Published in final edited form as:

Psychiatry Res. 2018 July ; 265: 271–278. doi:10.1016/j.psychres.2018.04.061.

A Bayesian Model Comparison Approach to Test the Specificity of Visual Integration Impairment in Schizophrenia or Psychosis

Tyler B. Grove^{a,*}, Beier Yao^b, Savanna A. Mueller^a, Merranda McLaughlin^c, Vicki L. Ellingrod^{c,d}, Melvin G. McInnis^c, Stephan F. Taylor^{a,c}, Patricia J. Deldin^{a,c}, and Ivy F. Tso^{a,c}

^aDepartment of Psychology, University of Michigan, Ann Arbor, Michigan, USA

^bDepartment of Psychology, Michigan State University, East Lansing, Michigan, USA

^cDepartment of Psychiatry, University of Michigan, Ann Arbor, Michigan, USA

^dCollege of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA

1. Introduction

Visual integration, the ability to combine discrete elements to form a holistic representation, underlies critical perceptual functions such as Gestalt grouping and is critical to cognitive processes within the environment (e.g., object identification, face processing; Butler et al., 2008). Deficits in visual integration are well-documented in schizophrenia (SZ) and have been shown to be related to clinical symptoms, cognition, and functional outcomes (Silverstein et al., 2006; Silverstein et al., 1996; Silverstein et al., 2000; Tso et al., 2014; Tso et al., 2012; Uhlhaas et al., 2006; Uhlhaas et al., 2005). Some evidence suggests that disruption in early perceptual processing may be one mechanism through which social functioning is compromised in SZ (Butler, 2009; Silverstein and Keane, 2011a). Recent data show that visual integration impairment is evident in first-episode psychosis and worsens with illness chronicity (Keane et al., 2016), suggesting that it may be a characteristic of psychosis or a function of illness severity rather than specific to the diagnostic category of schizophrenia. Given the functional and etiological relevance of visual integration in SZ and psychotic disorders, this question would have important implications for our understanding of the pathophysiology and treatment of severe mental illnesses. To this end, the current study aimed to test the diagnostic specificity of visual integration impairment in schizophrenia or psychosis.

Visual integration is an interactive process linking the bottom-up sensory data output of neurons that code local features of a scene to cells within downstream visual areas that code global and typically larger complex formations modulated by context and prior experiences. Within healthy individuals, effective visual integration relies on long-range connections in V2 or higher areas to produce grouping (Silverstein and Keane, 2011b). Successful visual integration has been shown to be related to the N_{cl} (closure negativity) event-related potentials (ERP) wave, localized in the lateral occipital complex (LOC; Butler et al., 2013).

*Correspondence concerning this article should be addressed to Tyler Grove, Department of Psychology, University of Michigan, 530 Church Street, Ann Arbor, Michigan 48109, USA. tylerg@umich.edu. Tel: 1-(734)-647-3872.

However, proper functioning of the visual system also depends much on top-down modulation of the visual cortex (Engel et al., 2001; Freeman et al., 2003; Gilbert and Li, 2013) and a balance in neuronal excitation/ inhibition, supported by NMDA receptor functions (e.g., to modulate lateral excitation) and GABAergic functions (e.g., to inhibit noise) (Butler et al., 2008). In fact, neural oscillations and synchronization, particularly at the beta and gamma frequency bands, are often implicated in visual processing and integration (Castelhano et al., 2015; Kloosterman et al., 2015; Uhlhaas et al., 2006).

Visual integration can be psychophysically assessed with perceptual closure tasks, grouping paradigms, and, most commonly, a contour integration task that requires participants to identify a contour comprised of elements within a background of similar noise elements (Butler et al., 2008). Individuals with SZ and psychosis typically perform worse than healthy controls on these tasks, suggesting impaired visual integration (review by Butler, 2009). The exact origin of visual integration deficits in psychosis is unclear. Distributed dysfunctions across the visual system, beginning from the retina (Adams and Nasrallah, in press), to primary visual cortex V1 (Anderson et al., 2017), to extrastriate visual cortex V2-V4 (Butler et al., 2013; Silverstein et al., 2009), and to association visual areas in the dorsal and ventral processing streams (Butler et al., 2013; Green et al., 2015; Silverstein et al., 2015b), have been reported. Regardless of the origin, visual integration impairment has been shown to be related to poorer social cognition and functional outcome in SZ (Silverstein and Keane, 2011b; Tso et al., 2014), suggesting that visual abnormalities may have downstream effects on higher-level cognition and social functioning in SZ. Given the scientific rigor of its measurement and functional relevance in SZ, visual integration offers a unique window to examine and understand the pathophysiology of psychotic disorders.

One question that needs clarification in the literature is whether visual integration impairment is specific to schizophrenia or common to other psychiatric disorders. This question arises as the field is moving toward a dimensional understanding of psychopathologies, led by the National Institute of Mental Health Research Domain Criteria (RDoC) initiative. This shift away from diagnostic categories (e.g., Diagnostic and Statistical Manual for Mental Disorders; DSM) to functional dimensions linked with pathophysiology (e.g., visual perception; Insel et al., 2010; Insel, 2014) may improve our understanding of psychopathology through a data-driven approach. In line with this effort, visual integration has been examined in other psychiatric disorders with clinical manifestations suggesting abnormal visual perception, including body dysmorphic disorder and obsessive-compulsive disorder; however, no impairment was found in these disorders when compared with healthy controls and schizophrenia (Silverstein et al., 2015a). It remains unclear, nevertheless, whether visual integration is affected in disorders in which psychosis is always present or highly prevalent, particularly those considered to be on the “schizophrenia-bipolar psychosis spectrum” (Keshavan et al., 2011). Bipolar disorder (BD) is a disorder frequently (>50%) affected by psychosis (Keck et al., 2003) and has substantial clinical, cognitive, neurobiological, and genetic overlap with schizophrenia (Brown, 2015; Hall et al., 2015; Pearlson, 2015; Pearlson and Ford, 2014; Tondo et al., 2015). Yet, no studies thus far have examined visual integration in BD. Additionally, there is evidence that BD patients with a history of psychosis (BDP+), compared with those without (BDP-), exhibit cognitive deficits (Hill et al., 2013; Ruocco et al., 2014) and neurobiological

abnormalities (Ivleva et al., 2013; Mathew et al., 2014) similar in extent and severity to those observed in SZ and SA. This suggests that the presence of psychosis, regardless of diagnostic category, might represent a distinct psychopathology that differentially impacts cognitive functions (including visual integration). Indeed, research studies often combine participants with SZ and schizoaffective disorder (SA) into one patient group, with the assumption that psychosis, rather than the DSM categories, is the underlying illness dimension causing the observed abnormalities of interest. This assumption is rarely explicitly tested in the schizophrenia literature, and visual integration is one of a well-researched topic in which the “schizophrenia” samples often comprise both SZ and SA (Butler et al., 2013; Chen et al., 2003; Silverstein et al., 2006). This makes it difficult to determine if the two diagnostic groups do indeed exhibit similar deficits to support the schizophrenia or psychosis hypothesis of visual integration deficits. Taken together, to address the question of specificity of visual integration impairment to schizophrenia or psychosis, it is necessary to include BD and stratify it by history of psychosis, as well as separate SA from SZ.

The current study aims to address the question whether visual integration impairment is characteristic of psychosis in general, specific to schizophrenia, or a function of DSM diagnosis. We assessed visual integration using a contour integration task in 116 participants: three patient groups along the “schizophrenia-bipolar psychosis spectrum” (SZ, SA, BDP+), BDP-, and HC. Participants were grouped according to three distinct models: 1) The Psychosis Model (psychosis, non-psychosis), where the psychosis group included SZ, SA, and BDP+, and the non-psychosis group included BDP- and HC; 2) The Schizophrenia Model (SZ, non-SZ); and 3) The DSM Model (SZ, SA, BD, and HC). We then used Bayesian model comparison to determine which model was a more likely generative model of the observed visual integration performance data. We hypothesized that visual integration in the psychosis group would be worse than the non-psychosis group, and the Psychosis Model would be the winning model among the three competing models. Additionally, we examined the relationship between visual integration and cognitive measures within the psychosis group and hypothesized that poorer visual integration would be associated with worse cognitive functions.

2. Method

2.1 Participants

A total of 116 participants completed the study: 25 SZ, 22 SA, 31 BD, and 38 HC. Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV; American Psychiatric Association, 2000) diagnoses were established using the Structured Clinical Interview for the DSM-IV (SCID-IV; First et al., 1997) for SZ, SA, and HC participants. BD participants were originally recruited via a separate study, which characterized participants using the Diagnostic Interview for Genetic Studies (DIGS Version 4.0; Nurnberger et al., 1994). BD participants were divided into two groups by history of prominent psychosis, defined as having had at least two mood episodes with psychotic features. Subsequently, 11 BD participants were assigned to the BDP+ group and 20 to the BDP- group. The clinical and HC groups were matched for age, sex, and parental education

(Table 1). Fifty-two participants of this study (29 SZ/SA and 23 HC) were part of a previous report (Tso et al., 2014). Eighty-seven participants of this study (37 SZ/SA, 27 BD, and 23 HC) participated in another study focusing on eye gaze perception, reported elsewhere (Yao et al., in press).

Participants were recruited via a university research registry, mental health clinics, other research studies, and advertisements. All participants were 18–65 years of age with at least 20/30 vision according to a Snellen chart. Participants who were unable to provide informed consent or had a history of substance dependence/abuse in the past 12 months were excluded. HC with a history of a DSM-IV Axis I diagnosis, significant medical conditions that affect brain functions, or family history of psychosis or mania among first-degree relatives were excluded. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and the research protocol was approved by the Institutional Review Board of the University of Michigan Medical School. Written informed consent was obtained from each participant prior to data collection.

2.2 Visual integration

A Contour Integration task was used to measure visual integration. The task was presented on a Windows PC using MATLAB (MathWorks, Inc.). A chin-rest was used to maintain a distance of 16 inches between the computer screen and the participant. The stimulus was presented on a screen and subtended visual angle of $18.6^{\circ} \times 14.3^{\circ}$. Participants were asked to locate (on the left or right side of the screen) a circle-like contour formed by 16 Gabor elements against a gray background consisting of approximately 250 distractor Gabor elements (Figure 1). The width of each Gabor element was 0.5° , and the Gabor wavelength was 2 cycles per degree. The distance between adjacent Gabor elements was 1° ($SD = 0.1^{\circ}$), well below the 2° necessary for contour integration to occur without input of higher-level cognition (Ciaramelli et al., 2007; Mandon and Kreiter, 2005; Stettler et al., 2002). The jitter angle of the contour-defining Gabor elements was manipulated so that larger degrees of jitter represent higher difficulty. This “jitter” method is recommended by the NIMH Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative (Carter and Barch, 2007) and used in validation studies of the Cognitive Neuroscience Test Reliability And Clinical applications for Schizophrenia (CNTRACS) Consortium (Butler et al., 2012; Butler et al., 2008; Gold et al., 2012; Sheffield et al., 2014; Silverstein et al., 2012; Strauss et al., 2014).

In each trial, stimuli were presented for 5 seconds and participants had to respond within this range. Participants were instructed to guess if uncertain. The task implemented a 3-up-1-down staircase method and was terminated after 12 performance reversals. For the first 2 reversals, the degree of jitter changed by units of 10° per reversal, and 5° per reversal for the remaining trials. The jitter degrees of the last 8 reversals were averaged to obtain a threshold. Participants completed a practice session (10 trials with feedback) followed by two blocks of the task. Thresholds for the two blocks were averaged to represent the overall threshold. Higher thresholds indicate better performance. Full methodological details of the task are available in Tso et al. (2014).

2.3 Clinical symptoms

Clinical participants were assessed with the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a), the revised version of the Beck Depression Inventory (BDI-IA; Beck and Steer, 1993), and the Young Mania Rating Scale (YMRS; Young et al., 1978). Young Mania Rating Scale (YMRS) data was not collected for participants who were part of a previous study of visual integration (see Tso et al., 2014). The current study includes YMRS assessments of 27 BD participants along with 6 SZ and 12 SA participants.

2.4 General cognition

Participants completed the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe, 1999) as a measure of general cognition. Standardized scores (z-scores) for BACS composite scores were computed with reference to test scores of 83 healthy individuals who are demographically similar to this study sample (41% female; average age = 42.2 ± 12.1 years; average years of education = 16.2 ± 2.4 ; average years of parental education = 14.8 ± 2.7 years).

2.6 Statistical analyses

Demographic and clinical differences between the psychosis and diagnostic groups were compared with one-way ANOVAs or chi-square tests. Tukey's HSD was used for post-hoc pairwise comparisons between the psychosis or diagnostic groups. Contour integration performance between groups within each of the three models (i.e., DSM, Schizophrenia, and Psychosis), along with the grouping of HC, BDP-, BDP+, SA, and SZ, was examined with one-way ANOVAs and Tukey HSD for post-hoc pairwise comparisons.

To address the question whether visual integration impairment is a characteristic of psychosis, specific to schizophrenia, or a function of DSM diagnosis, participants were grouped in three ways. The first grouping corresponds to the hypothesis that visual integration impairment is characteristic of psychosis (the "Psychosis Model"). As such, clinical participants were stratified by a history of prominent psychosis, resulting in a psychosis group (including SZ, SA, and BDP+) and a non-psychosis group (including BDP- and HC). The second grouping corresponds to the hypothesis that visual integration impairment is specific to schizophrenia (the "Schizophrenia Model"), resulting in a schizophrenia group (SZ only) and a non-schizophrenia group (including SA, BD, and HC). The third grouping corresponds to the hypothesis that visual integration impairment is a function of DSM-IV diagnosis (the "DSM Model") resulting in four groups: SZ, SA, BD, and HC.

Bayesian model comparison was then used to determine which among the Psychosis Model, the Schizophrenia Model, or the DSM model, was a more likely generative model of the observed visual integration performance data among the 116 participants. Specifically, Bayes factor (BF) of an ANOVA model based on each grouping model (the numerator model), compared against a null model containing only intercept (the denominator model), was computed using the 'anovaBF' function in the R package 'BayesFactor' (Morey and Rouder, 2015). BF is a ratio of the Bayesian evidence of two competing models. Because it

accounts for both data fit and model complexity in the model comparison process, it is superior to comparing R^2 of two regression models in classical frequentist statistics, in which R^2 always increases as the number of predictors (in this case, groups) increases and thus the results would always favor the more complex model, if everything else is held the same. In addition, because the three grouping systems being compared were not reduced version(s) of one another, a model comparison approach based on hierarchical regression would not be applicable.

The model with the highest BF was chosen as the winning model. Then, direct pairwise comparisons of the three models were performed by dividing the BF of one model by the BF of another model:

$$BF_1 = (\text{Evidence of Model 1}) / (\text{Evidence of Null Model}).$$

$$BF_2 = (\text{Evidence of Model 2}) / (\text{Evidence of Null Model}).$$

$$\text{Therefore, } (\text{Evidence of Model 1}) / (\text{Evidence of Model 2}) = BF_1 / BF_2.$$

Details of the R commands used and output of the Bayes factor analyses can be found in Supplementary Information 1.

We interpreted the BF values following accepted guidelines (Jarosz and Wiley, 2014). $BF > 1$ indicates evidence favoring the numerator model over the denominator model, while $BF < 1$ indicates evidence favoring the denominator model over the numerator model. Furthermore, BF between 1–3 provides “anecdotal” evidence for the numerator model, 3–10 “substantial” evidence, 10–30 “strong” evidence, 30–100 “very strong” evidence, and >100 “decisive” evidence. Similarly, BF between 0.33 and 1 provide “anecdotal” evidence for the denominator model, 0.10 and 0.33 “substantial” evidence, 0.033 and 0.10 “strong” evidence, 0.01 and 0.033 “very strong” evidence, and <0.01 “decisive” evidence.

Due to the consideration that benzodiazepines may impact visual cortex activity (Butler et al., 2008), the Bayesian analyses described above were repeated in participants not taking benzodiazepines (38 HC, 15 BDP-, 7 BDP+, 19 SA, and 21 SZ) for comparison purposes.

Finally, Pearson correlations were used to examine the relationships between visual integration and general cognition (BACS) and clinical variables (i.e., SAPS, SANS, and antipsychotic dose in daily chlorpromazine [CPZ] equivalents; Woods, 2003, 2011) for those with a history of prominent psychosis.

3. Results

Demographic and clinical characteristics of the groups (by diagnosis and by history of prominent psychosis) are summarized in Table 1. Performance on Contour Integration by each grouping model is illustrated in Figure 2. Results of one-way ANOVA showed a significant group effect when participants were divided into 5 different groups (SZ, SA, BDP+, BDP-, and HC), $F(4,111) = 2.88$, $p = 0.026$, and post-hoc pairwise group comparisons via Tukey HSD revealed that only SZ and HC were significantly different, $p = 0.038$ (Figure 2A). A significant group effect was observed when participants were grouped

according to psychosis, $F(1,114) = 10.20$, $p = 0.002$, with those with psychosis had significantly lower (worse) Contour Integration thresholds than those without psychosis (Figure 2B). When participants were grouped according to the schizophrenia model, the group effect did not reach statistical significance, $F(1,114) = 3.43$, $p = 0.067$. Finally, when participants were grouped according to the DSM model (Figure 2D), a significant group effect was obtained, $F(3,112) = 3.66$, $p = 0.015$, and post hoc comparisons indicated that SZ and SA both had significantly lower threshold than HC ($p = 0.024$ and $p < 0.05$, respectively).

3.1 Winning Model of Visual Integration Impairment

The Psychosis Model was the winning model, receiving the highest BF of 17.34 when compared against a null model, indicating “strong” evidence for a difference in Contour Integration according to a history of prominent psychosis. The Schizophrenia Model and DSM Model received a BF of 1.03 (“anecdotal” evidence) and 3.11 (“substantial” evidence), respectively.

The BF of the Psychosis Model vs. Schizophrenia Model was 16.89, and Psychosis Model vs. DSM Model was 5.58, indicating “strong” to “substantial” evidence favoring the Psychosis Model over the other two models. The BF of the DSM Model vs. Schizophrenia Model was 3.03, suggesting that the DSM model showed “substantially” more evidence than the Schizophrenia Model.

When BF analyses were repeated with participants not taking benzodiazepines, the findings were similar (see Supplementary Information 2).

3.2 Visual Integration Correlates in the Psychosis Group

Pearson correlation analysis showed that there was a significant relationship between Contour Integration and BACS (Figure 3). However, there were no significant correlations between Contour Integration and SAPS, SANS, or daily CPZ equivalents (p 's > 0.05).

4. Discussion

The current study compared three competing models of the specificity of visual integration impairment, namely the Psychosis Model, Schizophrenia Model, and the DSM Model. Results of Bayesian model comparisons based on data from 116 participants along the schizophrenia-bipolar-healthy spectrum indicated that the Psychosis Model was the winning model, showing evidence multiple times higher than the other two models. This suggests that visual integration impairment is characteristic of individuals with psychosis, rather than specific to the diagnostic category of SZ or a function of DSM diagnosis. Pairwise comparisons of the three models further revealed that although the DSM Model was far inferior to the Psychosis Model, it fit the data better than did the Schizophrenia Model. This relative merit of the DSM Model likely arises from its implicit assumption that the presence of prominent psychosis represents to some degree illness severity or constitutes a distinct class of disease, as reflected in its distinction between SZ, SA, and BD made partially based on the history of psychosis. Overall, the results of this study provided unambiguous support

that psychosis was an illness dimension driving the observed individual differences in visual integration performance.

Preliminary neuroimaging studies have provided some insight into the neural basis of visual integration deficits in psychosis. Silverstein and colleagues have shown that individuals with SZ exhibited underactivation in the extrastriate visual areas (V2-V4) when contour integration was difficult (i.e., higher jitter degree; Silverstein et al., 2009), but hyperactivation in the lateral occipital complex when the task was easier (Silverstein et al., 2015b). These suggest that deficient cortical activity in early visual areas and inefficiency of brain regions higher up in the visual processing stream may underlie the observed visual integration deficits in SZ. If these cortical dysfunctions are also present in those with a history of psychosis other than SZ (e.g., first-episode psychosis, SA, and BDP+), it would provide support that visual integration impairment observed in individuals with psychosis shares similar neural mechanisms. For example, in the context of visual processing of motion, similar brain dysfunction (reduced activation in the dorsal visual processing stream, including the superior parietal lobe) has been demonstrated in untreated first-episode schizophrenia and bipolar psychosis (Lencer et al. 2011), providing support that neural deficits in the visual system are related to the etiology of psychosis. Probing specific biological abnormalities that have been hypothesized to be causal factors of visual integration impairment (e.g., glutamatergic or GABAergic dysfunctions; Butler et al., 2008) in individuals with psychosis across diagnostic categories would help determine their roles in visual integration deficits and identify potential biological targets for treatment.

Visual integration was associated with general cognition in psychosis, suggesting that visual integration plays a role in cognitive operations required to efficiently process important intellectual information. This finding provides a rationale for improving functional outcome in psychotic disorders through interventions targeting early visual processing. Considering that normal learning does occur in SZ during early visual processing tasks (Silverstein and Keane, 2009), cognitive remediation focusing on visual integration tasks may improve occipital cortical functions and higher-order cognition that may be impacted by poor early visual processing in psychosis. Furthermore, given that the visual areas are relatively easy to localize and reach, applying brain stimulation such as transcranial direct-current stimulation (tDCS) and pairing it with neuroplasticity-based cognitive training (Nienow et al., 2016; Orlov et al., 2017) may be particularly applicable and help speed up the therapeutic process.

Previous findings indicate that more symptomatic SZ patients (especially those with more severe disorganization symptoms) show poorer early visual perceptual organization performance (Silverstein and Keane, 2011b). We did not find significant correlations between visual integration and psychotic symptoms in the current study. Because the majority of our clinical participants were clinically stable outpatients, this null finding could simply reflect the limited range of symptom severity (especially for disorganization symptoms), which made it less likely to detect statistical relationships. In addition to including a larger sample with a wider range of symptom severity, future research should also examine whether visual integration deficits are proportional to illness severity or the relative prominence of psychosis throughout the course of illness. This would help further establish the notion of visual integration deficits as a function of psychosis. Existing

assessment tools tend to focus on current symptoms only; research effort is required to develop reliable and valid tools to quantify these relevant dimensions of psychosis and consider the entire psychiatric history (including the prodromal phase) of the person instead of relying on a snapshot of the current state.

The use of mostly medicated patients in this study and previous studies presents the challenge of medication confounds. Preliminary findings of visual integration dysfunction in first-episode psychosis patients (Keane et al., 2016) provide some support that it is not merely caused by long-term medication use. However, these patients were all on antipsychotics and they showed less severe visual integration impairment when compared with chronic patients, making medication exposure still a possible, significant driving factor. Additionally, a significant portion (21%) of our patient sample (33% of the bipolar sample) were benzodiazepine users (60% of whom took this medication as needed). Benzodiazepines are known to affect cognition, including decreasing attention, slowing psychomotor response, and impairing memory (see for review Lader, 2014). However, the effect of benzodiazepines on visual processing in psychosis is unclear and may be paradoxical; there is evidence that they may actually improve visual cortical function (Taylor et al., 2014; Tso et al., 2015), potentially through normalizing pervasive GABAergic abnormalities found in the psychotic brain (Lewis, 2014). We did not find correlation between visual integration performance and antipsychotic dose among the participants with psychosis, and the Bayes factor findings comparing the three grouping models were similar after excluding the 18% of our clinical sample who used benzodiazepines (regularly or as needed), providing some support that medications may not fully account for the findings of this study. However, the question of to what extent visual integration deficits could be attributed to psychosis per se or medication exposure would be best clarified in genetic and clinical high risk studies. Preliminary studies on whether contour perception deficits are present in unaffected first-degree relatives of schizophrenia patients have yielded conflicting findings (Keri et al., 2004; Schallmo et al., 2013), and the presence of such deficits has yet to be investigated in ultra-high risk samples.

To summarize, this study tested the specificity of visual integration impairment to schizophrenia or psychosis using Bayesian model comparisons. Of the three grouping models tested (Psychosis Model, Schizophrenia Model, and DSM Model), the Psychosis Model showed the strongest evidence given the current data. Visual integration was found to be associated with general cognition in individuals with psychosis. The results together indicated that visual integration impairment is characteristic of psychosis and not specific to SZ or DSM categories, and may share common pathophysiologic pathways with abnormal neurocognition observed in psychosis. This study demonstrated that a Bayesian model comparison approach can be very useful in comparing competing disease categorization systems and extracting common psychopathological dimensions across diagnostic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported in part by grants from the National Institutes of Health (5KL2TR000434), National Institute of Mental Health (K23MH108823), American Psychological Foundation, and from the University of Michigan Horace H. Rackham School of Graduate Studies. The authors report no conflict of interest.

References

- Adams SA, Nasrallah HA, (in press). Multiple retinal anomalies in schizophrenia. *Schizophr. Res.*
- American Psychiatric Association, 2000. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC.
- Anderson EJ, Tibber MS, Schwarzkopf DS, Shergill SS, Fernandez-Egea E, Rees G, et al., 2017 Visual Population Receptive Fields in People with Schizophrenia Have Reduced Inhibitory Surrounds. *J. Neurosci.* 37, 1546–1556. [PubMed: 28025253]
- Andreasen NC, 1984a Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City, IA.
- Andreasen NC, 1984b Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City, IA.
- Beck AT, Steer RA, 1993 *Manual for the Beck Depression Inventory*. Psychological Corporation, San Antonio, TX.
- Brown AS, 2015 The Kraepelinian dichotomy from the perspective of prenatal infectious and immunologic insults. *Schizophr. Bull.* 41 (4), 786–791. [PubMed: 25964504]
- Butler PD, 2009 Early-stage visual processing deficits in schizophrenia, in: Javitt D.a.K., J. (Ed.), *Schizophrenia*. Springer Science and Business Media, LLC.
- Butler PD, Abeles IY, Silverstein SM, Dias EC, Weiskopf NG, Calderone DJ, et al., 2013 An event-related potential examination of contour integration deficits in schizophrenia. *Front. Psychol.* 4, 132. [PubMed: 23519476]
- Butler PD, Chen Y, Ford JM, Geyer MA, Silverstein SM, Green MF, 2012 Perceptual measurement in schizophrenia: promising electrophysiology and neuroimaging paradigms from CNTRICS. *Schizophr. Bull.* 38 (1), 81–91. [PubMed: 21890745]
- Butler PD, Silverstein SM, Dakin SC, 2008 Visual perception and its impairment in schizophrenia. *Biol. Psychiat.* 64 (1), 40–47. [PubMed: 18549875]
- Carter CS, Barch DM, 2007 Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. *Schizophr. Bull.* 33 (5), 1131–1137. [PubMed: 17630405]
- Castelhano J, Bernardino I, Rebola J, Rodriguez E, Castelo-Branco M, 2015 Oscillations or Synchrony? Disruption of Neural Synchrony despite Enhanced Gamma Oscillations in a Model of Disrupted Perceptual Coherence. *J. Cogn. Neurosci.* 27, 2416–2426. [PubMed: 26284991]
- Chen Y, Nakayama K, Levy D, Matthyse S, Holzman P, 2003 Processing of global, but not local, motion direction is deficient in schizophrenia. *Schizophr. Res.* 61 (2–3), 215–227. [PubMed: 12729873]
- Ciaramelli ELF, Del Viva MM, Burr DC, Ladavas E, 2007 The contributions of prefrontal cortex to global perception. *Exp. Brain Res.* 181, 427–434. [PubMed: 17401551]
- Engel AK, Fries P, Singer W, 2001 Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci.* 2, 704–716. [PubMed: 11584308]
- First MB, Spitzer RL, Gibbon M, Williams JBW, 1997 *Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version, Administration Booklet*. American Psychiatric Press.
- Freeman E, Driver J, Sagi D, Zhaoping L, 2003 Top-Down Modulation of Lateral Interactions in Early Vision. *Curr. Biol.* 13, 985–989. [PubMed: 12781139]
- Gilbert CD, Li W, 2013 Top-down influences on visual processing. *Nat. Rev. Neurosci.* 14, 350–363. [PubMed: 23595013]
- Gold JM, Barch DM, Carter CS, Dakin S, Luck SJ, MacDonald AW, 3rd, et al., 2012 Clinical, functional, and intertask correlations of measures developed by the Cognitive Neuroscience Test

- Reliability and Clinical Applications for Schizophrenia Consortium. *Schizophr. Bull.* 38 (1), 144–152. [PubMed: 22101961]
- Green MF, Horan WP, Lee J, 2015 Social cognition in schizophrenia. *Nat. Rev. Neurosci.* 16, 620–631. [PubMed: 26373471]
- Hall MH, Chen CY, Cohen BM, Spencer KM, Levy DL, Ongur, et al., 2015 Genomewide association analyses of electrophysiological endophenotypes for schizophrenia and psychotic bipolar disorders: a preliminary report. *Am. J. Med. Genet. B* 168B (3), 151–161.
- Hill SK, Reilly JL, Keefe RS, Gold JM, Bishop JR, Gershon ES, et al., 2013 Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *Am. J. Psychiat.* 170 (11), 1275–1284. [PubMed: 23771174]
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine D, Quinn K, et al., 2010 Research Domain Criteria (RDoC): Toward a new classification framework for research of mental disorders. *Am. J. Psychiat.* 167 (7).
- Insel TR, 2014 The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am. J. Psychiat.* 171 (4), 395–397. [PubMed: 24687194]
- Ivleva EI, Bidesi AS, Keshavan MS, Pearlson GD, Meda SA, Dodić D, et al., 2013 Gray matter volume as an intermediate phenotype for psychosis: Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *Am. J. Psychiat.* 170 (11), 1285–1296. [PubMed: 24185241]
- Jarosz AF, Wiley J, 2014 What Are the Odds? A Practical Guide to Computing and Reporting Bayes Factors. *J. Probl. Solving* 7 (1).
- Keane BP, Paterno D, Kastner S, Silverstein SM, 2016 Visual integration dysfunction in schizophrenia arises by the first psychotic episode and worsens with illness duration. *J. Abnorm. Psychol.* 125 (4), 543–549. [PubMed: 27030995]
- Keck PE, McElroy SL, Havens JR, Altshuler LL, Nolen WA, Frye MA, et al., 2003 Psychosis in bipolar disorder: phenomenology and impact on morbidity and course of illness. *Compr. Psychiat.* 44 (4), 263–269. [PubMed: 12923703]
- Keefe R, 1999 Brief Assessment of Cognition in Schizophrenia (BACS). Duke University Medical Center.
- Kéri S, Kelemen O, Benedek G, Janka Z, 2004 Vernier threshold in patients with schizophrenia and their unaffected siblings. *Neuropsychol.* 18 (3), 537–542.
- Keshavan MS, Morris DW, Sweeney JA, Pearlson G, Thaker G, Seidman LJ, et al., 2011 A dimensional approach to the psychosis spectrum between bipolar disorder and schizophrenia: The Schizo-Bipolar Scale. *Schizophr. Res.* 133 (1–3), 250–254. [PubMed: 21996268]
- Kloosterman NA, Meindertsma T, Hillebrand A, van Dijk BW, Lamme VA, Donner TH, 2015 Top-down modulation in human visual cortex predicts the stability of a perceptual illusion. *J. Neurophysiol.* 113, 1063–1076. [PubMed: 25411458]
- Lader M, 2014 Benzodiazepine harm: how can it be reduced? *Br. J. Clin. Pharmacol.* 77, 295–301. [PubMed: 22882333]
- Lencer R, Keedy SK, Reilly JL, McDonough BE, Harris MS, Sprenger A, et al. 2011 Altered transfer of visual motion to parietal association cortex in untreated first-episode psychosis: implications for pursuit eye tracking. *Psychiat. Res.* 194 (1), 30–38.
- Lewis DA, 2014 Inhibitory neurons in human cortical circuits: substrate for cognitive dysfunction in schizophrenia. *Curr. Opin. Neurobiol.* 26, 22–26. [PubMed: 24650500]
- Mandon S, Kreiter AK, 2005 Rapid contour integration in macaque monkeys. *Vision Res.* 45, 291–300. [PubMed: 15607346]
- Mathew I, Gardin TM, Tandon N, Eack S, Francis AN, Seidman LJ, et al., 2014 Medial temporal lobe structures and hippocampal subfields in psychotic disorders: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *J.A.M.A. Psychiat.* 71 (7), 769–777.
- Mayer JD, Salovey P, Caruso DR, 1999 Mayer-Salovey-Caruso Emotional Intelligence Test. Multi-Health Systems Inc, North Tonawanda, NY.
- Morey RD, Rouder JN, 2015 BayesFactor: Computation of Bayes Factors for common designs. R package version 0.9.12–12

- Nienow TM, MacDonald AW, 3rd, Lim KO, 2016 TDCS produces incremental gain when combined with working memory training in patients with schizophrenia: A proof of concept pilot study. *Schizophr. Res.* 172 (1–3), 218–219. [PubMed: 26852404]
- Nurnberger JI, Jr., Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al., 1994 Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch. Gen. Psychiat.* 51 (11), 849–859; discussion 863–844.
- Orlov ND, Tracy DK, Joyce D, Patel S, Rodzinka-Pasko J, Dolan H, et al., 2017 Stimulating cognition in schizophrenia: A controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. *Brain Stimul.* 10 (3), 560–566. [PubMed: 28057452]
- Pearlson GD, 2015 Etiologic, phenomenologic, and endophenotypic overlap of schizophrenia and bipolar disorder. *Annu. Rev. Clin. Psycho.* 11, 251–281.
- Pearlson GD, Ford JM, 2014 Distinguishing between schizophrenia and other psychotic disorders. *Schizophr. Bull.* 40 (3), 501–503. [PubMed: 24687045]
- Ruocco AC, Reilly JL, Rubin LH, Daros AR, Gershon ES, Tamminga CA, et al., 2014 Emotion recognition deficits in schizophrenia-spectrum disorders and psychotic bipolar disorder: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *Schizophr. Res.* 158 (1–3), 105–112. [PubMed: 25052782]
- Schallmo MP, Sponheim SR, Olman CA, 2013 Abnormal contextual modulation of visual contour detection in patients with schizophrenia. *PLoS One* 8 (6): e0068090.
- Sheffield JM, Gold JM, Strauss ME, Carter CS, MacDonald AW, 3rd, Ragland JD, et al., 2014 Common and specific cognitive deficits in schizophrenia: relationships to function. *Cogn. Affect Behav. Ne.* 14 (1), 161–174.
- Silverstein SM, Berten S, Essex B, Kovacs I, Susmaras T, Little DM, 2009 An fMRI examination of visual integration in schizophrenia. *J. Integr. Neurosci.* 8 (2), 175–202. [PubMed: 19618486]
- Silverstein SM, Elliott CM, Feusner JD, Keane BP, Mikkilineni D, Hansen N, et al., 2015a Comparison of visual perceptual organization in schizophrenia and body dysmorphic disorder. *Psychiat. Res.* 229 (1–2), 426–433.
- Silverstein SM, Harms MP, Carter CS, Gold JM, Keane BP, MacDonald A, 3rd, et al., 2015b Cortical contributions to impaired contour integration in schizophrenia. *Neuropsychologia* 75, 469–480. [PubMed: 26160288]
- Silverstein SM, Hatashita-Wong M, Schenkel LS, Wilkniss S, Kovacs I, Feher A, et al., 2006 Reduced top-down influences in contour detection in schizophrenia. *Cogn. Neuropsychiatry* 11 (2), 112–132. [PubMed: 16537237]
- Silverstein SM, Keane BP, 2009 Perceptual organization in schizophrenia: Plasticity and state-related change. *Learn. Percept.* 1 (2), 229–261.
- Silverstein SM, Keane BP, 2011a Vision science and schizophrenia research: toward a re-view of the disorder. Editors' introduction to special section. *Schizophr. Bull.* 37 (4), 681–689. [PubMed: 21700588]
- Silverstein SM, Keane BP, 2011b Perceptual organization impairment in schizophrenia and associated brain mechanisms: review of research from 2005 to 2010. *Schizophr. Bull.* 37 (4), 690–699. [PubMed: 21700589]
- Silverstein SM, Keane BP, Barch DM, Carter CS, Gold JM, Kovacs I, et al., 2012 Optimization and validation of a visual integration test for schizophrenia research. *Schizophr. Bull.* 38 (1), 125–134. [PubMed: 22021658]
- Silverstein SM, Knight RA, Schwarzkopf SB, West LL, Osborn LM, Kamin D, 1996 Stimulus configuration and context effects in perceptual organization in schizophrenia. *J. Abnorm. Psychol.* 105 (3), 410–420. [PubMed: 8772011]
- Silverstein SM, Kovacs I, Corry R, Valone C, 2000 Perceptual organization, the disorganization syndrome, and context processing in chronic schizophrenia. *Schizophr. Res.* 43 (1), 11–20. [PubMed: 10828411]
- Stettler DD, Das A, Bennett J, Gilbert CD, 2002 Lateral connectivity and contextual interactions in macaque primary visual cortex. *Neuron.* 36, 739–750. [PubMed: 12441061]

- Strauss ME, McLouth CJ, Barch DM, Carter CS, Gold JM, Luck SJ, et al., 2014 Temporal stability and moderating effects of age and sex on CNTRaCS task performance. *Schizophr. Bull.* 40 (4), 835–844. [PubMed: 23817024]
- Taylor SF, Demeter E, Phan KL, Tso IF, Welsh RC, 2014 Abnormal GABAergic function and negative affect in schizophrenia. *Neuropsychopharmacology.* 39, 1000–1008. [PubMed: 24154667]
- Tondo L, Vazquez GH, Baethge C, Baronessa C, Bolzani L, Koukopoulos A, et al., 2015 Comparison of psychotic bipolar disorder, schizoaffective disorder, and schizophrenia: an international, multisite study. *Acta. Psychiat. Scand.* 133 (1), 34–43. [PubMed: 26096273]
- Tso IF, Carp J, Taylor SF, Deldin PJ, 2014 Role of visual integration in gaze perception and emotional intelligence in schizophrenia. *Schizophr. Bull.* 40 (3), 617–625. [PubMed: 23666503]
- Tso IF, Fang Y, Phan KL, Welsh RC, Taylor SF, 2015 Abnormal GABAergic function and face processing in schizophrenia: A pharmacologic-fMRI study. *Schizophr. Res.* 168, 338–344. [PubMed: 26363970]
- Tso IF, Mui ML, Taylor SF, Deldin PJ, 2012 Eye-contact perception in schizophrenia: relationship with symptoms and socioemotional functioning. *J. Abnorm. Psychol.* 121 (3), 616–627. [PubMed: 22250658]
- Uhlhaas PJ, Linden DE, Singer W, Haenschel C, Lindner M, Maurer K, et al., 2006 Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J. Neurosci.* 26, 8168–8175. [PubMed: 16885230]
- Uhlhaas PJ, Phillips WA, Mitchell G, Silverstein SM, 2006 Perceptual grouping in disorganized schizophrenia. *Psychiat. Res.* 145 (2–3), 105–117.
- Uhlhaas PJ, Phillips WA, Silverstein SM, 2005 The course and clinical correlates of dysfunctions in visual perceptual organization in schizophrenia during the remission of psychotic symptoms. *Schizophr. Res.* 75 (2–3), 183–192. [PubMed: 15885509]
- Woods SW, 2003 Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J. Clin. Psychiat.* 64 (6), 663–667.
- Woods SW, 2011 Chlorpromazine Equivalent Doses for Atypical Antipsychotics: An Update 2003–2010. Yale University, <http://scottwilliamwoods.com/>, pp. 1–7.
- Yao B, Mueller SA, Grove TB, McLaughlin M, Thakkar K, Ellingrod V, et al. (in press). Eye-gaze perception in bipolar disorder: Self-referential bias but intact perceptual sensitivity. *Bipolar Disord.*
- Young RC, Biggs JT, Ziegler VE, Meyer DA, 1978 A rating scale for mania: reliability, validity and sensitivity. *Brit. J. Psychiat.* 133 (5), 429–435.

Contour Integration

Figure 1.

Examples of the stimuli of the Contour Integration task. In each trial, a circle-like contour formed by Gabor elements is presented against a background of random Gabor elements. Participants were instructed to locate the contour (on the left or right side of the screen). Arrows denote the locations of the contours (not present in task). Difficulty increases as the jitter angle of the contour-defining elements increases (depicted from left to right panels).

Figure 2.

Visual integration performance by different grouping models: (A) DSM diagnosis, with bipolar disorder further stratified by a history of prominent psychosis; (B) Psychosis Model; (C) Schizophrenia Model; (D) DSM Model. Group effects were tested using one-way ANOVAs followed by Tukey HSD for post-hoc pairwise comparisons. Y-axis indicates threshold on the Contour Integration task, with higher values indicating better performance. Vertical lines indicate standard errors. HC = healthy controls, BDP- = bipolar disorder without a history of prominent psychosis, BDP+ = bipolar disorder with a history of prominent psychosis, SA = schizoaffective disorder, and SZ = schizophrenia. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 3.

Scatterplot showing the relationship between visual integration and general cognitive measure z-score (Brief Assessment of Cognition in Schizophrenia; BACS) in the participants with a history of prominent psychosis. X-axis represents Contour Integration threshold. BDP+ = bipolar disorder with a history of psychosis. SA = schizoaffective disorder. SZ = schizophrenia. 95% confidence intervals for Pearson correlations are provided in brackets. $*p < 0.05$.

Table 1
Demographic, clinical, cognitive characteristics and use of psychotropic medications of each group

M (SD)	Group by Diagnosis					F statistic (dx groups only)	F or FET p-value (dx groups only)	Group by History of Psychosis ^h		F statistic (psychosis groups only)	F or FET p-value (psychosis groups only)
	HC (n = 38)	BDP- (n = 20)	BDP+ (n = 11)	SA (n = 22)	SZ (n = 25)			Non- psychosis ⁱ (n = 58)	Psychosis (n = 58)		
Age (years)	44.1 (11.8)	41.3 (11.6)	40.5 (12.7)	47.9 (10.4)	43.2 (10.8)	1.21	0.31	43.1 (11.7)	44.5 (11.2)	0.42	0.519
Gender (m/f)	21/17	7/13	3/8	11/11	18/7		0.057	28/30	32/26		0.577
Education (years) ^a	16.5 (2.5)	14.6 (2.4)	16.4 (2.5)	14.6 (2.4)	13.4 (1.9)	7.58	<0.001	15.9 (2.6)	14.4 (2.4)	9.21	0.003
Parental education (years) ^b	14.9 (2.6)	15.1 (3.6)	15.2 (3.0)	14.5 (3.6)	15.0 (3.5)	0.12	0.976	14.9 (3.0)	14.9 (3.4)	0.02	0.881
Age of onset (years)		16.0 (6.0)	17.9 (10.2)	18.4 (8.1)	18.5 (6.6)	0.50	0.681	16.0 (6.0)	18.3 (7.8)	1.5	0.224
Duration of illness (years)		24.3 (13.7)	22.5 (14.7)	29.5 (10.8)	24.8 (11.9)	0.96	0.418	25.3 (13.7)	26.1 (12.2)	0.07	0.798
CPZ (mg daily) ^c		287 (281)	150 (50)	467 (570)	475 (391)	0.81	0.494	287 (282)	450 (469)	1.0	0.322
SAPS		0.7 (1.1)	0.5 (0.8)	3.6 (2.5)	4.6 (3.6)	12.95	<0.001	0.7 (1.1)	3.4 (3.2)	14.58	<0.001
SANS		1.9 (2.0)	0.7 (1.5)	4.6 (3.5)	6.1 (2.8)	14.65	<0.001	1.9 (2.0)	4.5 (3.5)	10.48	0.002
YMRS ^d		3.2 (4.1)	2.0 (3.2)	2.3 (3.7)	2.5 (1.4)	0.29	0.835	3.2 (4.1)	2.6 (3.0)	0.82	0.371
BDI-IA ^e	1.2 (1.8)	10.1 (10.0)	8.5 (9.5)	13.4 (10.3)	11.2 (7.7)	11.43	<0.001	4.3 (7.3)	11.5 (9.1)	22.18	<0.001
BACS ^f	0.1 (1.0)	-0.6 (0.8)	-0.9 (1.1)	-1.5 (0.9)	-1.5 (1.0)	12.78	<0.001	-0.2 (1.0)	-1.4 (1.0)	38.41	<0.001
Medication use (%) ^g											
Atypical antipsychotics		10 (50%)	4 (36%)	18 (86%)	16 (67%)		0.021	10 (50%)	38 (68%)		0.183
Typical antipsychotics		0 (0%)	0 (0%)	2 (10%)	8 (33%)		0.004	0 (0%)	10 (18%)		0.055
Lithium		6 (30%)	5 (45%)	0 (0%)	1 (4%)		<0.001	6 (30%)	6 (11%)		0.07
Other mood stabilizers		14 (70%)	3 (27%)	3 (14%)	3 (13%)		<0.001	14 (70%)	9 (16%)		<0.001
SSRI or SNRI		7 (35%)	4 (36%)	3 (14%)	6 (25%)		0.382	7 (35%)	13 (23%)		0.377
NDRI		4 (20%)	3 (27%)	1 (5%)	0 (0%)		0.014	4 (20%)	4 (7%)		0.2
TCA		1 (5%)	1 (9%)	1 (5%)	2 (8%)		1.0	1 (5%)	4 (7%)		1.0
Benzodiazepines		5 (25%)	4 (36%)	2 (10%)	3 (13%)		0.202	5 (25%)	9 (16%)		0.502

Note. HC = Healthy control. BDP⁻ = Bipolar disorder with no history of prominent psychosis. BDP⁺ = Bipolar disorder with a history of prominent psychosis. SA = Schizoaffective disorder. SZ = Schizophrenia. FET = Fisher's Exact Test. SAPS = Scale for the Assessment of Positive Symptoms. SANS = Scale for the Assessment of Negative Symptoms. YMRS = Young Mania Rating Scale. BDI-IA = revised version of the Beck Depression Inventory. BACS = Brief Assessment of Cognition in Schizophrenia. CPZ = antipsychotic dose in chlorpromazine equivalent milligram daily. Other mood stabilizers = carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, or valproic acid. SSRI = selective serotonin reuptake inhibitors. SNRI = serotonin-norepinephrine reuptake inhibitors. NDRI = norepinephrine-dopamine reuptake inhibitors. TCA = tricyclic antidepressants.

^aYears of education was available for 37 HC and 19 BDP⁻.

^bYears of parental education was available for 17 BDP⁻, 21 SA, and 23 SZ.

^cCPZ available for 9 BDP⁻, 3 BDP⁺, 20 SA, and 22 SZ.

^dYMRS was available for 18 BDP⁻, 9 BDP⁺, 12 SA, and 6 SZ.

^eBDI-IA available for 24 SZ.

^fBACS data available for 34 HC and 21 SA; All 34 HC were part of the larger sample of 83 HC described in the Methods.

^gMedication data not available for one SA and one SZ.

^hPsychosis and non-psychosis data for each variable is the combination of available data in HC, BDP⁻, BDP⁺, SA, and SZ.

ⁱFor the non-psychosis group, clinical information was derived from BDP⁻ only.