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A VISION FOR PSYCHOSIS RESEARCH: COMMENTARY ON "NEW INSIGHTS INTO SCHIZOPHRENIA: A LOOK AT THE EYE AND RELATED STRUCTURES"

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Scientists have been examining the eye to understand the neurobiology of schizophrenia since 1908, when Diefendorf and Dodge published their landmark study, "ocular reactions of the insane". Using Raymond Dodge's new photochronograph technology, they proved that cases had significantly abnormal eye movements, which Allen Diefendorf had clinically observed in his patients. Deepening discoveries about perception, central processing and attention are still ongoing from this discovery.

Jurisic and colleagues (2019) have written a scholarly and comprehensive review of insights into the pathophysiology of schizophrenia that can be gleaned from the eye and related structures. Abnormalities in the neurovasculature, identified by Joe et al (2018), but also myelination, neuropil density, glia, cytokines, and immune function, all proposed to underlie schizophrenia, can be directly observed in the eye using increasingly sophisticated technologies. Developmental versus degenerative processes can also be discerned, which may predominate in single cases at different illness phases or characterize different subtypes of schizophrenia.

Beyond the neurons, glia, myelin and other neural ocular components, the examination of the eye can probe numerous facets of visual perception that may underlie the visual dysfunction observed in schizophrenia. Stimuli travel from the retina to brain and produce measurable perceptual responses that can be quantitated. This peripheral window to brain function is an exceptional opportunity to illuminate potential pathological mechanisms for schizophrenia.

Knowledge of the human visual system itself, including its anatomy and physiology, columnar organization and receptive fields, is so well understood that it provides an elegant model of brain function that can be viewed using the advancing methods of ophthalmology. For example, contrast detection is a seemingly simple task, but it is highly pertinent to general brain function and for understanding schizophrenia. Indeed, contrast detection is a prototypical example of gain control, which, along with integration, have been identified as core mechanisms underlying visual disturbances in schizophrenia by the NIMH-sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia initiative (Butler et al. 2008). Gain control refers to the homeostatic amplification or attenuation of signals to keep neural activity within an adaptively limited signaling range, preventing under- or over-stimulation, respectively. Gain control operates not only in the visual system but also in other brain areas. Contrast detection can be measured psychophysically and through visual evoked potentials and neuroimaging (Butler et al. 2005, Calderone et al. 2013). Such studies demonstrate reduced responding at low contrast presentations in subjects with schizophrenia, which exemplifies impaired gain control (Butler et al. 2005, 2009).

As noted by Jurisic and colleagues (2019), visual contrast detection is an important determinant of social function and other judgements about the environment. Indeed, the impaired capacity of schizophrenia cases to make accurate in judgments at low contrast is related to their inability to recognize the facial emotions of other persons, which handicaps them in reciprocal social interactions. Persons with schizophrenia require twice as much contrast as controls to accurately detect face emotion which does not accord with natural expressions (Butler et al. 2009). Such low-level visual dysfunction, including spatial frequency detection, also impacts perceptual organization, object recognition, reading, and measures of functional outcome (e.g., Butler et al. 2005, Silverstein et al. 2010). The difficulty in discerning whole images, gestures and other gestalts is consistent with involvement of the magnocellular visual system. There is complex interplay between magnocellular and parvocelluar visual pathways and other brain areas, in successful perceptual function and these systems may be awry in schizophrenia. Intracellular recordings from macaque monkeys following glutamatergic receptor blockade mirror the abnormalities observed in some schizophrenia patients (Butler et al. 2005, Kwon et al. 1992).

Examining contrast responding in schizophrenia can provide a model for a general impairment in brain function that could include decreased glutamatergic function and slower processing. Because incoming visual information propagates throughout the brain, the impaired initial visual input may produce widespread brain dysfunction, which can be useful to infer the impact of other sensory and internally generated stimuli.

The formation and integration of stored visual memories may be essential for navigating social interactions. Studies that assess the location along the visual pathway where the impairments arise can parse out the top-down as well as the bottom up contributions of the neural dysfunction producing the schizophrenia system. The association of neural elements that can quantitated through ocular imaging will permit the studies to move from the level of circuitry to tissue elements and ultimately to molecules.

Increased understanding of basic visual elements and processes that are disrupted in schizophrenia also may inform targeted perceptual cognitive remediations. Butler, Silverstein, and colleagues are conducting a randomized controlled trial of visual remediation to target ability to detect contrast and contour perception (low and mid-level visual functions). If the remediation successfully alters these visual functions, its impact on social, cognitive, and other outcomes will also be assessed.

With the advances in ophthalmologic techniques, including OCT and computational modeling, the nature of the impaired visual perception in schizophrenia, and its impact on other types of function, may become finally clarified. Many studies have found thinning of retinal structures in schizophrenia and further work looking at stage of illness and medical comorbidities is needed to understand the nature of these impairments (Silverstein et al. in press). In addition, we recently found good reliability across different OCT machines in schizophrenia (Miller et al. in press) which may be helpful in comparing studies between machines. Medical breakthroughs regularly follow advances in technology, but innovations in ocular assessments are truly salient to neuroscience, as they permit the direct investigation of central neural components, overcoming the constraints of the skull without the cost and complexity of neuroimaging.

Schizophrenia is actually a heterogeneous syndrome, for which precision medical approaches will require valid biomarkers of neural dysfunction, likely to differ significantly between groups of cases. There can be no better lens to identify subgroups than through the eye, and these approaches may set the way for precision treatment of particular subgroups of cases within this heterogeneous syndrome.

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References

1. *Butler PD, Abeles IY, Weiskopf NG, Tambini A, Jalbrzikowski M, Legatt ME, Zemon V, Loughead J, Gur RC & Javitt DC: Sensory contributions to impaired emotion processing in schizophrenia. Schizophr Bull 2009; 35:1095-1107*
2. *Butler PD, Silverstein SM, Dakin SC: Visual perception and its impairment in schizophrenia. Biol Psychiatry 2008; 64:40-47*
3. *Butler PD, Zemon V, Schechter I, Saperstein AM, Hoptman MJ, Lim KO, Revheim N, Silipo G & Javitt DC: Early-stage visual processing and cortical amplification deficits in schizophrenia. Arch Gen Psychiatry 2005; 62:495-504*
4. *Calderone DJ, Martinez A, Zemon V, Hoptman MJ, Hu G, Watkins JE, Javitt DC & Butler PD: Comparison of psychophysical, electrophysiological, and fMRI assessment of visual contrast responses in patients with schizophrenia. Neuroimage 2013; 67:153-162*
5. *Joe P, Ahmad M, Riley G, Weissman J, Smith RT & Malaspina D: A pilot study assessing retinal pathology in psychosis using optical coherence tomography: Choroidal and macular thickness. Psychiatry Res 2018; 263:158-161*
6. *Jurisic D, Cavar I, Sesar A, Sesar I, Vukojevic J & Curkovic M: New insights into schizophrenia: a look at the eye and related structures. Psychiatr Danub 2019; 31 in press*
7. *Kwon YH, Nelson SB, Toth LJ and Sur M: Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. J Neurophysiol 1992; 68:182-196*
8. *Miller M, Zemon V, Nolan-Kenney R, Balcer LJ, Goff DC, Worthington M, Hasanaj L & Butler PD: Optical coherence tomography of the retina in schizophrenia: Inter-device agreement and relations with perceptual function. Schizophrenia Research 2019; in press*
9. *Silverstein SM, All SD, Kasi R, Berten S, Essex B, Lathrop KL & Little DM: Increased fusiform area activation in schizophrenia during processing of spatial frequency-degraded faces, as revealed by fMRI. Psychol Med 2010; 40:1159-1169*
10. *Silverstein SM, Fradkin SI & Demmin DL: Schizophrenia and the retina: towards at 2020 perspective. Schizophrenia Research 2019 in press*

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