



## A vision science perspective on schizophrenia



Perceptual impairments in schizophrenia were described as long ago as 1903, when Kraepelin (1903) reported that patients demonstrated incomplete perception of briefly exposed objects on a laboratory task. Despite this early beginning, and despite the fact that the visual system is the most heavily researched area of cognitive neuroscience, there have been far fewer studies of vision in schizophrenia than of other cognitive functions (e.g., memory, cognitive control) (Silverstein and Keane, 2011b). In recent years, however, reports have accumulated indicating that visual processing impairments are both prevalent among individuals with schizophrenia, and significant in terms of advancing knowledge regarding etiology, pathophysiology, phenomenology, and course of illness. For example, approximately 25–30% of individuals with schizophrenia report visual hallucinations (Waters et al., 2014), and the number of patients reporting visual distortions (of brightness, motion, form, and color) is over twice that high (Phillipson and Harris, 1985). Importantly, reliable and valid laboratory measures of processing in these domains are available, and they have long histories of demonstrating specific impairments in schizophrenia (Cadenhead et al., 2013; Chen, 2011; Green et al., 2011; Silverstein and Keane, 2011a). These subjective and laboratory manifestations of visual abnormality are clinically significant. For example, visual distortions are associated with subjective distress and suicidal ideation (even after controlling for other factors such as psychotic symptoms and auditory distortions) (Grano et al., 2015). Laboratory-based markers of visual processing impairments have been shown to be related to poorer detection of facial affect (Tso et al., 2015; Turetsky et al., 2007), impaired reading ability (Martinez et al., 2012), poorer real-world functioning (Green et al., 2012; Rassovsky et al., 2011), and reduced short- (Silverstein et al., 2013) and long-term (Silverstein et al., 1998) treatment response. Visual abnormalities can also be observed in children, adolescents, and young adults at high-risk for schizophrenia (Hebert et al., 2010; Koethe et al., 2009; Mittal et al. in press; Revheim et al., 2014; Schubert et al., 2005), and findings suggest that they may be particularly sensitive (compared to other clinical phenomena) for predicting conversion to the disorder among high-risk (Klosterkotter et al., 2001) and general-population (Schubert et al., 2005) samples. Nevertheless, despite this growing body of evidence, visual processing measures are still rarely included in clinical trials or high-risk studies.

Because, as noted above, visual functioning is relatively well understood in the normal brain, it has the potential to shed light on many aspects of brain dysfunction in conditions such as schizophrenia. For example, because the basic architecture of local integrative circuitry, involving pyramidal cells and inhibitory interneurons, is the same in all regions of the cortex (Phillips and Singer, 1997), but expressed far less densely (i.e., with less associated complexity) in visual cortex compared to other regions (e.g., the frontal cortex) (Monaghan et al., 1989), visual cortex can serve as a useful model of broader aspects of coordinated

brain function (Douglas and Martin, 2007) and its breakdown (Phillips and Silverstein, 2003). In addition, laboratory tasks that emphasize local aspects of neural integration (e.g., those of gain control in vision) (Huang et al., 2006), as well as those that involve long-range connectivity, e.g., frontal-parietal connectivity as it is involved in contour integration (Castellano et al., 2014; Dima et al., 2009), can be useful in demonstrating the integrity of small- and large-scale networks in schizophrenia. These examples of connectivity, as they apply to vision, can also inform our models of specific symptom domains. Studies have already demonstrated relationships between alterations in specific processes (operationalized in reliable and valid laboratory tasks) and symptom clusters, namely between: 1) reduced application of prior knowledge to processing of sensory information and positive symptoms (Keane et al., 2013); 2) poor gain control and negative symptoms (Keri et al., 2005); and 3) reduced ability to organize visual information and disorganized symptoms (Uhlhaas and Silverstein, 2005). Moreover, these findings are consistent with theories positing that reduced illusion perception (which is observed in schizophrenia) and positive symptoms both reflect failures in Bayesian processing (i.e., altered predictive coding) (Clark, 2013; Corlett et al., 2009), and that reduced perceptual organization, poor selective attention, and formal thought disorder reflect failures of dynamic coordination of brain activity (Phillips and Silverstein, 2003). The link between abnormal gain control and negative symptoms is less clear conceptually, and is in need of further exploration. Overall, these findings highlight the potential for specific tasks to be useful as biomarkers of illness-related processes in treatment development studies and clinical trials.

Further information about schizophrenia has come from recent studies of retinal and ocular functions. Retinal (e.g., electroretinographic and retinal nerve fiber layer thickness) and ocular (e.g., eye alignment; retinal venule width) abnormalities have been found in individuals with schizophrenia, as well as in unaffected offspring, and some of these indices predict conversion to psychosis (see Silverstein and Rosen, in press, this issue, for review). This work is important for two reasons. One is that it suggests that for at least some individuals with schizophrenia, abnormal visual processing begins as early as the retina. Second, because the retina is part of the central nervous system, and because we know that the retinal changes observed in some neurological disorders (e.g. multiple sclerosis, Parkinson's disease, Alzheimer's disease) parallel illness progression, progressive white and gray matter loss, and cognitive decline (Martinez-Lapiscina et al., 2014; Ratchford et al., 2013; Saidha et al., 2013; Satue et al., 2014; Sedighi et al., 2014; Tian et al., 2011; Toledo et al., 2008), the question of whether, and to what extent, retinal and ocular measures could serve as biomarkers of changes in brain structure and function in schizophrenia is worthy of study. This includes the question of the extent to which changes in levels of dopamine and glutamate in the retina reflect disease processes

and/or medication effects (Silverstein and Rosen, *in press*), as well as the extent to which altered retinal function (as measured by, for example, electroretinography) reflects altered brain neurotransmitter levels (Lavoie et al., 2014), given that there are afferent projections from the brain to the retina (Gastinger et al., 2006).

This issue of *Schizophrenia Research: Cognition* focuses on these and related issues, and consists of papers that were presented, or grew out of discussions, at a conference on vision in schizophrenia, organized by Dr. Michael Herzog, at L'École Polytechnique Fédérale de Lausanne (EPFL) in Lausanne, Switzerland in July 2014. The paper by Javitt describes this meeting and summarizes each of the presentations. The paper by Silverstein and Rosen discusses ways in which schizophrenia, or its treatment, affects ocular and retinal function, and how this can impact visual processing in the disorder. The study by Joseph et al. highlights an innovative data reduction strategy for genetic data, and demonstrates how this can be useful in efforts to link specific single nucleotide polymorphisms with aspects of perceptual impairment in schizophrenia. Herzog and Brand review data on masking in schizophrenia, and conclude that impaired performance on masking tasks is a manifestation of a widespread impairment in neuromodulation, as opposed to abnormal activity in the magnocellular pathway. Schmack et al. present results from a percept stabilization task that support the hypothesis of altered predictive coding in vision in schizophrenia, and its relationship to delusions – further evidence that vision can be used to probe Bayesian processing abnormalities involved in higher-level disturbances. The study described by Giersch et al. also approaches perception from a predictive coding perspective, and demonstrates that patients have difficulty binding events in time, as well as in space, an impairment that can affect the subjective experience of the continuity of time. Tschacher et al. describe a study indicating that a reduced appreciation of incongruity in visual images is associated with a reduced perception of funniness in the same images, and so provide an additional example of the behavioral significance of perceptual changes. Modenato and Draginsky provide an overview of schizotypy, and how it relates to schizophrenia, with a focus on brain imaging findings. Shaqiri et al. demonstrate backward masking impairments in patients, students with self-reported schizotypal traits, and relatives, and show that in patients, nicotine use can partly normalize task performance, especially in those who are older – a finding that can help clarify our understanding of the cognitive effects of nicotine. Roché et al. demonstrate how the construct of intermittent degradation can account for performance impairments in schizotypy, and describe how this can be used to extend our understanding of perceptual and cognitive impairments in schizophrenia.

Findings such as those noted in the first three paragraphs above, in addition to the novel work presented in this special issue, have important implications for advancing translational research in schizophrenia and other psychoses. Specific questions that have become particularly relevant recently include: 1) Can, and should, visual processing impairments (in addition to those in visual acuity) be treated in schizophrenia, or high-risk cases? If yes, how? 2) Can the assessment of visual function via laboratory tasks, and/or clinical assessment of visual distortions, inform the prediction of risk for conversion/relapse, and/or treatment response? 3) Can screening for retinal and ocular abnormalities be useful in identifying illness risk and progression? The findings noted above also suggest directions for more basic research on schizophrenia, involving questions such as: 1) In what ways can aspects of visual function be used as examples of canonical cortical computations that can help clarify aspects of brain function in cognitive domains involving less concrete forms of information (e.g., abstract reasoning, planning)? 2) What are the relationships between perceptual disturbances and clinical symptoms, including both causal relationships and cases in which both emerge from similar mechanisms? Relatedly, 3) which visual changes are trait-like and associated with schizophrenia (including its genetic liability); which are related to severity of positive,

negative and/or disorganized symptoms; and which are related to other symptoms (e.g., depression, anxiety) or activity in functional dimensions (e.g., arousal, HPA axis functioning, positive and negative valence systems) that cut across current diagnostic categories, as emphasized by the NIMH Research Domain Criteria initiative (Cuthbert and Insel, 2010)? Generating answers to these questions may further our understanding of schizophrenia, similar to the way in which the intense focus on prefrontal cortex and hippocampal functioning has done over the past 25 years.

## References

- Cadenhead, K.S., Dobkins, K., McGovern, J., Shafer, K., 2013. Schizophrenia spectrum participants have reduced visual contrast sensitivity to chromatic (red/green) and luminance (light/dark) stimuli: new insights into information processing, visual channel function, and antipsychotic effects. *Front. Psychol.* 4, 535.
- Castellano, M., Plochl, M., Vicente, R., Pipa, G., 2014. Neuronal oscillations form parietal/frontal networks during contour integration. *Front. Integr. Neurosci.* 8, 64.
- Chen, Y., 2011. Abnormal visual motion processing in schizophrenia: a review of research progress. *Schizophr. Bull.* 37 (4), 709–715.
- Clark, A., 2013. Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav. Brain Sci.* 36 (3), 181–204.
- Corlett, P.R., Frith, C.D., Fletcher, P.C., 2009. From drugs to deprivation: a Bayesian framework for understanding models of psychosis. *Psychopharmacology (Berl)* 206 (4), 515–530.
- Cuthbert, B.N., Insel, T.R., 2010. Toward new approaches to psychotic disorders: the NIMH Research Domain Criteria Project. *Schizophr. Bull.* 36 (6), 1061–1062.
- Dakin, S., Carlin, P., Hemsley, D., 2005. Weak suppression of visual context in chronic schizophrenia. *Curr. Biol.* 15 (20), R822–R824.
- Dima, D., Roiser, J.P., Dietrich, D.E., Bonnemann, C., Lanfermann, H., Emrich, H.M., Dillo, W., 2009. Understanding why patients with schizophrenia do not perceive the hollow-mask illusion using dynamic causal modelling. *Neuroimage* 46 (4), 1180–1186.
- Douglas, R.J., Martin, K.A., 2007. Mapping the matrix: the ways of neocortex. *Neuron* 56 (2), 226–238.
- Gastinger, M.J., Tian, N., Horvath, T., Marshak, D.W., 2006. Retinopetal axons in mammals: emphasis on histamine and serotonin. *Curr. Eye Res.* 31 (7–8), 655–667.
- Grano, N., Salmijarvi, L., Karjalainen, M., Kallionpaa, S., Roine, M., Taylor, P., 2015. Early signs of worry: psychosis risk symptom visual distortions are independently associated with suicidal ideation. *Psychiatry Res.* 225 (3), 263–267.
- Green, M.F., Lee, J., Wynn, J.K., Mathis, K.L., 2011. Visual masking in schizophrenia: overview and theoretical implications. *Schizophr. Bull.* 37 (4), 700–708.
- Green, M.F., Helleman, G., Horan, W.P., Lee, J., Wynn, J.K., 2012. From perception to functional outcome in schizophrenia: modeling the role of ability and motivation. *Arch. Gen. Psychiatry* 1–9.
- Hebert, M., Gagne, A.M., Paradis, M.E., Jomphe, V., Roy, M.A., Merette, C., Maziade, M., 2010. Retinal response to light in young nonaffected offspring at high genetic risk of neuropsychiatric brain disorders. *Biol. Psychiatry* 67 (3), 270–274.
- Huang, P.C., Hess, R.F., Dakin, S.C., 2006. Flank facilitation and contour integration: different sites. *Vis. Res.* 46 (21), 3699–3706.
- Keane, B.P., Silverstein, S.M., Wang, Y., Papatomas, T.V., 2013. Reduced depth inversion illusions in schizophrenia are state-specific and occur for multiple object types and viewing conditions. *J. Abnorm. Psychol.* 122 (2), 506–512.
- Keri, S., Kiss, I., Kelemen, O., Benedek, G., Janka, Z., 2005. Anomalous visual experiences, negative symptoms, perceptual organization and the magnocellular pathway in schizophrenia: a shared construct? *Psychol. Med.* 35 (10), 1445–1455.
- Klosterkotter, J., Hellmich, M., Steinmeyer, E.M., Schultze-Lutter, F., 2001. Diagnosing schizophrenia in the initial prodromal phase. *Arch. Gen. Psychiatry* 58 (2), 158–164.
- Koethe, D., Kranaster, L., Hoyer, C., Gross, S., Neatby, M.A., Schultze-Lutter, F., Ruhrmann, S., Klosterkotter, J., Hellmich, M., Leweke, F.M., 2009. Binocular depth inversion as a paradigm of reduced visual information processing in prodromal state, antipsychotic-naïve and treated schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.* 259 (4), 195–202.
- Kraepelin, E., 1903. *Lehrbuch der Psychiatrie*. Barth, Leipzig.
- Lavoie, J., Illiano, P., Sotnikova, T.D., Gainetdinov, R.R., Beaulieu, J.M., Hebert, M., 2014. The electroretinogram as a biomarker of central dopamine and serotonin: potential relevance to psychiatric disorders. *Biol. Psychiatry* 75 (6), 479–486.
- Martinez, A., Revheim, N., Butler, P.D., Guilfoyle, D.N., Dias, E.C., Javitt, D.C., 2012. Impaired magnocellular/dorsal stream activation predicts impaired reading ability in schizophrenia. *Neuroimage Clin.* 2, 8–16.
- Martinez-Lapiscina, E., Ortiz-Pérez, S., Fraga-Pumar, E., Martínez-Heras, E., Gabilondo, I., Llufríu, S., Bullich, S., Figueras, M., Saiz, A., Sanchez-Dalmau, B., Villoslada, P., 2014. Color vision impairment is associated with disease severity in multiple sclerosis. *Mult. Scler.* 20 (9), 1207–1216.
- Mittal, V., Gupta, T., Keane, B. and Silverstein, S.M., *in press*. Visual context processing dysfunction in youth at high-risk for psychosis: resistance to the ebbinghaus illusion, symptoms, and social-role functioning. *Journal of Abnormal Psychology*
- Monaghan, D.T., Bridges, R.J., Cotman, C.W., 1989. The excitatory amino acid receptors: their classes, pharmacology, and distinct properties in the function of the central nervous system. *Annu. Rev. Pharmacol. Toxicol.* 29, 365–402.
- Phillips, W.A., Silverstein, S.M., 2003. Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behav. Brain Sci.* 26 (1), 65–82 (discussion 82–137).

- Phillips, W.A., Singer, W., 1997. In search of common foundations for cortical computation. *Behav. Brain Sci.* 20 (4), 657–683 (discussion 683–722).
- Phillipson, O.T., Harris, J.P., 1985. Perceptual changes in schizophrenia: a questionnaire survey. *Psychol. Med.* 15 (4), 859–866.
- Rassovsky, Y., Horan, W.P., Lee, J., Sergi, M.J., Green, M.F., 2011. Pathways between early visual processing and functional outcome in schizophrenia. *Psychol. Med.* 41 (3), 487–497.
- Ratchford, J.N., Saidha, S., Sotirchos, E.S., Oh, J.A., Seigo, M.A., Eckstein, C., Durbin, M.K., Oakley, J.D., Meyer, S.A., Conger, A., Frohman, T.C., Newsome, S.D., Balcer, L.J., Frohman, E.M., Calabresi, P.A., 2013. Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning. *Neurology* 80 (1), 47–54.
- Reveheim, N., Corcoran, C.M., Dias, E., Hellmann, E., Martinez, A., Butler, P.D., Lehrfeld, J.M., DiCostanzo, J., Albert, J., Javitt, D.C., 2014. Reading deficits in schizophrenia and individuals at high clinical risk: relationship to sensory function, course of illness, and psychosocial outcome. *Am. J. Psychiatry* 171 (9), 949–959.
- Saidha, S., Sotirchos, E.S., Oh, J., Syc, S.B., Seigo, M.A., Shiee, N., Eckstein, C., Durbin, M.K., Oakley, J.D., Meyer, S.A., Frohman, T.C., Newsome, S., Ratchford, J.N., Balcer, L.J., Pham, D.L., Crainiceanu, C.M., Frohman, E.M., Reich, D.S., Calabresi, P.A., 2013. Relationships between retinal axonal and neuronal measures and global central nervous system pathology in multiple sclerosis. *JAMA Neurol.* 70 (1), 34–43.
- Satue, M., Seral, M., Otin, S., Alarcia, R., Herrero, R., Bambo, M.P., Fuertes, M.I., Pablo, L.E., Garcia-Martin, E., 2014. Retinal thinning and correlation with functional disability in patients with Parkinson's disease. *Br. J. Ophthalmol.* 98 (3), 350–355.
- Schubert, E.W., Henriksson, K.M., McNeil, T.F., 2005. A prospective study of offspring of women with psychosis: visual dysfunction in early childhood predicts schizophrenia-spectrum disorders in adulthood. *Acta Psychiatr. Scand.* 112 (5), 385–393.
- Sedighi, B., Shafa, M.A., Abna, Z., Ghaseminejad, A.K., Farahat, R., Nakhiae, N., Hassani, N., 2014. Association of cognitive deficits with optical coherence tomography changes in multiple sclerosis patients. *J. Mult. Scler.* 1.
- Silverstein, S.M., Keane, B.P., 2011a. Perceptual organization impairment in schizophrenia and associated brain mechanisms: review of research from 2005 to 2010. *Schizophr. Bull.* 37 (4), 690–699.
- Silverstein, S.M., Keane, B.P., 2011b. Vision science and schizophrenia research: toward a re-view of the disorder. Editors' introduction to special section. *Schizophr. Bull.* 37 (4), 681–689.
- Silverstein, S.M. and Rosen, R., in press. Schizophrenia and the eye. *Schizophrenia Research: Cognition*.
- Silverstein, S.M., Schenkel, L.S., Valone, C., Nuernberger, S.W., 1998. Cognitive deficits and psychiatric rehabilitation outcomes in schizophrenia. *Psychiatry Q.* 69 (3), 169–191.
- Silverstein, S.M., Berten, S., Essex, B., Kovacs, I., Susmaras, T., Little, D.M., 2009. An fMRI examination of visual integration in schizophrenia. *J. Integr. Neurosci.* 8 (2), 175–202.
- Silverstein, S.M., Keane, B.P., Wang, Y., Mikkilineni, D., Paterno, D., Papatomas, T.V., Feigenson, K., 2013. Effects of short-term inpatient treatment on sensitivity to a size contrast illusion in first-episode psychosis and multiple-episode schizophrenia. *Front. Psychol.* 4, 466.
- Tian, T., Zhu, X.H., Liu, Y.H., 2011. Potential role of retina as a biomarker for progression of Parkinson's disease. *Int. J. Ophthalmol.* 4 (4), 433–438.
- Toledo, J., Sepulcre, J., Salinas-Alaman, A., Garcia-Layana, A., Murie-Fernandez, M., Bejarano, B., Villoslada, P., 2008. Retinal nerve fiber layer atrophy is associated with physical and cognitive disability in multiple sclerosis. *Mult. Scler.* 14 (7), 906–912.
- Tso, I.F., Calwas, A.M., Chun, J., Mueller, S.A., Taylor, S.F., Deldin, P.J., 2015. Altered attentional and perceptual processes as indexed by N170 during gaze perception in schizophrenia: relationship with perceived threat and paranoid delusions. *J. Abnorm. Psychol.*
- Turetsky, B.I., Kohler, C.G., Indersmitten, T., Bhati, M.T., Charbonnier, D., Gur, R.C., 2007. Facial emotion recognition in schizophrenia: when and why does it go awry? *Schizophr. Res.* 94 (1-3), 253–263.
- Uhlhaas, P.J., Silverstein, S.M., 2005. Perceptual organization in schizophrenia spectrum disorders: empirical research and theoretical implications. *Psychol. Bull.* 131 (4), 618–632.
- Waters, F., Collerton, D., Ffytche, D.H., Jardri, R., Pins, D., Dudley, R., Blom, J.D., Mosimann, U.P., Eperjesi, F., Ford, S., Laroi, F., 2014. Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease. *Schizophr. Bull.* 40 (Suppl 4), S233–S245.

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