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Review article

The role of the retina in visual hallucinations: A review of the literature and implications for psychosis

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ABSTRACT

Visual hallucinations are a psychotic symptom present in numerous clinical conditions such as eye disease, Parkinsonian syndromes, neurodegenerative disorders and psychosis. Alteration of low level visual processing is a common feature in these clinical conditions, and various stages of processing from the retina to visual cortices are involved. We undertook a literature review of abnormalities of the retina and their potential link with the occurrence of VHs in these clinical conditions of interest. We found that structural and functional abnormalities of the retina are frequently present. In Parkinson disease and eye disease, VHs have been related to dysfunctions of the retina. By contrast, in neurodegenerative disorders and psychosis, possible links have yet not been explored. We show that structural or functional abnormalities of the retina are given little consideration in cognitive models of VHs, which primarily postulate an alteration of sensory visual processing and a top-down attentional process. We conclude that contrast sensitivity measures and an exhaustive exploration of the retinal functions using the clinical electroretinography standards of the International Society for the Clinical Electrophysiology of Vision (ISCEV) are needed to explore retinal involvement in the occurrence of visual hallucinations.

1. Introduction

Visual hallucinations (VHs) are a common trans-diagnostic psychotic symptom that can occur in various clinical conditions, e.g. ophthalmologic disorders (eye diseases), neurologic disorders (migraine, epilepsy, neurodegenerative diseases, Parkinsonian syndromes, etc.), outcomes of substance use (delirium tremens, LSD abuse, etc.), and psychiatric disorders (schizophrenia, bipolar disorders, complex bereavement, etc.). VHs in these clinical conditions can be simple or complex manifestations. Simple VHs lack recognizable forms and are characterized by flashes of light, modification of light and shadow perception, shapeless colors (photopsia) and geometric patterns (lines, honeycombs, spirals, webs, etc.). Complex VHs can be defined as repetitive involuntary images of people, animals or objects experienced as real during the waking state, but for which there is no objective reality (Collerton et al., 2005). They can be distressing and affect quality of life (Dudley et al., 2012).

Numerous VHs studies have focused on functional cerebral abnormalities during the processing of visual scenes (Collerton et al., 2005 for review). Simple VHs are thought to arise principally from aberrant activity in the early visual processing involving thalamocortical circuitry and primary visual cortices (Anderson and Rizzo, 1994; Carter and Ffytche, 2015; Ffytche, 2009). Complex VHs are thought to involve a more complex network including visual cortices, executive and attention-related networks such as frontal lobe, superior parietal lobule and precuneus, memory-related networks such as posterior cingulate and hippocampus, and areas involved in sensory binding (Amad et al., 2014; Carter and Ffytche, 2015; Jardri et al., 2013; Oertel

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et al., 2007). Cognitive models of VHs postulate involvement of disturbed primary sensory processing together with a top-down attentional process (Collerton et al., 2005 for review). Despite these two lines of approach, VHs are classically explored by structural or functional brain studies. Low-level sensory processing also needs to be explored, given the involvement of the visual sense organ itself, and the retina is thus clearly a site of interest.

The retina is an extension of the diencephalon, and belongs to the central nervous system. The retina and the brain are connected by the optic nerve, the axons of the ganglion cells through the lateral geniculate nucleus. They share similar neurotransmitters such as dopamine (Reis et al., 2007), serotonin (Gastinger et al., 2006), glutamate and GABA (de Souza et al., 2013; Wu and Maple, 1998). The optic nerve is exposed to the same insults as the central nervous system, therefore brain anomalies have manifestations in the retina (London et al., 2013). The retina is a well-studied organ with a layered organization, facilitating the exploration of dysfunctional mechanisms. Functional or morphological measures of the retina thus offer a "window to the brain" (London et al., 2013) that can be of interest for exploring central nervous system disorders (Schwitzer et al., 2015). Moreover, retina is the first step of visual information processing. Hence, it is a critical stage of processing for studying VHs and if abnormalities of visual processing occur at this level it is possible that it could affect later stages of visual processing from the optic nerve to cortical visual areas. Together those particularities make retina an organ of great interest for studying VHs.

Clinical conditions with VHs also present ocular or retinal abnormalities. These are an etiopathogenic characteristic in eye disease, a well-known feature in Parkinsonian syndromes and an emerging topic in neurodegenerative and psychiatric disorders. Finally, recent studies have linked abnormalities of the retina and occurrence of VHs (Lee et al., 2014b).

VHs in psychiatric disorders have been largely neglected compared with VHs in eye disease or neurodegenerative disorders. Yet in a recent study, lifetime prevalence of VHs was 37% in non-affective psychosis, 37% in schizophrenia and 47.5% in schizoaffective disorders, and present state prevalence was 18.9% in non-affective psychosis and 36.2% in schizophreniform disorders (Ommen et al., 2016). As VHs in psychosis are mostly complex, we aim to review retina dysfunctions in clinical conditions characterized by complex VHs and to discuss cognitive models of VHs with respect to a possible role for the retina in the occurrence of VHs in eye disease characterized by the Charles Bonnet syndrome, Parkinson disease and Lewy body dementia, neurodegenerative disorders and more specifically psychosis.

2. Ophthalmologic techniques to investigate anatomical and functional retina dysfunctions in neurology and psychiatry

Recent research has focused on retinal dysfunctions in neurologic or psychiatric conditions, and suggests retinal involvement in the alteration of visual processing and/or VHs. Ophthalmologic medical imagery techniques such as optical coherence tomography (OCT), and functional measures of the retina such as electroretinogram (ERG) records, offer new approaches to explore retinal dysfunctions and study relationships between these dysfunctions and occurrence of VHs.

OCT is a non-invasive retinal imaging technique analogous to ultrasound imaging. It provides high resolution, cross-sectional images of the retina in vivo, and enables histopathological imaging of the retina (Fujimoto et al., 2000). OCT can assess the thickness of retinal nerve fiber layer (RNFL) around the optic nerve head, and provides a measure of the integrity of the retinal ganglion cell axons that exit the retina. The RNFL is a structure of interest because it can be considered as an extension of the brain, and axons are myelinized in the optic nerve. OCT enables measurements of macular volume and macular thickness. OCT imaging has been preferentially and primarily used in ophthalmology, but in the last few years it has appeared in neurology and psychiatry (Schönfeldt-Lecuona et al., 2015; Schwitzer et al., 2016, 2015) Several caveats of OCT use are noteworthy (for a review see Bodis-Wollner, 2013). For example, current OCT machines have different measuring protocols for specific ophthalmologic diseases, and so good reproducibility is possible only if the same equipment is used, which makes difficult the comparison of results across studies with different manufacturers (Watson et al., 2011). There is also no standard protocol to evaluate the retina in the clinical conditions of interest in our context (Lee et al., 2014a). Despite these current limitations, several authors view OCT as of potential utility to provide biomarkers for psychosis (Hébert et al., 2010), disease progression in Parkinson disease patients (Archibald et al., 2011), and neurodegenerative disorders (Ascaso et al., 2014; Bambo et al., 2014).

Besides structural anomalies, functional dysfunctions of the retina need to be explored when addressing a disorder such as VHs, which occur in many clinical conditions, with ranging probable causes. Several functional measures of the retina can be conducted. Three measures are principally studied in the present literature: the flash ERG, the pattern ERG and the multifocal ERG. Flash ERG is a frequently used technic in clinical ophthalmology to explore the retinal response. Hence clinical use of flash ERG permits diagnosis of disorders affecting the retina and more precisely the first two retinal layers (photoreceptors and bipolar cells). Nevertheless, flash ERG measures lack of sensibility and are affected only in case of wide lesions of the retina. Moreover it is difficult to correlate or compare flash ERG abnormalities to routine ophthalmological assessments such as contrast sensitivity or visual field examination as they are part of the subjective assessment of the visual function which can be disrupted by other deterioration (cognitive functions for example). Flash ERG provides retinal response to a photic stimulation. The retinal response is a light-evoked electric potential dominated by a biphasic waveform. Its two components are the negative a-wave (hyperpolarization of the photoreceptors) and the positive b-wave (depolarization of the bipolar cells). Flash ERG can provide photoreceptors and bipolar cell response in scotopic (dark-adapted, rod response) or photopic (light-adapted) conditions. Oscillatory potentials are also part of the flash ERG recording and permit to explore interplexiform retinal cells response, possibly dopaminergic amacrine cells (Wachtmeister, 1998). Oscillatory potentials response is dominated by rapid oscillations on the ascending phase of the b-wave (Wachtmeister, 1998). Pattern ERG investigates ganglion cell response and macula integrity. The stimulation employed is a black and white reversible checkerboard. The main retinal responses are the P50 wave and the N95 wave. Finally, multifocal ERG allows topographic mapping of retinal function in the macular area, and reflects bipolar cells and photoreceptors activity. Retinal electrophysiological measurements may have fewer flaws than OCT measures provided that it is recorded and analyzed by an experimented expert in ophthalmology and conducted following the International Society for the Clinical Electrophysiology of Vision (ISCEV) standards (Marmor et al., 2009).

In summary, besides structural and functional neuroimaging techniques to explore the hallucinator's brain, electrophysiological techniques focused on the retina could be crucial in gaining a better understanding of VHs.

3. Early visual processing and retinal dysfunctions in eye disease and Charles Bonnet syndrome

Eye disease is a well-known risk factor for the development of complex and recurrent VHs. Prevalence of VHs in ophthalmologic populations ranges from 0.4% to 63% (Menon, 2005; Tan et al., 2004). Visually impaired patients can experience stressful VHs known as Charles Bonnet syndrome (CBS), currently recognized as a set of symptoms including VHs that cannot be related to any psychiatric, neurologic or medical disorders (Lerario et al., 2013). VHs in CBS syndrome are generally characterized by abstract geometric patterns