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Schizophrenia and the eye

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ABSTRACT

Although visual processing impairments are common in schizophrenia, it is not clear to what extent these originate in the eye vs. the brain. This review highlights potential contributions, from the retina and other structures of the eye, to visual processing impairments in schizophrenia and high-risk states. A second goal is to evaluate the status of retinal abnormalities as biomarkers for schizophrenia. The review was motivated by known retinal changes in other disorders (e.g., Parkinson's disease, multiple sclerosis), and their relationships to perceptual and cognitive impairments, and disease progression therein. The evidence reviewed suggests two major conclusions. One is that there are multiple structural and functional disturbances of the eye in schizophrenia, all of which could be factors in the visual disturbances of patients. These include retinal venule widening, retinal nerve fiber layer thinning, dopaminergic abnormalities, abnormal ouput of retinal cells as measured by electroretinography (ERG), maculopathies and retinopathies, cataracts, poor acuity, and strabismus. Some of these are likely to be illness-related, whereas others may be due to medication or comorbid conditions. The second conclusion is that certain retinal findings can serve as biomarkers of neural pathology, and disease progression, in schizophrenia. The strongest evidence for this to date involves findings of widened retinal venules, thinning of the retinal nerve fiber layer, and abnormal ERG amplitudes. These data suggest that a greater understanding of the contribution of retinal and other ocular pathology to the visual and cognitive disturbances of schizophrenia is warranted, and that retinal changes have untapped clinical utility.

Visual processing impairments are well established in schizophrenia, including abnormalities in contrast sensitivity (Kelemen et al., 2013; Kiss et al., 2010); various excitatory and inhibitory functions (Kaplan and Lubow, 2011; Keri et al., 2005a; Robol et al., 2013) including those involved in masking (Green et al., 2011) and surround suppression (Tibber et al., 2013); and form and motion processing (Chen, 2011; Green et al., 2011; Javitt, 2009; Silverstein and Keane, 2011). There has been little work on color processing to date (Shuwairi et al., 2002), but clinical reports indicate frequent descriptions of increased intensity, or alterations in color perception (Chapman, 1966; Vollmer-Larsen et al., 2007). One study reported a 62% incidence of visual distortions in schizophrenia, with brightness, contrast, and motion increases being the most commonly reported (Phillipson and Harris, 1985). Visual distortions also had the highest predictive validity, among all basic symptoms, for conversion to a psychotic disorder (Klosterkotter et al., 2001), and visual distortions in help-seeking adolescents are associated with suicidal ideation, even after controlling for age, gender, depression, thought disorder, paranoia, and auditory distortions (Grano et al., 2015). Finally, visual impairments contribute substantially to poorer real-world functioning in people with schizophrenia (Green et al., 2012; Rassovsky et al., 2011).

In spite of this growing body of evidence, an unanswered question is the extent to which the problems observed in recent laboratory or clinical reports are due to changes in the eye vs. in the brain. It has already been shown that abnormalities (i.e., hypo- or hyper-activation) exist in occipital (Butler et al., 2013; Silverstein et al., 2009), temporal (Silverstein et al., 2010a), parietal (Dima et al., 2009), and prefrontal (Dima et al., 2009; Silverstein et al., 2009, 2010b) regions during visual processing tasks in schizophrenia, depending on the nature of the task requirements. These findings are thought to reflect both inefficient stimulus-driven (i.e., bottom-up) processing, as well as deficient top-down guidance or modulation of the feedforward sweep of information based on prior knowledge, expectations, and task strategies (Dima et al., 2009, 2010, 2011; Keane et al., 2013; Silverstein and Keane, 2009). However, degraded input to the visual system could contribute to both sets of findings, by adding noise to (or lowering the resolution of) sensory information, which would disrupt stimulus-driven processing, and by making it less likely that appropriate stimulus templates or memory representations would be activated to modulate processing. It is the purpose of this review to: 1) highlight potential mechanisms by which schizophrenia, or its treatment, can disrupt retinal function and lead to some of the common laboratory findings or visual distortions reported by patients; and 2) describe other types of ocular dysfunction that may contribute to these visual impairments. The extent to which these retinal and other ocular changes can serve as biomarkers for schizophrenia or psychosis will also be highlighted.

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1. Retinal cellular and vascular changes in schizophrenia and high-risk states

The retina is an active information processor, in which, among other things, early forms of transformations traditionally thought to occur only in visual cortex, take place. For example, in response to moving stimuli, cone photoreceptors produce motion blur, which has been shown to enhance information about orientation and direction of movement, shape contour orientation and completion, changes in texture between stimulus regions, spatial frequency, and depth (van Tonder, 2010). Motion blur can also affect perception of complex stimuli such as facial emotions. Importantly, much input to cone photoreceptors (the photoreceptor type involved in color vision) is dopaminergic, and, as reviewed below, retinal dopamine (DA) abnormalities could contribute to several forms of visual impairments in schizophrenia. An implication of this is that anything that affects retinal function may result in intensified, degraded or noisy input to higher levels of processing in LGN and visual cortex, depending on the nature of the abnormality.

The retina develops from the same tissue (neuroectoderm) as the brain, and is the only part of the central nervous system that can be seen with the naked eye in its natural state in living organisms. Given that retinal changes may parallel, or mirror the integrity of brain structure and function (Chu et al., 2012; Kemenyova et al., 2014; Lee et al., 2013; Tian et al., 2011), it has been suggested that retinal changes can serve as a marker of progressive brain tissue loss. Given this, the well-documented structural and functional brain changes in schizophrenia, and the obvious implications of altered retinal function for changes in visual processing, what is the evidence for retinal abnormalities in schizophrenia?

Data from the Dunedin longitudinal study indicated that, at age 38, individuals with schizophrenia had wider retinal venules than cohort members who did not have schizophrenia, suggesting a history of chronic insufficient brain oxygen supply (Meier et al., 2013). This finding was not secondary to other health issues. Moreover, wider retinal venules were associated with extent of psychotic symptoms in adulthood, and in childhood. The association between wider retinal venule width and psychosis (assessed 6 years after the eye exam) was recently replicated in two Australian twin studies (Meier et al., 2015). Moreover, retinal venule width in unaffected twins of a psychotic sibling was characterized by values intermediate between controls and psychotic siblings. Arteriole width was unaffected by presence of psychosis in twins with psychosis or their unaffected siblings. These data suggested that retinal venule widening may be a proxy marker of familial risk for psychosis. Other evidence indicates that retinal venule width is significantly correlated with childhood IQ and with neuropsychological functioning at midlife, in the general population (Shalev et al., 2013). A similar recent finding is that, in the general population, color vision impairments [implying DA dysregulation in cone photoreceptors (see below)] predict difficulties with cognitive control (Colzato et al., 2014) — a function thought to involve dopaminergic projections to the prefrontal cortex (van Schouwenburg et al., 2010), and that is characteristically impaired in schizophrenia (Lesh et al., 2011). These data suggest that basic aspects of retinal structure and function may indicate increased risk for schizophrenia, and be impaired in the disorder, via reflecting reduced vascular and brain health.

Other evidence for structural retinal changes in schizophrenia comes from studies of optical coherence tomography (OCT). OCT is a recently developed, rapid, non-invasive imaging technique that can reveal retinal structure *in vivo* with axial resolutions of 5 microns or less. It has recently proven useful for identifying thinning of certain retinal layers in several neurological conditions such as multiple sclerosis (MS) (Khanifar et al., 2010; Martinez-Lapiscina et al., 2014), Parkinson's disease (Satue et al., 2013, 2014; Tian et al., 2011), and Alzheimer's disease (Moschos et al., 2012), in addition to focal eye diseases (Leung et al., 2010). Retinal nerve fiber layer (RNFL) thinning – reflecting loss of ganglion cell axons that leave the retina as the optic nerve and synapse onto the lateral geniculate nucleus – as revealed by OCT, is thought to be a good model of brain neurodegeneration, since retinal cells are unmyelinated, and so any thinning directly reflects cell loss (Lee et al., 2013). Consistent with this, progressive RNFL thinning parallels disease progression in Parkinson's disease (Tian et al., 2011), where level of thinning correlates significantly with extent of visual hallucinations (Lee et al., 2014) and functional disability (Satue et al., 2014). In MS, RNFL thinning is associated with duration of illness, gray matter loss, poorer executive functioning, poorer overall cognitive functioning, illness progression, and relapse (Martinez-Lapiscina et al., 2014; Ratchford et al., 2013; Saidha et al., 2013; Sedighi et al., 2014; Toledo et al., 2008). Interestingly, even in healthy subjects, OCT indices correlate with intracranial volume (Saidha et al., 2013). OCT studies of schizophrenia have focused on RNFL thinning and reductions in macular volume (MV) (reflecting integrity of the fovea and surrounding tissue). While an initial small study (n=10 patients) reported RNFL thinning (Ascaso et al., 2010), this was not replicated in a subsequent study (Chu et al., 2012), although in the latter, reduced MV was related to increased positive symptoms. However, this study used an earlier generation (time domain) OCT device characterized by an ~10 micron axial resolution generating 400 scans per second. More recent studies, using spectral-domain OCT with resolution of ~5 microns and over 25,000 scans per second, have observed both RNFL and MV thinning (Lee et al., 2013), or RNFL thinning only (Cabezon et al., 2012), in schizophrenia (see Figs. 1 and 2). As with retinal venule widening, the functional significance of these findings is not yet clear, although one study found that RNFL thinning was related to illness chronicity in schizophrenia (Lee et al., 2013). Studies investigating the relationship between retinal degeneration and visual processing are just beginning to be carried out with schizophrenia patients. However, it is thought that problems in visual processing (including in contrast sensitivity, color perception, and reading) in Parkinson's disease may be due to retinal cell loss (Djamgoz et al., 1997; Harnois and Di Paolo, 1990; Hutton and Morris, 2001; Rodnitzky, 1998), and similar problems have been observed in schizophrenia (Butler et al., 2005; Cadenhead et al., 2013; Kelemen et al., 2013; Revheim et al., 2006b, 2014) (see below). In addition, as described in the next section, ganglion cell loss (which may be the primary cause of RNFL thinning) may be a marker of other cellular processes that have been linked to specific visual impairments. An additional consideration for studies of schizophrenia is that diabetic retinal changes (maculopathy) detectable by OCT (Sikorski et al., 2013) could contribute to visual processing disturbances, and so must be ruled out in both eyes of patients.

2. Dopamine and retinal function

DA is a major neurotransmitter in the vertebrate retina, and its cellular localization and functions are similar in organisms as diverse as fish and primates (Djamgoz et al., 1997; Masson et al., 1993). In the retina, DA originates in one class of amacrine cells (ACs) and in interplexiform cells. It is transmitted via standard synaptic transmission, as well as by volume transmission, where it can diffuse up to 3 mm through retinal tissue to potentially influence every type of retinal neuron, as all have receptors for DA (Yazulla and Studholme, 1995). One important function of DA in the retina is to weaken the gap junctions that couple horizontal cells (Piccolino et al., 1984; Teranishi et al., 1983). Because horizontal cells (HCs) pool the activity of photoreceptor cells across space, this DA-related uncoupling leads to significant reduction of the normally large HC receptive fields (Xin and Bloomfield, 2000), and to increased sensitivity to local (relative to contextual) stimulation (Brandies and Yehuda, 2008). A second effect of the uncoupling of HCs is reduced interaction between neurons signaling light and dark portions of space, leading to enhanced center responses (and reduced effects of surround responses) (Hedden and Dowling, 1978).

The DA receptor types found in the retina are the same as those found in the brain (e.g., D_1–D_5), and can be roughly divided into D_1