



Seeing more clearly through psychosis: Depth inversion illusions are normal in bipolar disorder but reduced in schizophrenia



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ABSTRACT

Schizophrenia patients with more positive symptoms are less susceptible to depth inversion illusions (DIIs) in which concave objects appear as convex. It remains unclear, however, the extent to which this perceptual advantage uniquely characterizes the schizophrenia phenotype. To address the foregoing, we compared 30 bipolar disorder patients to a previously published sample of healthy controls ($N = 25$) and schizophrenia patients ($N = 30$). The task in all cases was to judge the apparent convexity of physically concave faces and scenes. Half of the concave objects were painted with realistic texture to enhance the convexity illusion and the remaining objects were untextured to reduce the illusion. Subjects viewed objects stereoscopically or via monocular motion parallax depth cues. For each group, DIIs were stronger with texture than without, and weaker with stereoscopic information than without, indicating a uniformly normal response to stimulus alterations across groups. Bipolar patients experienced DIIs more frequently than schizophrenia patients but as commonly as controls, irrespective of the face/scene category, texture, or viewing condition (motion/stereo). More severe positive and disorganized symptoms predicted reduced DIIs for schizophrenia patients and across all patients. These results suggest that people with schizophrenia, but not bipolar disorder, more accurately perceive object depth structure. Psychotic symptoms—or their accompanying neural dysfunction—may primarily drive the effect presumably through eroding the visual system's generalized tendency to construe unusual or ambiguous surfaces as convex. Because such symptoms are by definition more common in schizophrenia, DIIs are at once state-sensitive and diagnostically specific, offering a potential biomarker for the presence of acute psychosis.

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1. Introduction

Three-dimensional (3-D) depth inversion illusions (DIIs) present a stunning class of visual phenomena in which concave objects produce the impression of convexity. A classic and well-known variant of DII is the hollow mask illusion, in which a face eerily floats in front of its true position along the depth axis (Gregory, 1970). A host of factors contribute to DIIs including object familiarity, convexity-consistent texture and perspective cues, and a general bias to interpret any ambiguous 3-D surface as convex (Hill and Johnston, 2007; Ramachandran, 1995; Sherman et al., 2011).

DIIs are of interest to clinical scientists because they arise to a lesser extent in schizophrenia and thus hold promise for detecting or gauging the severity of psychosis (Emrich et al., 1989). In a previous study, we had schizophrenia patients and healthy controls judge the convexity

of four concave objects (see Fig. 1), two of which were 3-D scenes (“reverse perspectives”) and two of which were hollow faces (masks) (Keane et al., 2013). One scene and one face were painted with misleading texture cues to magnify the illusion; the remaining objects were painted matte beige to mitigate the illusion. On half the trials, subjects viewed objects monocularly (with one eye) while continually swaying left to right, which allowed 3-D structure to be recovered via *motion parallax*, a phenomenon in which points at further distances appear to move more slowly relative to points closer. On the remaining trials, subjects remained still and observed objects binocularly, so that stereoscopic depth could disambiguate an object's structure (Papathomas and Bono, 2004). We found that between-group differences in overall illusion strength did not depend on object type or viewing condition and that each group responded normally to texture and viewing manipulations (i.e., responding more accurately with stereoscopic cues or uniformly colored surfaces). This suggested that reduced illusions in schizophrenia cannot be explained by poor processing of face, stereoscopic, or texture information, but instead can be ascribed to a reduced reliance on a generic convexity assumption, sometimes called a “visual

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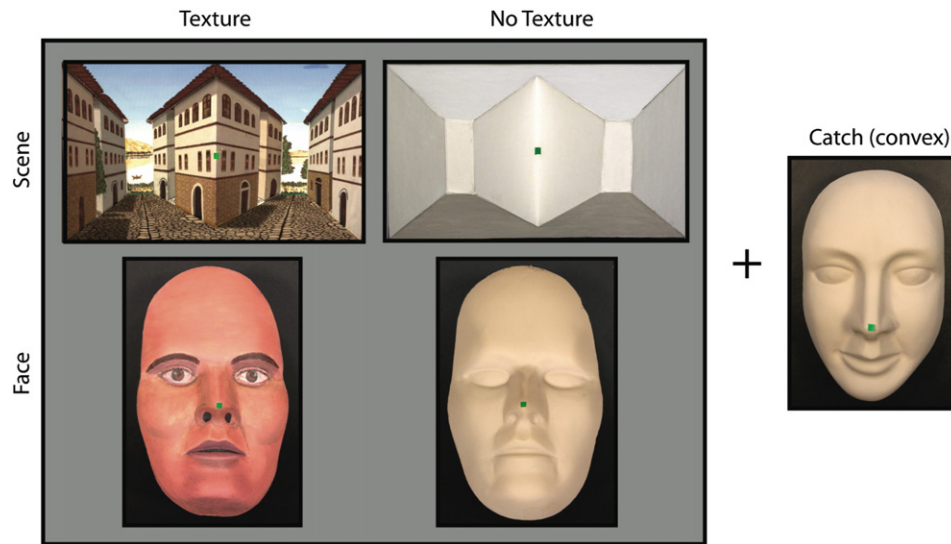


Fig. 1. Stimuli. Subjects viewed concave faces and scenes that were shown with or without misleading surface texture. Because of the concavity, the green fixation points were further from the observer than the surrounding regions (cheeks or landscape). An untextured beige face was convex and served as a catch.

prior". A critical qualification was that schizophrenia patients exhibited less illusion *only if* they demonstrated higher levels of positive symptoms or received care more recently within an acute psychiatric unit.

The experimental method just described has advantages over what has been used previously. DII tasks traditionally involve judging local and global convexity on a 5-item Likert-type scale, ranging from clearly convex to clearly concave. A problem pointed out by others is that different subject groups could conceivably use the scale in different ways (Schneider et al., 2002). For example, schizophrenia patients may need less evidence to categorize an object as "clearly concave" rather than "possibly concave", given that delusional patients more easily reach strong conclusions from weak evidence (Bristow et al., 2014; Garety et al., 1991). Our variant of the task minimizes differential evidential weighting biases by having subjects make simple, qualitative, binary judgments. Additionally, all prior DII studies in schizophrenia used shutter glasses or a Wheatstone stereoscope to present separate 2-D images to each eye, either as a normal stereo pair (eliciting true depth) or with the left and right eye images reversed (pseudoscopically) to invert the perceived depth. However, seeing images in this way is not the same as normal seeing. Only with physical object perception do accommodation cues (how much the eyes' lenses bend to focus on a stimulus) and vergence cues (how much the eyes turn inward to fixate on an object) provide congruent and veridical information about an object's true depth structure. Thus, the usage of physical objects removes oculomotor signal conflicts and allows the results to better generalize to everyday viewing circumstances.

Given the methodological advantages of the foregoing experimental approach and the novel findings that have already emerged from it, we sought in the present study to run the same protocol on bipolar disorder patients. Individuals with bipolar disorder were considered because they offer a nearly ideal comparison group for schizophrenia: they take some of the same anti-psychotic medications, experience some of the same psychotic symptoms, suffer from chronic medical problems (Birkenaes et al., 2007), have elevated rates of past substance abuse (Cassidy et al., 2001; Dixon, 1999), have below-average premorbid functioning (Cannon et al., 1997), and share a common genetic etiology (Lichtenstein et al., 2009). Therefore, if the two diagnostic groups end up differing in DII, then that would do much to demonstrate specificity to the schizophrenia phenotype and put to rest lingering confounds lurking in earlier schizophrenia studies of DII. Moreover, understanding the visual implications of bipolar disorder is important in its own right—there simply is not much literature on the topic. Performing a PubMed search of "visual perception" conjoined to either "bipolar

disorder" OR "bipolar affective disorder" yields about 11% as many entries as when conjoined to "schizophrenia" (search date: Feb. 12, 2016). If cognition is considered an important component of serious mental illness, then all aspects of cognition (broadly construed) should be considered, including those aspects that allow for adequate interpretation of the visual world around us. Third, with the advent of the NIMH Research Domain Criteria (RDoC) initiative, there has been a groundswell of interest in describing how impairments in core biobehavioral processes generate symptoms trans-diagnostically (Kozak and Cuthbert, 2016). Examining features that are common to patients across disorders or that segregate patients within a disorder, could help revamp the DSM nosology, which in turn could help personalize treatment, improve predictions of clinical outcomes, and deepen our understanding of the etiological origins of psychosis.

In the present investigation, we compared results from previously tested schizophrenia and healthy control participants to those of a new set of bipolar disorder patients. Three specific predictions were made. First, we expected increased positive symptoms to correlate with weaker DIIs, if not within the bipolar group, then across all patients combined. This was hypothesized not only because of our previously documented correlation with DII, but also because others have posited on theoretical grounds that abnormal dopamine neurotransmission and inappropriate prediction-error signaling will produce positive symptoms and abnormal interpretations of ambiguous visual information (Fletcher and Frith, 2009). A second prediction was that bipolar patients should demonstrate levels of DII that would be either closer to controls than to schizophrenia patients or intermediate between the two. The rationale is that the DII-relevant positive symptoms are present but muted in bipolar disorder and that other types of visual processing abnormalities in schizophrenia are reduced or absent in bipolar disorder (Jahshan et al., 2014; Kéri et al., 2005a; Yang et al., 2013). A final prediction was that DII differences between groups should not depend on the specific object type or viewing condition, since psychosis should alter a generic convexity assumption rather than the processing of any specific attribute that weakens or strengthens the illusion (Keane et al., 2013).

2. Methods

2.1. Subjects

The subject sample consisted of 30 patients who had type I ($N = 26$), type II ($N = 3$), or not otherwise specified ($N = 1$) variants of bipolar

Table 1
Demographic and clinical characteristics of participants.

Variable	Controls (N = 25)		Bipolar Disorder (N = 30)		Schizophrenia (N = 30)		Group comparison <i>p</i> -value	Follow-up comparison (<i>uncorrected</i>)
	Mean or %	SD	Mean or %	SD	Mean or %	SD		
Age (years)	45.8	10.2	40.4	13.1	46.6	13.6	0.125	–
Education, father (years)	12.1	3.0	13.1	3.0	12.4	4.4	0.578	–
Education, mother (years)	10.9	3.6	12.7	2.7	11.4	4.2	0.168	–
Education, self (years)	13.3	1.9	13.5	1.6	13.2	2.0	0.849	–
Ethnicity (% Caucasian)	24.0	NA	83.3	NA	60.0	NA	0.001	Ctrl < Bip***
FSIQ (Shipley)	89.7	13.0	92.5	10.8	88.5	12.9	0.447	–
Sex (% male)	48.0	NA	33.0	NA	70.0	NA	0.017	SZ > Bip**
Handedness (% right)	92.0	NA	93.3	NA	80.0	NA	0.277	–
Chlorp. Equiv. (mg/day)	–	–	274.3	211.4	444.0	208.3	0.016	–
Disorganization	–	–	3.7	0.8	5.2	2.1	0.001	–
PANSS, positive	–	–	12.2	3.5	14.7	4.7	0.025	–
PANSS, negative	–	–	12.7	3.5	17.3	5.4	<0.001	–
PANSS, general	–	–	30.3	6.4	29.8	8.1	0.819	–
Depression, BDI-II	–	–	15.4	12.0	–	–	–	–
Mania, YMRS	–	–	4.6	4.6	–	–	–	–

** *p* < 0.01.

*** *p* < 0.001.

disorder. Seven (6 type I) had psychotic features. These patients were compared to a previously published sample of 25 healthy control subjects and 30 schizophrenia patients (Keane et al., 2013). Special effort was made to match the three groups on age, education level (father/mother/self), full-scale IQ, and handedness (all *ps* > 0.12) (See Table 1). The bipolar disorder sample was recruited from a vertically integrated treatment facility (Smith et al., 1999) at Rutgers University Behavioral Health Care. The sample was composed of: 11 Acute Partial Hospital (APH) patients who were either recently discharged from an inpatient unit (<6 months) or recently admitted to the program in lieu of an inpatient hospitalization (in cases where there was no imminent danger to self or others); 10 Extended Partial Hospital patients who had been out of the hospital between 6 and 24 months but who were still undergoing stabilization and needed the daily structure of a partial hospital program; and 9 outpatients who had their last APH admission at least two years prior to testing and required only biweekly or monthly visits with treatment providers. By comparison, 30 schizophrenia patients had been recruited in equally sized subgroups from each of the three same treatment programs (10 per program, Keane et al., 2013).¹

For all subjects, the inclusion/exclusion criteria included: age 18–65 years; no history of neurological disease or clinically significant head injury (loss of consciousness or overnight hospitalization); no diagnosis of mental retardation or pervasive developmental disorder; no substance dependence in the past 6 months; sufficient spoken English so as to complete testing; normal stereoscopic vision; and the ability to give valid informed consent. An additional criterion for patients was having a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR) diagnosis of schizophrenia or bipolar disorder (APA, 2000). Four patients (all with bipolar disorder) were not taking antipsychotic medication at the time of testing. Additional criteria for controls were: no DSM-IV-TR diagnosis of schizophrenia or any other psychotic or mood disorder, and no current psychotropic- or cognition-enhancing medication. Written informed consent was obtained from all subjects after explanation of the nature and possible consequences of participation. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards at Rutgers. All participants were naïve to the study hypotheses and received monetary compensation for their time.

¹ The above guidelines were not deterministic: On infrequent occasions, a patient could skip one program to enter into another or stay longer in one program than is typical. Flexibility notwithstanding, patients in the different treatment programs differed starkly in their stabilization phase duration, namely, how long it had been (in log units) since the last APH admission (*ps* ≤ 0.001).

An experienced rater (YW) had established reliability with raters in other ongoing studies (ICC > 0.80) and administered the clinical instruments and perceptual task. Psychiatric diagnosis was established with the Structured Clinical Interview for DSM-IV (SCID), patient and non-patient editions (First et al., 2002a, 2002b). The Shipley Institute of Living Scale (vocabulary subtest, Shipley et al., 2009) provided an estimate for full-scale IQ; a Snellen eye chart was used to estimate visual acuity. We examined drug and alcohol history over the last six months using the Mini International Neuropsychiatric Interview, substance abuse module (MINI; Sheehan et al., 1998) and symptom levels over the last two weeks with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). For all bipolar disorder patients only, we assessed manic symptoms with the Young Mania Rating Scale (YMRS; Young et al., 1978) and depressive symptoms with the Beck Depression Inventory (BDI-II; Beck et al., 1996). Clinical symptom assessments were conducted within 8 days of perceptual testing. In accord with previous DII studies, we report the three-factor (positive, negative, general) PANSS scores (e.g., Dima et al., 2009, 2010, 2011; Keane et al., 2013; Schneider et al., 2002). We also examined cognitive disorganization, which was calculated as the sum of two PANSS items—poor attention and conceptual disorganization—and an additional item not originally included in the PANSS, inappropriate affect (Peralta et al., 1992). This last factor (also referred to as “disorganization”) was added since it has been routinely reported and found to be relevant in our previous perceptual studies in schizophrenia (Keane et al., 2013; Silverstein et al., 2000; e.g., Uhlhaas et al., 2006).

2.2. Stimuli

Front views of each of the five stimuli are shown in Fig. 1. (See Supplementary online material for stimulus movies, stereoscopic pictures and orthographic projections.) The faces were two geometrically identical plastic facial masks with maximum height, width, and depth of 21.45, 13.10, and 5.97 cm, respectively. The two differed in that one was painted with a uniform matte beige color and the other was painted on the hollow side with realistic human features so as to appear as a convex human face.

The scenes consisted of two geometrically identical truncated pyramids that were horizontally aligned and directed toward the viewer. The entire structure had a maximum height, width, and depth of 14.90, 24.90, and 4.10 cm, respectively. The space between the truncated pyramids can be perceived as concave (veridical) or convex (DII). The two scenes differed only in the addition of misleading convexity-consistent surface texture, which contained strong linear perspective cues. To ensure that subjects were responding non-randomly and

honestly, we also had subjects observe on certain trials a convex face stimulus (catch), which had the same color and size as the uniformly colored concave face.

A small green square fixation mark (side = 5 mm) was placed at the center of each object. This center was locally concave for all objects, except for the catch. Objects were mounted on a uniform matte black surface at eye level for each participant and were lit by two pairs of floodlights positioned symmetrically on either side to avoid cast shadows.

2.3. Procedure

At the beginning of the experiment, subjects were shown two sample stimuli up close—one ovoid shell painted matte beige and one miniature scene painted realistically. Each sample consisted of a thin shell that was convex on one side and concave on the other, and each had a green fixation point at its center. Participants were told that they would see similar objects from afar, and that—while fixating the green dot—they would report whether the object appeared to be “popping out” (convex) or “caving in” (concave).

On each of ten experimental trials, a stimulus was placed 200 cm from the subject—a distance known to produce an illusion of intermediate strength (Papathomas and Bono, 2004). A trial lasted for 2 min, during which subjects were prompted every 12 s to verbally report the object's appearance. The experimenter entered subjects' responses into a computer and a program quantified the fraction of total time spent in the veridical percept (proportion veridical response). Between trials, subjects received a break and were shown the two sample stimuli as a reminder.

The five objects—including the convex catch stimulus—were shown for each of the two viewing conditions. In the motion parallax condition, subjects wore an eye patch over their non-dominant eye (Crovitz and Zener, 1962) and laterally swayed back and forth between two vertical planks of wood—one on the left and one on the right. To clarify with an example, as an observer moves laterally in front of a stationary concave mask, the nose appears to move less than the surrounding parts of the face, indicating that the nose is further away and hence concave. The planks were separated by 35.6 cm, which created a swaying amplitude that greatly exceeds the average separation between the eyes (interpupillary distance) (6.3 cm, Dodgson, 2004). This ensured that—during movement—subjects would acquire substantially different views (retinal images) of the objects, and thereby obtain a robust motion parallax depth signal, comparable to the binocular disparity information in the binocular viewing condition. In the stereopsis viewing condition, subjects binocularly examined objects from a stationary chinrest. Stereoscopic viewing always occurred in the second half of the experiment because the visual system recovers depth better with stereopsis than motion parallax (Sherman et al., 2011) and because the aim was to minimize the chances that subjects would use their knowledge of a stimulus when making a response. The sequence of five objects was counterbalanced across participants and viewing conditions. Therefore, for each half of the experiment and across the whole experiment, 20% of the trials were dedicated to each of the five objects, including the convex catch stimulus.

2.4. Analysis

Performance on the catch stimulus was evaluated with a 3 (subject group) \times 2 (viewing condition) analysis of variance (ANOVA). Performance on the non-catch stimuli was assessed with a 3 (subject group) \times 2 (viewing condition) \times 2 (object category) \times 2 (texture type) ANOVA. As in our previous study, clinical stability was measured as the number of days (log units) between the date of perceptual testing and the date of last admission to the APH program (representing the beginning of the stabilization phase after the last relapse) (Keane et al., 2013). Bivariate relationships between variables were assessed with

Pearson correlations, unless individual symptom scores were considered in which case we used Kendall's tau. All tests were two-tailed and equal variances were assumed, unless noted. Corrections for multiple comparisons were implemented via the False Discovery Rate (FDR) controlling procedure (Benjamini and Hochberg, 1995).

3. Results

The patient and control groups identified the catch stimulus as convex on >98% of the occasions and did not differ in this regard (all $ps > 0.3$; Fig. 2). Across all subjects, there were fewer DII when objects were viewed with stereoscopic cues than without ($F(1, 82) = 73.2$, $p < 0.001$, $\eta_p^2 = 0.472$) and when objects were shown with realistic surface texture than without ($F(1, 82) = 63.6$, $p < 0.001$, $\eta_p^2 = 0.437$), which is consistent with previously documented findings in healthy adults (Sherman et al., 2011). The effect of texture modulation was amplified with binocular viewing, $F(1, 82) = 14.9$, $p < 0.001$, $\eta_p^2 = 0.154$. Most importantly, there was a main effect of group ($F(1, 82) = 3.7$, $p = 0.030$, $\eta_p^2 = 0.082$) that did not depend on viewing condition, texture, or object category (all $ps > 0.3$). Follow-up comparisons revealed that the bipolar disorder patients reported the correct shape as often as controls ($t(53) = -0.2$, $p = 0.821$) and less often than schizophrenia patients ($t(58) = 2.2$, $p = 0.030$, $d = 0.58$) and that (as already reported) schizophrenia patients reported fewer illusions than controls ($t(53) = -2.3$, $p = 0.028$, $d = 0.62$). An FDR correction for multiple comparisons did not change these results.

As in our prior study (Keane et al., 2013), we considered whether group differences remained if the data were restricted only to non-face stimuli or only to monocular viewings. It was found that in each case the bipolar disorder patients performed similarly to controls ($ps > 0.7$) but less accurately than schizophrenia patients ($ps < 0.03$), providing further evidence that group differences could not be attributed to abnormal stereoscopic or face processing.

Medication levels differed between groups (see Table 1). Is this a cause for serious concern? It is not. One reason is that chlorpromazine equivalents did not correlate with DII within either patient group ($ps > 0.17$). Another is that bipolar disorder patients expressed entirely normal levels of DII even though most were on antipsychotic medication. A third is that if the bipolar disorder patients receiving zero or small amounts of anti-psychotic medication were removed from the analysis (<100 mg/day; $N = 4$)—so that the two diagnostic groups were equated on CPZ equivalents ($p = 0.13$)—the ANOVA results turned out qualitatively identical, with bipolar disorder patients reporting the illusion more than schizophrenia patients ($p = 0.01$) and as often as controls ($p = 0.75$). Adding medication as a covariate into this ANOVA preserved the main effect of group ($p = 0.02$) without generating any medication effects or interactions ($ps > 0.24$). Therefore, antipsychotic dosage amounts do not predict abnormal DII and medication use is neither necessary nor sufficient for abnormal DII.

Of a priori interest was the effect of positive symptoms on DII. It was already reported that more severe positive symptoms predicted fewer illusions within the schizophrenia sample ($r = 0.42$, $p = 0.02$; Keane et al., 2013). Here, we report a similar correlation across all patients ($r = 0.269$, $p = 0.038$; Fig. 3A), but not within the bipolar disorder group alone ($r = -0.16$, $p = 0.40$). Interestingly, diagnosis significantly moderated the effect of positive symptoms on DII ($\Delta R^2 = 0.070$, $F(1, 56) = 2.47$, $p = 0.03$). However, this last effect must be regarded cautiously: the positive symptoms of the bipolar disorder sample fell within a more restricted range (see Table 1); it is not clear how much can be inferred about acutely psychotic bipolar patients on the basis of those who suffer few psychotic symptoms (as was the case in our sample); and psychotic-like symptoms in other populations alter DII in the expected direction (see Discussion).

For each group and across patients, we also considered in an exploratory fashion correlations with: general and negative PANSS symptoms, cognitive disorganization, ethnicity and sex (which differed between

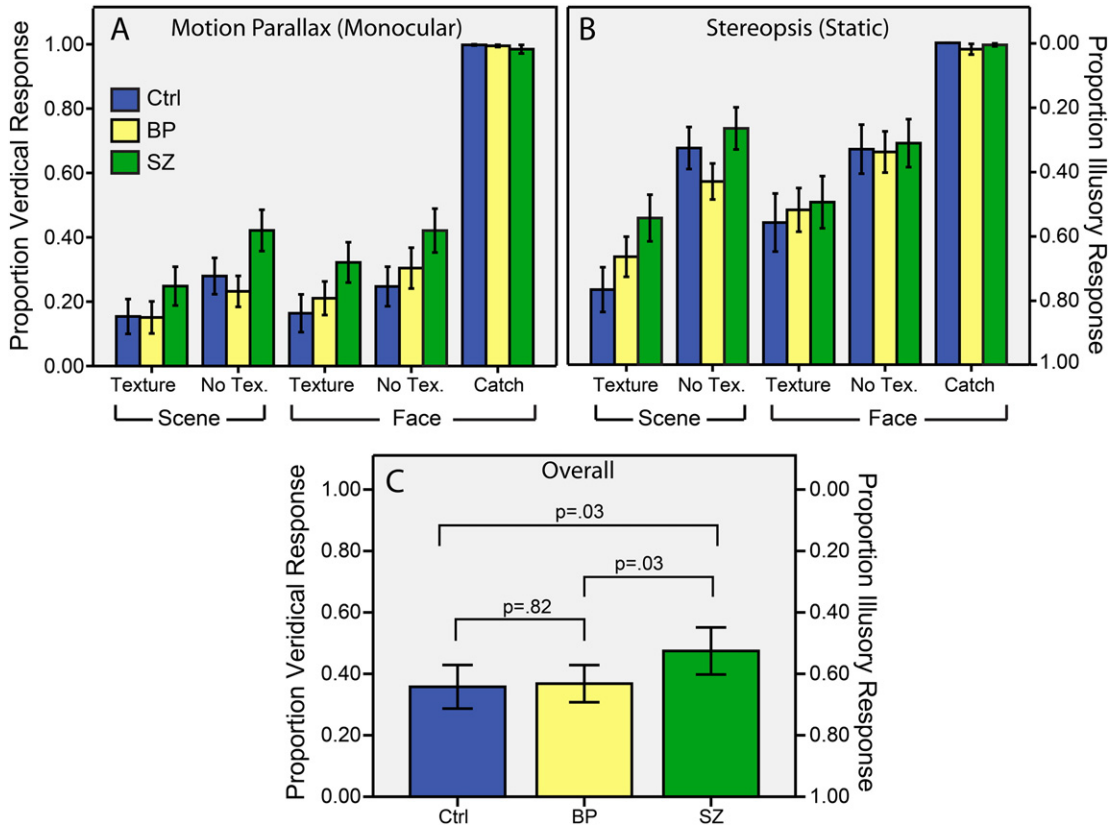


Fig. 2. DIIs for controls, schizophrenia patients, and bipolar disorder patients. (A–B) For concave objects, bipolar disorder patients gave similar responses to controls and less accurate responses than schizophrenia patients, regardless of object type or viewing condition. For the catch, each subject group was near ceiling. (C) When data were collapsed across conditions, group differences clearly emerged. Errors show \pm SEM.

groups; Table 1), and YMRS and BDI-II total scores. In the schizophrenia sample, there was a positive Pearson correlation with cognitive disorganization (Peralta et al., 1992) ($r = 0.410, p = 0.03$). In the bipolar disorder group, less veridical perception correlated with a higher level of PANSS general symptoms ($r = -0.372, p = 0.043$) and higher BDI-II scores ($r = -0.438, p = 0.036$). Across all patients, there was a strong DII correlation with disorganization ($r = 0.415, p = 0.001$; Fig. 3B). No other effects reached significance. If an FDR correction were applied to the above findings, only the disorganization correlation across patients would remain significant.

Two other exploratory findings across patients strengthen the case for disorganization's relevance: 1) FDR-corrected tests of the individual PANSS positive item scores yielded an effect of conceptual disorganization ($r = 0.33, p_{corr} = 0.007$); and 2) closely related (but different)

metrics of disorganization also produced correlations in the expected direction (Mueser et al., 1997; van der Gaag et al., 2006; Wallwork et al., 2012). These data suggest that however one wishes to define the term, cognitive disorganization—or the neural dysfunction that it reflects—paradoxically improves the ability to see hollow objects as hollow.

Previously, we reported that the duration since last admission into an acute psychiatric unit (log units) strongly predicted the extent to which depth inversion illusions were experienced by schizophrenia patients, with more accurate perception occurring nearer to the point of a psychotic episode ($r = -0.50, p = 0.006$, Keane et al., 2013). No such relation was found in our bipolar disorder sample ($r = -0.09, p = 0.63$). We probed whether the effect of clinical stability on DII significantly changed as a function of diagnosis. Using mean-centered

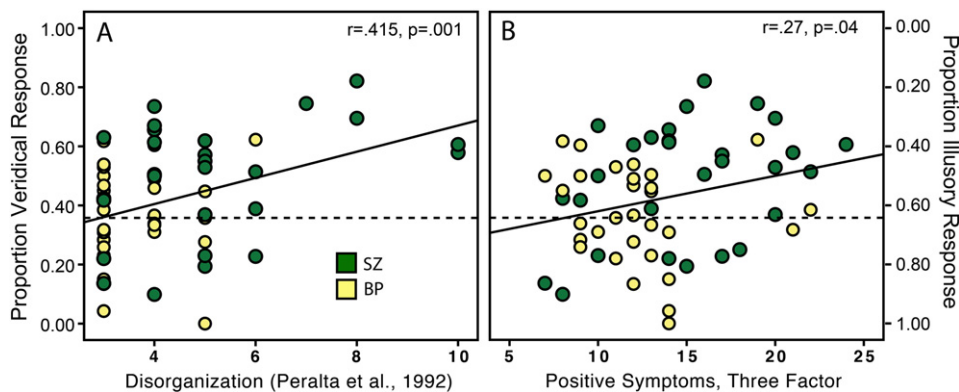


Fig. 3. More veridical perception was associated with (A) more cognitive disorganization and (B) positive symptoms. Regression lines accompany the scatter plots. Dotted lines denote controls' average proportion correct for the concave stimuli.

predictors, subject group did not significantly moderate the effect of days since acute APH admission on proportion veridical response ($\Delta R^2 = 0.032$, $F(1, 55) = 2.47$, $p = 0.12$).

4. Discussion

When judging the shape of physically concave objects, bipolar disorder patients were as accurate as healthy controls but less accurate than schizophrenia patients. Group differences in illusion susceptibility did not depend on object category (faces/scenes), viewing condition (parallax/stereopsis) or texture type (realistic/blank) and could not be explained in terms of a blind bias to respond “concave”, since subjects almost always identified the catch stimulus as convex. DIIs became less common when patients had more positive and disorganized symptoms but DIIs did not systematically change with the presence or dosage amounts of antipsychotic medication. Taken together, these data suggest that i) bipolar disorder patients exhibit a normal susceptibility to depth inversion illusions; ii) the likelihood of veridical perception increases monotonically with positive and disorganized symptoms but not other symptom types; and iii) between-group differences in convexity perception may arise from a reduced bias to construe any type of ambiguous object as convex.

4.1. State specificity of depth inversion illusions

Positive symptoms contributed to weaker DII in schizophrenia but not bipolar disorder and so it might be questioned whether they must accompany schizophrenia to enable more accurate hollow shape perception. There are several reasons to think otherwise. First, and most importantly, cannabis usage, sleep deprivation, and alcohol withdrawal all weaken the illusion (Emrich, 1989; Schneider et al., 1996, 1998; Semple et al., 2003), indicating that increased psychotic-like symptoms are associated with reduced DII independently of mental illness. Second, the non-significant symptom correlations in our bipolar disorder sample can readily be explained by the reduced symptom mean and variance in that group (Levene's test, $p = 0.045$; Table 1): Whereas 7 schizophrenia patients exhibited positive symptom scores exceeding the “average” symptom level documented in Kay and colleagues (> 18 ; Kay et al., 1987), only three bipolar disorder patients expressed scores above this same cut-off. The mean and variance of the disorganized symptoms were also systematically reduced ($ps < 0.01$). Therefore, had we included a sufficient number of actively psychotic bipolar disorder patients, DII-symptom correlates for that group very well could have reached significance, though, to be sure, this will need to be experimentally verified in future investigations.

It is worth emphasizing that positive and disorganized symptoms were not relevant solely because they are more common in and definitive of schizophrenia. Negative symptom scores were predictably more severe in the schizophrenia group ($p < 0.001$) but did not correlate with DII within or across groups ($ps > 0.10$). Therefore, positive and disorganized symptoms—or the brain states that they reflect—somewhat uniquely unshackle the visual system from convexity prejudices during the interpretation of unusually curved 3-D surfaces.

As described in the Methods section, all patients were treated within a single, vertically integrated system that makes level-of-care decisions on the basis of standard criteria (as set by external review agencies), facilitates rapid transfer between programs, and maintains continuity of treatment (Smith et al., 1999). Therefore the duration since last APH admission reflects the need for daily structure and treatment in a highly standardized way. While it is true that diagnosis did not significantly moderate the effect of clinical stability on DII, an intriguing possibility is that being more recently hospitalized indirectly increases veridical perception rates by way of reducing positive/disorganized symptoms or the neural disturbances associated with such symptoms (Fig. 4). This effect would arise only in the schizophrenia sample since psychotic symptoms are on average more common and more severe in that

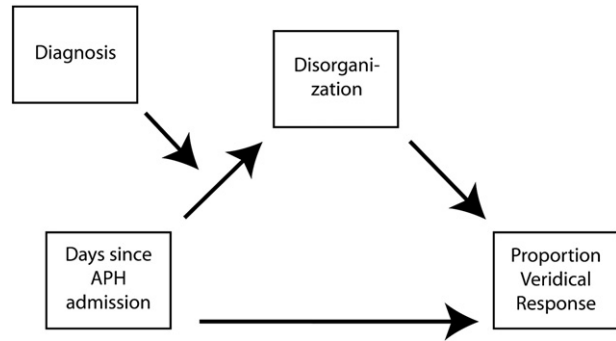


Fig. 4. A conceptual path analysis model of moderated mediation. According to the experimentally verified model, switching the diagnosis from schizophrenia to bipolar disorder blocks the indirect effect of clinical stabilization (days since last APH admission) on illusion resistance (proportion veridical response) by way of reducing disorganized symptoms.

disorder and thus have more opportunity to normalize in the months following a psychiatric hospitalization. To state this in another way, having bipolar disorder effectively blunts the causal/correlational link between clinical stabilization and positive/disorganized symptom severity, which in turn could eliminate any indirect effect of stabilization on DII. Lending support to this idea is a previous study showing that DIIs become more frequent and BPRS symptoms less severe as schizophrenia patients transit from inpatient hospital admission to discharge (Schneider et al., 2002). To test our conjecture more carefully, we conducted a moderated mediation analysis (Hayes, 2015 see Supplementary analyses and results). The results partly confirmed the suggested model: disorganized symptoms mediated the effect of days since AP hospital admission on veridical perception rates and the size of this indirect effect hinged on diagnosis. The confirmation was “partial” because the same model did not yield significant results for positive symptoms alone or in conjunction with disorganized symptoms. Note however that there was a direct effect of clinical stabilization on DII independent of symptomatology, indicating that symptoms need not change for there to be a concomitant normalization of vision. These outcomes—while intriguing and worthy of follow-up study—should be considered as provisional since the model was post-hoc and the comparison, cross-sectional.

4.2. What causes more accurate perception of object concavity?

We and others have suggested that state-related reductions of DII in schizophrenia may begin to be explained by disturbances in *prediction-error monitoring*, the statistical process by which the brain updates expectations about future states of the world on the basis of how past predictions matched with past experience. This Bayesian belief-updating process provides one way of characterizing the at-times fuzzy notion of “top-down influence”. The idea in its simplest form is that past experiences with mostly convex objects leads us to construe newly encountered ambiguous objects as also being convex and that this experientially established assumption may trump conflicting stimulus-driven (e.g., stereoscopic or motion-driven) information. People with schizophrenia are putatively less adept at detecting discrepancies (prediction errors) between sensory input and expectations for the purposes of appropriately updating their expectations as to how the world is supposed to look. These individuals will express under-confidence in the visual priors or relative over-confidence in the incoming sensory information (Adams et al., 2013; Moutoussis et al., 2011), leading to a lessened role of high-level visual priors on the interpretation of unusual visual input. There is at least suggestive neurobiological evidence for this view: dynamic causal modeling, functional imaging, and event-related potentials show that feedback from intraparietal sulcus (IPS) to lateral occipital complex (LOC) is stronger in healthy

controls than in schizophrenia patients and that this predicts reduced DII in patients (Dima et al., 2009, 2010). The exact neurobiological details as to how prediction error monitoring becomes maladapted or misused in schizophrenia remains a highly complex and largely unsettled debate, but some have argued that it is a product of large-scale network dysconnectivity, or dysregulation of the postsynaptic gain of principal cells through the interaction of NMDA receptors and dopaminergic projections (Fletcher and Frith, 2009; Friston et al., 2012; Stephan et al., 2009). However that debate turns out, a tantalizing possibility—and one that is seldom discussed in the schizophrenia literature but that merits further scrutiny in light of the current findings—is that the neurochemical and neurofunctional underpinnings of noisy visual priors may also undergird cognitive disorganization.

4.3. Visual perception in bipolar disorder

If DIIs are state-dependent, does this mean that inter-diagnostic differences arose in our study only because the schizophrenia participants happened to be more symptomatic at the time of testing? It should immediately be acknowledged that group differences could have been wiped out had we sampled more strategically, viz., by testing bipolar disorder patients with unusually severe psychotic symptoms or schizophrenia patients with unusually high levels of functioning. But such samples would not have been representative. It is consequently not a gross over-simplification to assert that depth inversion illusions are by-and-large normal in bipolar disorder and more common in schizophrenia. This conclusion is broadly consistent with other behavioral investigations which have documented either intermediate or absent visual deficits in bipolar disorder (Jahshan et al., 2014; Kéri et al., 2005b; Schallmo et al., 2015; Yang et al., 2013).

Our results also weigh in on the RDoC debate about whether the two illnesses differ categorically or dimensionally. In light of the discussion above, the current data support both views. On the one hand, positive/disorganized symptoms are by definition more common in schizophrenia, leading to an overall reduced level of DII. People with the two disorders share a host of similarities (below-average premorbid functioning, genetic risk for psychosis, antipsychotic medication usage, etc.), and so discovering reduced DII only in schizophrenia demonstrates specificity to the phenotype. At the same time, moderate-to-severe psychotic symptoms can in principle emerge in either disorder, opening up the possibility that at certain time points, patients who are diagnostically discordant will exhibit visual perceptual profiles that are more similar to one another than to those with the same diagnosis. Larger-scale investigations of DII are needed to explore this last suggestion more fully.

4.4. Limitations

Our study may have been limited in that the interviewer knew a subject's diagnosis when recording a subject's response, introducing the potential for experimenter bias. This confound is not particularly troubling since many of the findings were unanticipated and since the interviewer's role was merely to prompt a scheduled binary response. Another seeming shortcoming is that a standard interview for level of functioning was not administered. A caveat is that these measures do not always correlate highly with each other and may not reveal the need for daily structure and intensive treatment as does our metric of days since hospital admission (Silverstein et al., 2011). Third, even though group differences in medication were neither necessary nor sufficient for group differences in DII and even though dosages did not correlate with DII within or across patient groups, studies on never-before-medicated patients are still required. Limitations notwithstanding, the data show that—with physically concave objects—people with bipolar disorder express similar DIIs to healthy controls and more DIIs than schizophrenia patients, perhaps because of a differential tendency to construe any ambiguously curved surface as convex. The perceptual advantage in schizophrenia is closely linked to more severe positive/

disorganized symptoms and a more recent hospitalization, and may be generated by weakened top-down feedback from IPS to LOC. Therefore, the resulting perceptual advantage may potentially serve as a biomarker for predicting relapse and recovery in people with schizophrenia or acute psychosis.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2016.06.015>.

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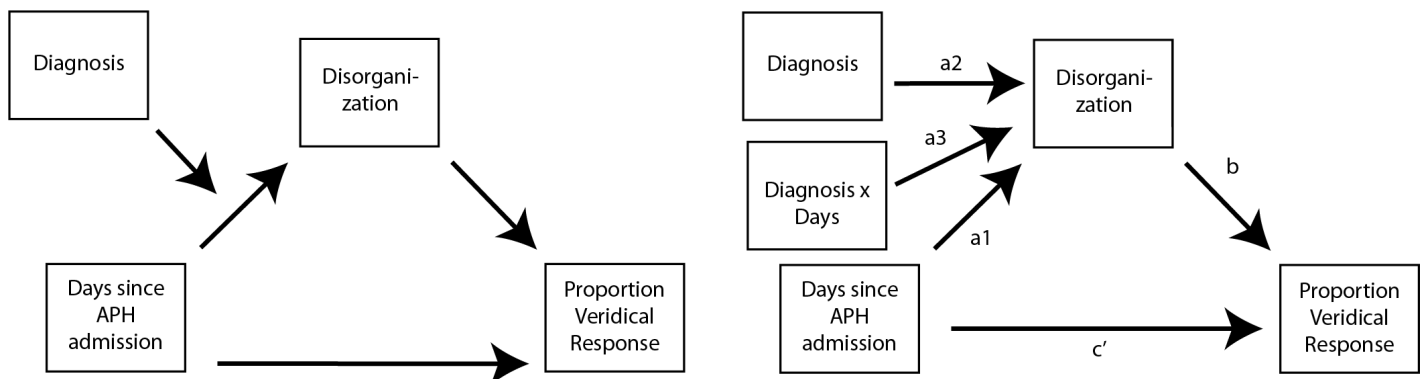
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Supplementary Analysis & Results

We conducted a test of linear moderated mediation (Hayes, 2015), which incorporated an ordinary least squares path analysis, bias-corrected and accelerated bootstrapped sampling (10,000 samples), and HS3 estimators to account for variance heterogeneity (Long & Ervin, 2000). The diagnosis dummy variable and AP hospitalization recency variable (in log units) were mean centered prior to being entered into the model. One schizophrenia subject's individual item scores were lost during an archiving process and were not available for calculating the cognitive disorganization and five-factor scores; also missing was the hospitalization history for one other schizophrenia patient.

A conceptual and statistical schema is shown below along with a table of key results. We found that when subjects had schizophrenia there was a significant conditional indirect effect of clinical stability (days since last AP hospital admission) on veridical response rates through five-factor disorganized symptoms, $ab = -.034$, 95% CI $[-.081 \text{ } -.004]$. That is, as schizophrenia patients were hospitalized a longer time ago, they exhibited fewer disorganized symptoms, which in turn lead to more DIIIs. When subjects had bipolar disorder, the indirect effect did not reach significance, $ab = -.006$, 95% CI $[-.0322 \text{ } .011]$. There was significantly moderated mediation: that is, the conditional indirect effect was larger in the schizophrenia than bipolar disorder group (index = $.028$, 95% CI $[\text{.0005 } \text{.0837}]$). There was also an overall direct effect of clinical stability across patients, $c' = -.071$ 95% CI $[-.132 \text{ } -.010]$.



		Disorganization (Five-factor)				Proportion Veridical Response		
		Coeff.	SE	p		Coeff.	SE	p
Days since APH Admission	a1	-.810	.284	.006	c'	-.071	.030	.024
Disorganization	--	--	--	--	b	.024	.011	.031
Diagnosis	a2	-1.61	.428	<.001	--	--	--	--
Days x Diagnosis	a3	1.17	.571	.045	--	--	--	--
Constant	--	6.55	.212	<.001	--	.262	.079	.002
R-squared=.388, F(3,54)=9.22, p<.001					R-squared=.181, F(2,55)=8.04, p<.001			

Qualitatively the same results emerged when the alternative "cognitive disorganization" was used in place of five-factor disorganization. A moderated mediation effect did not reach significance when either positive

symptom metric (three- or five-factor) was used as mediators or when either was added to either of the two disorganization metrics. Note that we did not closely consider alternative schemas such as subject group moderating the effect of positive/disorganized symptoms on DII since—as noted in the main article—there is little reason to think that symptoms lose their efficacy simply because they belong to a different diagnosis.

Overall, these results suggest that the longer that schizophrenia (but not bipolar) patients spent within their stabilization phase, the more their disorganization symptoms subsided, which in turn increased depth inversion illusions. Furthermore, when symptoms were held constant, visual perception became more normal as the most recent psychotic episode became less recent.

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