Functional Neuroanatomy of Visual Masking Deficits in Schizophrenia

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Context: Visual masking procedures assess the earliest stages of visual processing. Patients with schizophrenia reliably show deficits on visual masking, and these procedures have been used to explore vulnerability to schizophrenia, probe underlying neural circuits, and help explain functional outcome.

Objective: To identify and compare regional brain activity associated with one form of visual masking (ie, backward masking) in schizophrenic patients and healthy controls.

Design: Subjects received functional magnetic resonance imaging scans. While in the scanner, subjects performed a backward masking task and were given 3 functional localizer activation scans to identify early visual processing regions of interest (ROIs).

Setting: University of California, Los Angeles, and the Department of Veterans Affairs Greater Los Angeles Healthcare System.

Participants: Nineteen patients with schizophrenia and 19 healthy control subjects.

Main Outcome Measure: The magnitude of the functional magnetic resonance imaging signal during backward masking.

Results: Two ROIs (lateral occipital complex [LO] and the human motion selective cortex [hMT+]) showed sensitivity to the effects of masking, meaning that signal in these areas increased as the target became more visible. Patients had lower activation than controls in LO across all levels of visibility but did not differ in other visual processing ROIs. Using whole-brain analyses, we also identified areas outside the ROIs that were sensitive to masking effects (including bilateral inferior parietal lobe and thalamus), but groups did not differ in signal magnitude in these areas.

Conclusions: The study results support a key role in LO for visual masking, consistent with previous studies in healthy controls. The current results indicate that patients fail to activate LO to the same extent as controls during visual processing regardless of stimulus visibility, suggesting a neural basis for the visual masking deficit, and possibly other visual integration deficits, in schizophrenia.

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get, and the groups did not differ in the contrast levels needed for target detection. Third, backward masking deficits have been related to clinical aspects of schizophrenia, including negative symptoms. Fourth, initial evidence suggests that deficits on backward masking tasks are related to functional outcome, probably through key mediating variables. For example, visual masking has been found to be associated with performance on social cognitive tasks, which in turn are related to community functioning. Similar findings have been reported for other early visual processing tasks in schizophrenia.

A fifth reason for interest in backward masking paradigms is their detailed linkages to underlying neural systems. The visual masking deficits have been viewed in terms of the interactions of 2 key visual channels that form the basis for complex visual processing and are labeled in functional (transient and sustained) or anatomical (magnocellular and parvocellular) terms. The magnocellular pathway is characterized by fast phasic (transient) responses, while the parvocellular pathway has slower tonic (sustained) responses. Thus, magnocellular channels respond rapidly and briefly to stimulus onset, offset, and location, whereas parvocellular channels have a longer response related to stimulus identification. According to this model of masking, parvocellular activity elicited by the target conveys information needed to identify targets and masking results from disruption of this target information by either the magnocellular or parvocellular pathways of the mask, depending on the particular paradigm. Deficits in masking in schizophrenia have been attributed to abnormalities in the magnocellular pathway. However, there is also interest in possible schizophrenia-related abnormalities in high-frequency brain electrical activity (ie, gamma range, >30 Hz) that is associated with formation of visual representations.

Although the very brief temporal demands of backward masking present challenges for its application in the scanner, several recent studies have successfully examined masking paradigms with functional magnetic resonance imaging (fMRI) in healthy samples. While fMRI does not have the temporal resolution to examine the blood oxygen level–dependent (BOLD) response to the target and mask separately, it can yield an informative BOLD response to the target-mask sequence. There have been no studies, to our knowledge, on the neural basis of visual masking in schizophrenia using any functional neuroimaging procedure. Hence, the regional brain activity associated with these key deficits is not known. We previously examined visual masking in a group of healthy subjects to determine which areas are sensitive to masking effects (ie, show more activation with increasing duration between target and mask). Among the early visual processing areas identified a priori through localizer scans, the lateral occipital complex (LO) showed strong sensitivity to masking effects. Hence, LO was of particular interest as a possible substrate of the masking effect. Other areas showed similar effects on post hoc analyses, including inferior parietal lobe, anterior cingulate cortex, and thalamus.

For the current study, we used an approach similar to our previous study in which we first examined well-defined early visual processing areas for which there are established localizer tasks. We refer to these regions as a priori regions of interest (ROIs). Because areas outside of these early visual regions may be involved with masking, and may explain group differences, we also conducted exploratory whole-brain analyses (ie, post hoc analyses). We included samples of patients with schizophrenia (n = 19) and healthy controls (n = 19) to address several questions: (1) Among the visual processing areas identified a priori as ROIs, which show sensitivity to the effects of visual masking? (2) Of these ROIs, which show differences between patients and controls in level of activation? (3) Do other areas (identified post hoc) show sensitivity to masking effects? (4) Do patients and controls differ in activation on any of these areas?

**METHODS**

**PARTICIPANTS**

Twenty-four patients with schizophrenia (5 female) and 19 healthy controls (5 female) were recruited for this study. Participants were recruited from a larger National Institute of Mental Health study of early visual processing in schizophrenia. Schizophrenic patients were recruited from outpatient treatment clinics at the Veterans Affairs Greater Los Angeles Healthcare System and from local board and care facilities. Schizophrenic patients met diagnostic criteria for schizophrenia using the Structured Clinical Interview for DSM-IV (SCID) Axis I Disorders. Exclusion criteria for patients included (1) substance abuse or dependence in the last 6 months, (2) mental retardation based on review of medical records, (3) history of loss of consciousness for more than 1 hour, (4) an identifiable neurological disorder, and (5) not sufficiently fluent in English. We did not exclude patients for a history of substance dependence.

Normal control participants were recruited through flyers posted in the local community, newspaper advertisements in local newspapers, and Web site 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, (2) any of the following Axis II disorders: avoidant, paranoid, schizoid, schizotypal, or borderline, based on the SCID for Axis II disorders, (3) schizophrenia or other psychotic disorder in a first-degree relative, (4) any significant neurological disorder or head injury, and (5) not sufficiently fluent in English.

Schizophrenic patients and normal controls were comparable in terms of age and education (mean [SD], age: 38.2 [11.8] years and 42.7 [9.0] years, respectively; t(57) = -1.33; P = .19; education: 13.6 [1.6] years and 13.2 [1.3] years, respectively; t(57) = 0.95; P = .34). All patients were clinically stable at the time of testing and exhibited low levels of symptoms (for a more complete characterization of the patient sample for the larger project, see Sergi et al[26]). All of the patients were medicated (conventional antipsychotic, n = 1; single atypical antipsychotic, n = 16; 2 atypical antipsychotics, n = 2). Subjects did not take any sedatives during the 12 hours prior to assessment. All participants had normal or corrected to normal vision, and we did not select subjects on handedness.

All SCID interviewers were trained to a minimum of 0.75 for key psychotic and mood items through the Treatment Unit...
of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center. None of the research staff were blind to group membership. 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 boards at the University of California, Los Angeles (UCLA), and the Veterans Affairs Greater Los Angeles Healthcare System.

**DESIGN AND PROCEDURE**

All participants 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. The entire scanning session lasted 60 minutes. The visual backward masking task was presented using E-prime software (Psychology Software Tools, Pittsburgh, Pennsylvania) and the localizer tasks were presented using MATLAB (The Mathworks, Natick, Massachusetts). All tasks were presented with magnetic resonance-compatible LCD goggles (Resonance Technology, Northridge, California).

For the visual backward masking task, 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 of 4 smaller squares, overlapping the area occupied by the target (Figure 1). A mask was presented at 1 of 4 possible stimulus onset asynchronies (SOAs). These SOAs and stimuli durations were decided on after piloting with the magnetic resonance-compatible goggles. The beginning of each visual backward masking trial was signaled by two 100-millisecond flashes of a fixation point, followed by a 600-millisecond blank period. The target duration was held constant at 26.6 milliseconds and followed by a 53.3-millisecond mask at 1 of 4 possible SOAs: 26.6, 40, 80, and 200 milliseconds. The target subtended 5.7° and the mask 10.2° of visual angle. 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 6 runs, each with thirty 3-second trials (ie, 6 trials for each of the 4 SOAs and 6 null trials that included fixation but no stimuli). We used a rapid event-related design and the trials were presented in a permuted block design to maximize both hemodynamic response function estimation and signal detection power. To create trial sequences for each run, we first determined a random ordering of blocks, in which blocks contained 3 trials from a single condition (ie, 1 of the 4 SOAs or null). Then, we randomly swapped trials in the sequence until the first-order entropy of the sequence increased by a factor of 1.33. This procedure made the trial sequence appear random, and it was not easy for subjects to form expectations about the upcoming trial type. To generate the final sequence, this process was repeated 500 times and the trial sequence with the highest statistical efficiency was selected.

After the visual backward masking task, participants performed 3 functional localization tasks: LO, retinotopic areas, and hMT+. Full descriptions of the 3 functional localizer tasks are provided elsewhere and are summarized briefly herein. The LO localizer task consisted of alternating blocked presentations of pictures of abstract objects (ie, sculptures) and scrambled pictures of objects, with each block containing 10 images presented for a total of 12.5 seconds. The scrambled pictures were created by dividing each picture into 64 squares and randomly scrambling their positions. There were 6 blocks of each abstract objects and scrambled objects. Our definition of LO follows that of Malach and colleagues and includes lateral cortex between V3 and the medial temporal lobe but also continues into adjacent ventral cortex. To identify retinotopic areas, participants viewed slowly rotating wedges of a contrast-reversing checkerboard. The wedge made 5 rotations, with 1 rotation every 30 seconds. Retinotopic areas that respond well to the standard fMRI techniques for measuring retinotopic organization include V1, V2, ventral V3 (or VP), V3a, and V4. The motion-sensitive hMT+ localizer task consisted of alternating blocked presentations of moving rings and stationary rings, with each block presented for 15 seconds. There were 5 blocks each of moving and stationary rings.

**IMRI DATA ACQUISITION**

All scanning was conducted on a 3-T scanner (Siemens Allegra, Erlangen, Germany) located 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 milliseconds, echo time=54 milliseconds, flip angle=90°, 30 axial slices, field of view=20 cm). A T2*-weighted gradient-echo sequence was used to detect BOLD signal (repetition time=2000 milliseconds, echo time=42 milliseconds, 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.

**IMRI DATA ANALYSIS**

A detailed description of the IMRI data analysis is shown in the cText (http://www.archgenpsychiatry.com). In brief, we approached the IMRI data analyses in 2 complementary ways. First, we used an ROI-based approach in which we (1) identified 3 key visual processing areas separately for each subject using the functional localizer tasks, (2) examined the effect of SOA (that is, masking effect) for each ROI, and (3) examined between-group differences at each ROI. Second, we conducted a whole-brain analysis in which we (1) identified clusters of voxels that were sensitive to SOA (masking) effects outside the 3 ROIs and

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Figure 1. Schematic diagram of a single trial in a visual backward masking task. On each trial, participants identified the location of a gap in a target (up, bottom, or left) by pressing a corresponding button with their dominant hand. Stimulus onset asynchrony (SOA) was varied to manipulate the strength of the masking effect. The beginning of each visual backward masking trial was signaled by two 100-millisecond flashes of a fixation point, followed by a 600-millisecond blank period. A target was briefly presented for 26.6 milliseconds, followed by a 53.3-millisecond mask at one of the specified SOAs (26.6, 40, 80, and 200 milliseconds) and then an intertrial interval (ITI).
Five patients were excluded from analyses: 1 subject had excessive movement artifact due to tardive dyskinesia. 2 had technical problems during scanning, and 2 showed chance-level performance (defined as ≤38% accuracy) at the longest SOA (200 milliseconds). Therefore, 19 schizophrenic patients (4 female) and 19 normal controls (5 female) were included in the following analyses.

**RESULTS**

Behavioral data across SOAs are shown in Figure 2. A repeated-measures analysis of variance (ANOVA) yielded a significant effect of SOA ($F_{1,36}=350.9; P<.001$). Neither the main effect of group nor the group×SOA interaction was significant. Performance was comparable at all points except SOA3. Controls performed 0.50 effect size better than patients at this SOA but the difference was not significant at these sample sizes. As expected, both schizophrenic patients and normal controls showed improved performance as SOAs increased (ie, the masking became weaker). Because the performance data for SOA1 and SOA2 were close to chance performance for both groups, we combined the responses for these SOAs in all subsequent analyses.

**ROI-BASED ANALYSIS**

There were no significant differences (all $P$ values >.20) between groups in the number of voxels for any of the ROIs (Figure 3) (mean [SD], retinotopic areas: controls, 360 [46]; patients, 380 [50]; hMT+: controls 57 [11]; patients, 59 [12]; LO: controls, 34 [12]; patients, 56 [11]).

The time series of signal change for each ROI are presented for patients and controls in Figure 4. Our initial question was whether any of the ROIs showed sensitivity to masking (ie, an SOA effect at the middle time points) across groups. We conducted a 3 (SOA) × 7 (time points) × 2 (group) ANOVA separately for each ROI. Our interest was whether there was (1) an SOA×time point interaction or (2) an SOA×group interaction. Each ROI had a significant SOA×time point interaction ($F_{12,396}=2.54; P<.05$; and $F_{12,361}=1.92; P<.05$; and $F_{12,361}=2.68; P<.05$ for retinotopic areas, hMT+, and LO, respectively). None of the ROIs had a significant SOA×group interaction, so we combined groups and conducted post hoc ANOVAs at each time for each ROI to better understand the SOA×time point interaction. For retinotopic areas (Figure 4A and B), there was no significant effect of SOA at any time point. For hMT+ (Figure 4C and D), significant SOA effects were present at time points 6 and 8 ($F_{2,66}=3.23; P<.05$ and $F_{2,66}=4.04; P<.05$, respectively). For LO (Figure 4E and F), we also found significant SOA effects at time points 6 and 8 ($F_{2,66}=6.49; P<.01$ and $F_{2,66}=5.28; P<.01$, respectively).

While the SOA effect for LO was predicted, the one for hMT+ was not. To determine whether the SOA effect for LO was greater than that of hMT+, we conducted a 3 (SOAs) × 2 (LO and hMT+) repeated-measures ANOVA for time points 6 and 8 separately. For time point 6, we found significant interaction ($F_{2,66}=5.28; P<.01$) and time point ($F_{2,66}=3.23; P<.05$ and $F_{2,66}=4.04; P<.05$).
significant main effects of ROI ($F_{1,29}=10.40; P < .01$) and SOA ($F_{2,58}=5.49; P < .01$). Notably, the ROI × SOA interaction was significant ($F_{2,58}=3.27; P < .05$). Hence, LO showed more activation overall and a clearer SOA effect (more activation with increasing visibility of the target) compared with hMT+ (Figure 4C-F). For time point 8, we found a significant effect of ROI (larger for LO, $F_{1,29}=7.77; P < .05$) and a significant effect of SOA ($F_{2,58}=4.81; P < .05$), but not a significant ROI × SOA interaction.

Next, we considered any differences between groups by comparing their peak amplitude of percent signal change (ie, peak signal change) for each ROI (Figure 5). For retinotopic areas and hMT+, none of the main effects or interactions were significant. The groups were generally comparable in peak signal change for these ROIs ($P$ values = .59 and .37 for retinotopic areas and hMT+, respectively). For LO, we found a significant group effect ($F_{1,32}=11.74; P < .01$) and effect of SOA ($F_{2,64}=3.42; P < .05$); the SOA × group interaction was not significant. Hence, patients showed lower peak signal change on LO across SOAs, but a similar SOA effect, compared with controls.

Figure 4. Time series of signal change for each region of interest in patients and controls. A and B, Retinotopic areas. C and D, The human motion selective cortex (hMT+). E and F, Lateral occipital complex. SOA indicates stimulus onset asynchrony. Values are presented as mean (SE).
Some authors have separated out the dorsal and ventral portions of LO, with a particular interest in ventral LO for object representation. As an additional check on the findings, we examined the ventral portion of LO only. The results were essentially the same as for the entire LO: this region showed a clear effect of SOA and the patients showed lower amplitude responses (eFigure 1).

**WHOLE-BRAIN ANALYSIS**

For the whole-brain analyses, we first identified voxels that showed a parametric increase of SOA1 + 2 less than SOA3 less than SOA4. With both patients and controls combined, the activated brain regions included posterior cingulate cortex, right postcentral gyrus, bilateral inferior parietal lobe, bilateral superior temporal gyrus, bilateral middle temporal gyrus, left inferior temporal gyrus, bilateral fusiform gyrus, and thalamus (Table). The current study used 2 different approaches (an a priori ROI approach with localizer scans and whole-brain analyses) to examine the neural basis of visual masking in schizophrenia. Of the visual processing areas that were defined a priori through localizer scans, both LO and hMT+ showed sensitivity to the effects of masking, meaning that the activation increased as the SOAs became longer and the target more visible. The masking effect was significantly more pronounced in LO than in hMT+ at the 6-second time point. Compared with controls, patients showed lower peak signal change in LO, but not in the other visual processing areas. We identified areas outside of the visual processing areas that were sensitive to the effects of masking, including some areas that were implicated in our previous study (bilateral inferior parietal lobe and thalamus), but the groups did not differ in their activation of these areas.

The results of this study provide additional support for a key role in LO for visual masking, which is consistent with our previous study and with other fMRI studies of visual masking in controls. The current results also indicate that patients fail to activate LO to the same extent as controls across SOAs. The groups showed a nonsignificant 0.50–effect size difference on SOA3, so we computed the correlation between accuracy and peak signal change on LO at this SOA in each group. The correlation was moderate but nonsignificant in normal controls (r = 0.34) and small in schizophrenic patients (r = 0.09).

The blunted LO response was a general effect, observed for both short SOAs, where masking rendered the stimulus almost invisible, and the longest SOA, where masking had little effect. This pattern suggests that patients have generally weaker stimulus representations. Such a response from LO could not be inferred from behavioral masking studies of schizophrenia, in which it is common for patients to differ from controls at mid-range SOAs (ie, those without floor and ceiling effects). However, with fMRI it is possible to see a deficit across a range of visibility. Because of its generality, the blunted LO response could reveal itself as reduced performance in other tasks that depend heavily on precise readout of LO activity. Schizophrenia is associated with impairments in a range of visual integration tasks, including object recognition, grouping, perceptual closure, face processing, and reading, and deficits on any of these could be associated with a blunted LO response.

Other studies have used electrophysiology to suggest LO abnormalities in schizophrenia. For example, some have examined an event-related potential, closure negativity (Ncl), that is associated with object recognition. This wave has peak amplitude at approximately 290 milliseconds and is distributed over the lateral occipital scalp regions. Hence, its distribution would include region LO, which was significantly more pronounced in LO than in hMT+.
this wave differs in magnitude or pattern in patients with schizophrenia, thereby providing indirect, but consistent, support for LO abnormalities in schizophrenia.

What processes might be occurring in LO? One probable function of LO is to integrate different types of information from a variety of sources to provide a unified representation of visual shape. The reduced LO activity we observed in patients may indicate that patients have a weaker unified representation, at least under conditions of masking. Because LO dysfunction appears to be a key neural source of masking effects, we propose that patients’ weakened LO representations underlie the masking impairment observed in laboratory studies. It is possible that other brain areas supply a compensatory response for the weakened LO representation; however, the whole-brain analyses did not reveal group differences in regions outside LO that would suggest such compensation.

Patients’ increased susceptibility in masking could originate from either feed-forward or reentrant processing in LO. Visual masking has typically been interpreted in terms of feed-forward models of visual processing (ie, involving the flow of information from retina to cortex). In contrast to this model, more recent advances in cognitive neuroscience argue for the importance of reentrant (top-down or attentional) processes in early components of visual processing. Reentrant models of visual processing emphasize the iterative processing of visual stimuli within the cortex. One recent study used FMRI to examine a type of backward masking (+-dot masking) that is thought to involve primarily masking by reentrant processes. The results supported the idea that reentrant processes disrupted the neural representation of the target in LO. Hence, LO appears to be a critical site for neural representation of the target. Although our masking methods were not designed to separate feed-forward from reentrant processes, it is entirely possible that group differences in LO could be attributable to disruption in reentrant processes.

In the present study, we intentionally defined each ROI in a relatively restricted way, based on the largest single cluster for each activation task for each individual. This is a conservative approach that yields smaller, but hopefully more functionally homogeneous, regions. A previous publication from our laboratory used a more liberal approach to define ROIs to examine the extent of activation with the localizer tasks in the absence of any visual masking procedures. In that study, patients differed from controls in having a significantly broader area of activation with the LO localizer stimuli, but not with retinotopic or hMT+ localizers, again suggesting that LO is a critical area to consider regarding group differences in visual perception. To ensure that the present findings were not a result of using a more restricted approach for defining ROIs, we reanalyzed the fmri data using ROIs defined as in our previous study and found the same pattern of results with visual masking (ie, reduced LO activity in schizophrenic patients).

Patients and controls did not differ in performance in the scanner. On the surface, this appears to be inconsistent with performance data from many previous studies. 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. The backward masking methods in the present report were optimized to show a BOLD response. The 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 roughly 24 times as large as in our performance laboratory studies. In addition, we used fewer trials and assessed fewer SOAs than in our typical behavioral paradigms. Although the absence of large performance differences is unusual in the context of the masking literature, it provides an interpretive advantage in that performance level is not a confound in considering group differences in regional brain activity.

It remains possible that the lack of significant performance difference indicates that the patients in this study are atypical. To examine this possibility, we evaluated data from a subset of patients and controls who were also ex-

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Table. Activated Brain Regions

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Abbreviation: MNI, Montreal Neurological Institute.

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amined on visual masking performance out of the scanner as part of the larger masking protocol. Although the small number of subjects (10 patients, 17 controls) precludes formal statistical analysis, the between-group effect sizes for a similar masking task (i.e., high-energy identification) of these subjects were 0.05, 0.31, 0.61, and 0.73 for SOAs of 100, 125, 150, and 225 milliseconds, respectively. These effect sizes between groups were highly consistent with what is found in other studies when patients and controls are matched for sensory input values.

Hence, we do not consider the patient sample to be unusual in this regard.

Although fMRI does not lend itself well to separate examination of the parvocellular and magnocellular visual pathways, limited inferences can be made based on the input of these pathways to visual processing regions. Area MT is considered part of the dorsal pathway that receives predominant input from the magnocellular system, whereas LO is considered part of the ventral pathway and receives input from both the magnocellular and parvocellular systems. Hence, the current findings of abnormalities in LO are not inconsistent with previous evidence for a magnocellular abnormality in schizophrenia. Assuming that LO is a critical site for neural representation of a visual target, and that it underlies visual masking as well as other visual processing deficits in schizophrenia, our data raise questions about other consequences of a dysfunctional LO. For example, could abnormalities in this region contribute in part to the functional disability in schizophrenia? This view, while clearly speculative, would fit with behavioral performance findings that early visual processing tasks are associated with performance on social cognitive tasks, which are related to community functioning in schizophrenia. Hence, with sufficient samples it will be possible to test these speculations by using brain activation in selected ROIs as key variables in proposed pathways that run from brain to perception to basic and social cognition and eventually to functioning in schizophrenia.

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