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

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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 asynchronies (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 (3,15,16) 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 processing between striate and extrastriate cortex within the visual cortex (18,24). The other is a reentrant processing 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

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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 parents with a patient who met diagnostic criteria of schizophrenia using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (32). Probands of the siblings were recruited from the mental health clinics of the VA Greater Los Angeles Healthcare System and mental health clinics from the local community. Healthy control participants were recruited through flyers posted in the local community, newspaper advertisements in local newspapers, and Web site postings. The data from healthy control subjects were also included in an earlier study on neural activation patterns in schizophrenia using the same experimental procedure (31).

All participants underwent a diagnostic interview with SCID (32) and selected sections of the Structural Clinical Interview for DSM-IV Axis II disorders (33). Because siblings are more difficult to recruit than healthy control subjects, the parent study included siblings in the behavioral paradigms who were clinically affected. For the current fMRI component of the study, exclusion criteria for both groups of subjects were 1) diagnosis of schizophrenia or 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-sec 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