Biological Psychiatry: CNNI

Archival Report

Aberrant Cortical Connectivity During Ambiguous Object Recognition Is Associated With Schizophrenia

Victor J. Pokorny, Tori D. Espensen-Sturges, Philip C. Burton, Scott R. Sponheim, and Cheryl A. Olman

ABSTRACT

BACKGROUND: Dysfunctional connectivity within the perceptual hierarchy is proposed to be an integral component of psychosis. The fragmented ambiguous object task was implemented to investigate neural connectivity during object recognition in patients with schizophrenia (SCZ) and bipolar disorder and first-degree relatives of patients with SCZ (SREL).

METHODS: We analyzed 3T functional magnetic resonance imaging data collected from 27 patients with SCZ, 23 patients with bipolar disorder, 24 control subjects, and 19 SREL during the administration of the fragmented ambiguous object task. Fragmented ambiguous object task stimuli were line-segmented versions of objects and matched across a number of low-level features. Images were categorized as meaningful or meaningless based on ratings assigned by the participants.

RESULTS: An a priori region of interest was defined in the primary visual cortex (V1). In addition, the lateral occipital complex/ventral visual areas, intraparietal sulcus (IPS), and middle frontal gyrus (MFG) were identified functionally via the contrast of cortical responses to stimuli judged as meaningful or meaningless. SCZ was associated with altered neural activations at V1, IPS, and MFG. Psychophysiological interaction analyses revealed negative connectivity between V1 and MFG in patient groups and altered modulation of connectivity between conditions from right IPS to left IPS and right IPS to left MFG in patients with SCZ and SREL.

CONCLUSIONS: Results provide evidence that SCZ is associated with inefficient processing of ambiguous visual objects at V1, which is likely attributable to altered feedback from higher-level visual areas. We also observed distinct patterns of aberrant connectivity among low-level, mid-level, and high-level visual areas in patients with SCZ, patients with bipolar disorder, and SREL.

https://doi.org/10.1016/j.bpsc.2020.09.018

Psychosis is commonly associated with altered perceptual processes both experimentally and phenomenologically. Visual abnormalities in psychosis are especially pronounced in schizophrenia (SCZ), but these have also been reported in patients with bipolar disorder (BP) and first-degree relatives of patients with SCZ (SREL) (1,2). Past research has largely failed to elucidate the mechanisms by which perceptual abnormalities in these groups lead to (or result from) the heterogeneous clinical and subclinical symptomatology associated with psychosis and genetic predisposition for psychosis; however, recent Bayesian predictive coding models compellingly describe how aberrant top-down modulation (e.g., decreased precision of priors) and overreliance on bottom-up sensory information (e.g., increased precision of likelihood) may lead to a variety of psychotic symptoms including positive, negative, and interpersonal symptoms (3–5). Although predictive coding frameworks may be useful for understanding the relationship between neurobiology and psychopathology, the validity of such models is dependent on developing a better understanding of the neural pathways and architectures involved in perception. Thus, neuroimaging and electrophysiology experiments elucidating the nature of information flow between levels of perceptual hierarchies in the brain will be crucial for the advancement of such models.

Experimentally, most assays of perceptual processing deficits in psychosis have focused on questions of where and when in the perceptual stream deficits occur (e.g., low-level vs. high-level, early vs. late). Decades of such investigations have not produced a smoking gun; instead, there is evidence for processing abnormalities at multiple time points and locations in the perceptual stream (6–10). This is unsurprising given that perception is thought to be the result of iterative loops of bottom-up and top-down signals that coordinate and modulate information flow between brain regions (11). As such, there is a need to investigate interactions between low-level, mid-level, and high-level perceptual processes to better understand perceptual impairments in psychosis.

ISSN: 2451-9022

The primary visual cortex (V1) in particular is a promising candidate for exploring interactions between feedforward and feedback signals (12). Although V1 is commonly thought of as a simple retinotopic map that receives input from the lateral geniculate nucleus (LGN), only approximately 10% of connections to V1 are inputs from the LGN (13). The remaining connections consist of feedback connections from other brain regions and long-range horizontal connections within V1, both of which are thought to modulate neuronal activation in V1 (11). For example, V1 blood oxygen level–dependent (BOLD) activation to line drawings has been shown to be dependent upon higher-level shape perception in the lateral occipital complex (LOC) (14), which in turn means that observed V1 BOLD activation is likely the result of interactions between feedforward and inhibitory feedback connections.

A significant obstacle in successfully characterizing the influence of higher-level brain regions on V1 is the dearth of image sets that range in high-level features while controlling for low-level features. This study implemented a previously published set of images designed for this purpose (15), originally inspired by the work of Cardin *et al.* (12). The set of images depicts fragmented ambiguous objects that vary in the high-level property of recognizability (i.e., some objects are easier to discern than others) but are matched for low-level properties including image luminance, total number of line segments in the image, orientation distribution of line segments, number of line terminations, and contour probability [see (15) for more details]. Leveraging the well-characterized tuning properties of neurons in V1, we assume that changes in V1 activation in response to these images are likely the result of higher-level feedback connections rather than differences in feedforward input from the LGN. Given that psychosis is thought to be associated with reduced top-down inhibitory feedback, it is possible that the expected reduction in V1 activity for more recognizable stimuli (14) would be diminished in patients compared with control subjects.

This study explored associations between low-level, mid-level, and high-level visual areas and a spectrum of psychosis by acquiring functional magnetic resonance imaging (fMRI) data during viewing of fragmented ambiguous objects across a transdiagnostic sample of patients with SCZ, patients with BP, SREL, and healthy control (CON) subjects. In particular, we hypothesized that V1 activation would be affected by the feedback from mid-level and high-level visual areas and that psychosis would be associated with larger V1 activation to meaningful stimuli relative to meaningless stimuli from the fragmented ambiguous object task (FAOT) consistent with a predictive coding account of psychosis in which top-down inhibitory feedback (instantiated here as object recognition in LOC and/or other high-level regions) is diminished.

METHODS AND MATERIALS

Participants

A total of 34 patients with SCZ, 25 patients with BP, 25 CON subjects, and 20 SREL were recruited through the Minneapolis Veterans Affairs Medical Center, community mental health programs, and fliers posted throughout the community. Participants with a psychiatric diagnosis were stable outpatients. Exclusion criteria for SCZ, BP, and CON subjects included intellectual disability (IQ of $<$70), drug or alcohol dependence in the past 6 months, current or past central nervous system condition, epilepsy, history of electroconvulsive therapy, history of head injury with skull fracture or loss of consciousness longer than 30 minutes, age $<$18 or $>$60 years, and all standard MRI contraindications. CON subjects were also excluded if they had a history of primary psychotic disorder, current or past depressive episode, attention-deficit/hyperactivity disorder or learning disability, or a family history of depression, SCZ, or BP. SREL were only excluded if they had a general medical condition that made the study completion impossible. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2008.

Participants' IQ was estimated using the Wechsler Adult Intelligence Scale III Vocabulary and Block Design subtests. Psychiatric symptom severity was assessed through the Structured Clinical Interview for DSM-IV Axis I Disorders (16) and the Brief Psychiatric Rating Scale (BPRS) (17). Of the 23 patients with BP, 9 endorsed a previous psychotic episode. The Schizotypal Personality Questionnaire (SPQ) (18) was administered to all participants to characterize subclinical psychotic symptomatology. A minimum of 2 trained raters (advanced doctoral students in clinical psychology, post-doctoral researchers, or licensed doctoral-level psychologists) reached consensus on all diagnoses.

Stimuli

Stimuli were presented using PsychoPy on an iMac running MacOS 10.9 and were projected using an NEC NP4100 projector with a resolution of 1024 $\times$ 768 pixels and a 60 Hz refresh rate (19). Images were backprojected onto a translucent screen placed inside the scanner bore and were viewed through a mirror mounted on the head coil, positioned over the participants' eyes. The viewing distance was 112 cm, images subtended 8° of visual angle, and the mean luminance of the projected image was 110 cd/m^2.

Stimuli were generated by converting publicly available images of objects into spatially discrete line segments by applying a filter that emulates preferred orientation tuning in V1. Line segments representing the dominant orientation of local features sampled on a regular grid were then embedded in a background of parallel line segments. The orientation of parallel background line segments was determined randomly for each image. All line segments had a length of 7 pixels, and the total image size was 384 $\times$ 384 pixels. See Figure 1 for stimulus examples.

Images were categorized as meaningful or meaningless based on the recognizability of the embedded objects. Initially, images were categorized based on yes/no recognition ratings from 4 study staff (39 participants viewed this version of the task). For the remainder of the study, images were categorized based on yes/no recognition ratings made by the participants themselves in a separate behavioral iteration of the task. This second categorization method was implemented to ensure

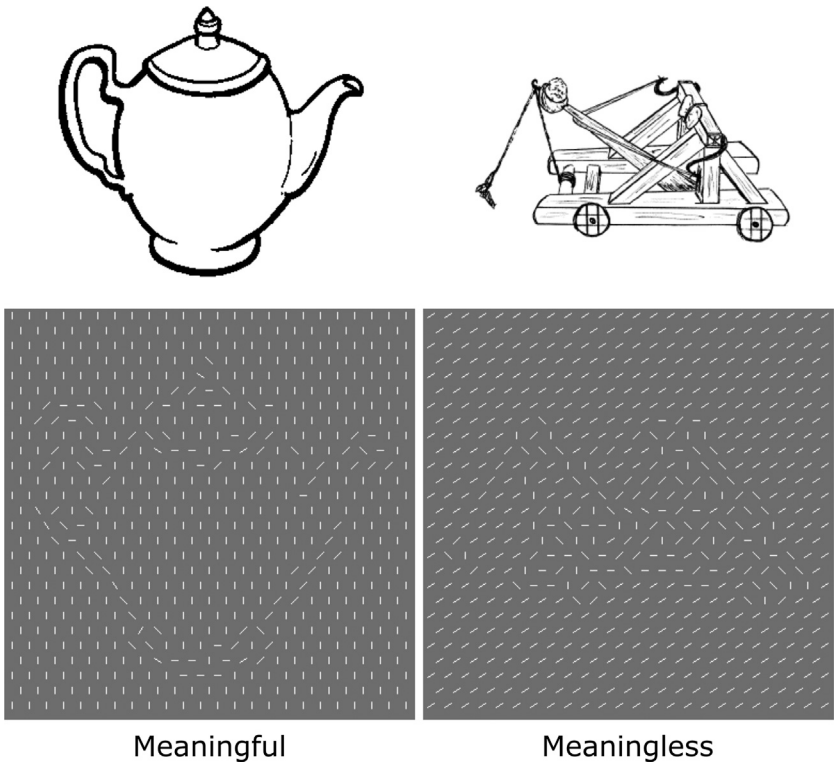

Figure 1. Stimulus examples. Stimuli were generated by converting publicly available images of objects into spatially discrete line segments by applying a filter that emulates preferred orientation tuning in the primary visual cortex. Participants rated images as "short and fat" (right button press) or "tall and skinny" (left button press). Images were deemed meaningful or meaningless based on recognition ratings made by participants in a separate iteration of the task.

that the ratings of stimuli reflected the recognition rates of the population of interest. For both the initial study staff categorizations and the participants' categorizations, the 63 images that were most frequently rated as recognizable were categorized as meaningful, whereas 60 images that were most frequently rated as unrecognizable were considered meaningless. Only 6.5% of the images (8 of 123) were categorized differently between study staff and participants. For more information regarding stimuli creation and properties, see (15).

Fragmented Ambiguous Object Task

The task consisted of 3 conditions: meaningful, meaningless, and rest. Participants were presented with a total of 26 blocks (9 blocks per stimulus condition; 8 blocks of rest) for a total scan duration of 312 seconds; block order was determined by an m-sequence (20). Each block was 12 seconds long and was composed of 8 trials (1.5-s duration each). Each stimulus was presented for 1 second followed by 0.5 second of blank screen before the next trial. Stimuli were sampled randomly with replacement within the given condition.

Participants were asked to indicate whether the fragmented ambiguous objects presented to them were "tall and skinny" or "short and fat" by pressing the left or right button, respectively, on a fiber-optic button box (Current Designs, Philadelphia, PA). This behavioral task was designed to ensure that participants engaged meaningfully with stimuli without activating overt object identification (i.e., naming) processes. By using this behavioral paradigm, we sought to eschew semantic processing and isolate brain activations that reflected naturalistic object perception.

fMRI Acquisition and Preprocessing

fMRI data were collected using a 3T Siemens Prisma system (Siemens, Erlangen, Germany) with a 32-channel head coil. Whole-brain echo-planar imaging data were acquired with a field of view of 208 mm and a matrix size of 88 $\times$ 88, resulting in an in-plane resolution of 2.4 mm isotropic. A total of 60 slices were collected every 1.5 seconds. The echo time was 30 ms, and the flip angle was 75°. Data were collected in the transverse orientation, and the phase encode direction was anterior-posterior. A T_1-weighted anatomical volume (magnetization prepared rapid acquisition gradient-echo) with 1-mm isotropic resolution was collected sagittally for anatomical reference.

Functional data were preprocessed using the Analysis of Functional NeuroImages (AFNI) software (21). For each scan, the initial echo-planar imaging was used as a reference volume for motion correction. Motion-corrected data were then unwarped with a reverse phase encode echo-planar imaging via AFNI's 3dQwarp function. Functional data were aligned with anatomical scans using AFNI's 3dAllineate and spatially smoothed (full width at half maximum = 2 mm).

Analysis

Participants were excluded from analysis for response rates of $<$60%, for statistically nonsignificant V1 responses, or if more than 30% of repetition times contained significant movement

Table 1. Participant Demographic Characteristics and Symptom Ratings

Index	SCZ (n = 27)	BP (n = 23)	CON (n = 24)	SREL (n = 19)	p Value	Post Hoc Contrasts
Age	43.52 (9.61)	45.22 (11.36)	47 (9.58)	46.8 (9.58)	$F_{3,89} = 0.65$, $p = .59$	
Percent Female	19	48	46	74	$\chi^2_3 = 14.07$, $p = .002$	SCZ < SREL
Education	13.56 (2.24)	15.04 (2.6)	15.92 (1.14) 1	14.8 (2.0)	$F_{3,89} = 5.68$, $p = .001$	SCZ < CON
Estimated IQ (From WAIS-III)	98.33 (15.05)	103.04 (13.91)	113.12 (12.46)	109.11 (17.87)	$F_{3,89} = 4.83$, $p = .004$	SCZ, BP < CON
CPZ Equivalent	10.6 (18.41)	1.85 (1.33)			$t_{19.2} = 2.12$, $p = .04$	BP < SCZ
Visual Acuity (LogMAR)	0.12 (0.14)	0.11 (0.13)	0.07 (0.13)	12 (0.12)	$F_{3,89} = 0.56$, $p = .639$	
Overall Symptomatology (BPRS Total)	39.37 (8.83)	36.3 (8.96)	25.7 (2.0)	30.9 (8.18)	$F_{3,89} = 15.77$, $p < .001$	CON < SCZ, BP, SREL SREL < SCZ
BPRS Positive	8.81 (4.32)	5.78 (1.13)	5.04 (0.2)	5.74 (2.54)	$F_{3,89} = 10.28$, $p < .001$	CON < SCZ, BP SREL < SCZ
BPRS Negative	3.93 (1.27)	3.87 (1.71)	3.17 (0.48)	3.21 (0.71)	$F_{3,89} = 2.91$, $p = .039$	CON < SCZ
BPRS Disorganized	7.07 (2.07)	6.26 (1.74)	4.38 (0.77)	5.74 (1.7)	$F_{3,89} = 11.76$, $p < .001$	CON < SCZ, BP, SREL SREL < SCZ
Schizotypal Characteristics (SPQ Total)	36.6 (16.5)	23.78 (15.41)	7.4 (6.3)	18.4 (13.2)	$F_{3,89} = 15.14$, $p < .001$	CON < SCZ, BP, SREL SREL < SCZ
SPQ Cognitive Perceptual	14.12 (9.23)	8.7(7.26)	1.17 (1.56)	5 (5.65)	$F_{3,89} = 16.23$, $p < .001$	CON < SCZ, BP, SREL SREL < SCZ
SPQ Disorganized	6.44 (4.48)	6.83 (3.81)	1.39 (1.5)	3.53 (3.85)	$F_{3,89} = 11.72$, $p < .001$	CON < SCZ, BP, SREL SREL < SCZ
SPQ Interpersonal	17.68 (8.5)	11.09 (9.02)	4.91 (4.96)	11.84 (7.62)	$F_{3,89} = 10.99$, $p < .001$	CON < SCZ, BP, SREL SREL < SCZ

All data are presented as mean (SD). A total of 20 patients with SCZ and 15 patients with BP were taking antipsychotics. Alpha for all post hoc contrasts was set at .05, and p values were false discovery rate–corrected for multiple comparisons when appropriate. SPQ total data were not obtained for 2 patients with SCZ and 1 CON subject.

BP, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; CON, control; IQ, intelligence quotient; SCZ, schizophrenia; SPQ, Schizotypal Personality Questionnaire; SREL, first-degree relatives of patients with schizophrenia; WAIS-III, Wechsler Adult Intelligence Scale, third edition.

(defined as greater than 0.5 mm). Analyses were performed on the remaining 27 patients with SCZ, 23 patients with BP, 24 CON subjects, and 19 SREL. A priori V1 regions of interest (ROIs) were defined by computing the intersection of significant positive whole-brain voxel activation and individualized probabilistic maps of V1 (22). Post hoc ROIs were identified by contrasting meaningful and meaningless conditions across participants; 6 post hoc ROIs were identified this way: right and left LOC with additional activation in the fusiform gyrus (LOC+), right and left intraparietal sulcus (IPS), and right and left middle frontal gyrus (MFG). Alpha for all ROIs was set at 0.001 voxelwise probability and 0.01 clusterwise probability with a minimum cluster size of 23.

To characterize stimulus-dependent connections between ROIs, we computed generalized psychophysiological interaction (gPPI) terms for V1, r/lLOC+, r/lIPS, and r/lMFG (23). The gPPI approach has been shown to be especially powerful for block design tasks such as the FAOT (24). False discovery rate (FDR)–corrected p values were calculated via the p.adjust function in R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/), and plots were created using ggplot2 (25).

RESULTS

Demographic, Clinical, and Behavioral Measures

Participant demographic information is presented in Table 1. Visual acuity and age did not differ across groups. Patients with SCZ exhibited lower IQ and reported fewer years of education than CON subjects. In addition, patients with SCZ exhibited the most symptomatology as indicated by highest totals on the BPRS and SPQ; patients with BP rated second highest and SREL totals fell between the totals for CON subjects and patients with BP. SCZ gender distribution skewed more male than any of the other groups, with post hoc pairwise comparisons revealing a significant difference between patients with SCZ and SREL. To partially account for this imbalance in gender distribution, all reported repeated-measures analyses of variance (RM-ANOVAs) included gender as a between-subjects factor. Visual acuity was included as a covariate in all models to account for variance that might be attributed to low-level differences in sensory processing. Moreover, 20 patients with SCZ and 15 patients with BP were taking antipsychotic medication; patients with SCZ were taking higher chlorpromazine equivalent doses than those with BP. We did not observe any significant correlations between chlorpromazine equivalent dose and any neural measures (Figure S2).

Behaviorally, we did not observe any differences in the left button (i.e., tall and skinny) vs. the right button (i.e., short and fat) responding between groups (interaction of group and response type, ANOVA, $F_{3,88} = 1.09$, $p = .359$, $\eta^2 = .03$). Furthermore, we did not observe strong evidence of differences in the frequency of responses between groups (main effect of group, $F_{3,88} = 2.55$, $p = .061$, $\eta^2 = .01$) and differences in the distribution of responses between groups (Levene's test of equal variances, $F_{3,180} = 0.71$, $p = .546$) (Figure S4).

V1 BOLD Activation

At V1 (Figure 2), we observed a difference between groups in the amount of BOLD modulation between conditions

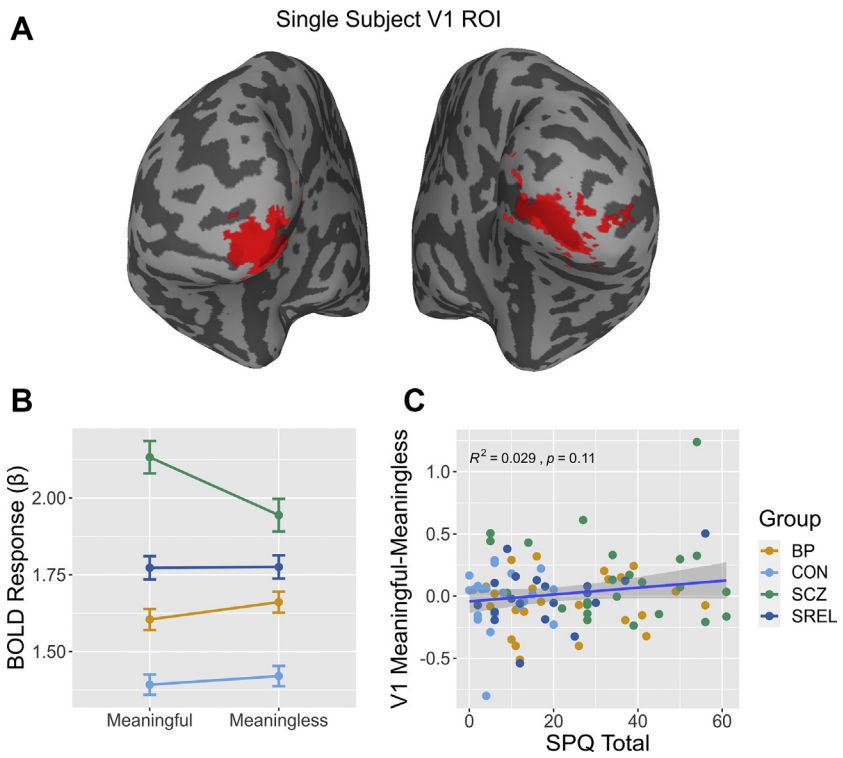

Figure 2. Primary visual cortex (V1) blood oxygen level–dependent (BOLD) activation. **(A)** Depiction of an example V1 region of interest (ROI) for a single participant. Individualized probabilistic maps of V1 (22) were restricted to positive clusters of voxels that modulated significantly between resting and meaningful + meaningless conditions. **(B)** V1 BOLD activation for each condition and group. Error bars are within-subjects SEM with a Morey correction factor according to an established method (38). **(C)** To characterize how a spectrum of clinical and subclinical psychotic symptoms relate to task manipulations, we correlated meaningful-meaningless difference scores with Schizotypal Personality Questionnaire (SPQ) totals. BP, bipolar disorder; CON, control; SCZ, schizophrenia; SREL, first-degree relatives of patients with schizophrenia.

(interaction of group and condition, ANOVA, $F_{3,87} = 3.30$, $p = .024$, $\eta^2 = .10$). This interaction was driven by patients with SCZ who were the only group to exhibit significantly larger activations during the meaningful condition relative to the meaningless condition (FDR-corrected $p = .003$). We did not observe significant main effects of condition or group on V1 BOLD activations. We then correlated meaningful − meaningless difference scores with scores on the SPQ and BPRS, but these correlations did not reach significance. In addition, IQ was not correlated with V1 difference scores, providing evidence that the group by condition interaction was not driven by a generalized deficit.

Post Hoc ROIs

It should be noted that RM-ANOVAs revealed significant main effects of condition for all post hoc ROIs because these ROIs were selected based on statistically significant modulation between conditions. Laterality was included as a within-subjects variable for all post hoc ROI RM-ANOVAs. Figure 3 depicts all post hoc ROIs and mean BOLD activation per group, per condition.

We did not observe a main effect of group or interaction of group by condition on LOC+ activation. There was a significant interaction between condition and laterality ($F_{3,87} = 8.73$, $p = .004$, $\eta^2 = .09$) that was driven by larger condition modulation in right LOC+ than left LOC+. We observed a difference in IPS activation between groups as a function of condition in IPS (group-by-condition interaction, $F_{3,87} = 3.78$, $p = .014$, $\eta^2 = .12$) that was driven by stronger modulation between conditions in the SCZ and SREL groups than in other groups. For MFG, we also observed an interaction of group and condition ($F_{3,87} = 4.57$, $p = .005$, $\eta^2 = .14$). Follow-up examination revealed again that the SCZ and SREL groups exhibited the strongest modulation between conditions. In addition, there was a main effect of laterality in which left MFG exhibited stronger activation than right MFG across groups ($F_{3,87} = 6.64$, $p = .012$, $\eta^2 = .07$). IQ, SPQ, and BPRS scores failed to correlate with meaningful-meaningless difference scores in IPS or MFG.

Context-Dependent Interactions: gPPI

We quantified a total of 42 connections of interest by assigning each ROI (V1, r/lLOC+ r/lIPS, and r/lMFG) as a seed region and computing interactions with the 6 remaining ROIs (7 seed regions × 6 ROIs) per condition per subject. We then tested the effect of condition for each gPPI connection of interest (COI) via dependent samples t tests. Of the 42 COIs, 19 showed a significant effect of condition after FDR correction for multiple comparisons ($ps < .001$). Figure 4A depicts this subset of COIs selected for further analysis. Although one cannot infer biological directionality from gPPI, we use arrows to illustrate the statistical directionality of gPPI results, e.g., if the connection between seed region rLOC+ to target region V1 is significant, we cannot assume that the connection between seed region V1 to target region rLOC+ is also significant.

To investigate connection strength within each group, we implemented a mass univariate approach in which we ran one-sample t tests against zero for each group for each condition for the 19 COIs selected for further analysis,

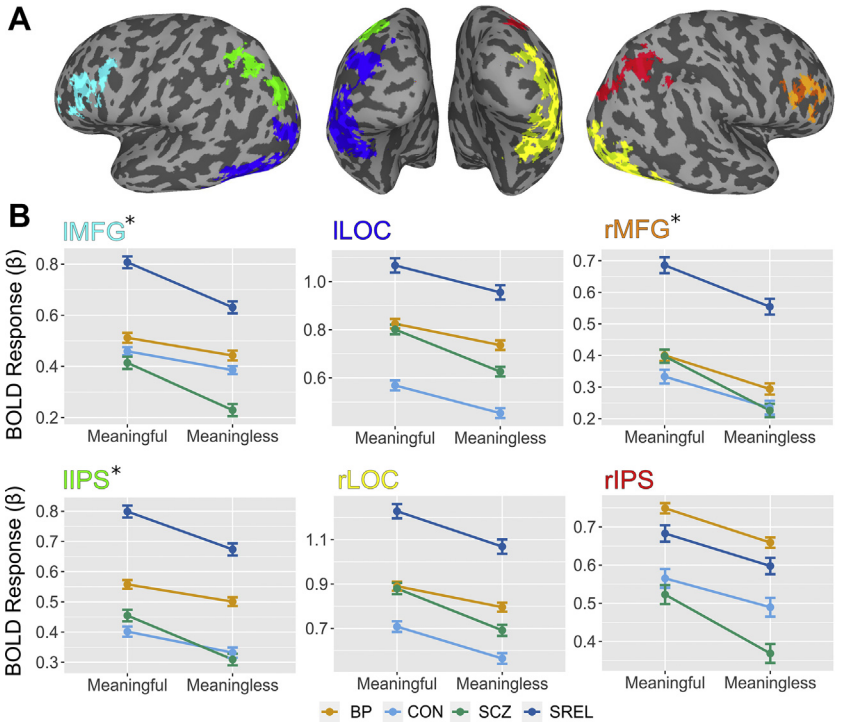

Figure 3. Post hoc regions of interest. **(A)** Depictions of group-level regions of interest that significantly modulated blood oxygen level–dependent (BOLD) activation between meaningful and meaningless conditions. Left lateral occipital cortex + ventral visual areas (lLOC+; dark blue), right LOC+ (yellow), left middle frontal gyrus (lMFG; teal), rMFG (orange), left intraparietal sulcus (lIPS; green), and rIPS (red). **(B)** Post hoc region of interest BOLD activations for each condition and group. The asterisk indicates significant interaction of group and condition. Similar to Figure 2, error bars are within-subjects SEM. BP, bipolar disorder; CON, control; SCZ, schizophrenia; SREL, first-degree relatives of patients with schizophrenia.

correcting for multiple comparisons via FDR (Figure 4B). In the context of gPPI, running one-sample *t* tests against zero for each interaction beta weight tests the null hypothesis that connection strength did not change during stimulus presentation.

COIs with V1 as the seed region showed varied patterns of activation across groups. SCZ and BP groups exhibited significantly negative V1→lMFG connections for the meaningless condition, whereas all groups except the SCZ group significantly increased connection strength from V1 to r/lLOC during the meaningful condition. CON subjects were the only group to increase V1→rIPS connection strength. For mid-level ventral (i.e., LOC+) seed COIs, all groups but CON exhibited increased connectivity from r/lLOC to V1. All mid-level IPS seed COIs were significant for all groups except rIPS→r/lMFG, in which SREL were the only group to increase connection strength between rIPS and lMFG. Finally, all groups exhibited a significant increase in connectivity relative to resting for all high-level (i.e., MFG) seed COIs.

To directly explore group differences and isolate task-related connection strengths that were specific to condition manipulation (meaningful vs. meaningless) rather than general visual system activation (resting vs. meaningless or resting vs. meaningful), we ran RM-ANOVAs with group as a between-subjects factor and condition as a within-subjects factor. We observed an interaction of group by condition at rIPS→lIPS ($F_{3,87}$ = 4.7, p = .004, η^2 = .14) and rIPS→lMFG ($F_{3,87}$ = 3.74, p = .014, η^2 = .11) that were both driven by SCZ and SREL groups modulating connectivity more between condition than the other groups (Figure 5). In addition, an interaction of group by condition at lMFG→lLOC ($F_{3,87}$ = 3.48, p = .019, η^2 = .11) was driven by SREL who exhibited a lack of modulation between conditions compared with the other groups (Figure 5). We did not observe any other group or group-by-condition effects.

Finally, to explore relationships between neural measures and symptom severity, we computed mass correlations between all neural measures of interest (i.e., individual ROI activations, connectivity indices, and meaningful-meaningless subtraction indices) and SPQ and BPRS scores corrected for FDR. These exploratory mass correlations are depicted in Figure S2.

DISCUSSION

Summary

This study identified neural correlates of fragmented ambiguous object recognition in a transdiagnostic sample of patients with schizophrenia, patients with bipolar disorder, first-degree relatives of patients with schizophrenia, and healthy control subjects. We found that SCZ was associated with altered V1 activations during object recognition. We identified bilateral mid-level visual areas in both the ventral (r/lLOC+) and dorsal (r/lIPS) stream and bilateral high-level areas (r/lMFG) that modulated between meaningful and meaningless conditions and found that the SCZ and SREL groups exhibited stronger modulation between conditions at IPS and MFG. Finally, we characterized

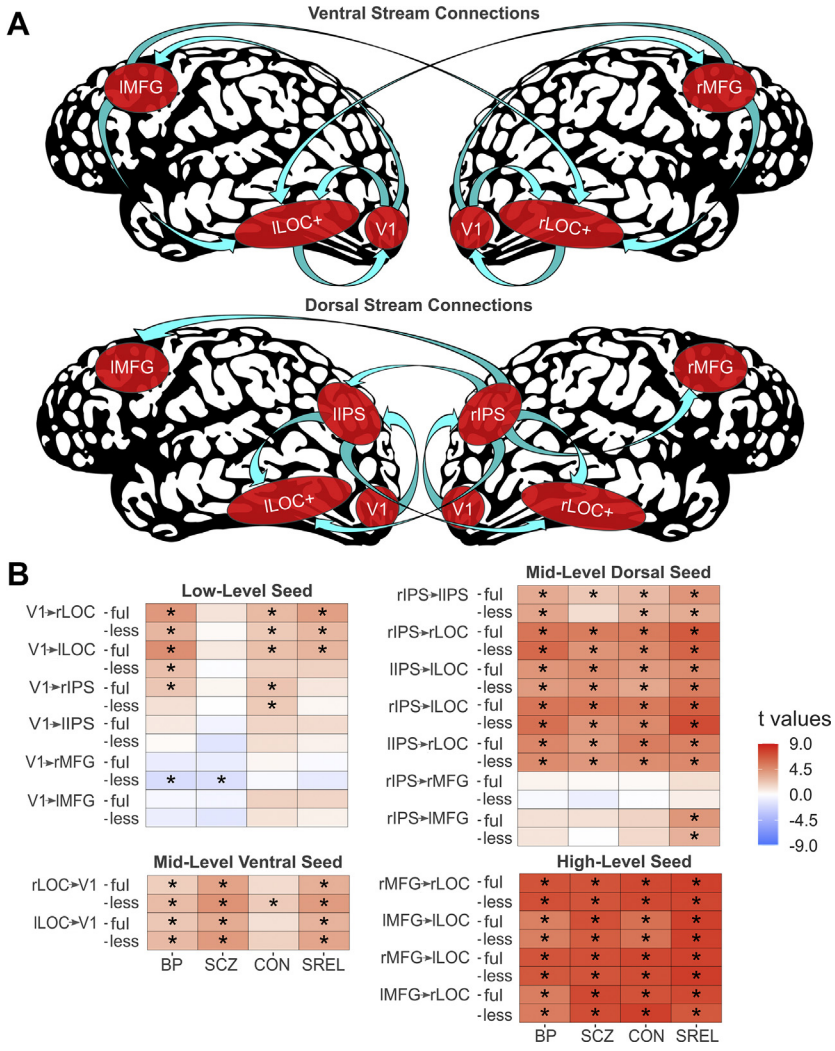

Figure 4. Generalized psychophysiological interaction results. **(A)** Illustration of the 19 connections that showed significant modulation between meaningful and meaningless conditions organized into ventral and dorsal connections. **(B)** Tile plot showing results of the first mass univariate analysis in which each connection for each condition for each group was tested against zero. The asterisk indicates significance at $p < .05$ after false discovery rate correction for multiple comparisons. + indicates plus ventral visual areas. BP, bipolar disorder; CON, control; IPS, intraparietal sulcus; l, left; LOC, lateral occipital cortex; MFG, middle frontal gyrus; r, right; SCZ, schizophrenia; SREL, first-degree relatives of patients with schizophrenia; V1, primary visual cortex.

distinct patterns of functional connectivity between ROIs for each group.

Low-Level ROI: V1

Because image sets were painstakingly matched for low-level features, including likelihood of collinear elements, modulation of V1 between conditions was likely a result of feedback from higher visual areas. The SCZ group exhibited patterns of V1 activation between conditions that were distinct from SREL, BP, and CON groups. This finding is consistent with a predictive coding account of SCZ in which aberrant predictive coding (instantiated here as aberrant feedback connections

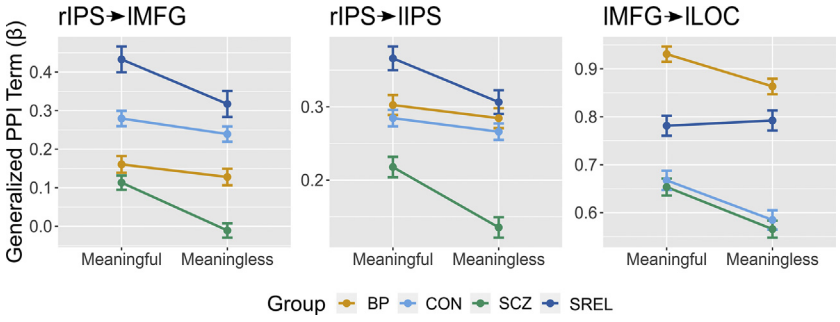

Figure 5. Generalized psychophysiological interaction (PPI) connections showing a group-by-condition interaction. Three connections of interest showed significant differences between conditions as a function of group. Interactions were primarily driven by altered modulation in patients with schizophrenia (SCZ) and first-degree relatives of patients with SCZ (SREL). Similar to Figures 2 and 3, error bars represent within-subjects SEM. BP, bipolar disorder; CON, control; l, left; IPS, intraparietal sulcus; MFG, middle frontal gyrus; r, right.

between brain regions) leads to (or stems from) downstream cognitive-perceptual distortions. However, it must be noted that we did not observe correlations between meaningful-meaningless difference scores and symptom severity ratings.

Our results shed light on previous studies of the modulatory effect of context and shape perception on V1 activation in normative populations (14,26–30). For example, Murray *et al.* (10) observed strongest V1 activation to stimuli composed of randomly oriented lines (i.e., meaningless line drawings) and weakest activation to stimuli composed of lines grouped into 3 dimensional shapes (i.e., meaningful line drawings). We did not observe this pattern of activation in CON, BP, or SREL groups and observed the opposite pattern in the SCZ group (i.e., greater activation to meaningful stimuli). These findings build on the work of Qiu *et al.* (30), who showed that previous discrepancies in the literature [see (14,26,27)] were likely caused by differences in the amount of visual clutter and contour alignment. Crucially, the FAOT stimuli were matched for both of these confounding factors and thus provide a novel account of the effect object recognition on V1 activation.

Mid-level ROIs: LOC+ and IPS

V1 participates in both ventral and dorsal visual streams with ventral activation commonly associated with identification/recognition processes and dorsal activation associated with location-oriented and behavior guidance processes. We did not observe strong evidence of deficits in mid-level ventral (LOC+) BOLD activation and instead found evidence of altered mid-level dorsal (IPS) BOLD activation in patients with SCZ and SREL. These results align with previous findings of aberrant dorsal stream visual processing in patients with SCZ during fragmented object recognition (10,31). For example, Doniger *et al.* (10) reported intact ventral N1 component generation but altered dorsal P1 component generation in SCZ during an object recognition task measured via electroencephalography. This convergent evidence across neuroimaging modalities and tasks suggests that IPS plays an important role in dysfunctional object recognition in SCZ and may extend to those with a genetic liability for SCZ (i.e., SREL). It is worth noting that others have observed ventral object processing deficits in SCZ (32); however, this discrepancy is likely caused by substantially different experimental manipulations and less well-controlled visual stimuli.

High-Level ROI: MFG

Similar to IPS, we observed stronger MFG modulation between conditions in patients with SCZ and SREL. MFG is commonly linked to the ventral attention network and is thought to play a role in reorienting attention (33). Thus, larger decreases in MFG activation to meaningless stimuli relative to meaningful stimuli in patients with SCZ and SREL may reflect reduced ability to allocate attention to more ambiguous stimuli.

Connectivity

We quantified task-dependent connectivity among ROIs (i.e., V1, r/lLOC+, r/lIPS, and r/lMFG) to clarify visual network activity during ambiguous object recognition. Across all participants, 19 of the 42 connections strongly modulated between conditions; 10 of these COIs shared striking similarities to proposed hierarchical models of the ventral stream in which V1 and LOC+ share information bidirectionally, consistent with feedforward and feedback between these regions (11,34,35). It is important to note that the significance of unidirectional versus bidirectional connectivity between regions in the context of gPPI is still unknown. gPPI terms certainly reflect a "statistical directionality," in that a seed area and target area are defined and cannot be assumed to be commutative; however, whether this statistical directionality can be translated to biological directionality is controversial. Previous studies have successfully used dynamic causal modeling to validate directionality of gPPI-derived connections (36); however, dynamic causal modeling itself has considerable limitations (37).

Mass univariate *t* tests of context-dependent interaction beta weights against zero revealed opposing connectivity between V1 and MFG for patients with SCZ and BP, which is consistent with overreliance on low-level sensory processes in these groups. In addition, patients with SCZ were the only group that failed to increase connection strength from V1 to r/lLOC during the meaningful condition consistent with reduced feedback from mid-level ventral regions although follow-up RM-ANOVAs did not reveal a significant effect of group or a group-by-condition interaction. Finally, we observed stronger modulation among conditions in patients with SCZ and SREL of rIPS→lIPS and rIPS→lMFG, suggesting that altered dorsal stream processing may be a feature of genetic predisposition for SCZ.

Conclusions

To the best our knowledge, this is the first study to assess the neural correlates of object recognition across a spectrum of psychosis using images that are matched for low-level features. Our results provide evidence that BOLD activation at V1 is modulated by other visual areas in SCZ, which has broad implications for the study of vision in SCZ and emphasizes that no brain region in the visual hierarchy can be considered an island. Clinically, this study identified aberrant processing of visual information in the dorsal stream and prefrontal regions in SCZ and relatives of patients with SCZ. Our findings highlight that SCZ is likely not the result of isolated low- or high-level perceptual deficits, but of aberrant connectivity between levels of the perceptual hierarchy.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the awards by the Department of Veterans Affairs Clinical Science Research and Development Service (Grant No. I01CX000227 [to SRS]) and the National Institute of Mental Health of the National Institutes of Health (NIH) (Grant No. R01MH112583 [to SRS]). This work is also supported by the National Institute of Neurological Disorders and Stroke of the NIH (Grant No. P30 NS076408), the National Eye Institute of the NIH (Grant No. P30 EY011374), the National Institute of Biomedical Imaging and Bioengineering of the NIH (Grant No. P41EB015894), and the NIH (Grant No. 1S10OD017974-01). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs or the NIH.

We would like to thank Isaac Hatch-Gillette, Joseph Lupo, and Haven Hafar for their assistance with data collection and Julia Longenecker for her assistance with task development.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Minneapolis Veterans Affairs Health Care System (VJP, SRS); and Department of Psychiatry and Behavioral Science (TDE-S, SRS), Department of Psychology and Center for Magnetic Resonance Research (CAO), and College of Liberal Arts (PCB), University of Minnesota, Minneapolis, Minnesota.

Address correspondence to Victor J. Pokorny, B.A., at pokor076@umn.edu.

Received Jun 23, 2020; revised Sep 25, 2020; accepted Sep 28, 2020.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2020.09.018.

REFERENCES

1. O'Bryan RA, Brenner CA, Hetrick WP, O'Donnell BF (2014): Disturbances of visual motion perception in bipolar disorder. Bipolar Disord 16:354–365.
2. Yeap S, Kelly SP, Sehatpour P, Magno E, Javitt DC, Garavan H, *et al.* (2006): Early visual sensory deficits as endophenotypes for schizophrenia: High-density electrical mapping in clinically unaffected first-degree relatives. Arch Gen Psychiatry 63:1180–1188.
3. Sterzer P, Adams RA, Fletcher P, Frith C, Lawrie SM, Muckli L, *et al.* (2018): The predictive coding account of psychosis. Biol Psychiatry 84:634–643.
4. Sterzer P, Voss M, Schlagenhauf F, Heinz A (2019): Decision-making in schizophrenia: A predictive-coding perspective. Neuroimage 190:133–143.
5. Adams RA, Brown HR, Friston KJ (2014): Bayesian inference, predictive coding and delusions. AVANT V 51–88.
6. Butler PD, Schechter I, Zemon V, Schwartz SG, Greenstein VC, Gordon J, *et al.* (2001): Dysfunction of early-stage visual processing in schizophrenia. Am J Psychiatry 158:1126–1133.
7. Neuhaus AH, Karl C, Hahn E, Trempler NR, Opgen-Rhein C, Urbanek C, *et al.* (2011): Dissection of early bottom-up and top-down deficits during visual attention in schizophrenia. Clin Neurophysiol 122:90–98.
8. Onitsuka T, Shenton ME, Salisbury DF, Dickey CC, Kasai K, Toner SK, *et al.* (2004): Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: An MRI study. Am J Psychiatry 161:1603–1611.
9. Keane BP, Joseph J, Silverstein SM (2014): Late, not early, stages of Kanizsa shape perception are compromised in schizophrenia. Neuropsychologia 56:302–311.
10. Doniger GM, Foxe JJ, Murray MM, Higgins BA, Javitt DC (2002): Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Arch Gen Psychiatry 59:1011–1020.
11. Lamme VA, Supèr H, Spekreijse H (1998): Feedforward, horizontal, and feedback processing in the visual cortex. Curr Opin Neurobiol 8:529–535.
12. Cardin V, Friston KJ, Zeki S (2011): Top-down modulations in the visual form pathway revealed with dynamic causal modeling. Cereb Cortex 21:550–562.
13. Peters A, Payne BR (1993): Numerical relationships between geniculocortical afferents and pyramidal cell modules in cat primary visual cortex. Cereb Cortex 3:69–78.
14. Murray SO, Kersten D, Olshausen BA, Schrater P, Woods DL (2002): Shape perception reduces activity in human primary visual cortex. Proc Natl Acad Sci U S A 99:15164–15169.
15. Olman CA, Espensen-Sturges T, Muscanto I, Longenecker JM, Burton PC, Grant AN, Sponheim SR (2019): Fragmented ambiguous objects: Stimuli with stable low-level features for object recognition tasks. PLoS One 14:e0215306.
16. First MB, Spitzer RL, Gibbon M, Williams JBW (2002): Structured Clinical Interview for DSM-IV-TR Axis I Disorders, research version, patient ed. (SCID-I/P). New York, NY: Biometrics Research, New York State Psychiatric Institute.
17. Overall JE, Gorham DR (1962): The Brief Psychiatric Rating Scale. Psychol Rep 10:799–812.
18. Raine A (1991): The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull 17:555–564.
19. Peirce J, Gray JR, Simpson S, MacAskill M, Höchenberger R, Sogo H, *et al.* (2019): PsychoPy2: Experiments in behavior made easy. Behav Res Methods 51:195–203.
20. Buracas GT, Boynton GM (2002): Efficient design of event-related fMRI experiments using M-sequences. Neuroimage 16:801–813.
21. Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173.
22. Wang L, Mruczek REB, Arcaro MJ, Kastner S (2015): Probabilistic maps of visual topography in human cortex. Cereb Cortex 25:3911–3931.
23. McLaren DG, Ries ML, Xu G, Johnson SC (2012): A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. Neuroimage 61:1277–1286.
24. Cisler JM, Bush K, Steele JS (2014): A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI. Neuroimage 84:1042–1052.
25. Wickham H (2009): ggplot2: Elegant Graphics for Data Analysis. New York: Springer.
26. Kok P, de Lange FP (2014): Shape perception simultaneously up- and downregulates neural activity in the primary visual cortex. Curr Biol 24:1531–1535.
27. Altmann CF, Bülthoff HH, Kourtzi Z (2003): Perceptual organization of local elements into global shapes in the human visual cortex. Curr Biol 13:342–349.
28. Murray SO, Boyaci H, Kersten D (2006): The representation of perceived angular size in human primary visual cortex. Nat Neurosci 9:429–434.
29. Naselaris T, Olman CA, Stansbury DE, Ugurbil K, Gallant JL (2015): A voxel-wise encoding model for early visual areas decodes mental images of remembered scenes. Neuroimage 105:215–228.
30. Qiu C, Burton PC, Kersten D, Olman CA (2016): Responses in early visual areas to contour integration are context dependent. J Vis 16:19.
31. Foxe JJ, Doniger GM, Javitt DC (2001): Early visual processing deficits in schizophrenia: Impaired P1 generation revealed by high-density electrical mapping. Neuroreport 12:3815–3820.
32. Plomp G, Roinishvili M, Chkonia E, Kapanadze G, Kereselidze M, Brand A, Herzog MH (2013): Electrophysiological evidence for ventral stream deficits in schizophrenia patients. Schizophr Bull 39:547–554.
33. Japee S, Holiday K, Satyshur MD, Mukai I, Ungerleider LG (2015): A role of right middle frontal gyrus in reorienting of attention: A case study. Front Syst Neurosci 9:23.
34. Felleman DJ, Van Essen DC (1991): Distributed hierarchical processing in the primate cerebral cortex. Cereb Cortex 1:1–47.
35. Hubel DH, Wiesel TN (1962): Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 160:106–154.
36. Minati L, Grisoli M, Seth AK, Critchley HD (2012): Decision-making under risk: A graph-based network analysis using functional MRI. Neuroimage 60:2191–2205.
37. Lohmann G, Erfurth K, Müller K, Turner R (2012): Critical comments on dynamic causal modelling. Neuroimage 59:2322–2329.
38. Morey RD (2008): Confidence intervals from normalized data: A correction to Cousineau (2005). Tutor Quant Methods Psychol 4:61–64.