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Disruptions in neural connectivity associated with reduced susceptibility to a depth inversion illusion in youth at ultra high risk for psychosis

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ABSTRACT

Patients with psychosis exhibit a reduced susceptibility to depth inversion illusions (DII) in which a physically concave surface is perceived as convex (e.g., the hollow mask illusion). Here, we examined the extent to which lessened susceptibility to DII characterized youth at ultra high risk (UHR) for psychosis. In this study, 44 UHR participants and 29 healthy controls judged the apparent convexity of face-like human masks, two of which were concave and the other convex. One of the concave masks was painted with realistic texture to enhance the illusion; the other was shown without such texture. Networks involved with top-down and bottom-up processing were evaluated with resting state functional connectivity magnetic resonance imaging (fcMRI). We examined regions associated with the fronto-parietal network and the visual system and their relations with susceptibility to DII. Consistent with prior studies, the UHR group was less susceptible to DII (i.e., they were characterized by more veridical perception of the stimuli) than the healthy control group. Veridical responses were related to weaker connectivity within the fronto-parietal network, and this relationship was stronger in the UHR group, suggesting possible abnormalities of top-down modulation of sensory signals. This could serve as a vulnerability marker and a further clue to the pathogenesis of psychosis.

1. Introduction

Accumulating evidence indicates that patients with schizophrenia experience abnormalities in visual perceptual processing (Silverstein, 2016). Some of this evidence suggests that the neurobiological mechanisms involved in these impairments are similar to those involved in some cognitive deficits and symptoms, suggesting that clarifying the altered neural circuitry involved in visual processing impairments could serve as a window for understanding diverse disease mechanisms in schizophrenia (Dima et al., 2009; Kantrowitz et al., 2009; Keane et al., 2013; Mittal et al., 2015; Phillips and Silverstein, 2003; Silverstein et al., 2015; Yoon et al., 2013). A relatively unanswered question, however, is the degree to which perceptual impairments occur in people at ultra high risk (UHR) for psychosis; that is, among people characterized by attenuated psychotic symptoms and a decline in socio-occupational functioning (Cannon et al., 2008; Haroun et al., 2006). The UHR period is critical for understanding important pathogenic processes and serves as a window of opportunity for early intervention before the onset of formal psychosis. Current research suggests that about 15%–35% of UHR individuals develop a psychotic disorder within 3 years of their baseline interview (Cannon et al., 2008; Fusar-Poli et al., 2013; Fusar-Poli et al., 2012). Additionally, individuals in this period tend to have fewer confounds that are often common in schizophrenia patients such as widely prescribed antipsychotic medications and substance abuse and dependence (Haroun et al., 2006; McGlashan et al., 2007; Mittal et al., 2010). If UHR individuals demonstrate some of the same perceptual changes that are observed in fully developed schizophrenia, this would provide important insights into the nature of psychosis, and could help to highlight novel biomarkers as well.

A small number of studies aimed at understanding perceptual processing during the psychosis risk period have focused on visual illusions

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(Koethe et al., 2009; Mittal et al., 2015; Parnas et al., 2001). Cross sectional studies of individuals at risk for psychosis and of schizophrenia patients report that both of these groups are less susceptible to visual illusions compared to patients with depression, bipolar disorder, and healthy controls (Koethe et al., 2009). Our group looked at visual context processing using the Ebbinghaus illusion task and found UHR youth to be less susceptible to this size-constancy-based illusion compared to healthy controls (Mittal et al., 2015). Other paradigms such as tasks using depth inversion illusions (DIIs), in which concave objects appear convex (to individuals with healthy visual processing), have demonstrated that patients with schizophrenia are less susceptible to these visual illusions as well (Dima et al., 2009; Keane et al., 2013; Schneider et al., 2002). However, limited work has been done looking at the DII paradigm with UHR individuals. Illusion paradigms provide critical information in understanding perceptual processing in schizophrenia because they reveal, among other things, the degree to which processing of feed-forward sensory signals is modulated in a "top-down" fashion by stimulus context, prior knowledge, and/or expectations (Bar, 2003; Cauller, 1995; Gilbert and Sigman, 2007; Schneider et al., 2002; Silverstein and Keane, 2011): when top-down signals override sensory input, illusions can result.

In the case of DII in healthy samples, top-down expectations signaling the likelihood that a facial stimulus will be convex suppress sensory signals indicating that the stimulus is concave (Dima et al., 2009; Koethe et al., 2009). DII studies of schizophrenia have found that there is less fronto-parietal top-down modulation of earlier visual cortex information, as well as stronger bottom-up feed-forward signals from the occipital lobe, resulting in more veridical stimulus perception during DII tasks, compared to healthy controls (Dima et al., 2009). This finding is important because evidence suggests that the fronto-parietal network is an important network for bottom-up and top-down processing of perceptual information (Corbetta and Shulman, 2002; Dima et al., 2009), and there is reduced connectivity in this network in people with schizophrenia (Poppe et al., 2016; Repovs et al., 2011). The purpose of this study was, therefore, to determine if DII and this network are impaired in UHR subjects.

The "dysconnectivity hypothesis" is of particular relevance in both schizophrenia and UHR research (Pettersson-Yeo et al., 2011). This hypothesis suggests that there are aberrant connections between networks that may be contributing to symptom formation and cognitive decline in schizophrenia patients and in UHR youth during the adolescent period (Mamah et al., 2013; Pettersson-Yeo et al., 2011). A recent review conducted by Schmidt et al. (2015) examined the fronto-parietal network, a network showing aberrant connectivity at rest in individuals along the psychosis spectrum, and findings suggest reductions in network connectivity which may contribute to the onset of psychosis (Schmidt et al., 2015). Other networks have been examined using resting state functional connectivity magnetic resonance imaging (fcMRI) in mental health populations as well. For example, investigations examining the salience network and the default mode network suggest abnormalities may be associated with increased symptoms and impaired processes in patients with schizophrenia and UHR populations (Mamah et al., 2013; Palaniyappan and Liddle, 2012; Pelletier-Baldelli et al., 2015; White et al., 2010; Whitfield-Gabrieli and Ford, 2012; Whitfield-Gabrieli et al., 2009).

There has been promise in using fcMRI as it has been found to provide critical information regarding the organization of connectivity patterns (Satterthwaite and Baker, 2015). Further, fcMRI has been shown to be advantageous because the task is simply to rest as opposed to completing a task in the MRI scanner, which is an important draw with patients that have impairing symptoms that hinder their ability to complete highly demanding and lengthy tasks inside the scanner (Fox et al., 2005; Mamah et al., 2013). Also, fcMRI allows for the identification of specific intrinsic functional networks without the potential confounds of introducing functional tasks (Whitfield-Gabrieli and Ford, 2012). The use of fcMRI as a tool to understand neural mechanisms related to disease has been a growing method and several studies examining populations such schizophrenia, aging, and autism have provided important insight into how the brain might be engaged during task performance outside the scanner (Bernard et al., 2013; Plitt et al., 2015; Sheffield and Barch, 2016). Further, fcMRI data sheds light on the intrinsic organization of the brain, and many of the patterns seen at rest are often quite similar to those seen during task performance (Biswal and Hyde, 1998). It is important to note though that with fcMRI, we are unable to make inferences and draw conclusions about causality and directionality. However, patterns of connectivity at rest measured during fcMRI do lend themselves to speculation about potential mechanisms involved in behavioral performance. Taken together, examining networks and associations with behavioral data at rest can provide a deeper understanding of underlying mechanisms fostering the etiology of disease and may have potential clinical utility.

Here, we investigated the susceptibility of UHR individuals to DIIs with respect to fcMRI and in comparison with healthy control subjects. We targeted the fronto-parietal network to test the hypothesis that abnormalities in illusion perception similar to those found in people with schizophrenia are present in UHR populations, and are related to dysfunction in networks implicated in top-down processing. Other studies have used similar approaches using seeds within the prefrontal cortex to reveal the fronto-parietal network. For example, one study used fcMRI and a behavioral performance task to examine associations between information processing and the fronto-parietal network, focusing on the dorsal lateral prefrontal cortex and intraparietal sulcus (IPS) to examine this network (Dosenbach et al., 2007). Further, Mamah et al. (2013) also used the noted regions to examine fronto-parietal network connectivity patterns using fcMRI to examine dysconnectivity in schizophrenia and bipolar disorder patients. Dima et al. (2009) examined top-down and bottom-up processes using seeds within the prefrontal regions.

In the present study, UHR and healthy control participants completed structured clinical interviews, a DII task, and a fcMRI scan. Based on findings from previous work in patients with schizophrenia, we predicted that the UHR youth would be less susceptible to the visual illusion compared to healthy controls. Specifically, we predicted that the UHR group would report more veridical responses (i.e., perceptions of concavity when viewing concave mask stimuli) compared to healthy controls, which would suggest a deficit in top-down modulation and potentially an excessive reliance on sensory (bottom-up) information. Similarly, we predicted that abnormalities in top-down modulation would be related to weaker functional connectivity in the fronto-parietal network compared to healthy controls.

2. Materials and method

2.1. Participants

A total of 73 adolescents and young adults (44 UHR and 29 Controls), aged 15–23 (UHR: mean = 19.09, SD = 1.51; Control: mean = 19.62, SD = 1.68) were recruited through the Adolescent Development and Preventive Treatment (ADAPT) program as a part of a larger, ongoing study. Participants were recruited using email, newspaper and media announcements, Craigslist, and flyers.

The exclusion criteria for all participants included history of significant head injury or other physical disorder affecting brain functioning, contraindication to the magnetic imaging environment, mental retardation (defined by an IQ of less than 70), or history of a substance dependence disorder in the prior 6 months. UHR exclusion criteria included a DSM-IV Axis I psychotic disorder diagnosis (e.g. schizophrenia, schizoaffective, bipolar disorder with psychotic features). Control exclusion criteria included any Axis I diagnosis or a first-degree relative with psychosis. UHR inclusion criteria included the presence of Attenuated Positive Symptoms (APS; 37 participants), and/or Genetic Risk and

Deterioration (GRD; 5 participants) (Miller et al., 1999). A total of 2 participants were included based of off both APS and GRD.

2.2. Clinical interviews

The Structured Interview for Prodromal Syndromes (SIPS; (Miller et al., 1999) was used to assess for positive, negative, disorganized, and general symptoms and to diagnose UHR syndromes. Additional inclusion for UHR participants included a decline in global functioning accompanying the presence of schizotypal personality disorder and/or a family history of psychosis (Miller et al., 1999). The Structured Clinical Interview for the DSM-IV (SCID, research version) (First et al., 1995), was used to rule out Axis I psychotic disorders and substance dependence. Training of interviewers (advanced doctoral students) was conducted over a 2-month period, and inter-rater reliabilities exceeded the minimum study criterion of Kappa ≥0.80.

2.3. Depth inversion illusion

Similar to methods from recent studies in patients with schizophrenia (Keane et al., 2016; Keane et al., 2013), a DII task was administered to all 73 participants. The task consisted of three mask conditions and the order of masks presented to the participants was counterbalanced. One condition included a concave, texture (painted) mask, and the other condition included a concave, no texture (unpainted) mask. There was also an unpainted, convex mask to ensure participants properly understood the task. Of note, the present study uses face stimuli, and research suggests that schizophrenia patients have impairments in facial recognition and processing, which has been attributed to regions such as the occipital and fusiform face areas (OFA and FFA, respectively) (Addington and Addington, 1998; Spilka et al., 2015; Walther et al., 2009). However, this is not expected to serve as a confound in the present study since: 1) no facial emotion processing or face recognition is involved in the DII paradigm, as in most studies of face processing in schizophrenia: only the more basic visual function of stereopsis is assessed; 2) we used extended viewing durations, which can compensate for basic visual processing impairments; 3) the DII paradigm has been used successfully in many past studies of schizophrenia (Dima et al., 2010; Dima et al., 2009; Keane et al., 2013; Koethe et al., 2009; Schneider et al., 2002; Silverstein and Keane, 2011) and it has generated a large body of evidence that has been consistent in its findings, and that motivated the present study; and 4) there is no basis for assuming that UHR participants have OFA and FFA impairments that are more severe than in schizophrenia and that should confound our study of top-down modulation during a DII task (Keane et al., 2016; Keane et al., 2013).

Participants were first given two miniature sample bistable stimuli (i.e., stimuli that could be perceived as concave or convex) – one hollow shell painted beige and one realistic painted scene, both with a fixation point in the center – and instructed that they would be seeing similar objects and to focus on the fixation points in the center. Further, participants were shown stimuli for 120 s each and told they would be asked every 12 s if they saw the 3-dimensional masks as “popping out” or “caving in” (10 responses per stimulus presentation). Subjects provided verbal responses, which was recorded by the instructor. Participants also viewed a convex, no texture catch mask to ensure that subjects properly understood the task and that they did not have a bias to respond “concave.” Participants were asked to make convexity judgments on each of these mask conditions using their dominant eye. After a stimulus was displayed, participants were asked to close both eyes while a new stimulus was put up. This inter-stimulus interval was standardized to 1 min in all cases. Participants were then told by the research assistant to open his/her eyes. Front views of each of the three stimuli are presented in Fig. 1. These faces were two geometrically identical plastic facial masks with maximum height, width, and depth measuring 21.45, 13.10, and 5.97 cm, respectively.

A small green fixation mark (size = 5 mm) was placed at the center of each object. This center was locally concave for all objects, except for the catch trial. Objects were mounted on a uniform matte black surface at eye level about 200 cm away from each participant. Overhead lights were turned off and the mask was only lit by two pairs of floodlights (75 W) positioned symmetrically on either side so as to minimize shadows on the mask. The presentation order of masks was counterbalanced.

2.4. Image acquisition and preprocessing

All individuals completed a brain imaging session that included a structural scan, resting state functional connectivity MRI (fcMRI), and DTI scans. For our purposes here, we focused on the fcMRI data. All of the scans were acquired using a 3-Tesla Siemens Tim Trio MRI scanner (Siemens AG, Munich, Germany) using a standard 12-channel head coil. Structural images were acquired with a T1-weighted 3D magnetization prepared rapid gradient multi-echo sequence (MPRAGE; sagittal plane; repetition time [TR] = 2530 ms; echo times [TE] = 1.64 ms, 3.5 ms, 5.36 ms, 7.22 ms, 9.08 ms; GRAPPA parallel imaging factor of 2; 1 mm^3 isomorphic voxels, 192 interleaved slices; FOV = 256 mm; flip angle = 7°; time = 6:03 min). A 5-minute 34 s resting state blood-oxygen-level dependent (BOLD) scan was acquired with a T2-weighted echo-planar functional protocol (number of volumes = 165; TR = 2000 ms; TE = 29 ms; matrix size = 64 × 64 × 33; FA = 75°; 3.8 × 3.8 × 3.5 mm^3 voxels; 33 slices; FOV = 240 mm). A 5-minute resting-state scan has been shown to have the same robust correlations as longer scans (Van Dijk et al., 2010). Participants were instructed to relax with their eyes closed during this time. A turbo spin echo proton density (PD)/T2-weighted acquisition (TSE; axial oblique aligned with anterior commissure-posterior commissure line; TR = 3720 ms; TE = 89 ms; GRAPPA parallel imaging factor of 2; FOV = 240 mm; flip angle: 120°; 0.9 × 0.9 mm^2 voxels; 77 interleaved 1.5 mm slices; time = 5:14 min) was generated to investigate incidental pathology. Studies indicate that the functional connectivity fcMRI duration utilized in the present study provides comparable power to longer scan times (Van Dijk et al., 2010). Furthermore, shorter scan durations may be optimal in developmental and clinical populations so as to minimize subject motion in the scanner.

Data were preprocessed in FSL (v. 5; http://fsl.fmrib.ox.ac.uk/fsl), which involved motion correction, brain extraction, high-pass filtering (100 s), and spatial smoothing (6 mm FWHM). Next, functional images were aligned to the MNI 2-mm brain template with a two-step procedure. First, the resting state scan was aligned to the high-resolution MPRAGE using a linear boundary-based registration method, which relies on white matter boundaries (Greve and Fischl, 2009; Jenkinson and Smith, 2001; Jenkinson et al., 2002). Second, the MPRAGE was nonlinearly aligned to the template and the two registrations were then combined to align the functional resting state scan to the template.

Recent papers have demonstrated the importance of properly correcting for motion by not only regressing out motion parameters, but also regressing out or eliminating specific frames with motion outliers (Power et al., 2012). To accomplish this, we used the Artifact Rejection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) to create confound regressors for motion parameters (3 translation and 3 rotation parameters), and additional confound regressors for specific image frames with outliers based on brain activation and head movement. In order to identify outliers in brain activation, the mean global brain activity (i.e., the mean signal across all voxels) was calculated as a function of time, and was then Z normalized. Activation outliers were defined as any frames where the global mean signal exceeded 3 SD. Similarly, frame-wise measures of motion (composite measure of total motion across translation and rotation) were used to identify any motion outliers (i.e., motion spikes). Motion outliers were defined as any frame where the motion exceeded 1 mm.

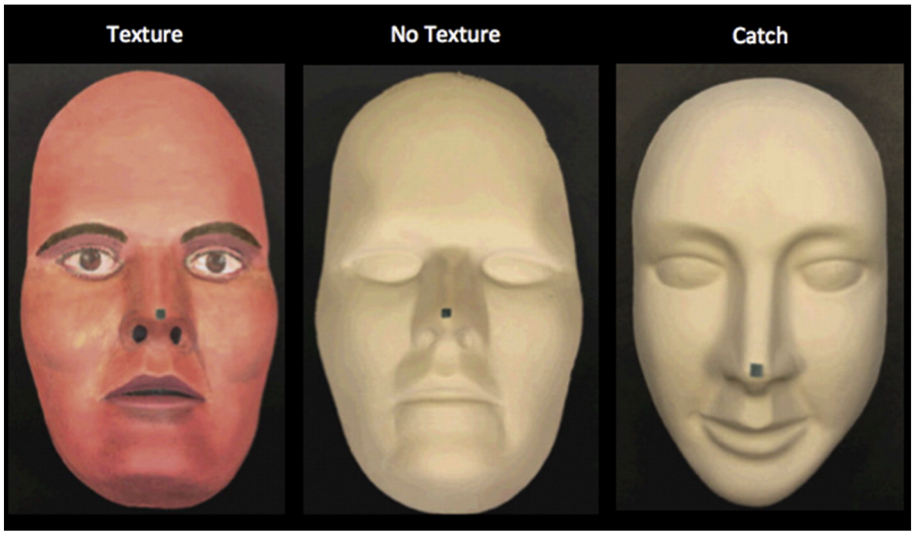

Fig. 1. Stimuli: Subjects observed concave faces that were shown with (left) or without (middle) misleading texture. Because of the concavity, the green fixation points were further from the observer than the surrounding regions (cheeks). A beige convex face (right) served as a catch. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Anatomical images were segmented into gray matter, white matter, and CSF with SPM8 in order to create masks for signal extraction. The CONN toolbox (Whitfield-Gabrieli and Ford, 2012) uses principal component analysis (PCA) to extract 5 temporal components from the segmented CSF and white matter, which were entered as confound regressors in the subject-level GLM. This approach corrects for confounds of motion and physiological noise without regressing out global signal, which has been shown to introduce spurious anticorrelations (Chai et al., 2011; Murphy et al., 2009). Motion from the ART toolbox was included as a confound regressor. From the motion translation parameters, the ART toolbox calculates mean displacement, and we used this measure as well as the number of motion and mean signal outliers in order to compare the degree of head movement between the groups. Further preprocessing included a band-pass filter (0.008 to 0.09 Hz), detrending, and despiking, in accordance with procedures used to target resting state data. The mean time-series, averaged across all voxels within each seed was used as a regression parameter, and correlated with all other voxels in the brain in seed-to-voxel connectivity analyses.

2.5. Behavioral analyses

SPSS Statistics 23 was used to conduct behavioral analyses. Independent *t*-tests and chi-square tests were employed to examine differences between groups in demographic and clinical status variables. We employed two-tailed tests for exploratory analyses (e.g., demographic analyses, fcMRI) and directional hypotheses (e.g., group comparisons on the DII task involving the no texture and texture conditions). Group differences in susceptibility to the depth inversion illusion were examined with a 2 × 2 repeated measures ANOVA (control/UHR × no texture/texture mask condition). Planned contrasts, examining group differences on specific conditions, employed independent *t*-tests. An independent *t*-test was used to compare group differences on the catch condition (i.e., control condition).

2.6. Imaging analyses

Functional connectivity analysis and corrections was performed using data from 37 UHR and 24 healthy control participants (7 UHR and 5 healthy control participants did not complete the scanning portion of the study) in the CONN toolbox 14.p (Whitfield-Gabrieli and Ford, 2012), with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm) using a voxel-level cluster forming threshold of $p_{uncorrected} < 0.001$ and then corrected at the cluster-level using a false-discovery rate (FDR) of $p < 0.01$ (Chumbley and Friston, 2009). A priori seeds for these networks were masked based on established literature identifying regions involved in top-down and bottom-up processing during performance of a DII task (Dima et al., 2009). Seeds were generated using the Wake Forest University Pick-Atlas with a 7 mm radius, consistent with the current literature (Dosenbach et al., 2007; Mamah et al., 2013). We investigated group comparisons in seed connectivity, as well as interactions between resting state connectivity and performance between groups. To appropriately account for false positives in multiple comparisons, results are thresholded at the voxel-level at $p_{uncorrected} < 0.001$ for cluster formation, and then corrected at the cluster-level using a false-discovery rate (FDR) of $p < 0.01$ (Chumbley and Friston, 2009). The inferior frontal gyrus (IFG), supramarginal gyrus (SMG), IPS, and lateral occipital cortex (LOC) were evaluated with fcMRI using seed-to-voxel connectivity across the whole brain and these data were correlated with DII task responses. The IFG, SMG, and IPS are regions within the fronto-parietal network thought to be related to top-down modulation processes. The LOC was used as a possible source of feed-forward (i.e., bottom-up) visual information about mask objects, where modulation by the fronto-partial network can occur (Dima et al., 2009). Limited ROI to ROI analyses were conducted in order to further unpack significant interactions. See Fig. 2 for ROI seeds.

3. Results

3.1. Demographic and symptom characteristics

There were no significant between-group differences in demographic characteristics including age, $t(71) = -1.41$, $p = 0.16$, parental education, $t(69) = -0.73$, $p = 0.47$, however gender, $\chi^2(1) = 4.24$, $p = 0.04$, differed significantly (UHR group had more males than females and the control group had more females than males). As expected, the UHR group showed significantly more positive symptoms, $t(1,71) = 14.90$, $p \leq 0.001$, $d = 3.20$, negative symptoms $t(1,71) = 7.28$, $p \leq 0.001$, $d = 1.57$ and disorganized symptoms $t(1,71) = 8.45$, $p \leq 0.001$, $d = 1.80$ when compared with controls. There were no controls on medications. In the UHR group, the most frequently prescribed medications were antipsychotics (8%) and SSRI's (14%), consistent with the current literature (Simon and Umbricht, 2010; Ziermans et al., 2011). Further, no controls used tobacco and 6.9% of controls used

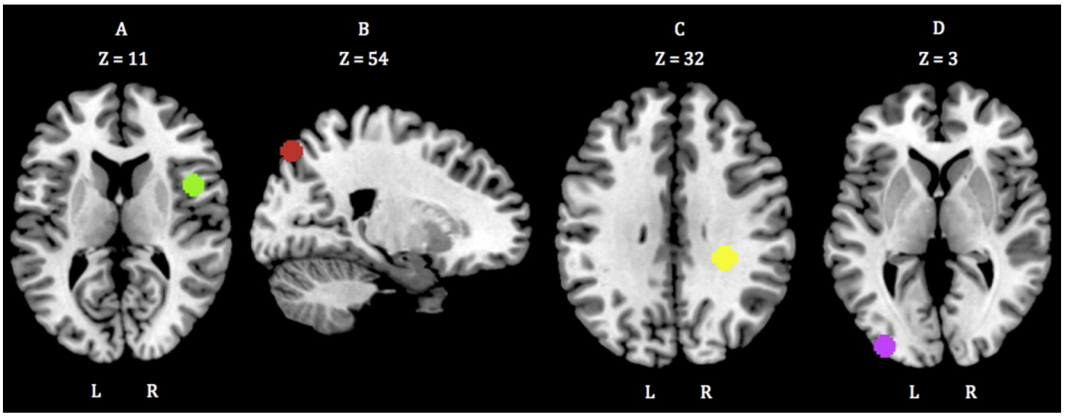

Fig. 2. Seed ROIs used. A.) IFG (green; MNI coordinates 46, 8, 9), B.) IPS (red; MNI coordinates 22, −73, 52) and C.) SMG (yellow; MNI coordinates 28, −31, 33). D.) LOC (violet; MNI coordinates −34, −90, 6). Results are thresholded at the voxel-level at $p_{uncorrected} < 0.001$ and then corrected at the cluster-level using a false-discovery rate (FDR) of $p < 0.01$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cannabis. In the UHR group, 4.5% used tobacco and 20.4% used cannabis. Each group was performing near ceiling and were undifferentiated on catch trial performance $t(71) = -0.21$, $p = 0.84$, indicating that both groups (UHR: mean veridical perception = 9.39, SD = 1.26; Control: mean veridical perception = 9.45, SD = 1.27) were paying adequate attention to, and were engaged in, the task. See Table 1 for means, standard deviations, and percentages.

3.2. Group differences in DII susceptibility

There was no significant interaction between group and condition across the 2 conditions, $F(1,71) = 0.006$, $p = 0.94$ consistent with Keane et al., 2013, 2016. There was a significant main effect of condition, $F(1,71) = 5.78$, $p = 0.02$, $\eta_p^2 = 0.08$. There was also a significant main effect of group, $F(1,71) = 6.37$, $p = 0.01$, $\eta_p^2 = 0.08$, indicating that UHR individuals experienced DIIs less frequently than healthy controls. In follow-up independent two-tailed *t*-tests, the UHR group exhibited more veridical responding (i.e., less susceptibility to DIIs) when compared to matched healthy controls in the texture condition $t(71) = 2.26$, $p = 0.03$. Group differences in the same direction were also detected for the no texture condition at a trend level of significance, $t(71) = 1.97$, $p = 0.053$. Thus, while the UHR and control groups were near ceiling on the catch (control trial condition), and verged on demonstrating a between-group difference on the no texture mask stimulus, there was a clear difference on the texture (painted) mask (see Fig. 3). These data suggest that the UHR group may be less susceptible, on average, to depth inversion illusions compared to controls.

Table 1
Sample demographics. *Note:* All demographic statistics are from all participants (N = 73). Positive, negative, and disorganized symptoms reflect total sums of domains from the Structured Interview for Prodromal Syndromes (SIPS). Parent education is the average of mother and father education.

	UHR	Control	Total	Statistic	*p*
Age					
Mean (SD)	19.09 (1.51)	19.62 (1.68)	19.30 (1.59)	$t(71) = -1.41$	0.16
Gender					
Male	26	10	36	$\chi 2(1) = 4.24$	0.04
Female	18	19	37		
Total	44	29	73		
Parent education (years)					
Mean (SD)	15.30 (3.13)	15.81 (2.55)	15.51 (2.90)	$t(69) = -0.73$	0.47
Symptoms domains					
Mean (SD)					
Positive	11.80 (5.02)	0.34 (0.72)	7.25 (6.86)	$t(1,71) = 14.90$	≤0.001
Negative	8.80 (7.41)	0.45 (1.38)	5.48 (7.10)	$t(1,71) = 7.28$	≤0.001
Disorganized	4.80 (3.60)	0.17 (0.38)	2.96 (3.60)	$t(1,71) = 8.45$	≤0.001

3.3. Group differences in IFG, IPS, SMG, LOC

Independent *t*-tests were performed to investigate group differences in total outliers and motion. Results show no significant group differences in the number of signal outliers, $t(59) = 0.55$, $p = 0.58$ and motion, $t(59) = 1.21$ $p = 0.23$. In contrast to expectations, there were no group connectivity differences when using the IFG, IPS, and SMG as seed regions. There were significant group differences in connectivity between the LOC and the right planum temporale revealed by whole brain seed-to-voxel analyses (see Fig. 4, Table 2).

3.4. Connectivity patterns and DII veridical perception

Connectivity analyses were conducted using the texture mask condition. Interactions were examined to investigate whether relationships between connectivity and behavioral performance (DII susceptibility) outside the scanner differed between the UHR and control groups. There was a significant interaction whereby lower connectivity between the IFG (within the fronto-parietal network) and the right lingual gyrus (LG) and right precentral gyrus was associated with veridical perception, and these correlations were stronger in the UHR group relative to the controls, signaling an aberrant interaction between sensory-perceptual and higher-cognitive regions in the UHR group (see Fig. 5). That is, individuals with less connectivity between these regions were less likely to perceive the DII illusion, and this was especially notable in the UHR group, who exhibited more veridical perception.

To further unpack this interaction, analyses were conducted within the UHR group alone. Interestingly, there was a negative association between IFG connectivity with the left and right LG and veridical perception in UHR youth, which may suggest impairments in top-down suppression of sensory signals when viewing a stimulus where there is a conflict between stimulus characteristics on the one hand, and expectations and prior experience on the other (see Fig. 6). There were similar negative correlations in ROI to ROI analyses with the UHR group alone in that lower connectivity levels between the IFG and the left LG ($t(59) = -3.52$, $p \leq 0.001$) and right LG ($t(59) = -3.92$ $p \leq 0.001$) were associated with greater veridical perception. Patterns within the UHR group suggest that the interaction is being driven by this group, and that decreased connectivity between prefrontal to visual

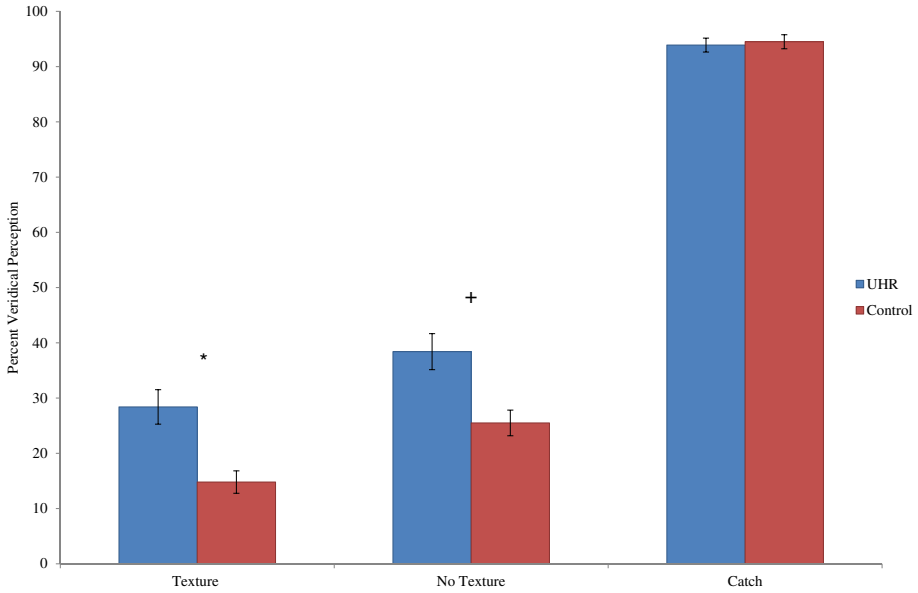

Fig. 3. Group differences in percent of veridical perception between UHR youth and matched controls. *Note:* Veridical perception is represented as the percentage of time participants spent perceiving the mask as concave, averaged across participants. *p ≤ 0.05; + indicates a trend level difference p ≤ 0.10. Error bars represent standard error.

regions is related to susceptibility to the visual illusion during DII task performance outside the scanner.

4. Discussion

To our knowledge, the present study is the first to explore the neural underpinnings of DIIs using the hollow mask illusion in UHR youth. We observed that UHR youth reported perceiving hollow faces more accurately compared to healthy controls. Additionally, we found lower connectivity between prefrontal regions within the fronto-parietal network and regions related to early visual processing in the UHR group. When viewed within the context of prior DII studies of schizophrenia, the present study indicates that DII reductions occur across the continuum of psychosis vulnerability (i.e., that they are not trait markers of schizophrenia), setting the stage for future biomarker research. An additional novel finding from this study was that abnormal DII performance was linked to aberrant connectivity in brain networks relevant to DII processing in our UHR group. As a result, this network metric and/or the behavioral DII task could be used as markers of network integrity during perceptual tasks requiring strong integration of feed-forward and modulatory processes in studies of UHR subjects.

The differences in the magnitude of between-group differences in the two concave mask conditions suggests a dose-dependent relationship. Specifically, in the condition with more stimulus details (e.g., texture, color), the difference between groups was larger. However, there

Table 2
Connectivity results. Findings show positive connectivity between the LOC and the right planum temporale and this was greater in the UHR group. Group interactions suggest there was an inverse relationship in connectivity between the IFG and the right lingual gyrus and veridical perception and this was higher in the UHR group compared to controls. Lastly, within the UHR group, there was a negative association in connectivity between the IFG and both the left and right lingual gyrus and veridical perception. Results of all analyses were thresholded at the voxel level at $p_{uncorrected} < 0.001$ and then corrected at the cluster-level using a false-discovery rate (FDR) of $p < 0.01$. * denotes an inverse relationship.

Group differences in seed to voxel connectivity from the LOC						
			MNI Coordinates			
Region	BA	Cluster Size	X	Y	Z	t-Value
Right Plaum Temporale	42	277	62	−30	18	5.30
Associations between seed to voxel connectivity from the IFG and veridical perception						
			MNI Coordinates			
Region	BA	Cluster Size	X	Y	Z	t-Value
*Right Lingual Gyrus	19	627	−26	−72	−10	4.31
Associations between seed to voxel connectivity from the IFG and veridical perception within UHR group						
			MNI Coordinates			
Region	BA	Cluster Size	X	Y	Z	t-Value
*Right Lingual Gyrus	19	166	26	−54	−02	4.20
*Left Lingual Gyrus	19	497	−20	−56	−06	5.63

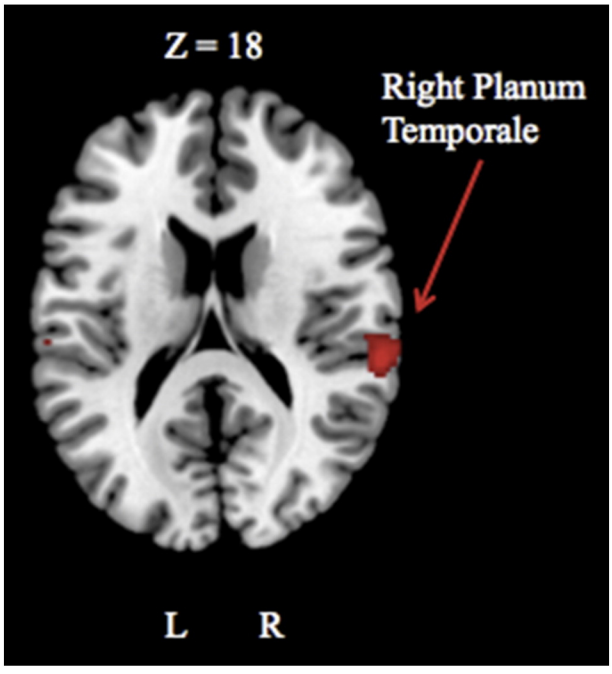

Fig. 4. Group differences in seed to voxel connectivity. *Note:* Results show greater connectivity between the LOC and the right planum temporale in the UHR youth relative to controls. Results are thresholded at the voxel-level at $p_{uncorrected} < 0.001$ and then corrected at the cluster-level using a false-discovery rate (FDR) of $p < 0.01$.

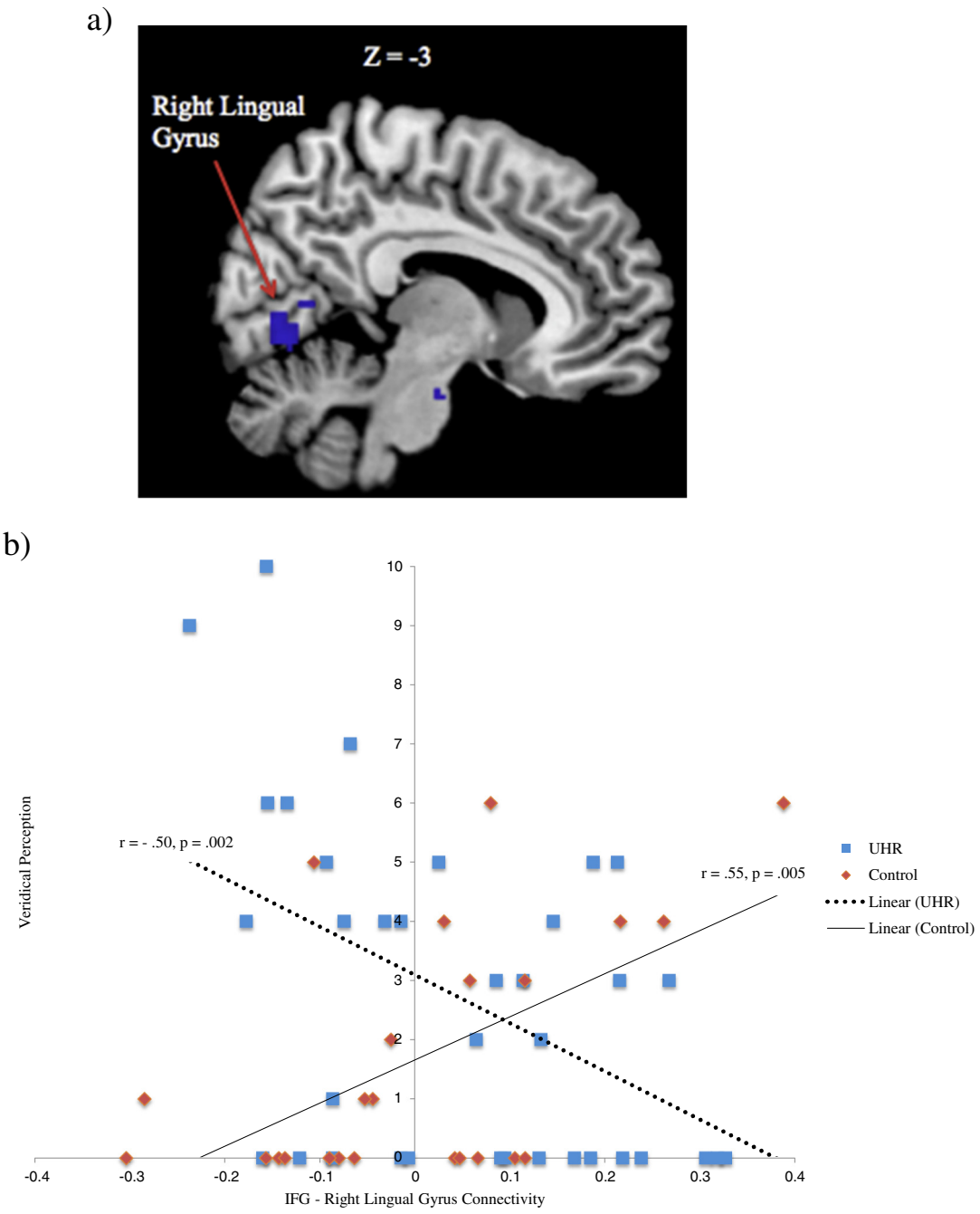

Fig. 5. a and b. Associations between connectivity and DII responses. Results indicate a group interaction in that there is a negative relationship (blue) between connectivity from the IFG to the right LG and the right precentral gyrus and this was related to veridical perception. Results are thresholded at the voxel-level at $p_{uncorrected} < 0.001$ and then corrected at the cluster-level using a false-discovery rate (FDR) of $p < 0.01$.

was a trend towards a between-group difference for the no texture stimuli as well, and with more statistical power we may have detected group differences here. It is important to note that some controls exhibited weak DII susceptibility, however, the UHR group showed far reduced DII susceptibility, on average, compared to the control group. Taken together, these results may indicate that the UHR youth are characterized by a reduced ability to modulate the representation of sensory input. Interestingly, a reduced ability to modulate the perception of stimulus size based on past experience was observed among UHR youth on the Ebbinghaus task (Mittal et al., 2015), replicating earlier results with schizophrenia patients (Horton and Silverstein, 2011; Silverstein et al., 2013; Uhlhaas et al., 2006).

Our findings are consistent with those from past studies of DII and other illusions in patients with schizophrenia. For example, just as these studies (Dima et al., 2010; Dima et al., 2009) demonstrated that disruptions in top-down processing are contributing to decreased illusion susceptibility, our study involving resting state functional connectivity suggests that a similar impairment is characteristic of a UHR sample. Specifically, findings from the present study strongly parallel the results of Dima et al. (2009, 2010) who, using a similar DII paradigm, found decreased connectivity from the IPS to LOC. Although our regions are not identical, our findings do also show abnormal and decreased prefrontal to visual region connectivity patterns that are associated with veridical perception when viewing stimuli that normally produce

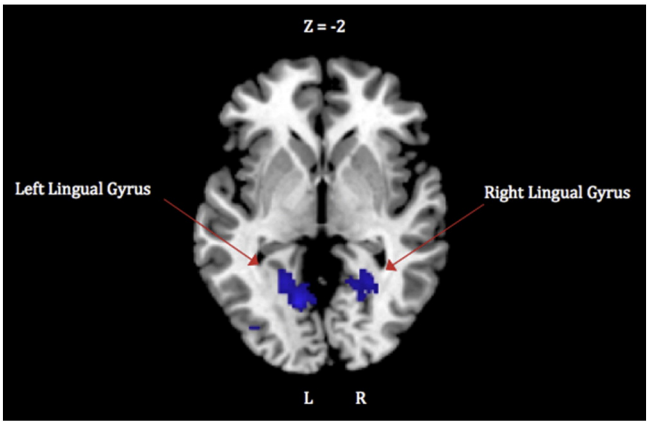

Fig. 6. Associations between connectivity and DII responses within the UHR group alone. Lower connectivity between IFG and the left and right lingual gyrus is associated with DII in UHR youth. Connectivity involving the fronto-parietal network was represented by analyzing seed to voxel connectivity among regions (IFG, IPS, SMG) within this network and part of the early visual system (LOC). There was an inverse relationship in connectivity between the IFG and the left and right lingual gyrus and veridical perception. Results of all analyses were thresholded at the voxel-level at $p_{uncorrected} < 0.001$ and then corrected at the cluster-level using a false-discovery rate (FDR) of $p < 0.01$.

illusions. According to a prior study, schizophrenia patients showed entirely normal reduction DII when the texture was removed from the concave stimulus; this result was replicated here (Keane et al., 2013). The data presented in the current study is consistent with that finding since both patients and controls benefitted to an equal extent (in terms of perceiving the stimulus veridically) by a removal of misleading surface texture. Further, another study examining the at risk period and DIIs using methodologies that differed from the current study (different measures of identifying at risk and perceptual paradigms) but that was similar in targeting top-down modulation found parallel behavioral results suggesting impairments in top-down modulatory control that occurs prior to the onset of psychosis. (Koethe et al., 2006). However, not all of our data are consistent with past studies of schizophrenia. In particular, our finding of decreased connectivity between the IFG and the precentral gyrus, suggesting reduced engagement of the primary motor cortex are difficult to interpret and additional studies are needed to better understand these results.

UHR youth may experience dysfunction in perception because visual information is less modulated by knowledge and experience than in the normal mental state. While this is advantageous during a DII task, it can be expected to lead to slowness in understanding the significance of visual stimuli in real-world settings, and to excessive modulation of sensory information by internally-generated mental activity that does not correspond to the current stimulus context, leading to misperceptions and to inappropriate behavioral reactions. This potential dysfunction in top-down modulation during visual perception in UHR youth may represent a vulnerability marker for schizophrenia risk. It is also possible that a reduced ability to integrate top-down and bottom-up information could contribute to other cognitive (e.g., context processing deficits in working memory; thought disorder) and social cognitive deficits (e.g., facial emotion perception misinterpretation), as well as symptoms (e.g., delusions, disorganization) (Clark, 2013; Phillips et al., 2015) experienced during the UHR period. Future modeling and experimental work is needed to determine the pervasiveness of this mechanism during the UHR period.

Broadly speaking, fcMRI has been a useful tool for studying UHR and schizophrenia populations and has provided important insights into the fronto-parietal network and visual systems. In the present imaging analyses, a more stringent cluster forming threshold ($p < 0.001$) and an additional conservative FDR correction ($p < 0.01$) was used to minimize false positives, which has been a concern within current neuroimaging research (Eklund et al., 2016). Here, we have further explored resting state patterns and have extended the literature to look at the LOC. Although we did not find group differences in resting state patterns of the IFG, IPS, and SMG, which has been suggested in previous literature (Repovs et al., 2011), these results may be related to the lower symptom severity of the UHR group compared to patients with schizophrenia (Mamah et al., 2013). Results showing greater connectivity within the UHR group relative to controls between the LOC and the right planum temporale contribute to our growing understanding of connectivity before the onset of psychosis. The current framework of connectivity between visual regions, and between visual and prefrontal regions, is not fully understood within the UHR group. However, it is known that the LOC is related to object recognition in healthy individuals and studies suggest schizophrenia patients may show impairment in these processes (Doniger et al., 2002; Grill-Spector et al., 2001; Harvey et al., 2011). Further, the LOC has been implicated in visual shape completion and visual backward masking (Altmann et al., 2003; Green et al., 2005; Wokke et al., 2013) both of which are disturbed in schizophrenia (Green et al., 2011; Keane et al., 2014). Future work is needed to further clarify the role of the LOC in abnormal network activity involving processing of visual stimuli.

Although our findings show promise in understanding DII susceptibility in UHR youth, there are still limitations. The current sample size is comparable to previous work in UHR and schizophrenia samples; however, future studies with larger samples are warranted. The current findings provide an important perspective on functional connectivity in a cross-section of UHR individuals. Follow-up studies are necessary to determine if susceptibility to the mask illusion continues as psychosis develops using longitudinal data. Future work including multiple time points will be necessary for examining the time course of visual information processing changes relative to other changes in the progression to psychosis. Further, it is important to note that fcMRI procedures involve examining correlations and do not provide any information regarding causation. Future task-based functional magnetic resonance imaging studies could help clarify the nature of disturbed bottom-up and top-down interactions and provide further evidence in understanding the neural patterns driving these perceptual dysfunctions. Although we chose our seeds based on previous studies, there may be variability in the exact location and size of these regions in individual brains and there is a possibility that important and relevant connectivity patterns were overlooked. This is an important limitation to acknowledge and it impacts all seed-based approaches.

Additional future directions include implementing a task-based approach using a computerized version of the DII paradigm, examining reaction times to understand timing of perceptual processing, assessing cannabis use and perceptual processing given the high percentage of users in the present sample and prior associations of cannabis use with reduced DII (Emrich et al., 1991), investigating further variability in symptoms, and using longitudinal data to map clinical course. Taken together, these findings suggest that impairments in visual processing among UHR youth provide important information regarding the nature of early neurobiological changes in people at high risk for developing a psychotic disorder.

Disclosure

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.09.022.

References

Addington, J., Addington, D., 1998. Facial affect recognition and information processing in schizophrenia and bipolar disorder. Schizophr. Res. 32, 171–181. http://dx.doi.org/10.1016/S0920-9964(98)00042-5.

Altmann, C.F., Bülthoff, H.H., Kourtzi, Z., 2003. Perceptual organization of local elements into global shapes in the human visual cortex. Curr. Biol. 13, 342–349. http://dx.doi.org/10.1016/S0960-9822(03)00052-6.

Bar, M., 2003. A cortical mechanism for triggering top-down facilitation in visual object recognition. J. Cogn. Neurosci. 15, 600–609. http://dx.doi.org/10.1162/089892903321662976.

Bernard, J.A., Peltier, S.J., Wiggins, J.L., Jaeggi, S.M., Buschkuehl, M., Fling, B.W., Kwak, Y., Jonides, J., Monk, C.S., Seidler, R.D., 2013. Disrupted cortico-cerebellar connectivity in older adults. NeuroImage 83, 103–119. http://dx.doi.org/10.1016/j.neuroimage.2013.06.042.

Biswal, B.B., Hyde, J.S., 1998. Functional connectivity during continuous task activation. Proc. 6th ISMRM. 537, p. 1997.

Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., 2008. Prediction at High Clinical Risk. 65 pp. 28–37.

Cauller, L., 1995. Layer I of primary sensory neocortex: where top-down converges upon bottom-up. Behav. Brain Res. 71, 163–170. http://dx.doi.org/10.1016/0166-4328(95)00032-1.

Chai, X.J., Whitfield-Gabrieli, S., Shinn, A.K., Gabrieli, J.D.E., Nieto Castañón, A., McCarthy, J.M., Cohen, B.M., Ongür, D., 2011. Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. Neuropsychopharmacology 36, 2009–2017. http://dx.doi.org/10.1038/npp.2011.88.

Chumbley, J.R., Friston, K.J., 2009. False discovery rate revisited: FDR and topological inference using Gaussian random fields. NeuroImage 44, 62–70. http://dx.doi.org/10.1016/j.neuroimage.2008.05.021.

Clark, A., 2013. Whatever next? Predictive brains, situated agents, and the future of cognitive science. Behav. Brain Sci. 36, 181–204. http://dx.doi.org/10.1017/S0140525X12000477.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 215–229. http://dx.doi.org/10.1038/nrn755.

Dima, D., Roiser, J.P., Dietrich, D.E., Bonnemann, C., Lanfermann, H., Emrich, H.M., Dillo, W., 2009. Understanding why patients with schizophrenia do not perceive the hollow-mask illusion using dynamic causal modelling. NeuroImage 46, 1180–1186. http://dx.doi.org/10.1016/j.neuroimage.2009.03.033.

Dima, D., Dietrich, D.E., Dillo, W., Emrich, H.M., 2010. Impaired top-down processes in schizophrenia: a DCM study of ERPs. NeuroImage 52, 824–832. http://dx.doi.org/10.1016/j.neuroimage.2009.12.086.

Doniger, G.M., Foxe, J.J., Murray, M.M., Higgins, B.A., Javitt, D.C., 2002. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Arch. Gen. Psychiatry 59, 1011–1020. http://dx.doi.org/10.1001/archpsyc.59.11.1011.

Dosenbach, N.U.F., Fair, D.a., Miezin, F.M., Cohen, A.L., Wenger, K.K., Dosenbach, R.a.T., Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., Schlaggar, B.L., Petersen, S.E., 2007. Distinct brain networks for adaptive and stable task control in humans. Proc. Natl. Acad. Sci. U. S. A. 104, 11073–11078. http://dx.doi.org/10.1073/pnas.0704320104.

Eklund, A., Nichols, T.E., Knutsson, H., 2016. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc. Natl. Acad. Sci. 201602413. http://dx.doi.org/10.1073/pnas.1602413113.

Emrich, H.M., Weber, M.M., Wendl, A., Zihl, J., Von Meyer, L., Hanisch, W., 1991. Reduced binocular depth inversion as an indicator of cannabis-induced censorship impairment. Pharmacol. Biochem. Behav. 40, 689–690. http://dx.doi.org/10.1016/0091-3057(91)90383-D.

First, M., Spitzer, R., Gibbon, M., Williams, J., 1995. Structured clinical interview for the DSM–IV Axis I disorders (SCID-I), patient edition. American Psychiatric Press, Washington, DC.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102, 9673–9678. http://dx.doi.org/10.1073/pnas.0504136102.

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., Barale, F., Caverzasi, E., Mcguire, P., 2012. Predicting psychosis. Arch. Gen. Psychiatry 69, 220–229. http://dx.doi.org/10.1001/archgenpsychiatry.2011.1472.

Fusar-Poli, P., Smieskova, R., Kempton, M.J., Ho, B.C., Andreasen, N.C., Borgwardt, S., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci. Biobehav. Rev. 37, 1680–1691. http://dx.doi.org/10.1016/j.neubiorev.2013.06.001.

Gilbert, C.D., Sigman, M., 2007. Brain states: top-down influences in sensory processing. Neuron http://dx.doi.org/10.1016/j.neuron.2007.05.019.

Green, M.F., Glahn, D., Engel, S.a., Nuechterlein, K.H., Sabb, F., Strojwas, M., Cohen, M.S., 2005. Regional brain activity associated with visual backward masking. J. Cogn. Neurosci. 17, 13–23. http://dx.doi.org/10.1162/0898929052880011.

Green, M.F., Wynn, J.K., Breitmeyer, B., Mathis, K.I., Nuechterlein, K.H., 2011. Visual masking by object substitution in schizophrenia. Psychol. Med. 41, 1489–1496. http://dx.doi.org/10.1017/S003329171000214X.

Greve, D.N., Fischl, B., 2009. Accurate and robust brain image alignment using boundary-based registration. NeuroImage 48, 63–72. http://dx.doi.org/10.1016/j.neuroimage.2009.06.060.

Grill-Spector, K., Kourtzi, Z., Kanwisher, N., 2001. The lateral occipital complex and its role in object recognition. Vis. Res. 1409–1422 http://dx.doi.org/10.1016/S0042-6989(01)00073-6.

Haroun, N., Dunn, L., Haroun, A., Cadenhead, K.S., 2006. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. Schizophr. Bull. 32, 166–178. http://dx.doi.org/10.1093/schbul/sbj007.

Harvey, P.O., Lee, J., Cohen, M.S., Engel, S.A., Glahn, D.C., Nuechterlein, K.H., Wynn, J.K., Green, M.F., 2011. Altered dynamic coupling of lateral occipital complex during visual perception in schizophrenia. NeuroImage 55, 1219–1226. http://dx.doi.org/10.1016/j.neuroimage.2010.12.045.

Horton, H.K., Silverstein, S.M., 2011. Visual context processing deficits in schizophrenia: effects of deafness and disorganization. Schizophr. Bull. 37, 716–726. http://dx.doi.org/10.1093/schbul/sbr055.

Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5, 143–156. http://dx.doi.org/10.1016/S1361-8415(01)00036-6.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17, 825–841. http://dx.doi.org/10.1016/S1053-8119(02)91132-8.

Kantrowitz, J.T., Butler, P.D., Schecter, I., Silipo, G., Javitt, D.C., 2009. Seeing the world dimly: the impact of early visual deficits on visual experience in schizophrenia. Schizophr. Bull. 35, 1085–1094. http://dx.doi.org/10.1093/schbul/sbp100.

Keane, B.P., Silverstein, S.M., Wang, Y., Papathomas, T.V., 2013. Reduced depth inversion illusions in schizophrenia are state-specific and occur for multiple object types and viewing conditions. J. Abnorm. Psychol. 122, 506–512. http://dx.doi.org/10.1037/a0032110.

Keane, B.P., Joseph, J., Silverstein, S.M., 2014. Late, not early, stages of Kanizsa shape perception are compromised in schizophrenia. Neuropsychologia 56, 302–311. http://dx.doi.org/10.1016/j.neuropsychologia.2014.02.001.

Keane, B.P., Silverstein, S.M., Wang, Y., Roché, M.W., Papathomas, T.V., 2016. Seeing more clearly through psychosis: depth inversion illusions are normal in bipolar disorder but reduced in schizophrenia. Schizophr. Res. 176, 485–492. http://dx.doi.org/10.1016/j.schres.2016.06.015.

Koethe, D., Gerth, C.W., Neatby, M.A., Haensel, A., Thies, M., Schneider, U., Emrich, H.M., Klosterkötter, J., Schultze-Lutter, F., Leweke, F.M., 2006. Disturbances of visual information processing in early states of psychosis and experimental delta-9-tetrahydrocannabinol altered states of consciousness. Schizophr. Res. 88, 142–150. http://dx.doi.org/10.1016/j.schres.2006.07.023.

Koethe, D., Kranaster, L., Hoyer, C., Gross, S., Neatby, M.A., Schultze-Lutter, F., Ruhrmann, S., Klosterkötter, J., Hellmich, M., Leweke, F.M., 2009. Binocular depth inversion as a paradigm of reduced visual information processing in prodromal state, antipsychotic-naïve and treated schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 259, 195–202. http://dx.doi.org/10.1007/s00406-008-0851-6.

Mamah, D., Barch, D.M., Repovš, G., 2013. Resting state functional connectivity of five neural networks in bipolar disorder and schizophrenia. J. Affect. Disord. 150, 601–609. http://dx.doi.org/10.1016/j.jad.2013.01.051.

McGlashan, T.H., Addington, J., Cannon, T., Heinimaa, M., McGorry, P., O'Brien, M., Penn, D., Perkins, D., Salokangas, R.K.R., Walsh, B., Woods, S.W., Yung, A., 2007. Recruitment and treatment practices for help-seeking "prodromal" patients. Schizophr. Bull. 33, 715–726. http://dx.doi.org/10.1093/schbul/sbm025.

Miller, T.J., McGlashan, T.H., Woods, S.W., Stein, K., Driesen, N., Corcoran, C.M., Hoffman, R., Davidson, L., 1999. Symptom assessment in schizophrenic prodromal states. Psychiatr. Q. 70, 273–287. http://dx.doi.org/10.1023/a:1022034115078.

Mittal, V.A., Walker, E.F., Bearden, C.E., Walder, D., Trottman, H., Daley, M., Simone, A., Cannon, T.D., 2010. Markers of basal ganglia dysfunction and conversion to psychosis: neurocognitive deficits and dyskinesias in the prodromal period. Biol. Psychiatry 68, 93–99. http://dx.doi.org/10.1016/j.biopsych.2010.01.021.

Mittal, V.A., Gupta, T., Keane, B.P., Silverstein, S.M., 2015. Visual context processing dysfunctions in youth at high risk for psychosis: resistance to the Ebbinghaus illusion and its symptom and social and role functioning correlates. J. Abnorm. Psychol. 124, 953–960. http://dx.doi.org/10.1037/abn0000082.

Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., Bandettini, P.A., 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? NeuroImage 44, 893–905. http://dx.doi.org/10.1016/j.neuroimage.2008.09.036.

Palaniyappan, L., Liddle, P.F., 2012. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. J. Psychiatry Neurosci. 37, 17–27. http://dx.doi.org/10.1503/jpn.100176.

Parnas, J., Vianin, P., Saebye, D., Jansson, L., Volmer, A., Volmer-Larsen, A., Bovet, P., 2001. Visual binding abilities in the initial and advanced stages of schizophrenia. Acta Psychiatr. Scand. 103, 171–180. http://dx.doi.org/10.1034/j.1600-0447.2001.00160.x.

Pelletier-Baldelli, A., Bernard, J.A., Mittal, V.A., 2015. Intrinsic functional connectivity in salience and default mode networks and aberrant social processes in youth at ultra-high risk for psychosis. PLoS One 10, 1–19. http://dx.doi.org/10.1371/journal.pone.0134936.

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., Mechelli, A., 2011. Dysconnectivity in schizophrenia: where are we now? Neurosci. Biobehav. Rev. 35, 1110–1124. http://dx.doi.org/10.1016/j.neubiorev.2010.11.004.

Phillips, W.a., Silverstein, S.M., 2003. Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. Behav. Brain Sci. 26, 65–82. http://dx.doi.org/10.1017/S0140525X0328002X discussion 82–137.

Phillips, W.A., Clark, A., Silverstein, S.M., 2015. On the functions, mechanisms, and malfunctions of intracortical contextual modulation. Neurosci. Biobehav. Rev. http://dx.doi.org/10.1016/j.neubiorev.2015.02.010.

Plitt, M., Barnes, K.A., Wallace, G.L., Kenworthy, L., Martin, A., 2015. Resting-state functional connectivity predicts longitudinal change in autistic traits and adaptive functioning in autism. Proc. Natl. Acad. Sci. 112, E6699–E6706. http://dx.doi.org/10.1073/pnas.1510098112.

Poppe, A.B., Barch, D.M., Carter, C.S., Gold, J.M., Ragland, J.D., Silverstein, S.M., MacDonald, A.W., 2016. Reduced frontoparietal activity in schizophrenia is linked to a specific deficit in goal maintenance: a multisite functional imaging study. Schizophr. Bull. 1–9. http://dx.doi.org/10.1093/schbul/sbw036.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 59, 2142–2154. http://dx.doi.org/10.1016/j.neuroimage.2011.10.018.

Repovs, G., Csernansky, J.G., Barch, D.M., 2011. Brain network connectivity in individuals with schizophrenia and their siblings. Biol. Psychiatry 69, 967–973. http://dx.doi.org/10.1016/j.biopsych.2010.11.009.

Satterthwaite, T.D., Baker, J.T., 2015. How can studies of resting-state functional connectivity help us understand psychosis as a disorder of brain development? Curr. Opin. Neurobiol. 30, 85–91. http://dx.doi.org/10.1016/j.conb.2014.10.005.

Schmidt, A., Diwadkar, V.A., Smieskova, R., Harrisberger, F., Lang, U.E., Mcguire, P., Fusarpoli, P., Borgwardt, S., 2015. Approaching a Network Connectivity-driven Classification of the Psychosis Continuum: A Selective Review and Suggestions for Future Research. 8 pp. 1–16. http://dx.doi.org/10.3389/fnhum.2014.01047.

Schneider, U., Borsutzky, M., Seifert, J., Leweke, F.M., Huber, T.J., Rollnik, J.D., Emrich, H.M., 2002. Reduced binocular depth inversion in schizophrenic patients. Schizophr. Res. 53, 101–108. http://dx.doi.org/10.1016/S0920-9964(00)00172-9.

Sheffield, J.M., Barch, D.M., 2016. Cognition and resting-state functional connectivity in schizophrenia. Neurosci. Biobehav. Rev. 61, 108–120. http://dx.doi.org/10.1016/j.neubiorev.2015.12.007.

Silverstein, S.M., 2016. The Neuropsychopathology of Schizophrenia. http://dx.doi.org/10.1007/978-3-319-30596-7.

Silverstein, S.M., Keane, B.P., 2011. Perceptual organization impairment in schizophrenia and associated brain mechanisms: review of research from 2005 to 2010. Schizophr. Bull. 37, 690–699. http://dx.doi.org/10.1093/schbul/sbr052.

Silverstein, S.M., Keane, B.P., Wang, Y., Mikkilineni, D., Paterno, D., Papathomas, T.V., Feigenson, K., 2013. Effects of short-term inpatient treatment on sensitivity to a size contrast illusion in first-episode psychosis and multiple-episode schizophrenia. Front. Psychol. 4, 1–11. http://dx.doi.org/10.3389/fpsyg.2013.00466.

Silverstein, S., Keane, B.P., Blake, R., Giersch, A., Green, M., Keri, S., 2015. Vision in schizophrenia: why it matters. Front. Psychol. 6. http://dx.doi.org/10.3389/fpsyg.2015.00041.

Simon, A.E., Umbricht, D., 2010. High remission rates from an initial ultra-high risk state for psychosis. Schizophr. Res. 116, 168–172. http://dx.doi.org/10.1016/j.schres.2009.10.001.

Spilka, M.J., Arnold, A.E., Goghari, V.M., 2015. Functional activation abnormalities during facial emotion perception in schizophrenia patients and nonpsychotic relatives. Schizophr. Res. 168, 330–337. http://dx.doi.org/10.1016/j.schres.2015.07.012.

Uhlhaas, P.J., Phillips, W.A., Mitchell, G., Silverstein, S.M., 2006. Perceptual grouping in disorganized schizophrenia. Psychiatry Res. 145, 105–117. http://dx.doi.org/10.1016/j.psychres.2005.10.016.

Van Dijk, K.R.a., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103, 297–321. http://dx.doi.org/10.1152/jn.00783.2009.

Walther, S., Federspiel, A., Horn, H., Bianchi, P., Wiest, R., Wirth, M., Strik, W., Müller, T.J., 2009. Encoding deficit during face processing within the right fusiform face area in schizophrenia. Psychiatry Res. Neuroimaging 172, 184–191. http://dx.doi.org/10.1016/j.pscychresns.2008.07.009.

White, T.P., Joseph, V., Francis, S.T., Liddle, P.F., 2010. Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. Schizophr. Res. 123, 105–115. http://dx.doi.org/10.1016/j.schres.2010.07.020.

Whitfield-Gabrieli, S., Ford, J.M., 2012. Default mode network activity and connectivity in psychopathology. Annu. Rev. Clin. Psychol. 8, 49–76. http://dx.doi.org/10.1146/annurev-clinpsy-032511-143049.

Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D.E., Seidman, L.J., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 106, 1279–1284. http://dx.doi.org/10.1073/pnas.0809141106.

Wokke, M.E., Vandenbroucke, a.R.E., Scholte, H.S., Lamme, V.a.F., 2013. Confuse your illusion: feedback to early visual cortex contributes to perceptual completion. Psychol. Sci. 24, 63–71. http://dx.doi.org/10.1177/0956797612449175.

Yoon, J.H., Sheremata, S.L., Rokem, A., Silver, M.a., 2013. Windows to the soul: vision science as a tool for studying biological mechanisms of information processing deficits in schizophrenia. Front. Psychol. 4, 681. http://dx.doi.org/10.3389/fpsyg.2013.00681.

Ziermans, T.B., Schothorst, P.F., Sprong, M., van Engeland, H., 2011. Transition and remission in adolescents at ultra-high risk for psychosis. Schizophr. Res. 126, 58–64. http://dx.doi.org/10.1016/j.schres.2010.10.022.