Visual hallucinations in eye disease
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Introduction
Visual hallucinations have been a recognized association of eye disease for more than a century, the classification of different ophthalmological circumstances in which they occur first outlined by Uhthoff [1] in 1899. Yet, our understanding of the cause, pathophysiology and treatment of the phenomena has advanced little in the intervening years so that controversies first outlined in the 1930s remain unresolved to this day. Indeed, most of the advances of the last 70 years have been epidemiological or descriptive. We know the prevalence of visual hallucinations in a range of ophthalmological populations, typically around 10% [2] but varying between 0.4% [3] and 63% [4], the factors that increase their risk, the types of hallucinations experienced and their consequences for patients. Current theory relates the phenomena to loss of visual input (traditionally termed release but more recently, deafferentation [5]). Given the static nature of the field, one would not expect a snapshot review of literature to identify a radical change in our understanding or treatment of the phenomena and the 2003–2005 period covered by Rovner [6] or 2007–2008 covered in the present review are no exceptions. However, this is not to say that important advances have not been made and these are dealt with in turn below.

Risk factor profile for hallucinations in eye disease
Several epidemiological studies in the period covered have examined the risk factor profile for visual hallucinations, together with new evidence to suggest that up to 40% of patients have long-term hallucinations. Scotoma size and specific eye pathology do not influence hallucination risk. Induced hallucinations in normal individuals provide a model for those in eye disease, revealing a shift in thalamocortical circuitry and neurophysiological links to states of drowsy wakefulness. Serotonergic therapy emerges as a potential treatment. Two ophthalmological interventions are added to the list of procedures provoking hallucinations. Historical accounts of Charles Bonnet, his syndrome and two novel visual syndromes highlight ongoing difficulties of case definition and the wider clinical context in which visual hallucinations occur.

Summary
Current research into visual hallucination is predominantly ophthalmology-led, with increasing recognition of the phenomena, their prevalence and prognosis within the specialty. Deafferentation remains the best available pathophysiological account, although it fails to explain the absence of hallucinations in the majority of patients with eye disease. Whether hallucinations require treatment and, if so, what that treatment should be remains unclear.

Keywords
Charles Bonnet syndrome, deafferentation, ophthalmology, release
Table 1 Risk factors for visual hallucinations in eye disease

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<tbody>
<tr>
<td>Mean age</td>
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<td>75</td>
<td>72</td>
<td>71</td>
<td>70</td>
<td>62</td>
<td>79</td>
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<td>80</td>
<td>74</td>
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<tr>
<td>AMD study</td>
<td>+</td>
<td>NS</td>
<td>NS</td>
<td>0.001°</td>
<td>0.002</td>
<td>0.001°</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Acuity</td>
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<td>NS</td>
<td>NS</td>
<td>0.001°</td>
<td>0.002</td>
<td>0.001°</td>
<td>0.08</td>
<td>0.28°</td>
<td>0.001</td>
<td>0.97</td>
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<td></td>
<td>28.1°</td>
<td>0.015</td>
<td>&gt; 0.2d</td>
<td>0.05</td>
<td>0.019</td>
<td>0.015</td>
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<tr>
<td>Cognition</td>
<td>0.009</td>
<td>0.015</td>
<td>0.015</td>
<td>0.015</td>
<td>0.05</td>
<td>0.18</td>
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<tr>
<td>Female</td>
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<td>NS</td>
<td>0.015</td>
<td>&gt; 0.2d</td>
<td>0.05</td>
<td>0.18</td>
<td>NS</td>
<td>0.019</td>
<td>0.2d</td>
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<td>Lives alone</td>
<td>0.03</td>
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\( P \) values are given in the risk factors cells. Cells marked with * are significant in the opposite direction (i.e. younger age and living with another). Cells are left empty when the risk factor has not been measured. AMD, age-related macular degeneration; NS, \( P \) value not provided but reported nonsignificant.

*For acuity \( n = 421 \) through combining two groups.

\( P \) values relate to pooled data from Holroyd et al. [12,14].

*For acuity \( n = 96 \) through combining two groups.

*Relates to low-vision group over 64 years old \( n = 221 \).

*Odds ratio for worst versus best acuity or worst versus best contrast sensitivity controlling for sex, age, depression (do you often feel sad or depressed) and independence (can you prepare your meals).

*Age more than 60 years.

derived from the central 7.3% of the retina [17]. Acuity is thus an indirect measure of deafferentation; worse acuity implying greater deafferentation in conditions restricted to the central retina. However, not all studies have found an association between acuity loss and hallucination risk, perhaps because of the inclusion of disorders such as glaucoma which dissociate deafferentation from acuity [18] or because of statistical issues related to limited acuity range. Deafferentation theory would predict that hallucination risk relates to the sum of visual loss from both eyes rather from one eye alone. The significant association of hallucinations with bilateral visual loss (\( P = 0.001 \)) reported by Khan et al. [11**] in 2008 is consistent with this view. It may be that combined-eye acuity measures better predict hallucination risk than best or worst eye acuity measures typically used in previous studies. A novel and potentially important contribution reported by Jackson et al. [8] in 2007 is that contrast sensitivity may be a more sensitive measure of hallucination risk than acuity. Older age has emerged as a risk factor in previous studies and was replicated for the over 60-year age group in the study by Kinoshita et al. [10] who used a database (National Comorbidity Survey Replication) to examine the association between responses to a question assessing visual hallucinations with responses to a question assessing visual impairment. Drug and sleep-related causes were excluded by other questions in the database. However, the association of old age and hallucinations in this study is difficult to interpret given the lack of supporting clinical information. It is also weighed against the study by Abbott et al. [7**] who found the opposite effect (increased risk of hallucinations in a younger age group). Of nine studies investigating age as a risk factor, only three have found a significant but small effect of older age. Part of the reason for this variability may be a statistical issue related to the age range in different studies. How age might relate to deafferentation theory is unclear. Lower cognitive score was a risk factor for visual hallucinations in two previous studies [12,14], suggesting a link between hallucinations and early dementia; however, this has not been replicated in the study by Abbott et al. [7**] or Crumbliss et al. [9]. The association found in previous studies may be related to the inclusion of patients with stroke, a factor likely to influence cognitive score and identified as a risk factor for visual hallucinations [12]. The more recent work suggests that when other causes are excluded, visual hallucinations in patients with eye disease are not indicators of early dementia, a view supported by the finding that at 3-year follow-up, cognitive function in such patients had not declined [19]. Female sex has also been identified as a risk factor in several previous studies and replicated at trend level in the study by Khan et al. [11**]. The effect is small and only reaches significance or trend significance in larger scale studies, with the exception of the study by Teunisse et al. [15] in which the predominance of female participants (67%) may have influenced the ability to identify a gender effect. Living alone was identified as a risk factor in two previous studies [12,14], the implied lack of social stimulation interpreted as an indirect measure of sensory deprivation. However, this finding has not been replicated since, and Khan et al. [11**] found a significant association in the opposite direction. Although sensory deprivation additional to that caused by eye disease might be expected to increase the risk of hallucinations on theoretical grounds, it seems unlikely that the crude measure of living alone or in partnership usefully assesses this factor.

**Prognosis of visual hallucinations**

Patients with visual hallucinations and eye disease are typically informed that the hallucinations will pass with time, an impression based more on anecdote than...
evidence. Khan et al. [11**] cast doubt on this prognostic optimism. To date, the only longitudinal study to have investigated prognosis [19] found that out of 10 patients followed for 3 years, 40% were still hallucinating, 20% at unchanged hallucination frequency and 20% with reduced frequency. For the 60% without hallucinations, the average time for the symptom to resolve was 18 months, although in 20% this was directly related to the timing of laser treatment. The study by Khan et al. [11**] was cross-sectional and thus does not provide direct longitudinal data, nor did it assess measures of improvement such as changes in the duration or frequency of hallucinations; however, 36% (35/97) of patients had been hallucinating for at least 2 years, a percentage similar to that identified at 3-year follow-up in the longitudinal study. The implication is that although more than half of hallucinating patients recover, a significant proportion will continue to hallucinate for several years. More evidence is needed to help advise patients of their likely outcome.

### The eye in visual hallucinators

Beyond visual acuity, detailed examination of the eye has not been an important focus of most previous surveys of visual hallucinations in eye disease. Two studies in the period under review add to this literature. Abbott et al. [7**] used Bjerrum perimetry to plot the scotoma in each eye and calculated the area of overlapping field loss. They found a trend towards a larger area binocular scotoma in patients with visual hallucinations (P < 0.06) that became less significant when controlling for age and acuity, although the reduction in significance could be due to statistical issues such as the covariance of acuity and scotoma area. The lack of association with scotoma area has also been noted in a previous study using scanning laser ophthalmoscopy [13]. Deafferentation theory would predict lower hallucination risk with a smaller scotoma, so the absence of an effect is surprising. It may be that even a small macular scotoma crosses a threshold of deafferentation to place individuals at risk of hallucinations. If correct, one would only expect to find an association between scotoma area and risk for the very smallest scotomata. Alternatively, it may be that the level of deafferentation is better assessed by the summed scotoma area from both eyes than by the area of binocular overlap measured by Abbott et al. [7**]. Khan et al. [11**] found no difference in the relative proportion of choroidal neovascular and geographical atrophy AMD subtypes in patients with and without visual hallucinations, suggesting that visual hallucinations are not linked to a specific ocular pathology in AMD. Although an earlier study found a link between hallucinations and bilateral cicatrix in the macular region [20], it seems unlikely that hallucinations are linked to a specific class of retinal disease, given that they can also be caused by cataracts [21] and blindfolding [22].

### Neurophysiology of visual deafferentation

The neurophysiological link from deafferentation to hallucinations remains unclear; however, new evidence of relevance to the issue emerged in my 2008 study of induced hallucinations in normal individuals [23]. Purkinje’s doctoral thesis described a method of inducing hallucinations of geometrical patterns, colours and motion using flashing light. Termed Purkinje patterns, these induced hallucinations closely match geometrical hallucinations described by patients with eye disease (Fig. 1) and can be switched on and off in normal individuals by altering the luminance and frequency characteristics of the flash. The brain activity underlying induced hallucinations as measured by electroencephalography and functional MRI is consistent with a shift in the behaviour of thalamocortical circuitry from tonic firing, in which retinal signals are faithfully transmitted to the visual cortex, to burst firing in which retinal input and cortical output are partly dissociated, in effect leading to a transient form of thalamic blindness. The finding is of relevance to the neurophysiology of hallucinations in eye disease as loss of visual inputs would be expected to cause thalamocortical networks to shift to burst firing, or a threshold close to it. Burst firing is also linked to states of drowsy wakefulness, explaining why the combination of eye disease and drowsiness is particularly likely to lead to hallucinations.

### Treatment: cause and effect

Two case reports add to the range of ophthalmological treatments precipitating visual hallucinations. Meyer et al. [24*] raise the possibility that intravitreal bevacizumab (Avastin) for neovascular AMD causes hallucinations, although the mechanism is unclear. Two patients with left eye injections developed visual hallucinations from the first to third postinjection days without a change in acuity, an incidence of 3–5% in the case series (author reply to [25]). Details are not provided as to the temporal relationship of prior visual loss with the injection so the association may be coincidental; however, there is a compelling consistency in the two reports. Furthermore, one of the patients developed visual hallucinations after a second injection. In a different treatment setting, Wagle and Au Eong [26] describe the onset of hallucinations in the second postoperative day. Acuity had dropped from 6/120 to counting fingers in the operated eye although the intact eye may have been occluded by the prone position. The hallucinations resolved after 8 days by which time acuity had returned to preoperative levels. The case reemphasises the fact that ‘deafferentation’ need not imply neuronal loss, and that decreased visual stimulation...
Current evidence of whether or how to treat visual hallucinations in eye disease is largely derived from the case report literature as no controlled clinical trials have been reported. Lang et al. [27] add to this literature, describing a 78-year-old woman with a 1-year history of hallucinations with visual acuity of hand movements only, who became depressed (no ophthalmological diagnosis given). The patient was treated with venlafaxine (75 mg), a drug influencing both serotonergic and noradrenergic systems but predominantly serotonergic at this dose. Fortuitously, it was noted that her visual hallucinations ceased after 4 days, contrasting with the antidepressant effect of the medication that, as expected, took several weeks. Venlafaxine was changed to another serotonergic drug (citalopram 20 mg) because of side effects without recurrence of hallucinations, and the patient remained hallucination free at 6-month follow-up. The serotonergic system has been linked to visual hallucinations in other contexts (see below), and the report adds this class of drugs to anticonvulsant, antideimentia and antipsychotic classes reported as effective in some patients [28*]. Crumbliss et al. [9] examined whether acuity improvement through the use of visual aids helped treat hallucinations in 11 patients. Using a simple percentage change rating scale, three patients (27%) had a modest decrease in the frequency of hallucinations (10–70% decrease) measured between 2 weeks and 2 months after training in the use of visual aids, although the decrease in hallucination frequency was not correlated with acuity improvement. As the study did not have a control group without visual aids, it is difficult to determine whether the decrease in hallucination frequency is better than would be expected by spontaneous remission; however, the study outlines a simple method for monitoring changes in hallucination frequency that could be adapted for future longitudinal studies.

Charles Bonnet and his syndrome(s)
Bartlet [29] referred to Charles Bonnet in passing in the 1950s, but it was not until the 1980s that Bonnet entered the English speaking visual hallucination literature, remaining a prominent figure ever since. Most clinicians know only a handful of facts about him, and in the period under review, Hedges [30**] provides a biography of
Bonnet aimed at clinicians. Bonnet became interested in insectology when 16 years old, adding his own observations to the major works of the time culminating in a paper on parthenogenesis in aphids sent to the French Academy of Sciences that resulted in him becoming, at 20 years of age, its youngest corresponding member. He was awarded membership of the Royal Society of London when 23 years old on the basis of his work on insect metamorphosis, the respiratory pores of caterpillars and butterflies and the regeneration of fresh water hydra and tapeworms. Turning to botany, his observation of bubbles emitted from submerged illuminated leaves is still used in school classrooms today. It was only the emergence of visual problems limiting his use of the microscope that made him turn to psychology and philosophy when 34 years old and at the peak of his natural science career. Hedges [30**] provides the first complete translation of the relevant paragraphs in Bonnet’s Analytical Essay on the Faculties of the Soul remembered in the Charles Bonnet syndrome (CBS) eponym. CBS has its own history and complex usage, which is outlined in my general review of visual hallucinatory syndromes [28*]. Bonnet’s description of visual hallucinations contained three key elements: an elderly patient with intact cognition, eye disease and hallucinations with preserved insight, each of which have been emphasised as the core component of CBS in different uses of the term (Fig. 2a–c). The syndrome was coined in the 1930s by de Morsier who was struck by the fact that Bonnet’s case report, and others of a similar nature,
described elderly patients with intact cognition, thus differing from patients in whom visual hallucinations occurred in the context of dementia. De Morsier introduced the CBS eponym to differentiate those patients without cognitive impairment from those with Alzheimer’s and Pick’s disease and hypothesised that CBS related to a localized neurodegenerative brain condition unrelated to eye disease (Fig. 2a). The CBS eponym was well received but not the lack of role for the eye, and in the 1950s and 1960s, de Ajuriaguerra used the term to refer to visual hallucinations in the context of eye disease, arguing that the syndrome was caused by a combination of eye and cerebral disorders (Fig. 2b). The final use of the term emphasises the nature of the hallucinations rather than their cause. Gold and Rabins argued that CBS should be divorced from aetiology in a manner similar to the Capgras syndrome, in which a complex set of symptoms can be related to a range of different neurological and psychiatric disorders (Fig. 2c). Misunderstandings of the use of the term remain a problem for the literature. For example, Kinoshita et al. [10] found an association between visual impairment and auditory hallucinations and suggest that auditory hallucinations be incorporated into CBS. This makes no sense under the CBS definition in Fig. 2c or 2a, in which auditory hallucinations are specifically excluded.

Each of the three uses of CBS are correct in their own ways, the difference between them related to whether the intention is to refer to a specific cause of the hallucinations. Another difference between the three traditions of CBS usage is the attitude to whether eye disease can be held as a true cause of visual hallucinations when visual hallucinations do not occur in a significant proportion of patients with eye disease. Studies of visual hallucinations caused by eye disease typically rely on a range of exclusion criteria to avoid including subjects whose hallucinations may be related to another condition. An example of this use of exclusions is found in the correspondence of Tan and Au Eong [31] and Mckoy and McGartland over whether a relationship with sleep is consistent with the diagnosis of CBS. However, the
results of the study by Abbott et al. [7**] question the necessity for stringent exclusion criteria. Two sets of criteria for CBS were used, one excluding all possible confounding conditions and medications, the other more lenient. When compared, the two groups of CBS patients did not differ in terms of cognitive score, acuity, age, binocular field loss or types of hallucination reported. The finding questions the necessity and usefulness of the exclusion criteria used in previous studies.

Visual hallucinatory syndromes
Not all visual hallucinations are related to the eye, and it is important to keep in mind the spectrum of associated conditions when making the diagnosis. I have reviewed the type and distribution of visual symptoms in a range of conditions and found the three distinct but overlapping visual hallucinatory syndromes illustrated in Fig. 3 [28*]. The first syndrome is linked to deafferentation and consists of a range of simple phenomena associated to varying degree with more complex hallucinations to form subsyndromes. The second syndrome lacks simple hallucinations and consists of illusions and complex hallucinations, typically of figures or animals, extracampine hallucinations (a feeling of something being present), hallucinations in other modalities and delusional elaboration. It is found in conditions such as Parkinson’s disease, dementias and peduncular lesions and relates to ascending brainstem neurotransmitter dysfunction, particularly in the cholinergic system. The third syndrome consists of simple hallucinations and illusions without complex hallucinations, delusions or hallucinations in other modalities. It is found in lysergic acid diethylamide flashbacks, migraine and as a side effect of a variety of drugs related to the serotonergic system. By recognizing the different syndromes and their causes, clinicians may be prompted to further investigate or review treatment options when the visual symptom profile of a given patient fails to match their diagnosis.

Conclusion
Behind modest advances in the period 2007–2008 lies an important trend not yet mentioned. Whereas 10 years ago, most of the work relating visual hallucinations to eye disease would have been led by other specialties, today, ophthalmology and its related disciplines are setting the research agenda, largely within its own journals. The field has turned full circle and returned to the ophthalmology-led era of the 1920s and 1930s. That this is as it should be seems obvious given that ophthalmologists are the clinicians most likely to encounter the disorder and are in the best position to investigate it further. However, as recognized by previous generations and highlighted again above, the eye is part but not all the explanation for visual hallucinations in eye disease, the elusive missing factor likely to reside in the brain. Until we understand why most patients with eye disease do not have visual hallucinations, deafferentation theory remains incomplete. Further advances will require ophthalmology, neurology and psychiatry to work in partnership.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 110).


This study links visual hallucinations in eye disease to burst mode firing in thalamocortical circuits using induced hallucinations in normal sighted individuals.


A novel risk factor requiring further study. It is of potential importance because of increasing use of the treatment.


Potentially important report highlighting the possible therapeutic effect of a drug class previously untested in the context of visual hallucinations but theoretically linked to them.


A history of the Charles Bonnet syndrome emphasising different uses of the term.


A biography of Charles Bonnet aimed at clinicians, with translated excerpts of key passages related to visual hallucinations.