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Revisiting visual dysfunctions in schizophrenia from the retina to the cortical cells: A manifestation of defective neurodevelopment

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ABSTRACT

This review highlights morphological and functional anomalies found along the entire visual pathway in schizophrenia, from the retina to the cortex. Based on the evidence of widespread anatomical and functional visual abnormalities, we posited that a neurodevelopmental anomaly occurring early in life was likely to explain those. Incidentally, support to the neurodevelopmental theory of schizophrenia is strongly emerging from many neurobiological domains. In vertebrates, the first visual structures migrate toward the orbit position at the end of the fourth week of gestation. A neurodevelopmental defect around that time on these embryonic structures could account for the visual anomalies in schizophrenia. Retinol activity might be involved in the process. Future research in schizophrenia should focus on early visual testing, on trials combining multiple visual anomaly assessments and a closer look to retinol activity during the pregnancy.

Contents

1. Introduction

Ophthalmic and visual anomalies, in the presence of normal vision, have been documented in schizophrenia since the middle of the 20th century (Cohen, 1949; Venables & Tizard, 1956). Recent discoveries suggest that such subtle visual anomalies are spread over the entire visual system. The goal of this review is to demonstrate how visual information, from the basic photoreceptor to the visual cortical areas, is affected in this major psychopathology. Since so many structures along the visual track are affected, it is proposed that developmental anomalies are susceptible to account for those dysfunctions. We also postulate that these developmental anomalies could account for other features of the disease such as the increased prevalence of congenital morphological defects (cardiac, craniofacial, limb) (Goodman, 1996) and eye tracking defect (O'Driscoll & Callahan, 2008). Those will be discussed in the last part of the manuscript.

This review included trials corresponding to two main criteria: 1) reporting a significant visual defect either morphological or physiological and 2) with no task involving cognitive function with the exception of the eye tracking task. The later exception was made because it requires only minimal cognitive resource from the subject and is one of the most documented deficits in SZ.

Abbreviations: BA, Brodmann area; ERG, Electroretinogram; ETD, Eye tracking dysfunction; fMRI, Functional magnetic resonnance imagery; LGN, Lateral geniculated nucleus; OP, oscillatory potentials; PET, Positron emission tomography; RAR, retinoic acid receptor; RGC, Retinal ganglion cells; RNFL, Retinal nerve fiber layer; SZ, Schizophrenia.

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The second criterion dramatically reduced the number of studies with large samples. However it has the advantage to focus more specifically on pure visual deficiencies that are independent of cognitive function or of the subject compliance. This distinguishes this review from other recent exhaustive manuscript describing visual disturbances in schizophrenia such as Silverstein et al. (2015).

2. Visual anomalies or visual differences in schizophrenia patients when compared to healthy controls

2.1. The retinal level

The retina is the first structure to receive and process environmental visual information. The phenomenon of vision begins when light stimuli penetrate the eye, and reach the layer containing the classical photoreceptors (rods and cones) which become hyperpolarized. The cone hyperpolarization leads to the depolarization of specific bipolar cells (called ON bipolar cells) connected to ON retinal ganglion cells (RGC). RGC then form the optic nerve that projects for the most part to the visual cortex to generate vision. The pathway of rods is slightly more complex with rod ON bipolar cells reaching RGC via amacrine cells that connect to cone ON bipolar cell. Other interneurons such as horizontal cells are also implicated to link photoreceptors together (Masland, 2001). The type of photoreceptor implicated will depend on the ambient light intensity. It could be either rods for scotopic vision (night; under 0.001 cd/m^2; less than 1 lux), cones for photopic vision (day; above 3 cd/m^2; more than 10 lux) or both for mesopic vision (between 0.001 cd/m^2 and 3 cd/m^2; between 1 and 10 lux) (Boyce, 2003).

In schizophrenia (SZ), the first steps of phototransduction seem to be affected in both scotopic and photopic conditions as suggested by studies using the electroretinogram (ERG) (Balogh et al., 2008; Dong et al., 2004; Gerbaldo et al., 1992; Raese et al., 1982; Warner et al., 1999). The ERG is a non-invasive technique recording the light-evoked electric potential originating from the retina in response to standardized flash stimuli. The hyperpolarisation of photoreceptors, i.e. the a-wave, is followed by the depolarisation of bipolar cells, i.e. the b-wave. Both of them are quantified with an amplitude and a latency (Brown, 1968; Green & Kapousta-Bruneau, 1999; Karwoski & Xu, 1999). The first observation of a decrease in b-wave amplitude in schizophrenia was reported in 1992 (Gerbaldo et al., 1992), but this finding was only observed in patients with a history of sun gazing and who showed an increased tolerance to extremely intense eye light exposure. Even though this decrease was independent of the medication, staring at the sun could have caused retinal damages, yielding to a reduced ERG response. Two small ERG reports demonstrated a decrease in cone driven a-wave in schizophrenia patients (Balogh et al., 2008; Warner et al., 1999). This was not observed in patients affected by bipolar disorder medicated with the same drugs for at least two weeks before the assessment (Balogh et al., 2008) and this anomaly was found to be independent of the antipsychotic dose received prior to ERG recording (Warner et al., 1999).

In yet the largest study so far (SZ = 105; Controls = 150), Hebert et al. (2015) recently reported various ERG anomalies in SZ patients including the cone a-wave deficit and rod b-wave amplitude decrease reported by others (Balogh et al., 2008; Warner et al., 1999) but also novel anomalies namely a slower and reduced cone b-wave.

Abnormalities on oscillatory potentials (OPs), which are small wavelets superimposing on the ascending b-wave (Dong et al., 2004), have been anecdotally reported in schizophrenia patients but results are conflicting (Raese et al., 1982; Schechter et al., 1987). Since patient samples were small and because of the heterogeneity of the medication, we can only conclude that OPs definitely warrant further investigations as they are too rarely assessed in ERG studies.

A study using optical coherence tomography, a non-invasive imaging technique that measures the macular thickness and volume as well as the thickness of the retinal nerve fiber layer (RNFL), revealed that all those retinal areas of SZ patient are affected. Indeed, the volume of the macula was reduced, the thickness of both macula and RNFL was decreased and the thinning/reduction were correlated with the duration of the disease (Lee et al., 2013). Using the same technique, another team failed to replicate the thinning of the macular and the RNFL but found that the macular volume was negatively correlated with the severity of positive symptoms (Chu et al., 2012).

Finally, it was recently reported that SZ patients demonstrate wider eye microvessels than controls (Meier et al., 2013). All the participants were members of the Dunedin Multidisciplinary Health and Development Study. They were evaluated for childhood psychosis symptoms at 11 years old and for vessel caliber at the age of 38. The authors observed that SZ patients (N = 27) had wider retinal vessel. Those with the widest retinal vessels had also exhibited more psychotic symptoms in childhood. The authors suggested that early defective vascular mechanisms could contribute to the trajectory toward schizophrenia. This is concordant with the hypothesis of a childhood risk trajectory leading to schizophrenia (Insel, 2014). Of interest, some of the findings observed in Hebert et al. (2015) were indeed observed in offspring at risk of developing schizophrenia and bipolar disorder, namely decreases in photopic a-wave and scotopic b-wave amplitudes (Hebert et al., 2010). These findings were highly relevant due to their presence many years before the eventual disease onset and highlight a vulnerability to the disease. It was concluded by the authors that the ERG response could represent an early risk biomarker with a neurodevelopmental basis.

Table 1 summarizes the anomalies found at the retinal level.

2.2. The relay structures

The visual information originating from the retina is transmitted to the visual cortex following a transition through a relay structure: the lateral geniculated nucleus (LGN). This retino-geniculo-cortical

Table 1
Summary of the retinal physiological and anatomical findings reported in schizophrenia.

Retinal physiological and morphological findings in schizophrenia		
Authors (N = SZ patients)	Physiological findings	Anatomical findings
Gerbaldo et al. (1992) (N = 9)	-Reduced cone ERG response (b-wave) -Increased tolerance to extremely intense light	
Warner et al. (1999) (N = 9)	Reduced a-wave amplitude of rod and cone	
Balogh et al. (2008) (N = 26)	-Reduced cone response (a-wave) -Rod response not assessed	
Hebert et al. (2015) (N = 105)	-Reduced cone and rod ERG response (b-wave) -Slower cone a-wave -Reduced cone a-wave amplitude	
Raese et al. (1982) (N = 9)	OP desynchronization	
Chu et al. (2012) (N = 38)		Macular volume correlates with symptom severity
Lee et al. (2013) (N = 30)		-Reduced volume of the macula -Reduced thickness of the RNFL and the macula
Meier et al. (2013) (N = 27)		Wider retinal vessels