identifying the target in the presence of a visual mask (3,4). Impaired backward masking performance may be a vulnerability marker for schizophrenia because deficits have been reported in patients in clinical remission (5,6) and show stability over 18 months in first-episode patients (7). In addition, some studies (8–10), but not others, (11,12), have reported masking impairment in first-degree relatives of schizophrenia patients compared with healthy control subjects. Masking deficits have been observed in psychosis-prone individuals (13,14). These studies suggest that visual masking deficits may be an indicator of genetic liability for schizophrenia, but some studies have shown impaired backward masking performance in patients with bipolar disorder (15,16) or learning disabilities (17), so the impairment is not limited to schizophrenia. To understand better the putative genetic nature of the visual masking deficit in schizophrenia, it is helpful to study people who are unaffected but at risk for the disorder. In this study, we explore the functional neuroanatomy of visual backward masking in unaffected siblings of schizophrenia patients.

There are two primary paths for processing visual information in backward masking paradigms: a feed-forward pathway that travels from retina to visual cortical areas and a recurrent or reentrant pathway in which neural feedback from visual (or higher) cortical areas affect early components of visual processing (18–20). Although earlier research on visual backward masking emphasized feed-forward processing (1), recent studies suggest that backward masking may occur because of disrupted reentrant or feedback signals that are necessary for conscious perception of a target (21–23). Further, there are at least two levels of reentrant processes. One is a short reentrant process between striate and extrastriate cortex within the visual cortex (18,24). The other is a reentrant process occurring over longer distances between visual and higher brain regions (including frontal, parietal, and cingulate cortices) (18–20). It remains to be determined whether schizophrenia patients show backward masking deficits due to impaired feed-forward processing, deficient reentrant processing, or both (25,26).

Several studies have examined visual cortical areas during the backward masking task and suggested that the lateral occipital complex (LO), which is associated with object recognition (27), plays an important role in visual backward masking (28,29). During a backward masking task, a target is initially processed but fails to reach visual awareness, especially when the mask follows a target very quickly. By examining differential activation of brain areas as a function of target visibility, one can identify brain regions that are important for visual backward masking performance. In a healthy sample, we previously found increased LO activation with increasing duration between target and mask (30). The same study also found similar sensitivity to the masking effect in several areas outside early visual cortical...
areas, including inferior parietal lobule and anterior cingulate cortex. These areas may be associated with reentrant processing of visual information or with effortful visual processing. In a subsequent study, we examined neural mechanisms associated with backward masking deficits in schizophrenia (31). Although schizophrenia patients showed sensitivity to target visibility in area LO, similar to that of healthy control subjects, they showed lower activations in LO compared with healthy control subjects. This study suggested that reduced LO activation may play an important role of understanding backward masking deficits in schizophrenia.

In the present study, we examined the neural substrates of visual backward masking performance in unaffected siblings of schizophrenia patients using functional magnetic resonance imaging (fMRI). If visual masking deficits in schizophrenia reflect a vulnerability to the illness, unaffected siblings would be expected to show differences in regional brain activity compared with control subjects. To our knowledge, this is the first study to investigate neural activity of backward masking performance in unaffected siblings of schizophrenia. We focused primarily on three key visual processing regions of interests (regions of interest [ROIs]): LO, the human motion-sensitive area (hMT+), and the retinotopic area. We selected these three ROIs because they represent key early and middle visual processing regions and have well-established localizer tasks. After identifying three functionally defined ROIs with localizer tasks, we compared neural activation during the backward masking task between siblings and control subjects. To examine the masking effect systematically, we varied the stimulus-onset asynchronies (SOAs) between target and mask, which enabled us to create a range of masking effects (from strong to weak). We employed the following: 1) an ROI approach to determine whether siblings and control subjects differ in activation of key visual processing areas during visual masking and 2) an exploratory whole-brain approach to determine whether siblings and control subjects show different response to the masking effect in areas outside of the key visual processing regions.

Methods and Materials

Participants

Twenty-three (11 female) unaffected siblings of patients with schizophrenia and 19 (five female) healthy control subjects participated in this study. All participants were part of a larger National Institute of Mental Health–funded study of early visual processing in schizophrenia (principal investigator: author M.F.G.). Participants in the sibling group shared both biological and environmental risk factors, including an important role of understanding backward masking deficits in schizophrenia. For the current fMRI component of the study, exclusion criteria for both groups of subjects were: 1) diagnosis of schizophrenia or any other psychotic disorder or any substance abuse in the previous 6 months; 2) any of the following Axis II disorders: avoidant, paranoid, schizoid, schizotypal, or borderline; 3) history of loss of consciousness for more than 1 hour; 4) any significant neurologic disorder or head injury; or 5) insufficient fluency in English. In addition, healthy control subjects were excluded for recurrent episodes of major depression and history of substance dependence. Finally, to separate further the control and sibling groups, control subjects were excluded if they had a first-degree relative with schizophrenia or other psychotic disorder. All participants had normal or corrected to normal vision (of at least 20/30).

All SCID interviewers were trained to a minimum kappa of .75 for key psychotic and mood items through the Treatment Unit of the Department of Veterans Affairs Veterans Integrated Service Network 22 Mental Illness Research, Education and Clinical Center (MIRECC). All 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 Board at the University of California at Los Angeles.

Design and Procedure

All participants completed six runs of the visual backward masking task followed by three localizer tasks (retinotopic areas, hMT+, and LO) in the MRI scanner. The entire scanning session lasted 60 min. The visual backward masking task was presented using E-prime software (Psychology Software Tools, Inc., Pittsburgh, Pennsylvania), and the localizer tasks were presented with the Psychophysics Toolbox (34) for MATLAB (Mathworks, Inc., Natick, Massachusetts). All tasks were presented with MR-compatible LCD goggles (Resonance Technology, Northridge, California). These experimental procedures are described in detail elsewhere (31).

For the visual backward masking task, we used 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 (35–37). The target was a square with a gap on one of three sides (up, down, or left) that appeared at the center of the screen. The mask was a composite square made up of four 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-msec flashes of a fixation point, followed by a 600-msec blank period (Figure 1). A target was then presented for 26.6 msec, followed by a 53.3-msec mask at one of four possible SOAs: 26.6, 40, 80, or 200 msec. The only component that varied from a trial to a trial was the SOA, resulting in a slight difference between the offset of a mask and the start of the next trial across trials depending on the SOA. 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 visual backward masking tasks consisted of six runs, each with thirty 5-s trials (i.e., six trials for each of the four SOAs and six null trials that included fixation but no stimuli).

After the visual backward masking task, participants performed three functional localization tasks: retinotopic areas, and hMT+, and LO. Full descriptions of the three functional localizer tasks are provided elsewhere (31,38) and are summarized briefly here. To identify retinotopic areas, participants viewed slowly
rotating wedges of a contrast-reversing checkerboard (39). The
wedge made five rotations, with one rotation every 30 sec. The
localizer task for the motion-sensitive hMT+ consisted of alter-
nating blocked presentations of moving rings and stationary
rings, with each block presented for 15 sec. There were five
blocks each of moving and stationary rings. The LO localizer task
consisted of alternating blocked presentations of pictures of
abstract objects (i.e., sculptures) and scrambled pictures of
objects, with each block containing 10 images presented for a
total of 12.5 sec (27,40). There were six blocks each of abstract
objects and scrambled objects.

fMRI Data Acquisition

All scanning was conducted on a 3-T scanner (Siemens Allegra,
Erlangen, Germany) located in the University of California
at Los Angeles Ahmanson Lovelace Brain Mapping Center.
For anatomic reference, a high-resolution echo planar axial
T2-weighted series was obtained for each subject before func-
tional scanning (repetition time = 6000 msec, echo time = 54
msec, 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 signal (repetition time = 2000 msec,
echo time = 42 msec, 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 Data Analysis

Data were analyzed using the Functional Magnetic Resonance
Imaging of the Brain (FMRI) Software Library (FSL) (41). The
prestatistics processing included motion correction (42), non-
brain removal (43), spatial smoothing using a Gaussian kernel of
full width at half maximum of 5 mm, and high-pass temporal
filtering (Gaussian weighted least-squares straight line fitting
with sigma = 25.0 sec). To facilitate multisubject analyses,
statistical images created for each subject were normalized into a
standard space of Montreal Neurological Institute coordinates.
To examine neural activations associated with visual backward
masking in unaffected siblings of schizophrenia patients, we
approached the fMRI data analyses in two complementary ways:
an ROI-based approach and a whole-brain analysis.

For the ROI analysis we were interested in the activation
patterns of the ROIs during the backward masking task. First, we
identified the three key visual processing areas (retinotopic
regions, hMT+, and LO) in each individual subject based on the
localizer scans. Retinotopic regions were defined as those in
which activity was temporally correlated with a sinusoid at the
stimulus modulation frequency at a level above a defined
threshold (p < .001, uncorrected) (39). To identify hMT+, the
blocked time series (moving vs. stationary rings) were convolved
with a model HRF and used as regressors in a multiple regression
analysis. The contrast of moving rings versus stationary rings
produced a statistical parametric map of t values with a specified
threshold (p < .001, uncorrected). Area hMT+ was identified on
the basis of contiguously activated voxels within the occipital
cortex bilaterally. A similar approach was employed to identify
LO. Specifically, blocks (abstract vs. scrambled images) were
modeled, and the contrast of abstract images greater than the
scrambled images created a statistical parametric map of t values
with a specified threshold (p < .001, uncorrected). LO was
identified as a group of contiguously activated voxels within the
lateral occipital cortex bilaterally.

Second, we modeled the hemodynamic responses at each
SOA during the visual backward masking task using seven finite
impulse response (FIR) functions, one for each peristimulus time
point (total window = 14 sec) (44,45). With fewer assumptions
about the exact shape of the hemodynamic responses (44,45),
the FIR model can capture any shape of hemodynamic response
and makes it possible to average each trial type selectively for a
fast-event-related design. After fitting the FIR function, response
amplitude (i.e., percent signal change) was calculated by aver-
aging event-related responses across trials, separately for each
SOA. Third, we determined whether the early visual processing
areas showed the expected masking effect (i.e., increased neural
responses with longer SOA) by examining percent signal change
using a repeated-measure analysis of variance (ANOVA) with
group as a between-subject variable and time point and SOA as
within-subject factors.

For the whole-brain analyses, fMRI data for each SOA were
convolved with our model HRF and used as regressors in a
multiple regression analysis. The six motion parameters were
included as covariates of no interest to increase statistical sensi-
tivity. The contrast of interest was a parametric change: increased
activity as a function of increased SOA. After voxels were
selected in this manner, we considered any group differences
using a mixed-effects model of FLAME (FMRIb’s Local Analysis of
Mixed Effects) Stage 1 only (46,47). Statistical images were
thresholded using the cluster threshold of z ≥ 3.2 and p ≤ .05,
corrected for multiple comparisons using Gaussian random field
theory (48).

Results

Two siblings were excluded from analyses: one had excessive
movement artifact and another showed chance-level perform-
ance (defined as at or below 33% accuracy) at the longest SOA.
Therefore, 21 siblings of schizophrenia patients and 19 healthy
control subjects were included in the following analyses.
**Table 1.** Demographics of Unaffected Siblings of Schizophrenia Patients and Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Unaffected Siblings</th>
<th>Healthy Control Subjects</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.0 (10.3)</td>
<td>42.7 (9.0)</td>
<td>$t_{15} = 2.18, p &lt; .01$</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.9 (1.6)</td>
<td>13.2 (1.3)</td>
<td>$t_{15} = -5.64, p &lt; .001$</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>11/10</td>
<td>5/14</td>
<td></td>
</tr>
<tr>
<td>Racial Breakdown</td>
<td>Caucasian 9/16</td>
<td>3/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Latino 3/1</td>
<td>1/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asian 1/0</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>African American 5/2</td>
<td>2/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other/unknown 1/2</td>
<td>1/2</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as mean (SD).

**Demographic Information and Performance Data**

Siblings of the schizophrenia patients were younger and had higher education compared with healthy control subjects (Table 1). Figure 2 shows behavioral performance of the visual backward masking task in the scanner. A repeated-measures ANOVA with SOAs as a within-group factor and group as a between-group factor showed a significant main effect of SOA $F(3,114) = 313.72, p < .001$, but no SOA by group effect $F(3,114) = .38, p = .76$ and group effect $F(1,38) = 80, p = .37$. Because siblings were younger than control subjects and a previous study found association between age and masking performance (49), we also performed an analysis of covariance with age as a covariate, which did not change the findings. As expected, both groups showed improved performance as SOAs increased (i.e., masking effect became weaker and the target became more visible). Because both groups showed close to chance-level performance for SOA 1 and SOA2, we combined the responses for these SOAs in all subsequent analyses.

Figure 3 presents the time series of percent signal change for each ROI during the backward masking task. For retinotopic areas (A for control subjects and B for siblings) and hMT+ (C for control subjects and D for siblings) the main effect of time was significant $F(6,210) = 54.61, p < .001$ for retinotopic; $F(6,210) = 26.71, p < .001$ for hMT+. For LO (E for control subjects and F for siblings), we found a significant main effect of time $F(6,198) = 33.92, p < .001$ and a significant SOA by time interaction effect $F(12,396) = 3.26, p < .01$. The group effect was not significant. To examine further the SOA by time interaction for LO, a repeated-measures ANOVA was performed with SOA as a within-subject factor for each time point separately. We found a trend toward significant SOA effect $F(2,68) = 2.44, p = .09$ at Time Point 6 and a significant main effect for SOA $F(2,68) = 8.22, p < .001$ at Time Point 8. These findings indicate that across groups, LO activation increased as SOA became longer and the target became more visible.

**Whole-Brain Analyses**

For the whole-brain analyses, we were interested in regions in which groups differed in their sensitivity to the masking effect. Hence, we focused on areas that 1) showed a parametric increase of SOA $1,2 < SOA < 3 < SOA 4$ and 2) showed differences between siblings and control subjects (Table 2). Areas in which control subjects showed increased parametric activations compared with siblings included anterior cingulate cortex, posterior cingulate cortex, inferior prefrontal cortex, inferior parietal lobe, precentral gyrus, and precuneus (Figure 4). There was no region in which siblings showed more activation than control subjects.

**Discussion**

Visual backward masking performance has characteristics suggesting it is a vulnerability marker for schizophrenia (7–12,50,51). Hence, we expected unaffected siblings to show differential patterns of neural activation as a function of a masking effect during backward masking compared with healthy control subjects. In this study, we used two complementary approaches to investigate neural activity associated with visual backward masking in unaffected siblings of schizophrenia patients. First, we used an ROI approach to examine the neural response for siblings and control subjects in three key visual processing areas: retinotopic areas, hMT+, and LO. Both groups showed an increase in LO activation with increased visibility of the target, but this pattern was not observed in hMT+ and retinotopic areas. The groups did not differ in any of these three areas. The modulation of LO activation as a function of the target visibility is consistent with our previous studies (30,31). Second, we conducted exploratory whole-brain analyses to examine neural activation to target visibility in areas outside the key visual processing ROIs. Several brain areas demonstrated significant group differences in a parametric increase of activation as a function of the target visibility, including the anterior cingulate cortex, posterior cingulate cortex, inferior prefrontal gyrus, precuneus, and inferior parietal lobule. Some of these regions, such as the anterior cingulate cortex and inferior parietal lobule, have shown sensitivity to masking effects in our previous study with healthy individuals (30). Current findings indicate that during a backward masking task, compared with control subjects, siblings use LO in a similar way but show reduced task-related activations in several polymodal brain regions.

We did not find a behavioral performance difference between siblings and control subjects in the scanner, in contrast to our previously published psychophysics studies (10,51). There are several possible reasons for this lack of difference. First, the current backward masking task was designed principally to generate and detect neural activation and was not optimal for...
detecting group differences between siblings and control subjects. Specifically, it included stimuli that were much larger and of higher contrast than those used in our behavioral masking studies \((10, 49, 51, 52)\), which may have overridden any subtle deficits that siblings may have shown. Second, although some studies find that siblings show impairment in backward masking \((8 – 10)\), others do not \((11, 12)\). Third, our sample was relatively small. In contrast, the absence of performance difference provides an interpretative advantage for the fMRI findings because the group differences in regional brain activity were not confounded with performance level.

A closer examination of the brain regions that distinguish siblings from control subjects on a whole-brain analysis suggests the specific cognitive and perceptual processes that may be closely related to impaired backward masking performance seen in siblings of schizophrenia patients. One explanation is that these individuals may have reduced attentional resources compared with healthy control subjects, which could influence alertness, readiness to respond, or response selection. Most of areas that showed group differences in whole-brain analyses are involved in attention. For example, inferior frontal gyrus and inferior parietal lobule are considered part of an attention network \((53, 54)\), and the anterior cingulate cortex is frequently associated with attentional control or cognitive effort necessary to perform a task \((55)\). In addition, the precuneus is involved in variety of cognitive tasks, including shifting attention to visual stimuli \((56, 57)\). If siblings failed to use attentional resources effectively \(e.g., \) have inefficient resource allocation or response selection), they would show decreased task-related activations of these regions in response to the target visibility during a backward masking task. Reduced task-related activation in siblings in this study may indicate other cognitive dysfunction \(i.e., \) attention) that could affect early visual processing, instead of directly reflecting impaired early visual processing.

Another feature shared by several of these regions is their association with awareness of a visual perception \((54, 56)\). A visual stimulus activates the visual system through either a cascade of feed-forward connections or reentrant pathways that can be short or long. There is increasing support for the theory that visual masking, under most conditions, is mainly a result of

**Table 2. Activated Brain Regions**

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Regions</th>
<th>Brodmann’s Area</th>
<th>MNI Coordinates</th>
<th>z Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Inferior Frontal Gyrus</td>
<td>46</td>
<td>(-50) \ 32 \ 2</td>
<td>4.34</td>
</tr>
<tr>
<td>Left</td>
<td>Inferior Frontal Gyrus</td>
<td>9</td>
<td>(-56) \ 10 \ 26</td>
<td>3.94</td>
</tr>
<tr>
<td>Left</td>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>(-46) \ -36 \ 48</td>
<td>4.25</td>
</tr>
<tr>
<td>Left</td>
<td>Precentral Gyrus</td>
<td>6</td>
<td>(-58) \ 2 \ 34</td>
<td>3.87</td>
</tr>
<tr>
<td>Right</td>
<td>Anterior Cingulate Cortex</td>
<td>32</td>
<td>0 \ -40 \ 18</td>
<td>3.94</td>
</tr>
<tr>
<td>Left</td>
<td>Posterior Cingulate Cortex</td>
<td>30</td>
<td>2 \ -50 \ 18</td>
<td>3.67</td>
</tr>
<tr>
<td>Left</td>
<td>Precuneus</td>
<td>31</td>
<td>(-4) \ -46 \ 38</td>
<td>3.52</td>
</tr>
</tbody>
</table>

MNI, Montreal Neurological Institute.

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disrupted reentrant processes, rather than impaired feed-forward processes (59). Most of the brain regions that showed group differences in our study (i.e., anterior cingulate cortex, posterior cingulate cortex, inferior prefrontal gyrus, precuneus, and inferior parietal lobule) have been implicated in awareness of visual stimuli or reentrant processing of visual information (20,60,61). Hence, this pattern of results suggests that siblings of schizophrenia patients may not use these neural regions associated with reentrant pathways as efficiently as control subjects do. The patterns of neural activation observed in schizophrenia patients from our previous study could be due to short reentrant processing, whereas the pattern observed in the current study with unaffected siblings might represent disrupted long reentrant processing. A recent study with healthy control subjects and a specialized masking task showed that activation in LO during masking is primarily related to reentrant processing (62). In contrast, unaffected siblings may have relatively spared LO but show differences in areas associated with long reentrant processing, including inferior parietal lobule and the anterior cingulate cortex (18–20). However, this speculation does not explain why schizophrenia patients show deficits in a short, but not long, reentrant processing.

In this study, we used a visual backward masking, a task that is heavily dependent on LO activation (28–30). This study is distinct from previous studies on early visual processing in schizophrenia using fMRI, most of which focused on area hMT+ or the primary visual cortex (63–65). The results from this study with unaffected siblings differ in some respects from our previous finding using fMRI to assess backward masking in schizophrenia (31). With schizophrenia patients, we found lower activation of LO compared with control subjects but did not find any differential activation patterns in whole-brain analyses outside three key visual areas between patients and control subjects. The results from the current analyses are the reverse: no group difference in LO or other visual ROIs but notable differences in activation with increasing visibility in other brain regions. One may argue that the absence of a behavioral difference could explain the lack of a group difference between siblings and control subjects in LO. However, we found blunted LO activation of patients in our previous study despite comparable behavioral performance. In addition, another study from our laboratory also showed increased extent of LO activation in patients using the LO activation task (38). On the basis of these findings, we speculate that LO differences between siblings and control subjects would not have emerged even if we had detected performance differences. However, this prediction needs confirmation with a different masking paradigm that yields performance differences. The absence of group differences in LO activation in this study raises questions as to whether an aberrant LO is a disease indicator, rather than reflecting genetic vulnerability for schizophrenia. This view is consistent with a finding of impaired performance of patients, but normal performance of individuals at risk for schizophrenia, in a perceptual organization task, which is strongly associated with intact object recognition (66). Hence, reduced attentional resources or reentrant processing may be associated with vulnerability to schizophrenia, but that dysfunctional activation of LO may be a disease-specific factor instead of a risk factor.

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