Cognition and morphological brain changes in Charles Bonnet syndrome

A thesis submitted to the University of Manchester for the degree of Doctor of Medicine in the Faculty of Medical and Human Sciences

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Abstract

This thesis is entitled ‘Cognition and morphological brain changes in Charles Bonnet syndrome’. It has been prepared by Dr Gregor Russell, and has been submitted in pursuance of the degree of Doctor of Medicine at The University of Manchester.

Charles Bonnet syndrome (CBS) is defined as complex persistent visual hallucinations in the absence of mental disorder. It is associated with advanced age and poor vision. It is common, with prevalence estimates of up to 63% among older people with significant visual impairment. CBS would not be diagnosed in the presence of dementia, but its relationship to milder cognitive impairment is unclear. The few studies that have examined this are underpowered and provide contradictory results. There are 16 case reports of dementia emerging in people with a diagnosis of CBS. These cases raise the possibility of an association between impaired insight at diagnosis of CBS and the subsequent development of dementia.

This thesis reports the findings of a prospective cohort study which describes changes in cognitive functioning over one year in patients with CBS and age-matched controls. Participants were recruited from low vision and glaucoma assessment clinics. A clinical assessment was carried out by an old age psychiatrist, and participants had a detailed assessment of visual functioning. This thesis also describes the findings of the first study to use voxel-based morphometry (VBM) to investigate changes in volume of grey and white matter in CBS. Participants were recruited from the same clinics as the cohort study, and underwent MRI scanning on a 1.5T scanner, to a protocol designed to produce 1mm³ voxels.

Twelve participants with CBS and ten controls were followed up. Two people in the CBS group developed dementia, while none did in the control group. The CBS group showed a mean change in the score on the Addenbrooke’s cognitive examination (ACE-R) of -3.7 points, compared to a change of +1.4 in the control group. This difference was not statistically significant. The CBS participants performed worse on the verbal fluency item of the ACE-R, a difference which was statistically significant. The VBM analysis was conducted on 11 CBS participants and 11 controls. The CBS group showed an increase in grey matter volume in the right cerebellar hemisphere. This difference retained significance after family-wise error correction, non-stationary correction, and ANCOVA to control for the effects of possible confounders.

As far as the author is aware, these are the most methodologically robust studies to date to have investigated cognition and morphological brain changes in CBS. The findings of the cohort study were inconclusive. However, the two cases of dementia in CBS patients add weight to the suspicion that this is a clinically important outcome in the condition, and the finding of abnormalities in frontal lobe testing in participants with CBS fits with a theoretical model of visual hallucination generation. Moreover, this type of research appears to be acceptable to a frail and visually disabled population, and studies powered to investigate this issue more fully would be feasible. The VBM findings report the presence of underlying structural brain abnormalities in CBS, in a region not usually associated with visual hallucinations. Possible links with Lewy body dementia, and implications for theories of visual hallucinations, are discussed.
Lay Abstract

This thesis is entitled ‘Cognition and morphological brain changes in Charles Bonnet syndrome’. It has been prepared by Dr Gregor Russell, and has been submitted in pursuance of the degree of Doctor of Medicine at The University of Manchester.

Charles Bonnet syndrome (CBS) is a common condition among older people with poor eyesight. People with this condition experience visions of people and objects which are not actually there. In CBS these visions are not caused by mental health problems. People with dementia can also experience visions, and the relationship between these conditions is uncertain. A diagnosis of dementia would exclude CBS, but milder problems with memory would probably not be picked up by eye specialists who see most cases of CBS.

This thesis reports the findings of two linked studies. In the first, a group of patients with CBS, and a group of people of similar age and visual functioning, had their memory tested by a psychiatrist and their vision measured by an optometrist. They were then followed up for a year and the tests were repeated. The number of people who developed dementia in each group was counted. In the second study, a group of people with CBS, and a comparison group, underwent MRI scans of their brain. The scans of each group were combined and then the two groups were compared to see if any regions of the brain were different in people with CBS.

The first study found that two patients with CBS did develop dementia, while none of the comparison group did. The CBS group also did worse on memory tests after a year, while the comparison group did a little better. However, because the study was small, these results could have happened by chance. The people with CBS did worse on the part of the test that examines the frontal lobe of the brain; this difference was unlikely to have happened by chance. The MRI scans showed the brains for patients with CBS were different, with more grey matter in a part of the brain called the cerebellum. It is unlikely that this difference was just chance.

The most important finding of the first study is that this sort of research is acceptable to the participants, despite their age and health problems. It is therefore feasible to consider a larger, more powerful study that could determine the nature of the relationship between CBS and dementia. As this would be important in the planning of services for the timely diagnosis of dementia, this would be a worthwhile study to conduct. It also suggested that the frontal lobe may be abnormal in CBS, and this may be partly responsible for why some people with poor eyesight get CBS while others do not; this is a very tentative finding but worth looking at further. The MRI study reports that the brains of people with CBS are different from those without it. The area of the brain affected is not usually thought of as related to visual hallucinations, but it is involved in the control of rapid eye movements and has been shown to be abnormal in a form of dementia where visions commonly occur. This finding could have implications for theories of how visual hallucinations develop, and which parts of the brain are involved in producing them.
Declaration

I declare that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.
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I would like to thank the following people, without whose kind and patient support, encouragement and assistance this work would not have been possible:


I would also like to thank all the participants, and their families, who willingly gave up their time to assist with this research; without their generosity, there would be no study to report on.
The Author

I am a consultant old age psychiatrist working with Bradford District Care Trust, and hold the degrees of MB ChB and BSc (Hons) from the University of Glasgow, and MMedSc from the University of Leeds. My research experience includes working as a research assistant while an undergraduate on studies on immunocytochemistry in rat spinal cord, and on intestinal helminth infection in twins in The Gambia. I have carried out research on polyamine production by protozoa as part of my BSc degree, and on outcomes of self harm following assessment by different professional groups as part of the MMedSc degree. The latter led to a publication in the journal *Crisis* as lead author. More recently, I have acted as Principal Investigator for two National Institute for Health Research portfolio studies at Bradford District Care Trust, and assisted as a local collaborator for a further two portfolio studies.
The Extent of My Personal Contribution

I originated the concept of this work, and developed the study it describes. I designed and executed the literature review that is set out here. I completed the ethics and R&D applications, and designed the study documents. I put together the team of clinicians contributing to the work, and conducted around 80% of the consenting and data gathering contacts. I prepared all the study amendments for ethics and I was present for all the MRI scans conducted. I carried out all the data analysis, including the statistical testing, and conducted the VBM analysis.

I had assistance from my supervisors and advisor in reviewing the study design and progress, and in reviewing the drafts of this thesis. I had assistance from colleagues in the optometry team at Manchester Royal Eye Hospital in designing the vision assessment components of the study, and in interpreting the findings in this area. These colleagues also carried out the majority of recruitment screening. The remainder of recruitment screening was conducted by a colleague from Dendron, Lewis Harpin. I had support from Dr Varinder Singh with consent and data gathering; Dr Singh carried out around 20% of these contacts. I had assistance from Dr Roland Zahn, Dr Sha Zhao and staff at the Wellcome Trust clinical research facility in developing the scanning protocol from the MRI component of the study, and in actually conducting the MRI scans. Dr Zahn also provided tutorials in VBM techniques and reviewed my progress and findings during the VBM analysis, and Garry Byrne helped with updating software in order that I could complete the
necessary work. Finally, Julie Morris provided advice on what statistical tests would be appropriate to use when analysing the data obtained in this work.
Dedication

I would like to dedicate this thesis to my wife and family. Their patience, love, and cups of coffee, have been essential to the completion of this work.
Part I

Introduction, Literature Review and Study Development
1. Introduction and Background

1.1 Introduction

Medicine has a long tradition of eponymous syndromes, whose names commemorate the significant contributions to our understanding of ill health by our predecessors. Some of these describe conditions whose importance grows over time, and pass into everyday usage; an example would be the dementia described by Alois Alzheimer and which took his name. Others, such as the syndrome of believing that familiar people have been replaced by imposters, first described by Joseph Capgras, have become redundant, being seen now as symptoms of other disorders.

There is a third group whose status remains unclear; while their pathological basis is not yet certain, they describe interesting phenomena which are not entirely explained by the current understanding of their field. One such condition is Charles Bonnet syndrome, widely held to describe the presence of complex visual hallucinations in eye disease- though in fact this is a misunderstanding of its complex and controversial history. As a diagnosis, it is approaching its 80th birthday, but it remains a ‘medical curiosity’, due to the remarkable complex and vivid visual hallucinations experienced by those who develop it, rather than being the focus of a major research effort. Indeed, it has faced questions over whether it describes a valid diagnosis at all, and at times there have been calls for its use to be abandoned. However, as our understanding of the neurological basis of psychiatric phenomena develops, its status as a syndrome where prototypically ‘psychiatric’ symptoms occur with preserved insight into their unreal nature seems likely to bring it to greater prominence, and makes research into its aetiology, and its relationship to other disorders where complex visual hallucinations are experienced, of increasing relevance.
This thesis describes work undertaken to try to address these two areas. It explores the relationship between Charles Bonnet syndrome and impaired cognitive functioning; and it attempts to characterise changes in brain structure that may underlie the condition. The thesis is divided into four parts. In Part I, the current understanding of Charles Bonnet syndrome is set out with a review of the published literature relating to it. In particular, the literature describing its relationship to cognitive impairment is reviewed in a systematic way. This leads into Part II, in which a clinical study of a cohort of patients with Charles Bonnet syndrome is reported. This prospective study follows the cohort, and a comparison cohort, up for a year to monitor changes in their cognitive functioning and detect the development of dementia. In Part III, a neuroimaging study using the technique of voxel-based morphometry, applied to MRI scanning, is reported. This study sets out to detect changes in the grey or white matter in people with Charles Bonnet syndrome, and so attempts to relate the condition to underlying neurological abnormalities. Finally, Part IV includes appendices where material related to the main body of work is presented.

In chapter 1, I will introduce Charles Bonnet syndrome, setting out in 1.2 the reasons for my interest in it, and for making it the subject of this thesis. In part 1.3, I present a brief history of the condition, describing the emergence of controversies over its aetiology and relationship to dementia which remain unresolved until the present day. Part 1.3 also sets out the current most widely accepted diagnostic criteria for Charles Bonnet syndrome. In parts 1.4, 1.5 and 1.6, I present a review of the literature relating to its phenomenology, epidemiology and aetiology, respectively. Finally, in part 1.7, I summarise the findings of this review, and set out the next step, focussing on the relationship with cognitive impairment and dementia in more detail.
1.2 Background

The eponym “Charles Bonnet syndrome” was introduced in 1936 by a Genevan neurologist, Georges de Morsier, in a paper discussing the nature and classification of visual hallucinations (de Morsier 1936). It was initially intended to describe the occurrence of visual hallucinations in the elderly, in the absence of cognitive impairment. The name chosen was a reference to his fellow Genevan, the natural philosopher Charles Bonnet, who in 1760 published an account of the hallucinations experienced by his grandfather, Thomas Lullin. Of his grandfather’s experiences, Bonnet wrote:

‘I know a respectable man full of health, of ingenuousness, judgement and memory, who, completely alert and independently from all outside influences, sees from time to time, in front of him, figures of men, of women, of birds, of carriages, of buildings… The tapestries in his apartment appear to change suddenly; these tapestries cover themselves with paintings displaying different landscapes. All these visions appear to him in perfect clarity and affect him as strongly as if the objects themselves were present. However, they are only paintings because the men and women do not talk and no noise comes to his ear’

Bonnet reported that Lullin underwent procedures to remove cataracts from both eyes, and that the hallucinations did not begin until several months after the second such operation. The hallucinations lasted around six months, but ceased when Lullin’s vision deteriorated further. Lullin’s case, as described by Bonnet, illustrates well the features that would later be ascribed to the condition: he was of advanced age, and had a condition which significantly impaired his vision. The hallucinations he experienced were varied in content, but were vivid, complex, and formed; and they occurred in clear consciousness in a person of intact cognition. They developed as his visual impairment progressed, but then remitted as the impairment advanced towards blindness.
My first clinical contact with Charles Bonnet syndrome came in 1999, as a junior doctor. I had been involved in managing a gentleman in his 70s on an inpatient old age psychiatry ward. He reported vivid and complex visual hallucinations which were present at some point of every day. He saw people who he described as “gypsies”, who would sit and watch him in silence. The people he saw were of varying size, but were in general very small, at only around a foot tall. At times there were very many of these people, to the point where every available surface was occupied by them. He found the experience unsettling.

At first he was able to recognise the unreality of these experiences, and his cognitive functioning, while not entirely normal, was relatively good. However, as time passed he became more convinced that these were real people, and formed a belief they could enter and leave his room using a tunnel under his bed. His cognition deteriorated and a diagnosis of dementia was made.

I recalled that he was initially given a diagnosis of Charles Bonnet syndrome, and I was intrigued by the eponym, and the remarkable clinical experiences it described. I reflected that in subsequent years I had come across a few other patients who presented in a similar way, with complex visual hallucinations preceding the development of a clear dementia syndrome. On discussion with colleagues in old age psychiatry, many of them reported seeing patients with similar histories. Given my experiences, I wondered whether a relationship between Charles Bonnet syndrome and dementia was recognised in the literature.

My first step was to look in established textbooks to determine if this was a well understood phenomenon. I consulted Lishman’s Organic Psychiatry (ed. David, Fleminger, Kopelman et al., 2009) and the Oxford Textbook of Old Age Psychiatry (ed. Jacoby, Oppenheimer, Dening and Thomas, 2008), but found that there was little information on Charles Bonnet
syndrome in either book. The Oxford Textbook did cite a study (Pliskin et al. 1996) which suggested that some cognitive impairment is present in many cases of Charles Bonnet syndrome, but concluded that ‘the link between Charles Bonnet syndrome and Dementia with Lewy bodies is uncertain’.

I then went on to carry out a brief investigation of the literature published in journals relating to Charles Bonnet syndrome. This initial, non-systematic review focussed on a number of review articles (Menon et al. 2003, ffytche 2005, Menon 2005, Rovner 2006, Hedges 2007), and established that, while the potential for an association had been commented on, the issue awaited resolution.

I found this exciting. The National Dementia Strategy (Department of Health, 2009) had recently been published, and had made the early diagnosis of dementia one of its priorities. My clinical experience suggested that there may be a population of people who present with symptoms suggestive of an ophthalmological condition, but who actually have early symptoms of dementia. If this was in fact the case, then it offered the prospect of recognising and offering treatment earlier for this group. My initial review of the literature suggested this was a gap, and one that could be addressed by relatively straightforward epidemiological study design, and which could be of clinical significance.

1.3 Visual hallucinations and the Charles Bonnet syndrome- a brief history

Charles Bonnet (1720-1793) was a Swiss naturalist and philosopher, and was a resident of Geneva for most of his life. He made important contributions to the fields of entomology and botany in the mid-18th century. He was recognised for this work by being made a Fellow of the Royal Society at the age of only 23. As his eyesight began to fail, his work turned to philosophy, and in 1760 he published a book entitled *Essai analytique sur les facultes de*
l’ame. It contained a detailed and vivid account of the visual hallucinations suffered by his
grandfather, which is set out in chapter 1.1 above. This account was of considerable
significance, and has been described as ‘arguably the beginnings of a modern approach to
psychiatric phenomenology’ (ffytche 2005).

In the following 170 years, the phenomenon of visual hallucinations in people in whom no
mental illness was present was documented by a number of authors. Colman (1894)
described three such cases, and noted that these were:

‘…far from infrequent. They are usually extremely definite, so that the patient can give an
extremely vivid and detailed account of them. Unless he is much out of health, he rarely
believes in their reality’.

Flournoy (1902) published Lullin’s own account of his experiences, which provided even
more detail relating to the hallucinations, noting in particular the presence of many simple
hallucinations, which Bonnet had omitted to mention. More cases were described in the
French literature, including by Naville (1908) and Flournoy (1923).

The phenomenon was also described in the British Medical Journal in 1925, by Ormond. He
described a case of an ‘old woman’ who saw ‘faces’ peering at her through windows, making
‘grotesque grimaces’ which she grew to find ‘unpleasant and disturbing’, while all along
being ‘quite aware that they were not real’. Ormond speculated on the aetiology of the
condition, in particular whether it was caused by pathology affecting the eye, or the brain;
and noted that during his work among ‘totally blind men’, he ‘never had a patient who related
similar symptoms’.

In 1936, another resident of Geneva, a neurologist named Georges de Morsier, published a
paper entitled ‘Les automatismes visuels. (Hallucinations visuelles retrochiasmatiques)’. In
this paper, de Morsier described six cases of patients presenting with visual hallucinations, and posed the question as to whether the visual hallucinations found in neurological disease were different from those seen in chronic psychosis. He felt they were not, but that they could instead be differentiated by the presence of other neurological symptoms. He went on to describe several separate syndromes of hallucinations, one of which he named ‘Charles Bonnet syndrome’ (CBS), after his fellow Genevan. In de Morsier’s initial description, this was to indicate hallucinations in elderly people, with ‘complete integrity of other cerebral functions’, and without eye disease.

Figure 1: Charles Bonnet (left) and Georges de Morsier (right)

A further significant addition to the literature took place in 1951, with Bartlett’s detailed description of the hallucinations described by a man of 84, who had undergone bilateral cataract extractions and suffered a probable haemorrhage of the choroid. In his discussion Bartlett drew a parallel between the visual hallucinations described in patients with significant visual impairment, and the phantom pain syndrome seen in patients who have
undergone an amputation. He stated: ‘an important factor in the production of hallucinations is the absence of normal stimuli to the part of the brain concerned’. This is the deafferentation hypothesis- that the impairment of afferent stimuli to the visual cortex leads to the production of hallucinations- and it has been widely held to be an important part of the aetiology of the syndrome ever since.

A further significant development took place in 1956, with the publication of a paper by Hecaen and Garcia Badaracco. They disputed de Morsier’s rejection of a role for the eye in CBS, and instead defined the condition as visual hallucinations in the presence of eye disease- entirely the opposite of what de Morsier intended (ffytche 2007). This redefinition was adopted by de Ajuriaguerra, a contemporary of de Morsier at the University of Geneva, where he was Director of Psychiatry. He further altered the definition of the condition by including patients with cognitive disorders in the case series he published with colleagues (Burgermeister et al. 1965).

The inclusion of patients with cognitive impairment ignited a controversy which has persisted ever since, and caused de Morsier to return to the subject despite having retired. In 1967 he presented a review of 18 cases of CBS, and noted that in five of the cases vision was recorded as being normal, or nearly normal. In his conclusion he explicitly states that

‘il n’existe pas de correlation entre les hallucinations visuelles et les lesions des globes oculaires’.

He denied that impairment in visual afferents could lead to hallucinations, and claimed that they are always caused by pathology of the brain. He speculated that the abnormality responsible may be found in pulvino-cortical pathways (ffytche 2007). However, this failed to resolve the matter, and the debate over the contribution of eye disease to the development of CBS continues to the present time.
Also within the same paper, de Morsier addressed a further controversy which has proved persistent: the relationship of CBS to cognitive impairment. He made a pointed rebuttal of Burgermeister et al. (1965), noting that all 11 patients presented in the paper suffered from dementia. In the light of this he stated that, ‘by definition, none of these cases had Charles Bonnet syndrome, contrary to what the authors think’.

Further significant contributions were made by Cogan (1973) and Lance (1976). Cogan expanded on Bartlett’s visual afferent hypothesis, describing the resulting hallucinations as ‘release phenomena’; and Lance described complex visual hallucinations in a range of conditions, noting that the hallucinations were confined to the area of the visual field deficit. Neither however used the term ‘Charles Bonnet syndrome’; and nor did White (1980), when describing three patients who, from the descriptions given, would have attracted this diagnosis.

The modern study of Charles Bonnet syndrome in the English language literature began in 1982, with the publication of two papers, both in the psychiatric literature, by Berrios and Brook, and Damas-Mora et al. It was not an auspicious start: two of the three cases presented by Berrios and Brook had dementia. Their discussion notes that the definition of the syndrome had been broadened to such an extent that they felt there was little point in using the eponym at all.

Damas-Mora et al., however, suggested a set of diagnostic criteria which could narrow the focus of the condition to a more specific group of patients. In the absence of clear evidence as to the role of eye disease, or of specific brain lesions, they took a phenomenological approach, avoiding issues of aetiology. Podoll (1989) and Gold and Rabins (1989) both made a further attempt to define clear diagnostic criteria, further developing the phenomenological approach; and the Gold and Rabins criteria were later refined by
Teunisse et al. (1996). The Teunisse criteria are set out in table 1 below, and a summary of all the criteria, showing the evolution of the syndrome over time, is provided in Appendix 1.

Table 1: The Teunisse et al. (1996) criteria for diagnosis of Charles Bonnet syndrome

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<td>1. At least one complex visual hallucination within the past four weeks</td>
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<td>2. A period between the first and last hallucination exceeding four weeks</td>
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<td>3. Full or partial insight into the unreal nature of the hallucinations</td>
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<td>4. Absence of hallucinations in other sensory modalities</td>
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<td>5. Absence of delusions</td>
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<td>6. Hallucinations cannot be explained by the presence of a psychiatric disorder</td>
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In clinical practice, there is still a lack of precision in the use of the term ‘Charles Bonnet syndrome’. The association of hallucinations with eye disease remains the key feature of the condition in many clinicians’ understanding. The operationalised definitions set out in Appendix 1 are helpful in giving the opportunity to apply the diagnosis of Charles Bonnet syndrome in a consistent and replicable manner, and have allowed research to progress in the years that have followed. However, there is still no universally accepted set of diagnostic criteria for CBS, and many published studies still make no reference to any of the criteria described here, raising questions over whether the population they describe is the same as that which would have been obtained by using one of the explicit frameworks. In recent work where the researchers have explicitly stated which criteria they have used, it has most often been those of Teunisse et al.. These have the advantage of being operationalised in a clear and unambiguous manner, and are constructed so as to avoid contentious questions around aetiology.
1.4 Charles Bonnet syndrome: Phenomenology

The visual hallucinations seen in CBS are well illustrated by Lullin’s original case. They are complex, well defined and localised in external space (Menon 2003). Faces and people are very frequently seen, and are sometimes distorted, in miniature, or wearing unusual clothing (Fernandez et al. 1997, Rovner 2006). Animals or even landscapes are often seen, as are grid-like or branching patterns (Menon 2003). The content of hallucinations can be repetitive, or can vary extensively over time. The duration and frequency of hallucinations is also very variable, from brief episodes weeks or even months apart, to continuous (Fernandez et al. 1997). ffytche (2005) proposed that the phenomenology of the hallucinations could give an indication as to their origin, with hallucinations characterised by ‘grid patterns, distorted faces, unfamiliar figures in bizarre costume and extended landscape scenes’ being related to ophthalmic and visual pathway pathology, and those including ‘isolated animals and [often familiar] figures’ being more suggestive of dementia or other psychiatric conditions. Subjects’ reactions to hallucinations can also vary but are frequently negative, with a quarter of patients reporting anger, anxiety, paranoia, or even terror (Menon 2003).

1.5 Charles Bonnet syndrome: Epidemiology

While most of the literature relating to CBS remains in the form of case reports, there have been a number of observational studies which have attempted to define the prevalence of the condition. A systematic consideration of the evidence relating to prevalence is beyond the scope of this thesis, but Appendix 2.2 provides a summary of studies in this area. These studies have given values for prevalence of between 0.4% and 63%. This wide variation seems to relate to differences in the population studied. Studies looking at patients attending old age psychiatry outpatient clinics (Berrios and Brook 1984, Norton-Willson and Munir 1987, Cole 1992) found low rates of CBS (in 2/150, 8/434 and 13/2000 cases respectively).
Howard and Levy (1994) examined a population of old age psychiatry inpatients, and diagnosed CBS using the Damas-Mora criteria in 18/101. There have been no studies of CBS in the old age psychiatry population since that time.

Low rates have also been found when unselected patients attending ophthalmology outpatient clinics have been studied. Holroyd et al. (1994) found CBS in 8/127 ophthalmology clinic attenders, all of whom were over the age of 60. Tan et al. (2004) only found 4 cases in 1077 patients attending a ‘comprehensive ophthalmology clinic’; and Shiraishi et al. (2004) also found low rates of CBS, with only 5/1000 consecutive new referrals to low vision and optometric clinics meeting Teunisse criteria. However, both populations retained relatively good visual acuity. Both populations also contained a high proportion of younger patients, with the mean age of the Shiraishi et al. sample being 51.3 years.

In contrast, when populations with high rates of visual impairment, or greater mean age, are studied, much higher rates are found. These studies report a prevalence of between 11% and 63%, the latter in Menon (2005). Of particular note are the studies by Teunisse et al. (1995) and Khan et al. (2008). Teunisse et al. compared a population attending a low vision clinic with attenders at an optometry clinic; the latter group had relatively good visual acuity. It used clear, operationalised diagnostic criteria; and recruited large numbers of patients. CBS was found in 33/300 of the low vision patients, but only 2/200 of the patients with preserved visual acuity. The authors reported a clear association between bilateral impaired visual acuity and CBS, with acuity of logMAR 0.3 or worse in the better eye being associated with considerable risk. Khan et al. (2008) studied 360 people with end stage age-related macular degeneration, and found that 97 (27%) satisfied the Teunisse criteria for CBS. They found that worse visual acuity was strongly related to CBS, with an odds ratio of 3.5 (95% confidence interval 1.6-7.5) for being given a diagnosis of CBS in those with a Snellen visual
acuity in the better eye of worse than 6/36, compared to those with a visual acuity of better than 6/12.

While most of the literature suggests an association between visual impairment and CBS, there are some studies that have reported contradictory findings. Crumbliss et al. (2008) found no correlation between the severity of visual loss and the presence of CBS, though the number of participants was small (50) compared to Teunisse et al. (1995) and Khan et al. (2008). Both Abbott et al. (2007) and Khan et al. (2008) looked at the complexity of visual hallucinations, and found no increase in this with increased visual loss.

Three other factors reported to confer a risk of developing CBS are increased age, female sex, and social isolation. Holroyd et al. (1994) and Teunisse et al. (1995) both report a significant association between CBS and increased age. However, no such association was found by Khan et al. (2008); indeed, they go further, noting that Teunisse et al. did not correct for visual acuity in their analysis, and speculating that if they had done so, then the association with age may not have proved significant. It remains the case, however, that most patients diagnosed with CBS are over the age of 65; while there are a few case reports describing the syndrome in younger adults (Hartman 1995, Gittinger et al. 1989, Ugas Ballester 2008), and even children (Alao et al. 2000, Mewasingh 2002), the mean ages in epidemiological studies is generally in the range of 75-85.

Literature relating to gender seen in CBS generally shows a preponderance of cases in females. However, as is noted above, most cases are found in the over 70s age group, in which there are higher numbers of females. When this is controlled for, there is little consensus between studies, with Teunisse et al. (1995) reporting no statistically significant gender effect, but Holroyd et al. (1994) and Scott et al. (2001) claiming to detect a significant association with female sex.
The literature relating to social isolation is similarly contradictory. Holroyd et al. (1994) claimed that living alone was a risk factor for developing CBS. Cole (1992) reported that out of six cases felt to be socially isolated, five immediately ceased having hallucinations when moved to a more stimulating environment. Teunisse et al. (1999) found no association between living alone per se, but did report that the quality rather than the number of social contacts was a relevant factor. Gilmour et al. (2009) reported that living alone was not a risk factor; and Khan et al. (2008) report that those living alone actually had reduced rates of CBS.

In summary, there is reasonably good evidence that bilaterally impaired visual acuity is a significant risk factor for the development of CBS. While the condition is seen in those with preserved visual acuity, this is uncommon, whereas in those with significant acuity impairments rates of 12-25% are commonly found, with even higher rates reported in some studies. Though there is some debate in the literature, CBS is generally a condition affecting the elderly, while the literature on gender and social isolation is less clear, and allows no firm statements to be made on these matters.

1.6 Charles Bonnet syndrome: Aetiology

The diagnostic criteria for CBS discussed in chapter 1.3 are set up to avoid reference to aetiology, and there is little in the way of robust research into the relationship of the condition with specific underlying brain or eye abnormalities. Most of the evidence that does exist is in the form of case reports or case series.

However, the evidence that does exist does not support de Morsier in his contention that there is no relationship between CBS and visual impairment. While the studies reported in chapter 1.5 above show some disagreement, on balance they appear to demonstrate a link
between CBS and significantly reduced visual acuity. Among the case reports, a wide range of eye pathology has been reported to be associated with the condition. This includes age related macular degeneration, cataract, glaucoma, retinal detachment, enucleation, optic neuritis in multiple sclerosis, retinitis pigmentosa, and CMV retinitis in AIDS (Menon et al. 2003). There is no robust research reporting the relative frequency of CBS in different ophthalmological conditions; though in studies which did not select cases on the basis of a pre-existing ophthalmological diagnosis, age related macular degeneration is usually the most common diagnosis found in people with CBS (Teunisse et al. 1996, Nesher et al. 2001, Tatlipinar et al. 2001, Vukicevic and Fitzmaurice 2008, Crumbliss et al. 2008, Gilmour et al. 2009).

However, it is clear that eye disease is neither necessary nor sufficient to explain the development of Charles Bonnet syndrome, and de Morsier’s insistence that there must be an underlying brain abnormality in order for the hallucinations to be manifest appears to have some validity to it. Little research has considered this area, with there being only three neuroimaging studies of the Charles Bonnet syndrome in the literature. Shedlack et al. (1994) report MRI findings which suggest an increase in small vessel cerebrovascular disease in the posterior white matter, and so offer some support to de Morsier’s hypothesis of involvement of pulvino-cortical pathways. ffytche et al. (1998) carried out fMRI and found increased activity in the visual accessory areas; while a small study, with only eight participants with CBS, 15 years on this remains the most robust evidence of abnormal underlying brain processes in the condition. Adachi et al. (2000) used MRI and SPECT to investigate five participants diagnosed as having Charles Bonnet syndrome. They found increased perfusion in the temporal lobe, striatum and thalamus of all five participants on SPECT. There was also evidence of cortical atrophy posteriorly in 3/5 participants.

Several case reports of SPECT in CBS have found a range of abnormalities, most frequently hypoperfusion of the occipital cortex (Sichert and Fuchs, 1992; Guerra-Garcia, 1997;
Kanzaki *et al*., 1998; Kishi *et al*., 2000; Holroyd and Wooten, 2006; Kazui *et al*., 2009; Gil Navarro *et al*., 2011). However, the functional imaging reports are all unable to comment on whether the abnormalities found were the cause of the condition, or whether they emerged as a result of it.

In addition to the imaging studies reported above, a number of case reports have described a range of neurological conditions as being associated with CBS. These have included cranial arteritis, meningioma, multiple sclerosis, pituitary tumours, temporo-parietal trauma, and occipital infarction (Menon *et al*., 2003).

Finally, a number of authors have attempted to develop overarching theories of visual hallucinations which have included Charles Bonnet syndrome within a broader framework. These have included de Morsier (1936, 1938, 1967), who described a classification of visual hallucinations which included 12 categories, of which CBS was one. More recently, Manford and Andermann (1998) suggested three categories of visual hallucinations, related to epilepsy, visual pathway lesions and ascending cholinergic and serotoninergic pathways. ffytche (2007) developed this concept further, placing Charles Bonnet syndrome as the prototype of disorders where visual hallucinations arise as a result of de-afferentation. Finally, Collerton *et al*., (2005) suggest a ‘perception and attention deficit’ model of visual hallucinations, where either a reduction in the information from the retina or a disturbance in the brain’s systems of sustaining attention can both lead to abnormal perceptions being experienced. In Charles Bonnet syndrome, the former situation is likely to play a more significant role, but a combination of both factors is believed to be involved.
1.7 Summary

Of the two significant controversies relating to the diagnostic scope of Charles Bonnet syndrome, one has seen reasonable progress in recent years. The balance of evidence suggests that de Morsier was incorrect, and there is a relationship between visual impairment and Charles Bonnet syndrome, with significant loss of visual acuity conferring an increased risk of developing the condition.

The other controversy - the relationship to cognitive impairment and dementia - appears to have seen less progress. The widely used diagnostic criteria are constructed so that absent insight or clear dementia excludes a diagnosis of Charles Bonnet syndrome. Major reviews of the subject (Menon et al. 2003, ffytche 2005, Rovner 2006, Hedges 2007) note the possibility that some cases of CBS may progress to dementia, but overall recommend reassurance be given to those with the condition that it does not signify the presence of significant psychiatric morbidity.

However, the evidence they base these judgements on is limited, and the situation in clinical practice is not necessarily so clear cut. Most CBS is seen by eye specialists, who will be unfamiliar with making a diagnosis of dementia. Moreover, they may not be aware of less common types of dementia such as Lewy body dementia, where visual hallucinations are more common, and severe memory impairment less common, early in the progress of the disease. Even in old age psychiatry settings, where there is a familiarity with both dementia and CBS, it is not always possible to be certain of diagnosis at the outset of the condition, and it is only with follow-up that the nature of the condition becomes clear.

This raises a number of important questions. It is likely that some people who are diagnosed with Charles Bonnet syndrome will go on to develop dementia, but given the advanced age of many of those with this condition, this relationship may just be coincidence and not
represent a causal association. In order to understand the relationship better, it would be necessary to know answers to the following questions: what proportion of people initially diagnosed with Charles Bonnet syndrome subsequently go on to develop dementia? Which types of dementia do they develop? Are there characteristics, such as performance on cognitive testing, or phenomenology of visual experiences, that predict which people will go on to develop dementia? Are there underlying brain abnormalities common to patients with CBS? Lastly, are these abnormalities similar to the patterns of abnormality recognised in other conditions associated with visual hallucinations, such as Parkinson’s disease, Lewy body dementia, or Alzheimer’s disease?

These are the questions that this thesis will set out to address. I will first set out evidence from a systematic review of the literature relating to cognitive impairment and dementia in Charles Bonnet syndrome. I will then outline the process by which the studies this thesis describes were developed. Following this I will set out the methodology and findings relating to two related studies:

- firstly, a prospective cohort study investigating changes in cognitive functioning and the development of dementia among patients with Charles Bonnet syndrome.

- secondly, a neuroimaging study using voxel-based morphometry to look for evidence of underlying brain abnormalities in the condition.

Finally, I will discuss the results and significance of the findings of these studies in relation to existing theories about how visual hallucinations are produced; and I will make some suggestions regarding further research that this work indicates may be of value.
2. Systematic Review of Literature

2.1 Introduction

This chapter presents a systematic review prepared during the first year of the degree programme. I have subsequently updated and edited it, and prepared it as a paper which has been submitted to the Journal *International Psychogeriatrics*. A copy of this manuscript is included in appendix 3.

The role of insight in, and the relation of cognitive impairment to, Charles Bonnet syndrome was been a matter of debate throughout the history of the condition. In the case that provided the inspiration for the diagnosis, that of Charles Lullin, the patient was fully aware of the unreality of the abnormal percepts, despite their vividness. This requirement for there to be insight into the nature of the experiences has been incorporated into most diagnostic criteria ever since, including those of Damas-Mora *et al.* (1982). The Gold and Rabins (1989) criteria softened the stance a little, allowing for insight to be ‘fully or partially retained’, and this acceptance of ‘partial’ insight was retained by Teunisse *et al.* (1995) when they revised the criteria.

It has been claimed that the extent of insight may change over time; Menon (2005) found that insight was gained following initial deception in 18/30 cases. Gilmour *et al.* (2009) found a higher rate of initial insight, with 80% of cases demonstrating insight from the outset. However, in 6% of cases, insight took 10 or more episodes of hallucination to develop. Deception has been described as more common when the hallucinated objects fit realistically into their surroundings (Teunisse *et al.* 1996, Menon 2005, Vukicevic and
Related to the concept of insight is cognitive impairment. The criteria of Damas-Mora, Gold and Rabins and Teunisse make no mention of cognitive impairment or dementia; indeed, Gold and Rabins (1989) specifically state that their criteria ‘do not exclude or require eye pathology or brain lesions’. As the use of the term ‘Charles Bonnet syndrome’ broadened, some authors departed from the criteria set out by de Morsier, and included patients with a diagnosis of dementia (Berrios and Brook 1982, Cole 1992). However, as noted above, this practice was controversial from the outset (de Morsier 1967), and most authors would agree that a diagnosis of Charles Bonnet syndrome should not be made in the presence of dementia, or other medical/psychiatric conditions known to lead to visual hallucinations (Podoll 1990, Hedges 2007). Even Teunisse et al. (1996), while not placing dementia as a specific exclusion in their criteria, state that for a diagnosis of CBS to be made, the hallucinations ‘cannot be explained by the presence of a psychiatric disorder’.

So, while the presence of frank dementia would generally be seen to preclude a diagnosis of CBS, the frequency of cognitive impairment falling short of dementia, and its significance if present, is less certain. Much of the research on CBS has been carried out by ophthalmologists, who are less familiar with the clinical presentation of mild cognitive impairment, or the tools to detect it. Moreover, the mini-mental state examination (Folstein et al. 1975), the most frequently used psychometric instrument used to quantify cognitive impairment, is known to be poor at detecting both mild cognitive impairment, and the patterns of impairment seen in Lewy body dementia (Bak 2006).

This uncertainty should be a source of concern. Many authors recommend that reassurance be given to patients with Charles Bonnet syndrome that their symptoms are benign and not
an indication of developing mental health problems (Norton-Willson and Munir 1987, Teunisse et al. 1996, Menon et al. 2003, Hedges 2007, Crumbliss et al. 2008). However, concerns have been raised by a number of authors that, for some patients, Charles Bonnet syndrome may actually be the first indication of the development of dementia (Holroyd et al. 1994, Pliskin et al. 1996, Terao 2001, Menon et al. 2003, Schadlu et al. 2009). This is a particular concern with Lewy body dementia, where visual hallucinations may often appear early and dominate the clinical picture (Terao and Collinson 2000). This raises the possibility that some people presenting with visual hallucinations may be given a diagnosis of Charles Bonnet syndrome, and reassured, when in fact they are developing a serious neurodegenerative condition for which there is treatment potentially available.

To date, no review has specifically set out to examine the relationship between Charles Bonnet syndrome and cognitive impairment. Given the potential significance of this relationship were it to be shown to exist, this is a significant gap in the literature. It is the intention of this review to systematically assess the existing literature on Charles Bonnet syndrome to determine if there is evidence for such a relationship.

2.3 Methods

I conducted a systematic review using the search engine Ovid, and searched the databases Medline, PsychINFO and Embase. The multi-field option was selected, and searches using the following terms were executed: Charles Bonnet$ AND dementia; Charles Bonnet$ AND cognitive impairment; Charles Bonnet$ AND Alzheimer$; Charles Bonnet$ AND Lewy body.

The abstracts were reviewed, and papers satisfying the following criteria were obtained for further review:
1. The paper described the results of an observational study of good methodological quality.

2. Charles Bonnet syndrome was confirmed using recognised diagnostic criteria.

3. Examination of the relationship between Charles Bonnet syndrome and cognitive impairment was a significant part of the study design.

Despite the large numbers of papers identified by the search strategy, none met all the criteria for inclusion. However, most of the papers published on Charles Bonnet syndrome were in the form of case reports and therefore not eligible for inclusion in this review. These reports sometimes made mention of the results of a cognitive examination, and some of these described changes in cognitive functioning over time. There were also descriptive studies where some of the inclusion criteria were met.

I was also aware from the reference lists of the papers identified that there were articles that our search strategy had failed to identify, but which seemed no less relevant than those that were found. I therefore revised the search strategy and sought to review all studies and case reports relating to people with Charles Bonnet syndrome. I used the same databases and search engine, but used the search term ‘Charles Bonnet$’, initially using the multi-field function. The search dates included were from the start of the period covered by the database to January 2012. A brief review of the results indicated that a high proportion of them were of no relevance. The search was repeated with ‘Charles Bonnet$’ in the title field. The results seemed to be much more relevant to the purpose of the review. The abstract for each was reviewed and the paper obtained if it was either a case report, or an observational study, on a patient or patients reported as having Charles Bonnet syndrome. Rigorous application of diagnostic criteria was not possible as there was often insufficient information. However, where the information provided was in direct conflict with the Teunisse criteria the paper was excluded. Papers in languages other than English or Spanish were also excluded.
2.4 Results

After duplicates were removed our search identified 316 papers. One hundred and ninety papers were excluded, and table 2 summarises the reasons for exclusion.

Table 2: Reasons for excluding papers identified by search strategy

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language other than English or Spanish</td>
<td>50</td>
</tr>
<tr>
<td>Not a case report or study (mostly letters, poster presentations)</td>
<td>49</td>
</tr>
<tr>
<td>Other relevant medical, psychiatric or medication related problem present</td>
<td>19</td>
</tr>
<tr>
<td>Review article</td>
<td>18</td>
</tr>
<tr>
<td>Not a clinical article</td>
<td>18</td>
</tr>
<tr>
<td>Duplicate report, not removed by search engine</td>
<td>17</td>
</tr>
<tr>
<td>Explicitly in conflict with Teunisse criteria</td>
<td>16</td>
</tr>
<tr>
<td>Paper not obtainable</td>
<td>3</td>
</tr>
</tbody>
</table>

One hundred and twenty six papers were included in the review, consisting of 26 observational studies and 100 case reports or case series. The references of the papers obtained were scrutinised and the abstract of any other paper which looked like it might be relevant was obtained; the paper was included if it met the above criteria. The search also identified 18 review papers on the subject of Charles Bonnet syndrome. The reference lists of these were scrutinised for any relevant papers not found by the other methods. A further 55 relevant papers were identified by this method (19 observational studies and 36 case reports), bringing the total to 45 observational studies and 136 case reports/series. These are discussed in the results section below.
2.5 Results - Review Papers

These are not strictly part of the systematic review, as they represent summaries of the evidence themselves rather than primary evidence. However, they are of some interest as many comment on the relationship between Charles Bonnet syndrome and cognitive impairment, and they are likely to have a greater influence on the attitudes of clinicians to this subject than the primary studies. The reviews are split on the issue, with 5/12 (Fernandez et al. 1997, Terao 2001, Menon et al. 2003, ffytche 2005, Schadlu et al. 2009) suggesting that CBS may represent the onset of dementia in some cases, and 4/12 (Gurwood and Abdal 2003, Jacob et al. 2004, Hedges 2007, Walsh and Hilas 2009) concluding that there is no link between the conditions, and that reassurance should be given. It is perhaps worth noting that none of the authors who recommended reassurance had a background in psychiatry, while in 3/5 of the reviews which raised concerns that a relationship may exist the authors were psychiatrists. These review papers, sitting outside the systematic review proper, are summarised in Appendix 2.1.

2.6 Results - Observational Studies

Schultz and Melzack (1993) carried out psychometric testing on 14 patients with Charles Bonnet syndrome over a period of up to 12 months. The tests used included the Minnesota multiphasic personality inventory, the Beck depression inventory, the trait form of the state-trait anxiety inventory, and the MMSE. They found no evidence of abnormalities in cognitive function in this group, and concluded that they had “ruled out the hypothesis that the hallucinations were caused by dementia”.

The study was important, as it was the first to administer a range of psychometric instruments to people with Charles Bonnet syndrome. It did have a number of weaknesses
however. The criteria by which Charles Bonnet syndrome was diagnosed were not made clear; and, although there was contact with participants at two points, testing was only carried out at one of these, so change in cognition with time could not be assessed. The instrument used to assess cognition was the MMSE, which is known to be poor at detecting early dementia; and the sample size was small. Given these limitations, the evidence does not seem to support the robust conclusion the authors reach.

These findings contrast with Pliskin et al. (1996), who described cognitive abnormalities in 14 of 15 cases with Charles Bonnet syndrome. They used measures including the Wechsler Adult Intelligence Scale-Revised, the Dementia Rating Scale, the MMSE and the Wechsler Memory Scale. They proposed that Charles Bonnet syndrome can be an indication of the early stages of dementia. They used the Gold and Rabins criteria for making the diagnosis of Charles Bonnet syndrome. However, their study was criticised by Teunisse (1997) for including a substantial number of cases (8/15) who did not have insight, contrary to these criteria. The authors responded by noting that even among those who did have insight, 6/7 had cognitive abnormalities, and that the one patient with normal cognition was found to have developed dementia 16 months later.

The instruments used in this study did seem more appropriate for detecting potential cognitive impairment than those in Schultz and Melzack (1993). However, the inclusion of people lacking insight, and even suffering from delusions, is a weakness, as most clinicians would not consider these people had Charles Bonnet syndrome. There was no longitudinal component to the study to determine if the abnormalities found were progressive, and the sample size (in effect only seven) was too small.

Holroyd and Rabins (1996) described findings in 13 patients reporting symptoms consistent with CBS who were contacted by telephone 39 months after their participation in a cross sectional study (Holroyd et al. 1994). Only 10 of the 13 could be contacted. The Telephone
Interview for Cognitive Status was administered, and scores compared to TICS scores at baseline. There was no significant change in the scores on the TICS over the study period. The authors conclude that this should be reassuring information for patients with macular degeneration who experience visual hallucinations. However, there were a number of limitations of the study; it was again very small, and the loss of 3/13 to follow up could be significant. There are also limitations in the breadth of a cognitive assessment delivered by telephone. While the authors cite data suggesting good correlation with the MMSE, a telephone test must be limited in its coverage of visuo-spatial items.

In addition to the paper described above, there were eight studies where cognitive functioning was described as one of the study parameters, though it was not the main focus of the study. These are described in Table 3. A number of these are large studies. Four included 30 or more people experiencing complex visual hallucinations. All of them assessed cognitive functioning using a validated instrument, the MMSE in seven and the TICS in the other. All but one of these studies reported no significant relationship between cognitive impairment and CBS. Only Holroyd et al. (1994) found an association with a lower score on the TICS; but the participants they reported on were the same cohort which was described in the subsequent study discussed on page 43 (Holroyd and Rabins, 1996), and where no deterioration in cognitive performance was reported over time.

However, there are some concerns over these findings. The studies were generally samples of convenience, mostly being consecutive attenders at out-patient clinics. Only Teunisse et al. (1995) and Gilmour et al. (2009) provided data on the number of potential participants who declined to participate, and no study gave information on whether those that did agree to participate were different from those who declined. This limits confidence in how applicable these results are to other populations.
Moreover, only the three studies authored by Teunisse and colleagues confirmed diagnosis of CBS with reference to broadly accepted criteria. In three there was no psychiatric history and mental state examination undertaken by a psychiatrist (Menon, 2005; Crumbliss et al. 2008; Gilmour et al. 2009). This is of particular importance given the cognitive test used was the MMSE in all but one study. The lack of a significant difference in the scores found cannot therefore be taken as having excluded significant impairments in cognitive functioning. The milder abnormalities reported in MMSE scores in some studies (Shedlack et al. 1994, Teunisse et al. 2005) could be consistent with clinically relevant deficits in functioning.

Indeed, Gilmour et al. (2009) explicitly mention that people taking medication for Alzheimer’s disease were included in the study, but do not provide further details of how many people this applied to or what group they were in. It is likely that some of the participants labelled as having CBS in Gilmour et al. (2009) had mental disorders accounting for their visual hallucinations, invalidating the CBS diagnosis.

Of the studies described, Teunisse et al. (1995) and Teunisse et al. (1998) appear the most robust. Large numbers of participants were recruited, accepted CBS criteria applied, an examination by a psychiatrist was part of the protocol and the control group was relevant. The finding of no impairment in cognitive functioning is therefore of interest. However, even these studies relied on the MMSE, and so were unable to rule out the presence of mild but important deficits in cognitive functioning.

2.7 Results - Case Reports and Series

The 136 papers where cases consistent with CBS were described were reviewed to determine whether a comment was made on the patient’s cognitive functioning, and whether any follow up observations were made in regard to this. These papers reported details of
225 cases where the information provided was not explicitly in conflict with the Teunisse criteria, though it should be noted that in many cases the information provided was very limited. Some details of these case reports are provided in Appendix 2.3.

A total of 16 papers describe 22 cases where cognitive functioning was described at baseline and follow up. Of these, 11 papers detail 15 cases where dementia was reported as developing after a period of follow up. These were published between 1988 and 2011, and are summarised in Table 4. Six of the cases were in males, and nine in females, and the ages ranged from 70-87 at time of diagnosis of CBS, with a mean age of 79.2 years. A range of ophthalmic diagnoses were involved, though this information was frequently not given in the case report.

In 11/14 cases insight was reported as being partial or fluctuating; this was a much higher rate of partial insight than in reported cases of CBS as a whole. The period of time that visual hallucinations were present before diagnosis varied, but was only one year or less in three cases. In five cases it was over three years before dementia emerged, with the longest delay being five years. The type of dementia was recorded as Lewy body dementia in five cases and Alzheimer’s disease in four cases. In the remaining six cases, a specific diagnosis was not given.

In the cases where dementia did not develop (Levine 1980, Sadananda Unni 1994, Ukai 2004, Bourgeois et al. 2010 and Hartney et al. 2011), there were 4 males and 3 females. The periods of follow up ranged from one to six years. Of note, the mean age of this group was younger, at 67.3 years, and more of the group had full insight at the time of diagnosis (5/6 where insight was referred to).

In addition to the cases presented above, there were a number of other cases identified by the literature review which were worthy of commenting on. Cole (1992) documents a series
of 13 cases who were seen by old age psychiatry services and who experienced complex visual hallucinations. Five had mild dementia at the time of assessment, but in the other eight cognitive impairment was absent or minimal. In three of these patients, after one year a severe and rapid decline in their cognitive functioning had taken place. However, insight was recorded as absent at baseline, so they would not meet recognised criteria for CBS.

Guerra-Garcia (1997) records the case of an 83 year old woman who presented with complex visual hallucinations in the context of bilateral glaucoma, diabetic retinopathy and corneal transplants. The author does not note how long the hallucinations had been taking place prior to referral, but comments that the patient had full insight into the unreality of the experiences and that the hallucinations occurred ‘with normal mentation’. Her MMSE was noted to be 24/30. However, the author notes that ‘further neuropsychological testing disclosed early dementia’, which would be generally held to rule out a diagnosis of CBS. However, the cognitive changes were mild enough that they may well have been missed had the patient presented first in an ophthalmological setting, rather than care of elderly, and so the case may still be of interest.

A further case is described by Kishi et al. (2000), of a 73 year old woman who suffered from retinitis pigmentosa from the age of 32. She developed complex visual hallucinations at the age of 70, with full insight into the unreality of the experiences. She scored 25 points on the MMSE, excluding vision dependent items, and no evidence of significant cognitive impairment could be found. At follow up 18 months later she demonstrated no signs of cognitive decline. Her MRI showed some atrophy which was more notable in the left medial occipital lobe, but SPECT scanning showed ‘marked hypoperfusion’ throughout the left occipital lobe. No vascular cause was found for this, and the authors speculate that the cause may be a parieto-occipital variant of Alzheimer’s disease.
2.8 Discussion- Methodology and Findings of the Review

This review establishes a number of points. The recording of insight and cognitive ability in the literature relating to CBS has generally been limited in completeness and quality. There are no well-constructed, adequately powered epidemiological studies which describe the rates or patterns of cognitive impairment in this condition, or which establish the rates of emergence of dementia of any type. The three studies that directly address this question are too small, have methodological weaknesses, and come to contradictory conclusions. All are now over 17 years old.

The cross sectional study data does not significantly advance the position. While there has been much work looking at the relationship between aspects of visual functioning and CBS, few studies have assessed cognitive functioning at all, and none have done so with instruments of sufficient sensitivity to reliably detect clinically relevant but mild deficits. While in general the studies do not provide evidence of cognitive impairment being present in CBS, the larger studies all had limitations which prevent this being taken as a robust finding. This is not unexpected, as these studies were not designed primarily to investigate the relationship between CBS and cognition.

The case report literature does contain a number of cases where CBS appears to have been a pre-dementia state. As predicted from diagnostic criteria, the commonest dementia type diagnosed in this group was Lewy body dementia. However, beyond indicating that this is a relationship that is sometimes observed, the data these cases provide is of limited value in determining the frequency of this outcome, as they may not be representative of CBS cases as a whole. Information in the case reports was often patchy, and recognised diagnostic criteria were commonly not referred to. The finding that dementia did develop in 15 cases (16 including the case described in Pliskin et al. 1996) is therefore hard to interpret. The mean age of this group was nearly 80, and so the background incidence of dementia would
be relatively high. It would be expected in a large group of cases in this age group, followed up for five years, that some would develop dementia anyway, and that the presence of CBS would be coincidental. The finding that the cases that did not develop dementia at follow up were younger on average is relevant to this.

However, the data on insight does provide some potentially interesting observations. Partially impaired insight was far more common in cases where dementia subsequently developed than in CBS cases as a whole; and in those who were followed up, partially impaired insight was far more likely to be associated with the development of dementia than full insight. These are highly tentative findings, given the potentially unrepresentative nature of the cases that have been reported, but they do raise the possibility that the subgroup of CBS cases who experience fluctuating insight may be different from those where insight is preserved, and that this group may be at a considerably higher risk of going on to develop dementia.

With regard to the methodology, the over-inclusive nature of the search strategy, and robust checking of the reference lists, should have ensured that no major published work on CBS was overlooked. However, by no means all the published papers made reference to the condition in the title, or even in the body of the text, so it is possible that some papers were missed as a result. This is less likely with the observational studies, as these are fewer in number and more likely to be referenced by other authors in the field. It is possible that some case reports were missed, but these were overall more likely than the observational studies to use the term ‘Charles Bonnet syndrome’ in the title of the published report. Overall, there is a good level of assurance that the strategy was successful in systematically identifying the population of published studies and case reports that were the target of this work.

There were however, as table 2 sets out, a total of 50 published papers which were in languages other than English and Spanish, and which were therefore beyond the resources
of this project to translate for inclusion. These were in a wide range of languages, including French, German, Portuguese, Japanese, Turkish and Serbian. This raises the possibility that significant contributions to the literature may have been missed due to the problem of their language of publication.

On balance I think this is unlikely to have been the case, for the following reasons. I was able to obtain abstracts in English for all the papers concerned, and so was able to make some assessment of the relevance of their contents. None of the published works related to a report of an observational study or clinical trial; all were case reports. None of the abstracts made reference to the development of dementia in the cases they pertained to, and given the significance of this as an outcome, it seems unlikely that this would not have been referred to in the abstract. Finally, none of these reports were cited in other works in ways that suggested that important new information, such as a diagnosis of dementia in the cases reported, was being missed. Overall, there is a low likelihood that the exclusion of these 50 papers has resulted in data which would have had an important bearing on the outcome of this review being missed.

2.9 Discussion - Implications for Aetiology of CBS

CBS has been defined in terms that avoid reference to aetiology throughout its existence in English-language literature. However, advances in cognitive science and neuroimaging have allowed some progress to be made in relating the syndrome to underlying disturbances in brain structure and functioning. Three studies have used a range of neuroimaging modalities to investigate CBS, and found abnormalities were present in those with the condition. Shedlack et al. (1994) found excess posterior white matter ischaemic changes; ffytche et al. (1998) found increased activation in the fusiform gyrus; and Adachi et al. (2000) used a combination of MR and SPECT, reporting occipital atrophy, and hyperperfusion in the
temporal lobe, striatum and thalamus. In addition to these studies, there have been numerous case reports, mostly using SPECT, but a consistent picture of where abnormalities are located has failed to emerge.

Another approach has been to try to develop an overarching theory of how visual hallucinations are generated, and to locate CBS within this framework. Significant contributions in this area have been made by Collerton et al. (2005) and ffytche (2007). Collerton et al. (2005) introduced a ‘perception/attention deficit’ model of visual hallucinations, in which afferent stimuli are ‘compared’ to proto-objects present in the visual accessory cortex, with the ‘best fit’ being experienced as the conscious percept. In states of reduced afferent information, or impaired attention, errors in selecting the proto-object are more likely to occur, which may be experienced as a hallucination. In the Collerton model, the content of the hallucinations is held to be similar whatever the underlying cause. The association with impaired visual acuity in CBS fits with the ‘perception’ part of the Collerton model; but as discussed above, this is not sufficient to explain why most people with poor vision do not experience hallucinations, suggesting that a co-existing abnormality leading to reduced attention may also be present in the condition.

ffytche (2007) made an attempt to distinguish the aetiology of different visual hallucinatory syndromes on phenomenological grounds. He described three separate syndromes, related to deafferentation, acetylcholine deficits in the midbrain, and excess serotonin, which he suggested differed in the content of hallucinations experienced. In this framework CBS is the prototypical deafferentation syndrome, and the symptoms emerge as a result of abnormalities in the retinogeniculocalcarine syndrome.

Neither of these models has yet been supported by conclusive empirical evidence in relation to CBS, but they offer frameworks which are testable and which should help shape future
research in the area; and they offer the prospect of both moving CBS onto a clear aetiological footing, and defining its relationship to other visual hallucinatory disorders.

The findings of this review are unable to offer much new evidence to support either of the models described. The cases that developed dementia would be classified in a different category in the ffytche (2007) framework, and would potentially have differences in the content of the hallucinations experienced. However, the descriptions of the hallucinations provided in the reports lacked sufficient detail to allow this theory to be tested.

The findings of the review in relation to insight are of interest in relation to the perception/attention deficit model of Collerton et al. (2005). In cases where a period of follow-up was described, partially impaired insight was more likely to be associated with the development of dementia than full insight. It is possible that the subgroup of CBS cases who show partial insight may be different from those where insight is preserved, and that this group may be at a higher risk of going on to develop dementia. In the Collerton model, the cases where dementia develops would be likely to form a group where the ‘attention deficit’ component of the model is of greater importance than the ‘perception’ component. They would potentially be indistinguishable on the content of the hallucinations, but the presence of impaired or fluctuating insight early in the course of the syndrome could alert clinicians to the possibility of a different aetiology.

2.10 Conclusion

The findings of this systematic review clearly establish that the relationship between Charles Bonnet syndrome and dementia is not well understood. The existing literature is contradictory and has methodological shortcomings. Many authors still advise that CBS is a benign, self-limiting condition, with no relationship to serious mental disorder. However,
reports of severe and progressive cognitive impairment occurring in patients with CBS have occurred with sufficient frequency to suggest that CBS may on some occasions represent the first signs of an emerging dementia. This offers the possibility of a new pathway to early diagnosis and treatment.

Conditions causing visual impairment are common in the elderly population at risk of dementia. For example, Owen et al. (2012) report prevalence rates of age related macular degeneration among those aged over 80 to be around 12%. Epidemiological studies indicate that the prevalence of CBS in the elderly population with significant visual impairment may be as high as 63% (Menon 2005); so there are potentially large numbers of people who could be identified as being higher risk of dementia. If this relationship was confirmed it could lead to closer working between ophthalmology departments and memory assessment services, and could offer another way to help meet the Prime Minister’s challenge of increasing rates of timely diagnosis of dementia (DoH, 2013).

Moreover, progress in the understanding of the neurological basis of CBS is likely to lead to a better understanding of visual hallucinations as a whole. Explanatory frameworks have been developed that offer the prospect of more clearly defining the relationship between CBS and other disorders which cause visual hallucinations. The case for carrying out well designed, adequately powered studies to investigate the rates of dementia in CBS, the factors which predict development of dementia, and the neurological abnormalities which underlay the condition, is now compelling. In chapter 3 I will briefly report on the process that led to the development of a study to investigate this issue, and on the related development of a neuroimaging study to address the related issue of the aetiology of CBS.
<table>
<thead>
<tr>
<th>Study design and focus</th>
<th>Population</th>
<th>Cognitive Assessment</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holroyd et al. (1994) Cross sectional, compares prevalence of visual hallucinations (VH) in low vision population and general medical population.</td>
<td>127 visual disorder patients, 100 general medical patients. 8 in total had VH. Other medical or psychiatric causes of VH excluded</td>
<td>Telephone interview of Cognitive status (TICS).</td>
<td>Lower cognitive score on TICS significantly associated with VH, p&lt;0.001 on ANOVA</td>
<td>Follow up in Holroyd and Rabins (1996) did not show progression of cognitive impairment</td>
</tr>
<tr>
<td>Shedlack et al. (1994) Cross sectional. MRI scanning to quantify the severity of white matter ischaemic changes in VH patients and controls.</td>
<td>5 patients with VH, no primary psychiatric disorder; 12 normal controls, health volunteers</td>
<td>MMSE</td>
<td>Scores among VH patients 21-27/30; and among controls 28-30/30. No mean/median score given, no comment on differences</td>
<td>Significantly more white matter changes posteriorly in the VH group. Controls younger than patients (74.6 vs 81.4), no comment on significance of this</td>
</tr>
<tr>
<td>Teunisse et al. (1994). Cross sectional. Evaluation of factors associated with CBS.</td>
<td>14 patients with CBS from psychiatry/geriatric medicine. Gold and Rabins criteria applied. Mean age 81.8 years, gender ratio 13:1 F:M</td>
<td>MMSE</td>
<td>Mean score on MMSE 26.2/29.4. Four patients excluded, two with severe cognitive impairment present, one who was very uncooperative with testing and one who was very hard of hearing</td>
<td>Source of patients different from many other studies, so may represent a different population. No follow up of cohort to monitor changes in cognition over time</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Measures</td>
<td>Findings</td>
<td>Comments</td>
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</tr>
<tr>
<td>Teunisse et al. (1995)</td>
<td>500 patients attending ophthalmology services (300 low vision patients, 200 general elderly ophthalmic patients). 11% of low vision patients vs 1% general patients had CBS, as diagnosed by Teunisse criteria.</td>
<td>MMSE</td>
<td>Mean score 26.5 in CBS patients (22-30); scores for those without CBS in each group not given.</td>
<td>Large study, using accepted criteria, applied robustly, so findings of interest. Scores on cognitive testing were difficult to interpret, as mean age of CBS group not given and no comparison data for those with no VH.</td>
</tr>
<tr>
<td>Teunisse et al. (1998)</td>
<td>Low vision clinic; 52 patients with CBS and 80 clinic attenders with no VH.</td>
<td>MMSE</td>
<td>No connection of CBS with cognitive impairment was found.</td>
<td>Large study, relevant and similar control group. Widely accepted criteria for diagnosis of CBS used.</td>
</tr>
<tr>
<td>Menon (2005)</td>
<td>48 participants with visual acuity of 20/200 or worse in better eye compared with 48 controls with VA of 20/40 in better eye. 30/48 of low vision group had VH, compared to only 2/48 controls</td>
<td>MMSE (excluding 2 items designated as visually dependent)</td>
<td>VH low vision group MMSE 27.2/28, non-VH low vision group 26.8/28, normal vision controls 26.4/28. Differences reported as non-significant.</td>
<td>Insight also commented on- all attained this, but in 18/30 there was an initial period of deception. Reasonably sized study, but limited by use of MMSE.</td>
</tr>
</tbody>
</table>

**Legend:**
- **CBS**: Cognitive Behavioral Symptoms
- **MMSE**: Mini-Mental State Examination
- **VH**: Visual Impairment
<table>
<thead>
<tr>
<th>Study Authors &amp; Year</th>
<th>Study Design</th>
<th>Sample Description</th>
<th>Outcome Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crumbliss et al. (2008)</td>
<td>Longitudinal study</td>
<td>50 consecutive patients presenting at visual rehabilitation centre, 12 found to have CBS.</td>
<td>MMSE</td>
<td>No significant correlation found between improved visual acuity and reduction in VH. MMSE not repeated at follow up, which was of too short duration to be of value in tracking changes in cognition.</td>
</tr>
<tr>
<td>Gilmour et al. (2009)</td>
<td>Cross sectional case/control study</td>
<td>258 low vision clinic attenders and 251 controls; CBS in 34% LVC patients, &lt;2% of controls</td>
<td>MMSE. Those scoring &lt;22 excluded; this included 12 LVC patients and 1 control</td>
<td>No significant differences in MMSE scores between any groups. Precise scores not given, graph appears to show scores around 25 in all groups. Large study. Exclusion for low MMSE presumably to exclude dementia, but some participants were taking medication for Alzheimer’s disease. Calls into question validity of findings, as Alzheimer’s diagnosis would rule out CBS.</td>
</tr>
</tbody>
</table>
Table 4: Details of case reports of patients with CBS who went on to develop dementia

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Age/gender</th>
<th>Ophthalmic diagnosis</th>
<th>Visual acuity in best eye</th>
<th>Insight status</th>
<th>Cognition assessed at baseline?</th>
<th>Neuroimaging or other investigations</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal et al. (1988)</td>
<td>70, female</td>
<td>Not given</td>
<td>20/50</td>
<td>Present initially</td>
<td>'borderline normal score on the Blessed test of orientation, memory and concentration'</td>
<td>CT and EEG were normal</td>
<td>Alzheimer's disease emerged 1 year after onset of visual hallucinations</td>
</tr>
<tr>
<td>Gold and Rabins (1989)</td>
<td>84, female</td>
<td>Not given</td>
<td>No comment</td>
<td>Partial, fluctuating</td>
<td>MMSE 27</td>
<td>Normal</td>
<td>Alzheimer’s disease after 2 years, MMSE then 14</td>
</tr>
<tr>
<td>72, male</td>
<td></td>
<td>Not given</td>
<td>No comment</td>
<td>Partial, fluctuating</td>
<td>MMSE 25</td>
<td>Normal</td>
<td>'Dementia' after 18 months, MMSE then 15</td>
</tr>
<tr>
<td>Brabbins (1992)</td>
<td>79, female</td>
<td>Bilateral cataracts</td>
<td>No comment</td>
<td>Partial, present at times but fluctuating</td>
<td>Clinical assessment-‘memory testing revealed minor deficits’</td>
<td>No comment</td>
<td>Probable Lewy body dementia developed 2-3 years after onset of VH</td>
</tr>
<tr>
<td>80, female</td>
<td></td>
<td>No comment</td>
<td>No comment</td>
<td>Partial, present at times but fluctuating</td>
<td>No comment</td>
<td>No comment</td>
<td>Over 1 year period, fluctuating and increasing impairment in cognitive functioning; probable Lewy body dementia</td>
</tr>
<tr>
<td>Study</td>
<td>Age, Gender</td>
<td>Visual Acuity</td>
<td>Visual Field</td>
<td>Cognitive/Neurological Assessment</td>
<td>Neuroimaging</td>
<td>Diagnosis Considerations</td>
<td></td>
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</tr>
<tr>
<td>Haddad and Benbow (1992)</td>
<td>84, female</td>
<td>Not given</td>
<td>'corrected visual acuity satisfactory'</td>
<td>partial</td>
<td>Blessed Roth Cognitive function scale 25/26; Wechsler adult intelligence scale, Benton visual retention task, cognitive scale of Clifton assessment procedure for elderly. Isolated problems with visuospatial skills noted</td>
<td>EEG normal; CT carried out after emergence of cognitive symptoms showed involutional change, most pronounced parietally</td>
<td>General cognitive decline evident 9 months after emergence of VH; patient died 21 months after VH started. Authors felt diagnosis was either Alzheimer’s disease or Lewy body dementia</td>
</tr>
<tr>
<td>Lefroy (1999)</td>
<td>87, female</td>
<td>'retinal degeneration' and cataracts</td>
<td>'unable to count fingers'</td>
<td>full</td>
<td>Clinical assessment 'normal', MMSE30/30</td>
<td>CT- moderate atrophy; EEG- 'abnormal, did not support epilepsy'</td>
<td>Unspecified dementia after 3 years</td>
</tr>
<tr>
<td>Johnson and Barnes (2001)</td>
<td>87, male</td>
<td>Age related macular degeneration</td>
<td>Finger counting at 1 metre</td>
<td>No comment made</td>
<td>Clinical assessment, 'no short or long term memory problems'</td>
<td>No comment</td>
<td>Unspecified dementia</td>
</tr>
<tr>
<td></td>
<td>72, male</td>
<td>Not given</td>
<td>6/60</td>
<td>partial</td>
<td>'performed well on cognitive testing'</td>
<td>CT- moderate vascular changes and frontal atrophy</td>
<td>Unspecified dementia</td>
</tr>
<tr>
<td>Magoub and Serby (2007)</td>
<td>78, female</td>
<td>Venous occlusion, cataracts</td>
<td>Not stated</td>
<td>Present initially, then lost</td>
<td>MMSE 28/30</td>
<td>CT 'normal'</td>
<td>Unspecified dementia, treated with donepezil, after around 18 months of VH</td>
</tr>
<tr>
<td>Archibaldo Donoso <em>et al.</em> (2007)</td>
<td>84, female</td>
<td>Cataracts bilaterally, traumatic injury left eye</td>
<td>Right eye- complete loss of vision</td>
<td>Partial- not present initially</td>
<td>Clinical assessment 'normal'</td>
<td>CT showed mild generalised atrophy</td>
<td>Alzheimer’s disease after 4 years</td>
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<tr>
<td></td>
<td>80, male</td>
<td>Glaucoma</td>
<td>Finger counting</td>
<td>Partial- fluctuates</td>
<td>MMSE 22/27, ‘mild cognitive impairment’</td>
<td>EEG- diffuse slowing; CT- age related involutional change, white matter changes</td>
<td>Alzheimer’s disease after 5 years</td>
</tr>
<tr>
<td>Hanyu <em>et al.</em> (2008)</td>
<td>81, female</td>
<td>Cataracts</td>
<td>No comment</td>
<td>full</td>
<td>MMSE 27/30</td>
<td>MR showed mild generalised atrophy, SPECT showed mild hypoperfusion in medial occipital lobe</td>
<td>Three years of VH prior to assessment; after further 3 year follow up, Lewy body dementia emerged</td>
</tr>
<tr>
<td>Walker and Keys (2008)</td>
<td>72, male</td>
<td>Progressive diabetic macular oedema</td>
<td>20/100, worsening to finger counting over years</td>
<td>Partial (present initially then lost)</td>
<td>No comment</td>
<td>No comment</td>
<td>Lewy body dementia diagnosed after 3 years</td>
</tr>
<tr>
<td>Gil Navarro <em>et al.</em> (2011)</td>
<td>78, male</td>
<td>Optic nerve ischaemia</td>
<td>No comment</td>
<td>Full insight</td>
<td>No comment</td>
<td>Two years later: EEG- unremarkable. SPECT- severe perfusion impairment bilaterally, posterior structures more affected</td>
<td>Lewy body dementia developed after 2 years</td>
</tr>
</tbody>
</table>
3. Development of the Studies

The systematic review set out in chapter 2 demonstrates that the issue of the relationship of Charles Bonnet syndrome to cognitive impairment is currently uncertain, and is of sufficient clinical significance to warrant further investigation.

Previous significant studies in this area (Schultz and Melzack 1993, Holroyd and Rabins 1996, Pliskin et al. 1996) have attempted to characterise changes in cognitive functioning seen in CBS, but it is the development of dementia which is the outcome of greatest interest to clinicians. I believed that a study which investigated this potential outcome would be a significant addition to the literature and decided to make this the focus of my work.

I considered that the study should be designed to meet the following objectives:

1. To identify possible cases of CBS from a defined target population
2. To characterise the visual hallucinations in detail, including their phenomenology and participants' reactions to them, to allow a diagnosis of CBS to be made using recognised criteria.
3. To identify any other relevant psychiatric or medical disorders that may be present, that would invalidate the diagnosis of CBS.
4. To characterise participants' cognitive functioning, both to make a diagnosis of dementia, if present, and to describe the pattern of milder degrees of cognitive impairment.
5. To obtain an informant history to support the diagnostic process.
6. To repeat the measurements of cognitive functioning and dementia diagnostic assessment after a year, so as to calculate the incidence of dementia in a population with CBS.
To meet these objectives would require a study with a longitudinal design, and so I adopted a prospective cohort methodology for this work. As part of the cohort study, I considered that neuroimaging would be desirable, as this would assist with the process of diagnosis of dementia. However, I felt it would be possible and desirable to develop this aspect of the study further. As discussed in chapter 1.3, CBS has been defined in purely phenomenological terms since its introduction to the English language literature by Damas-Mora et al. (1982). de Morsier always considered that there was some form of brain abnormality underlying the condition though, and some of the papers identified in the review (Shedlack et al. 1994, Guerra-Garcia 1997, Kishi et al. 2000) described neuroimaging studies which demonstrated abnormal findings in the brains of those diagnosed with CBS. However, all these papers described single cases, or small case series, and made use of clinical descriptions of scan findings, except for one report (Shedlack et al. 1994) where a semi-quantitative rating scale was used. I decided to develop a linked neuroimaging study, which would make use of a more powerful analytic technique, voxel-based morphometry, to investigate the nature and site of any abnormalities present in the brains of participants with CBS.

I made an application to use the Wellcome Trust clinical research facility 1.5 Tesla MRI scanner. Dr Roland Zahn assisted me in developing the protocol to include a voxel-based morphometry analysis (VBM) of MRI scans of participants with CBS. This would seek to determine if there were characteristic patterns of change in the grey or white matter of patients with Charles Bonnet syndrome, and so try to provide insight into the aetiological basis of the condition.

This development meant that, in essence, I was now proposing to undertake two linked studies. The first of these was a prospective cohort study, looking to follow up
a cohort of patients with CBS, and a group of controls drawn from the same population. The second was a case-control study using voxel-based morphometry to analyse MRI brain scans of patients with CBS and a control group. I anticipated that participants would be included in both studies, as the data collection would overlap considerably. A detailed account of the methodology and results of these two studies will be described in parts II and III of this thesis below.
Part II

Clinical Cohort Study of Charles Bonnet syndrome and Dementia
4. Clinical Study- Hypothesis and Aims

4.1 Summary

In this chapter I describe the development of the clinical cohort study introduced in chapter 3. Chapter 4.2 describes the aims of this study, and the hypotheses it sets out to test. It also discusses important concerns over expected sample size and study power, and the reasons these concerns led to the work being designated as a pilot study. In chapter 4.3, the issue of power calculations is considered in more detail, with worked examples showing the potential power in a range of scenarios. In chapter 4.4 the development of the study is described, including how the clinical setting for recruitment was chosen, how inclusion and exclusion criteria were set and how the protocol was translated into standard operating procedures. Chapter 4.5 develops the issue of sample size further, taking into account information about the recruitment setting to arrive at recruitment targets, and discusses the assumptions made to arrive at estimates of the proportion of clinic attenders who would be eligible, and the proportion of eligible patients who would agree to become participants. In chapters 4.6 and 4.7 the pilot nature of the study is explored further. Chapter 4.6 looks at the differences between feasibility and pilot studies, discusses the concept of ‘clinical significance’ in relation to effect sizes, and explores value and utility of pilot studies in general. These discussions are then applied to this study in chapter 4.7. Finally, in chapter 4.8 the progress of the study is briefly discussed, including amendments made to the protocol in the light of recruitment proving a greater challenge than anticipated.
4.2 Aim and Hypotheses

The aim of the project, as set out in chapter 3, is to investigate the relationship between Charles Bonnet syndrome and dementia. The study sets out to explore the possibility that within the group of patients who meet the criteria for the diagnosis of Charles Bonnet syndrome, there is a sub-group who are in fact presenting with the early symptoms of dementia. While this group would not present as sufficiently impaired to attract a diagnosis of dementia at the outset of the study, as that would invalidate the CBS diagnosis, the study aims to explore whether they show a measurable decline of their cognitive functioning over the course of the study, and to determine what proportion meet diagnostic criteria after a year of follow up. A further aim is to determine if the group who show progressive impairment in cognitive functioning are identifiable at entry to the study by abnormalities on measures of cognitive functioning, by the content of their visual hallucinations, and by abnormalities on MRI.

These aims led to the development of the following experimental hypotheses:

1. The incidence of dementia in a population who satisfy diagnostic criteria for Charles Bonnet syndrome is significantly higher than in a population of controls who are of similar age and visual impairment.

2. The prevalence of abnormalities in cognitive functioning that are not severe enough to warrant a diagnosis of dementia is higher in people diagnosed with Charles Bonnet syndrome than among controls of similar age and visual impairment.

3. There are characteristics, identifiable at baseline assessments, which predict which members of a population with Charles Bonnet syndrome will go on to develop
dementia. These include the content of the hallucinations, performance on baseline cognitive testing, and abnormalities detectable on MRI scanning.

However, sections 4.3 and 4.5 below explore the issue of the sample size the study could expect to recruit, and raise significant concerns over whether this would be sufficient to reject the null hypotheses derived from these experimental hypotheses. I thus recognised that there was a risk that the study may be underpowered. Nevertheless, the limited work previously carried out in this area had significant methodological shortcomings, as discussed in chapters 2.6 and 2.8. This study would be the first to attempt to recruit a defined population using clear and rigorously applied diagnostic criteria for CBS, to include a control group, and to use a longitudinal methodology. It would call for collaboration between departments with no history of working together, and include participants who were likely to be of an advanced age, and may be reluctant to participate in research perceived as onerous.

This work would therefore have considerable value as a pilot study. Three further aims were therefore defined for the project:
1. To test out the protocol to determine if joint working across old age psychiatry and ophthalmology departments was possible in a real clinical setting.
2. To test whether the instruments and assessments which comprised the study were acceptable to an aged and frail target population.
3. To test which venues and strategies led to successful recruitment, and inform the development of potential future studies with greater power.

The aim of investigating the relationship between CBS and dementia was retained, on the basis that existing work provides insufficient information to allow the effect size for any relationship to be estimated, and so makes the precision of estimates of
the necessary sample size very low. It would still be the intention to test the hypotheses set out above, if the sample size proved sufficient to do so.

4.3 Power Calculations

This section explores the issue of effect sizes and power calculations in a little more depth, and discuss how these relate to the process of determining sample size. As part of this process, I consulted Dr Julie Morris, honorary reader in statistics at the University of Manchester. Power calculations depend on a number of parameters, including:

- the study population. A study which recruits large numbers of participants will clearly have greater power than a smaller study.

- the value of alpha, the likelihood of accepting a type I statistical error (rejecting the null hypothesis when it is in fact correct). This is by convention set at 0.05, and this value will be adopted in the calculations below.

- the effect size of the event that is the subject of the hypothesis. In this case, the event of interest is the diagnosis of dementia at the review interview after one year. The effect size is the increase in the relative risk of developing dementia in the CBS population compared to the control group. This value is unknown, and there are no previous epidemiological studies in the area to guide estimation of it. However, from the case report literature, which is incomplete and not specifically designed to record the frequency of this outcome, the development of dementia does not seem to be a rare event. This is supported by the clinical experience of colleagues working in the field of old age psychiatry. For there to be a widely held clinical suspicion that there is
a relationship between CBS and dementia, there is good reason to think that the increase in the relative risk is clinically significant. It seems reasonable to make assumptions of a relative risk in the region of 2-5, and to model power calculations based on a range of values in this region. I will use relative risks of 2, 3, and 5 in the calculations below.

- the incidence of the event of interest in the study population. The age of participants was likely to be in the older elderly given epidemiological work in CBS, which has suggested greater age as a risk factor for the development of the condition (Holroyd et al. 1994; Teunisse et al. 1995). The incidence of dementia in a European population in the age group 80-84 is around 60 per 1000 (Jorm and Jolley, 1998). However, in this meta-analysis, the incidence changed significantly with age. In the age group 75-79 it was 33/100, and in the group 85-89 it was 104/1000. For this reason, in the power calculation modelling below, I used a range of estimates of incidence to show the effect this would have on the required sample size. I took incidences of 40/1000, 80/1000 and 120/1000, which would correspond roughly to the three age bands in Jorm and Jolley (1998).

With regard to sample size, for the purpose of the modelling below I took a conservative estimate of potential recruitment to the study. All previous studies in the area (Schultz and Melzack 1993, Holroyd and Rabins 1996, Pliskin et al. 1996) had recruited between 10-15 participants with CBS. I planned to include a control group, so doubling the number of participants I intended to recruit. Recruitment was originally intended to take place over one year, and a recruitment rate of two participants per month seemed realistic to expect. This would give 12 participants with CBS and 12 controls, in line with previous studies, and the modelling was conducted using these values as anticipated sample sizes.
The results of these power calculations are shown in tables 5a, 5b, and 5c below. These were generated using continuity corrected Chi squared tests, with the software package nQuery advisor. Each assumes a sample size of 12 in both CBS and control groups. Each shows the power a study of this size would have to correctly reject the null hypothesis- that there is no difference in the rate of development of dementia between the groups- to a 95% level of significance, for different relative risks of developing dementia.

Table 5a: Power (relative risk of 2)

<table>
<thead>
<tr>
<th>Incidence (CBS vs. control)</th>
<th>Power (for N=12)</th>
<th>Sample size to achieve power= 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>240/1000 vs. 120/1000</td>
<td>6%</td>
<td>176</td>
</tr>
<tr>
<td>160/1000 vs. 80/1000</td>
<td>4%</td>
<td>283</td>
</tr>
<tr>
<td>80/1000 vs. 40/1000</td>
<td>2%</td>
<td>602</td>
</tr>
</tbody>
</table>

Table 5b: Power (relative risk of 3)

<table>
<thead>
<tr>
<th>Incidence (CBS vs. control)</th>
<th>Power (for N=12)</th>
<th>Sample size to achieve power= 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>360/1000 vs. 120/1000</td>
<td>13%</td>
<td>57</td>
</tr>
<tr>
<td>240/1000 vs. 80/1000</td>
<td>6%</td>
<td>94</td>
</tr>
<tr>
<td>120/1000 vs. 40/1000</td>
<td>2%</td>
<td>204</td>
</tr>
</tbody>
</table>

Table 5c: Power (relative risk of 5)

<table>
<thead>
<tr>
<th>Incidence (CBS vs. control)</th>
<th>Power (for N=12)</th>
<th>Sample size to achieve power= 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>600/1000 vs. 120/1000</td>
<td>52%</td>
<td>19</td>
</tr>
<tr>
<td>400/1000 vs. 80/1000</td>
<td>25%</td>
<td>33</td>
</tr>
<tr>
<td>200/1000 vs. 40/1000</td>
<td>7%</td>
<td>76</td>
</tr>
</tbody>
</table>

As can be seen, variations in the parameters can have a dramatic effect on the power of the study, and on the numbers of participants required to adequately power
it. Even assuming the highest incidence rates and relative risk, with only 12 participants in each arm of the study, the study would be underpowered. However, if the mean age of participants fell towards the older of the age bands, where there would be a higher risk of dementia in the control group, and if the relative risk conferred by a diagnosis of CBS proved to be towards the higher of the values considered in the testing illustrated above, then it might be possible to construct an adequately powered study with fewer than 100 participants in each arm.

4.4 Developing Collaborations and Plans for Recruitment

The next step was to identify where recruitment would take place, given that I would be based in Manchester. One of the epidemiological studies found in the literature review (Abbott et al. 2007) had been carried out in the Manchester Royal Eye Hospital and Professor Richard Abadi, a co-author, still worked at the University of Manchester. I made contact with Professor Abadi, and discussed my proposal with him. He put me in contact with Dr Robert Harper, an Optometry Consultant at the Manchester Royal Eye hospital (MREH). Dr Harper was keen to be involved and felt that the Low Vision Clinic at the MREH was a good place to recruit participants. This clinic dealt with a population who had significant visual impairment, and rates of Charles Bonnet syndrome among those attending should therefore be high.

I then considered the issue of recruitment procedures. For issues of practicality, I felt it was not possible to carry out recruitment myself. The assessments of new patients attending the low vision clinic could take up to an hour; this meant that on any given day, the number of patients seen was small. I felt this would be a rather inefficient use of my time, and that this was a procedure that could be carried out by my optometrist collaborators. We agreed that they would administer a screening
instrument for visual hallucinations to all patients attending the Low Vision Clinic, and take the details of any patients that screened positive and expressed an interest in the study. I defined inclusion and exclusion criteria: being over 65, having a friend or relative able to act as an informant, being fluent in English and having a visual acuity in the best eye of between logMAR 0.3 and 1.3. These criteria were designed to try to direct the study effort at the population where the prevalence of CBS was likely to be highest. The restriction to fluent English speakers was due to the lack of resource for translation services, and the potential lack of validity of some of the psychometric instruments used in the study in languages other than English. Those that expressed an interest in participating had their details taken and were contacted by me to arrange a visit to discuss the study in more detail, and to obtain consent from those willing to participate. I also agreed with the optometrists that they would arrange to see the participants in order to carry out a more detailed examination of their visual functioning. This would include contrast sensitivity testing and visual field testing.

Controls were also sought from the low vision clinic, and were intended to be of a similar age and level of visual impairment to participants with CBS. Patients that screened negative for visual hallucinations were identified as possible controls, and offered information about the study. Those that expressed an interest, like those screening positive, had their details taken and were contacted by me to arrange a visit to discuss the study in more detail, and to obtain consent from those willing to participate.

4.5 Determination of Sample Size

In chapter 4.3, I set out power calculations based on a sample size of 12 participants with CBS and 12 controls. These figures were based on the sample sizes attained in
previous published work. In this section, I explore further aspects of the clinic setting in which recruitment was planned, the low vision clinic of Manchester Royal Eye hospital, to determine if this was a realistic figure to aim for.

Determining the number of patients attending clinic that would require to be screened proved to be a difficult task. Two parameters were key to the calculation: the proportion of clinic attenders who met the inclusion criteria, and the proportion of those meeting the criteria who would agree to be recruited. When attempting to estimate these parameters, the usual practice is to look at similar studies in the published literature, and to make a judgement based on their recruitment rates as a proportion of the eligible population. This process was hampered by there being no sufficiently similar studies to make a comparison with. A lot of the previous work focussing on the relationship between CBS and cognition was conducted in other settings- for example recruiting from a database of a low-vision charity in Schultz and Melzack (1993), and taking referrals from neurology, psychiatry and ophthalmology clinics (Pliskin et al. 1996). Holroyd et al. (1994) did recruit from a low vision clinic, and so was closer to the setting this work was conducted in. Another study, Abbot et al. (2005) was actually conducted in the same department as the current work, and so was potentially even more relevant.

However, Abbott et al. (2007) report recruiting 66 consecutive attenders at clinic, and do not mention any potential participants declining to take part. This suggests a recruitment rate of 100% of eligible candidates, which is a remarkable figure. The protocol in Abbott et al. (2007) however, made fewer demands on participants than in this work, with no neuroimaging component or requirement for a period of follow-up. Holroyd et al. (1994) reported a similar situation; they claim to have approached 127 consecutive patients attending clinic, and report all of them agreed to participate. Again, the protocol was less onerous, and so may have made the study seem more
attractive, and the mean age was much lower at 66; but such high rates of recruitment raise questions over how similar attitudes to participation in research were in the target population of Holroyd *et al.* (1994) to this work. I felt caution should be exercised before assuming that I would find near complete acceptance by potential participants.

The other two studies were less clear about recruitment procedures: neither Schultz and Melzack (1993) nor Pliskin *et al.* (1996) make any comment about whether any potential recruits declined to participate, nor was their target population so clearly defined. Again neither made similar demands on participants to those that participants in this study faced, and overall they offer no useful information to guide my estimations of recruitment rates. In summary, the existing published literature is not able to offer any guidance on the proportion of eligible people in the target population who will agree to take part in this study.

In such circumstances, where the literature is of no help, then pilot/feasibility studies and clinical experience may offer some guidance. This work was intended to be a pilot study, but some of its aims do overlap with those of feasibility studies; and estimating proportions of clinic attenders who meet eligibility criteria, and of eligible people who agree to participate, were important aims of this work. However, no feasibility studies existed at the point of the study design that were able to inform development of this work.

This meant that clinical experience and judgement were the only factors available to help guide estimation of these parameters. I therefore discussed the matter with Dr Robert Harper, as a senior and experienced clinician within the department where recruitment was to take place, and sought his opinion on the proportions of people attending who were likely to be eligible, and who would be prepared to be recruited.
Dr Harper stated that there were around 1600 new patient assessments each year in the low vision clinic at Manchester Royal Eye hospital. Not all of those attending would be over 65; and not all of the optometrists would be involved actively in recruitment, but he felt we could aim to screen around 1/3 of this number per year. This would equate to approximately 550 patients screened over this period.

Assuming that the rates of CBS in the population attending MREH were broadly in line with those seen in previous research carried out in the department (Abbott et al. 2007), and in line with previous work in low vision populations elsewhere, then a conservative estimate would be that 15% of this population would be experiencing symptoms consistent with CBS. This would translate to around 80 people screening positive for CBS over a year. However, not all people screening positive would meet inclusion criteria or wish to take part in the research. I assumed only 30% would be eligible for and express an interest in the study. This assumption had no good evidence to guide it, and was merely an estimate based on clinical experience and judgement. It was however a conservative estimate, and was far short of the 100% participation reported in Abbott et al. (2007). I assumed many people would be unwilling to undergo the 5 contacts over a year, including two which required attendance at hospital, especially given the likely advanced age of the cohort I was looking to recruit. This gave an estimate that around 25 people with CBS would be willing to participate over the course of a year.

With regard to controls, I assumed that the interest rate for being a control would be significantly lower, and took a value of 10% of eligible people being willing to participate; however, with around 470 people expected to screen negative, this would lead to an estimate of around 45 people who may be interested in acting as controls.

I therefore considered that it may be possible to aim to recruit more than the 12 CBS participants assumed in the modelling. If the figure of around 30% of eligible
participants recruited was achieved, that would translate to around 25 participants with CBS. The targets of 12 participants in each group were therefore retained, but I hope it may be possible to exceed these and potentially recruit up to 25 participants in each group.

4.6 Discussion of Pilot studies

As discussed in 4.3, the anticipated sample size I could realistically aim to recruit was unlikely to result in the study being adequately powered to exclude a type II statistical error. The primary role of this piece of work was therefore as a pilot study. In this section, I will explore pilot studies in more detail, considering their place in the landscape of research, their utility, and their limitations.

Firstly, there is sometimes misunderstanding of the differences between pilot studies and feasibility studies. I will discuss the relationship between these, and consider the proposed work in relation to their definitions. In each case, I have taken the definitions from the National Institute of Health Research website glossary (NIHR 2014).

Feasibility studies are pieces of preliminary work which address the question, ‘can this study be done?’ They are used to help inform the design of the main study and have the characteristics shown in table 6 below.

Pilot studies are a smaller version of the main study used to test whether the components of the main study can all work together. They test the processes of the main study, including recruitment, randomisation, treatment and follow-up assessments. They can be internal pilots, where the data generated will be included
in the final analysis alongside that generated by the substantive study; or external pilots, where the data may be analysed but will be set aside of that from the main study.

Table 6: characteristics of feasibility studies

<table>
<thead>
<tr>
<th>Pieces of research done before a main study</th>
<th>Used to estimate important parameters that are needed to design the main study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility studies for randomised controlled trials may not themselves be randomised</td>
<td>The do not evaluate the outcome of interest; that is left to the main study</td>
</tr>
</tbody>
</table>

The goals of this study were to test out how the protocol performed when it was put into practice, and to generate information on how effectively it can be delivered, in relation to key areas such as recruitment and retention of participants, and whether the disparate clinical teams involved can work effectively together. There was no intention to include the data generated with that of any subsequent large-scale study, so I consider that this work has the characteristics of an external pilot study. I will discuss pilot studies further below, and consider issues arising from their conduct.

As set out in the NIHR definition, pilot studies are preliminary in nature, and usually involve using the proposed protocol on a small group taken from the target population, in advance of a larger definitive study. They may have a number of functions, including testing how the protocol works in the field, training staff to carry out the work involved in the study, and contributing to power calculations to help define the sample size for the definitive study.

The first two aspects of pilot studies are largely uncontroversial. A large RCT or epidemiological study may intend to recruit hundreds of participants, may have many
staff across a number of sites, and as a result be very costly. There is therefore potentially great value in determining whether the protocol works when put into practice; whether the documents are clear and understandable to staff that were not involved in designing them; whether participants find the burdens placed upon them acceptable; and whether the training for staff has adequately equipped them to use the study instruments. It is also possible to assess if the proposed recruitment procedures are likely to deliver the expected number of participants. The pilot allows weaknesses and flaws in the protocol or planning to be identified and rectified before the large scale study begins, and should reduce the risk of unforeseen problems jeopardising the viability of the project.

The third aspect of pilot studies is more contentious. The pilot may be used to estimate an effect size, in order to inform power calculations. By convention, the study should be powered to have at most a 20% chance of failing to reject the null hypothesis if there is a real, and clinically significant, difference between the groups. By carrying out power calculations, the sample size can that would achieve this can be determined, and so in theory two undesirable alternatives can be avoided: an underpowered study that is incapable of achieving the study aims, and an overpowered study, which is far larger, and therefore costlier, than is needed.

The concepts of clinical significance and effect size warrant discussion in more detail at this point. These concepts have become more important over time in the design of studies, to ensure the correct level of powering, and in the interpretation and communication of findings. They address the problem inherent in testing for statistical significance: that showing a result is statistically significant only demonstrates that there is a non-random effect being observed. It allows no judgement to be made as to the clinical relevance of that effect. A very large, well designed study could potentially have great power, and be able to show a clinically significant difference
between an intervention group and a control group that was clinically trivial in magnitude. Conversely, failure to achieve statistical significance, and so to refute the null hypothesis, only indicates that the study was poorly designed; it does not rule out the possibility that there is a real, and clinically relevant, difference between the groups being studied that the study failed to detect (Kraemer and Kupfer 2006).

By introducing the concept of clinical significance, this shortcoming can be addressed. Clinical significance is a measure of the practical importance of a treatment effect in real-life practice. It is likely to vary between conditions and settings; for example, even a very small reduction in the long term risk of suffering a serious event such as a myocardial infarction may be clinically significant, if the treatment is well tolerated and resources exist to fund its use on a population scale. In designing studies, the best practice is to set an effect size a priori which the investigators would consider to be clinically significant given the setting (Kraemer and Kupfer 2006). This will then inform power calculations, to ensure that the probability of rejecting the null hypothesis at the desired level of statistical significance is greater than 80% whenever the true effect size is greater than the threshold taken to confer clinical significance.

In relation to effect size, there are a number of ways to quantify this. One of the most commonly used is the Cohen’s d, defined as the difference between two means divided the standard deviation for the data. Cohen offered definitions for small, medium and large effect sizes (of 0.2, 0.5, and 0.8 respectively) (Cohen 1988). These have become widely used, though they have been criticised. Moreover, the Cohen’s d itself is noted to have drawbacks, including not conveying a readily understandable message to clinicians (Kraemer and Kupfer 2006). Kraemer and Kupfer (2006) suggest other measures of effect size are preferable for this reason, as
they are more easily interpreted by clinicians; they include the Number Needed to Treat (NNT), and the Area Under ROC Curve (AUC).

This does raise a conundrum: there should be a reasonable expectation that there is likely to be an effect size that would be regarded as clinically significant in order to proceed with the study. However, the effect size is likely to be unknown, as part of the aim of the research is to determine this. How then can an estimated effect size be derived, so as to inform the power calculations?

One approach is to carry out calculations based on widely accepted values for small, medium and large effect sizes, based on previous research. However, there may not be previous relevant research, which risks inappropriate values being used. Another is to carry out a pilot study, with the goal of determining the effect size; this can then be used to inform the power calculations, and so determine a study size.

While a superficially attractive approach, Kraemer et al. (2006) draw attention to a serious problem inherent in this approach. A pilot study will generate an estimate of the true effect size of the area being investigated in the target population, but this is a single estimate drawn from the total population of estimates of the effect size. By definition the pilot study is likely to be small, and so the standard error of that effect size is likely to be large. This means that there is a significant chance that the effect size generated by the pilot will be a considerable underestimate, or overestimate. Both possibilities are potentially serious; if the effect size is underestimated, then a full scale study may not go ahead, and an intervention or epidemiological relationship that would be of value will not be investigated. On the other hand, if it is overestimated, this will lead to power calculations which indicate smaller numbers of participants, underpowering the study and leaving it unable to confirm or refute the hypothesis.
4.7 Application of principles of pilot studies to this work

In the light of the concerns over the use of pilot studies to estimate effect sizes set out in section 4.6 above, I planned to focus the aims of the current work on testing protocol delivery in a clinical setting. The study would demand close collaboration between two departments who do not have any history of joint working, and are unfamiliar with each other’s field. The acceptability and tolerability of the proposed study, both from its subject matter, and from the practicalities of the protocol in a very elderly population, were uncertain. Given the low vision of participants, adaptations would need to be made to study instruments, principally the Addenbrooke’s cognitive examination; this work could assess whether these adaptations were sufficient for purpose. The extensive documentation could be trialled to see if it was understandable and usable in the field. Different potential sources of recruitment could be evaluated, and the attitudes of staff in these settings assessed to reach a view on their level of commitment to any future work in this area. As the Chief Investigator, I could develop skills and competencies in putting together and managing a study using this protocol, learning what areas work well and what needs revising, and so prepare myself for any larger study that follows from this.

Finally, while using the study explicitly to determine an effect size would be unwise given the arguments that Kraemer et al. (2006) advance, if there was a large difference in the rates of development of dementia, this would offer some support to any subsequent proposal to undertake a larger-scale cohort study in future. Indeed, if the changes in cognitive functioning in the CBS group proved to be larger than anticipated, it remained possible that some form of hypothesis testing could still be undertaken; though given that this was felt to be unlikely, it was not the primary focus of the research.
4.8 Progress of Study and Amendments to Protocol and Study Team

An application to the South Manchester NHS Research Ethics Committee was prepared and submitted, based on the protocol attached in appendix 4. The application was reviewed and ethical approval granted in December 2009. Copies of a selection of the study documents approved for use are provided in appendix 5; where more than one version of the document has been used during the study, the most recent version is the one that has been included. I then had to secure R&D approval from the various organisations involved in the research, which was successfully completed to allow recruitment to begin in April 2010.

Recruitment was initially promising, but soon slowed down. As a result a number of amendments were made to the study, including opening the study for recruitment in a glaucoma assessment clinic at MREH, and removing exclusion criteria relating to visual acuity. Making arrangements for participants to attend for optometry assessments proved challenging and these were reduced to one contact per participant. I also received assistance from a higher specialist trainee in Old Age psychiatry, Dr Varinder Singh. I discussed with my supervisors the level of involvement Dr Singh could have without compromising the educational validity of the project. The outcome was that Dr Singh could provide some assistance with recruitment and data collection, but that I must retain overall responsibility for the design and management of the research, and for writing any papers that arose.

A final strategy to improve recruitment was also put into place at this point. Professor Burns contacted colleagues in Dendron, the Dementia and Neurodegenerative Diseases Research Network, to investigate whether they may be able to offer any support to the project. A clinical studies officer offered to help with recruitment, attending clinics to support the staff in the glaucoma and low vision clinics who were
at times too busy with clinical work to reliably administer the screening instrument. With this support in place, recruitment did improve and was completed in June 2012.

The methodology of the study will be set out in detail in chapter 5, and its findings in chapter 6 below.
5. Clinical Study: Methods

5.1 Introduction

In this chapter the methods used in the clinical cohort study are described. Recruitment methods and the screening instruments used to identify potential recruits are set out in section 5.2, and the processes relating to eliciting informed consent are noted in section 5.3. The study instruments used in the data collection interview, and how these were chosen, are discussed in section 5.4. Optometry assessments are described in section 5.5, and neuroimaging procedures in 5.6. Arrangements for the follow-up interview, and special considerations around capacity at this contact are discussed in section 5.7, and some brief considerations around statistical testing are noted in section 5.8.

5.2 Screening

Recruitment was conducted in the low vision clinic and glaucoma assessment clinic at Manchester Royal Eye hospital, between April 2010 and June 2012. Participants were seen by staff working in these clinics, and as part of the clinical assessment, the four-item screening section of the North East Visual Hallucination Interview (Mosimann et al. 2008) was administered. This instrument is designed to detect evidence of visual hallucinations, and to elicit information regarding the details of the experiences, so as to allow classification of the hallucination as simple or complex. Those that screened positive for having complex visual hallucinations, and met the inclusion criteria of being aged 65 or older and having a friend or relative able to act
as an informant, were provided with an information sheet and asked if they would be willing to be contacted by the study investigators. If they agreed, then they were contacted by telephone and offered an appointment, either as a domiciliary visit or in clinic at Manchester Royal Eye hospital, at their preference.

Those that screened negative during this process were also provided with information about the study, and asked if they would be willing to act as controls. For those that did express an interest, the same process of providing an information sheet and arranging contact by investigators was followed.

5.3 Consent and Inclusion/Exclusion Procedures

Those that agreed to the initial visit were seen and the nature of the study was explained to them. They were taken through the information sheet to make sure that they had understood its contents, and their capacity to consent to the study was assessed by one of the investigators. Both investigators carrying out this task were old age psychiatrists, working as consultant or higher specialist trainee in the discipline, and so had considerable experience of working with the Mental Capacity Act 2005 and of taking informed consent. For those that agreed to take part, informed consent was elicited and the consent form signed.

Once recruited to the study, the next step was to establish that they did in fact have Charles Bonnet syndrome, or, for controls, that they did not. In order to do this, the full North East Visual Hallucination Interview (Mosimann et al. 2008) was administered by the investigator, and the results were used to determine if the Teunisse criteria (Teunisse et al. 1996) for CBS were met.
In addition, a full medical and psychiatric history was taken, and permission was sought via the consent form to approach the participant’s General Practitioner, in order to determine if any relevant medical conditions known to be responsible for hallucinations were present. These included dementia, Parkinson’s disease, schizophrenia, depression, alcohol dependency and chronic delirium.

Any participant agreeing to be a control who developed visual hallucinations between screening and giving informed consent was recruited as having CBS instead, if they met the criteria and were agreeable to taking part.

5.4 Data Collection Interview

Participants who gave consent and were deemed to have CBS, or to be able to act as a control, had a further assessment arranged with an investigator. At this first data collection visit, a number of instruments were administered which would form the central part of the study. These were as follows:

i) An extension to the NEVHI. In his paper of 2005, ffytche identified a number of aspects of the phenomenology of hallucinations that he proposed were more often associated with ‘true’ CBS, and a number that were suggestive of the hallucinations being an early presenting symptom of a dementia. I developed a tool to derive a score to reflect this, with the intent of testing whether it had any predictive value in detecting the presence of dementia.

ii) A measure of cognitive functioning. This should be a well-recognised and validated measure, that was capable of detecting small changes in cognitive
functioning, and that had a good coverage of a wide range of cognitive domains. Ideally, it should be validated in a vision impaired population. For practical purposes, it would need to be available without charge to the user, and it should not need extensive training to administer. Given the advanced age of many of the probable participants, it should not take too long to administer, so as to maximise acceptability. Finally, given that a possible outcome could be that the instrument will be shown to have a clinical role in identifying people with CBS who are at risk of developing dementia, it would be an advantage if it was an instrument that was already well recognised and accepted by clinicians. The Addenbrooke’s Cognitive Examination-Revised (ACE-R) (Mioshi et al. 2006) was adopted as the instrument that met more of the criteria than any of the others. This is scored out of 100, and incorporates items which test domains of cognitive functioning which are covered poorly by the MMSE, such as frontal-executive and visuospatial skills (Bak and Mioshi 2007). It is now widely used in clinical settings and is capable of being administered by staff with relatively little training, and in a clinically manageable timescale.

I contacted a member of the team who developed the ACE-R (Eneida Mioshi) to inquire whether she was aware if there was a version of the ACE-R validated for low vision populations. She was not aware of any such version. I recognised this was a potential problem, as the ACE-R is quite heavily vision dependant. There are 34 items that have some reliance on visual functioning, and to omit these items would result in poor coverage of the visuo-spatial and language subscales, potentially undermining the validity of the instrument. I therefore developed large print versions of the vision dependant items. I consulted with Robert Harper to ensure that these would be sufficiently large to be understood by people with the levels of visual impairment we were likely to encounter in the study; and piloted it on a number of patients attending the low vision clinic, with encouraging feedback about their acceptability and utility.
iii) A full medical and psychiatric history taken by an experienced old age psychiatrist. This would include a brief neurological examination and a mental state examination. This would seek to identify the presence of any pre-existing mental disorder, including dementia or psychotic disorders. In seeking to make a diagnosis, well recognised operationalised diagnostic criteria for mental disorders would be taken as the reference point. These would be as follows: the NINCDS-ADRDA criteria for Alzheimer’s disease (McKhann et al. 1984); the NINDS-AIREN criteria for vascular dementia (Roman et al. 1993); the consensus criteria for Lewy body dementia (McKeith et al. 1996); and the ICD-10 criteria for functional mental disorders and alcohol dependency.

Diagnosis would be made by the clinician conducting the assessment, based on an evaluation of the material generated during the assessment process, including the informant history and cognitive testing. Diagnostic criteria for dementia include a requirement for there to be cognitive decline of sufficient magnitude to interfere with social or occupational functioning. The coexisting visual impairment posed a diagnostic challenge, as in many cases it would be likely that this would independently interfere with functional ability. In the absence of validated instruments to determine the contribution of visual loss to observed functional deficits, the decision over the significance of changes in cognitive functioning to these deficits would lie with the investigator. Although this is a less robust procedure than the gold standard, of clinical consensus among at least two experts, blinded to participant group, after review of the clinical material, it would be achievable with the resources available to the study. It would represent the sort of real-world clinical decision making challenge that experienced old age psychiatrists face, and so would be a task the investigators would be familiar with. This practical solution would come at the
cost of a potential reduction in diagnostic validity, but represented the best option available given the limitations the study faced, both in resource and in the applicability of existing diagnostic tools to the study population.

iv) An informant history, including a structured questionnaire, in addition to an unstructured interview with an old age psychiatrist. The Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) (Jorm et al. 1996) seemed to meet the criteria I had established, of being well validated, and simple to complete. This would increase its acceptability to a potentially very aged population who would be asked to complete it. It has shown to be very sensitive in detecting the impairments of skills of daily living seen in dementia. In addition to the full IQCODE, there is also a short version (Jorm 2004). This is a 16 item questionnaire completed by someone that knows the participant well, and assesses their ability to carry out everyday tasks currently when compared to a point in the past. The items included in it seemed less likely to be affected by the poor vision present in this population than the longer version. I therefore adopted the Short IQCODE for this study.

v) A semi-structured and validated measure of psychiatric morbidity. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) was chosen for this task. This is a well-established instrument which can be used to systematically elicit psychopathology suggestive of the presence of any mental disorder which could render the diagnosis of CBS unreliable. A low score on this would add weight to the clinical assessment findings, and offer further evidence that there was no mental illness present that could account for the presence of the visual hallucinations. As all of the CBS patients, by definition, would score points on the BPRS item relating to
hallucinations, while none of the controls would, again by definition, I took the decision to exclude this item from the total score generated.

Copies of the study instruments are included in Appendix 6.

At the end of the data collection interview, if a diagnosis of dementia, or any of the other disorders known to feature hallucinations that are listed above, was made, the participant was excluded. Otherwise, they were invited to take part in two subsequent data collection contacts.

5.5 Optometry Assessment

The participant also would have an assessment arranged at the low vision clinic at the Manchester Royal Eye hospital. During this assessment, their history of ophthalmological disorders would be clarified, and their visual acuity determined in logMAR units. In addition, two other aspects of visual functioning were measured. The first of these was contrast sensitivity, using the Pelli-Robson scale. The second was visual fields testing, using an Amsler grid chart.

5.6 MRI Scan

Thereafter, the participant was invited to attend at the Wellcome Trust clinical research facility in the University of Manchester, where they would undergo an MRI brain on the 1.5 Tesla scanner. This would look for the presence of abnormalities consistent with the presence of any of the exclusion diagnoses mentioned above. Following an amendment granted by the Research Ethics Committee, this part of the
study was made optional, due to its lower level of acceptability to potential participants.

5.7 Follow-up Assessment

Finally, one year after the initial data collection interview, the participant was contacted again and, if agreeable, a follow-up interview was arranged. At this, the nature and purpose of the study was explained again, and the participants continued consent to participate was examined. It was anticipated that some participants may lose capacity to consent over the year of follow up, and so provision was made for this, with a separate information sheet prepared for persons acting in the role of consultee, as set out in the Mental Capacity Act (2005).

For those agreeing to undergo the follow-up interview, the format was very similar to the initial interview. The NEVHI was re-administered to determine if the criteria for CBS continued to be met, and to characterise the nature of the hallucinations if they were. A full history, informant history, mental state examination and neurological examination were undertaken. Finally, the ACE-R, IQ-CODE and BPRS were administered again. Given the number of tasks to be completed at this interview, provision was made to divide them between two visits, according to the participant’s wishes.

5.8 Outcomes and Statistical Testing

As described in chapters 4.3 and 4.7, the study was likely to be underpowered to detect differences in the outcome measures with enough precision to reach statistical
significance. The primary outcome of the study would therefore be to meet the goals associated with its status as pilot work, in assessing the performance of the protocol when it was applied to a group of frail elderly patients. Nonetheless, the data collected would be assessed to see if the aims of the study set out in chapter 4.2 were met. Statistical testing would be used where appropriate, for example subjecting the proportions of each cohort who developed dementia to significance testing with Fisher’s exact test, and carrying out t-testing on differences in scores on the ACE-R at baseline assessment and follow-up, using SPSS version 20.
6. Clinical Study: Results

6.1 Introduction and Summary of Results

Chapter 6 sets out the results of the clinical cohort study. Section 6.1 deals with recruitment, describing how a total of 70 people screened positive for possible Charles Bonnet syndrome over the course of the study, and how a total of 12 participants with CBS and 10 controls completed all required data collection. The representativeness of the cohorts recruited is addressed, and the reasons people gave for declining participation are considered. In chapter 6.3, the demographics of the cohorts are described; the CBS group and controls were found to be very similar in age, but to differ in gender, with more females in the CBS group and more males in the control group. Chapter 6.4 documents the findings of the history and examination. No participants were found to have dementia at the initial data collection interview, and none were found to have medical conditions or be taking medication which could explain the presence of hallucinations. This finding was supported by the results of the Brief Psychiatric Rating Scale (BPRS), shown in chapter 6.5, where the low scores found made the presence of significant psychiatric morbidity at diagnosis of CBS very unlikely.

In chapter 6.6, the characteristics of visual hallucinations experienced are described. This includes a detailed description of the content of the hallucinations. The hallucinations were found to be persistent, with most participants experiencing them for over one year at the point of diagnosis of CBS. At follow up after one year, 7/12 participants continued to meet criteria for CBS. Emotional responses to the hallucinations were largely neutral, and while insight was good, participants reported
little control over the experiences. When the experiences were categorised, participants were found to have on average 4 different categories of visual hallucination.

Chapters 6.7 and 6.8 deal with the findings of the optometry testing conducted as part of the study. This showed that age-related macular degeneration and cataracts were the commonest diagnoses among both participants with CBS and controls. Visual functioning was impaired in all participants, with the mean visual acuity of both the CBS participants and control group being poorer than the threshold of logMAR 0.3 found to confer an increased risk of developing CBS (Teunisse et al. 1995). Both groups also showed relevant and significant impairments on measures of contrast sensitivity and scotoma testing.

Chapter 6.9 presents the findings of the neuroimaging conducted as part of the study. Given that both the participants with CBS and controls were of advanced age, it was not unexpected to find that there were frequently abnormalities present on the scans, with many participants showing cerebral atrophy and small vessel ischaemic changes. However, the extent of ischaemic changes in the cohort with CBS appeared to be greater than that seen in the control group.

The emergence of dementia in two of the twelve participants with CBS is documented in chapter 6.10. This is contrasted with the control group, where none of the participants developed dementia over the course of the study. This difference was not found to be statistically significant.

Chapters 6.11 and 6.12 report more findings relating to cognitive functioning. Using a cut-off point on the Addenbrookes Cognitive Examination (Revised) (ACE-R) previously identified as indicating abnormal cognitive functioning, 3/12 participants
with CBS were found to score below this at baseline, rising to 6/12 at follow-up. This compared to 0/10 controls scoring in the abnormal range at baseline, and only 1/10 at follow-up. These differences did not attain statistical significance. The use of a cut-off point could be criticised however, as this was not derived from a vision-impaired population, so in chapter 6.12 changes in the raw scores on the ACE-R were investigated. The mean score on the ACE-R at follow up in the cohort with CBS (83.6) was lower than in the control group (92.0), and the magnitude of the difference was likely to be clinically significant. Statistical analysis of the change in scores on the ACE-R using a t-test appeared to confirm a significant difference. However, the presence of potential confounders, such as the differences in visual acuity between the CBS cohort and control group, made this finding unreliable. Further testing using the technique of Analysis of Covariance was conducted, which failed to replicate the finding of statistical significance in the change in the ACE-R scores between the groups. These findings are set out in chapters 6.13 and 6.14.

In chapter 6.15 results from an analysis of the five subscales of the ACE-R, each describing a different cognitive domain, are looked at in more detail. This analysis suggests that frontal lobe functioning in people who receive diagnosis of CBS may be more impaired than in controls. The detailed analysis of the ACE-R results is continued in chapter 6.16, where a comparison of the ACE-R scores on visually-dependent items and visually-independent items is carried out. This provides evidence that the poorer performance on the ACE-R among CBS participants is not restricted to the visually-dependent items of the test, but instead is seen in both visually-dependent and visually-independent items. Moreover, the difference in the mean score on the visually-independent items of the ACE-R between the CBS participants and controls at follow-up was statistically significant. This provides some support for the view that the changes seen represent a real effect, rather than confounding effects of the CBS participants’ poorer visual acuity.
Finally, chapter 6.17 presents results relating to the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Mean scores on this were higher among participants with CBS than controls. This may have again reflected the poorer visual acuity among this group. However, it was notable that the highest scores on the IQCODE were found in the two participants who went on to develop dementia, suggesting that this instrument may have some value in predicting who may be at risk of this outcome.

6.2 Recruitment

Between April 2010 and June 2012 a total of 70 people screened positive during clinic visits at Manchester Royal Eye Hospital. Of these 20 were seen and gave consent to be included in the study. However, four subsequently withdrew consent before the initial data collection was complete, and one was excluded, leaving 15 participants with Charles Bonnet syndrome for whom initial data collection took place.

Of the 15 where initial data collection was completed, one had considerably poorer visual functioning than any other participants in the study. As a result, they were unable to complete the vision dependent items in the ACE-R, even with the low vision modifications. This meant they obtained a score out of 65 rather than 100. While it would have been possible to scale the result obtained up to give a score out of 100, the items that were incomplete clearly test different aspects of cognitive functioning than the ones that were done, so the validity of this approach would have been very much in doubt. Moreover, on this approach, the participant was an outlier, with an adjusted ACE-R score more than 2 standard deviations below the mean,
despite clinically showing no evidence of dementia. I therefore took the decision to exclude this participant from the analysis.

There were also two participants where initial data collection was done, but the follow up data collection could not be completed before the study end date. This meant that a total of 12 participants with Charles Bonnet syndrome completed the initial and follow up data collection.

Within the control group, a total of 15 participants were recruited over the course of the study. Three controls withdrew before data collection commenced, and one participant died after recruitment but before data collection. Another control died during the course of the study, before the follow up data collection took place. Therefore, a total of 10 controls completed the study, with data collection at both time points.

With regard to CBS participants, Table 7 sets out the number of those screening positive that fell into each category.

Given that only 21% (15/70) of those screened actually progressed to data collection in the study, I was concerned that those included could be in some way unrepresentative. I did have access to the age and gender of those that declined contact or were excluded/withdrawn, and was able to compare these to the study participant group. The results were reassuring, with a mean age in the participant group of 81.7, compared to 81.2 among those who did not take part. The gender balance was 17% male in the study group compared to 25% male in those that did not take part. Thus, in the limited attributes that were available to compare those who participated with those that did not, the groups appeared similar, lending support to
the view that the participants were likely to be representative of the sample population.

Table 7: Results of Screening for Charles Bonnet syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declined further contact at screening</td>
<td>41</td>
</tr>
<tr>
<td>Did not meet Teunisse criteria: no hallucinations in month leading up to screening contact</td>
<td>4</td>
</tr>
<tr>
<td>Did not meet Teunisse criteria: duration of hallucinations less than one month</td>
<td>1</td>
</tr>
<tr>
<td>Did not meet Teunisse criteria: auditory hallucinations also present</td>
<td>1</td>
</tr>
<tr>
<td>Hallucinations possibly medication related or due to medical condition</td>
<td>2</td>
</tr>
<tr>
<td>Not able to speak or read English</td>
<td>1</td>
</tr>
<tr>
<td>Recruited too late to complete follow up</td>
<td>1</td>
</tr>
<tr>
<td>Withdrew</td>
<td>4</td>
</tr>
<tr>
<td>Consented and initial data collection completed</td>
<td>15</td>
</tr>
<tr>
<td>Of this 15, number that completed study</td>
<td>12</td>
</tr>
</tbody>
</table>

I did look at the screening data sheets for those who declined participation, to see whether any comment was made as to why they declined. In a number of cases, people did comment on why they did not wish to take part, and the actual responses given are quoted in table 8. Where a reason for being unwilling to participate was given, this tended to fall into one of three categories. These were an unwillingness to be involved in research at all, a feeling that the person’s health was too fragile to tolerate the rigours of the research process, or a specific unwillingness to undergo the MRI scan. It was this final reason that led to the protocol being amended to
remove the requirement for a scan, though in the end only two participants did not undergo this procedure as part of the study

Table 8: Reasons given for declining participation

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too many other clinic appointments</td>
</tr>
<tr>
<td>Not keen to be involved in research</td>
</tr>
<tr>
<td>Not keen on leaving wife to have MRI scan</td>
</tr>
<tr>
<td>Not keen on idea of scan</td>
</tr>
<tr>
<td>Feels has too many medical conditions and it would be too much</td>
</tr>
<tr>
<td>Doesn’t want to be part of research</td>
</tr>
<tr>
<td>Feels has enough on with eyes, knees and hearing requiring hospital appointments</td>
</tr>
<tr>
<td>Does not want to have MRI</td>
</tr>
<tr>
<td>Too tricky to attend</td>
</tr>
<tr>
<td>Does not want to take part in any kind of study</td>
</tr>
<tr>
<td>Too old</td>
</tr>
</tbody>
</table>

.  

6.3 Demographics

The mean age of participants with Charles Bonnet syndrome was 81.7. This was similar to that of the controls, where the mean age was 81.3. The ethnic background of the two groups was largely comparable; 11 of the 12 CBS participants were of white British ethnicity, with one being of white Irish. Among the controls, 9 of the 10 were of white British ethnicity, and one was of black ethnicity. However, the two groups did differ in gender (82% male in the control group, compared to 17% in the
CBS group). I also looked at the living circumstances of the participants. Ten of the
12 CBS participants lived alone, compared to four of the ten controls.

6.4 Findings of history taking and examination

All participants underwent an interview with an experienced old age psychiatrist as
part of the protocol. All participants had a range of medical diagnoses, as would be
expected for a cohort of this age. None were felt to be acutely unstable, or to be
responsible for the presence of the hallucinations in the Charles Bonnet syndrome
group. Five of those with Charles Bonnet syndrome had a past psychiatric history,
three with depression, one with an anxiety disorder and one with an adjustment
reaction. None felt that they were experiencing current symptoms of these conditions,
and none had ever been referred to secondary care mental health services. None
were on medication that was felt could be contributing to the hallucinations, such as
dopamine agonists or narcotic analgesics. Four CBS participants had minor
abnormalities on neurological examination: in three cases a tremor, one
accompanied by reduced arm swing when walking, and in one, peripheral
neuropathy. The mental state examinations in the CBS group were remarkably
normal, with only one participant showing signs of mild word finding problems and
reduced reactivity of affect.

Two participants reported increased forgetfulness, but this did not appear to be
significantly interfering with practical skills of daily living, and none of the informants
raised concerns over significant problems with cognitive functioning. None of the
participants met diagnostic criteria for dementia during the initial interview, nor were
any diagnosed with other exclusion conditions, such as Parkinson’s disease, alcohol dependency, delirium, psychosis or significant depression.

6.5 Brief Psychiatric Rating Scale (BPRS) scores

The participants also underwent the BPRS as a means of objectively quantifying their level of psychiatric morbidity. As noted in the methods section, a modified version of the 18 item BPRS was used, with the item relating to hallucinations excluded. The results of this are set out in table 9.

The mean score on the BPRS was higher in the CBS group than the controls, even when the item scoring for the presence of hallucinations was omitted. However, the possible range of scores available on this assessment is from 17 to 119, so the mean score of 22.3 in the CBS group, though higher than the controls, is still low. These generally low scores on the BPRS support the evidence from history taking and mental state examination that none of the participants had a recognisable mental disorder which was relevant to their presentation.

Table 9: Scores on the BPRS

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS: Initial</td>
<td>18</td>
<td>29</td>
<td>22.3</td>
<td>3.7</td>
</tr>
<tr>
<td>CBS: Follow-up</td>
<td>17</td>
<td>42</td>
<td>22.6</td>
<td>6.4</td>
</tr>
<tr>
<td>Control: Initial</td>
<td>17</td>
<td>27</td>
<td>19.7</td>
<td>2.95</td>
</tr>
<tr>
<td>Control: Follow-up</td>
<td>18</td>
<td>28</td>
<td>20.3</td>
<td>3.7</td>
</tr>
</tbody>
</table>
6.6 Characteristics of Visual hallucinations

The visual hallucinations experienced by the Charles Bonnet syndrome participants were characterised in detail, and the participants descriptions of their experiences are set out in table 10.

The data generated by the North-East Visual Hallucination Inventory (NEVHI) included information on the duration and frequency of the visual hallucinations. Of the 12 participants who experienced these, eight had done so for over one year by the point of recruitment. Among the remaining four, two had experienced them for less than six months, and two for between six months and one year. Five participants experienced hallucinations daily, while six experienced them less often than daily, but at least once every week. For one participant, the experiences were less frequent, happening monthly.

The NEVHI also elicited information about the response of the participant to the hallucinations. Four dimensions were investigated, generating response on a five point Likert scale (0-4). Three dimensions (‘pleasantness’, ‘distress’ and ‘awareness’) each had two questions, so giving a score of from 0 to 8; ‘control’ had three questions, and had a potential score of 12. The results for each dimension are shown in table 11. Higher scores indicate a stronger response in that dimension, and the number of participants scoring five or higher, indicating a strong response, is shown in the table.
Table 10: content of visual hallucinations

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>Age</th>
<th>Gender</th>
<th>Description of visual hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>002</td>
<td>83</td>
<td>F</td>
<td>&quot;easter eggs&quot;, about 1 foot long, sometimes 3d, sometimes flat; around and inside real objects. &quot;a sheet of paper&quot; over garden. Things &quot;hanging from ceiling&quot;- jewellery, wrought iron. Tries to touch them. &quot;two little girls&quot;- her great-grandnieces- didn't move or speak; also on awakening- saw mother (deceased). Images of real people, behind and left, with no heads.</td>
</tr>
<tr>
<td>005</td>
<td>81</td>
<td>M</td>
<td>sees large mauve toads on carpet; floating disembodied heads which disappear when he focusses on them; brickwork patterns spread onto surrounding objects; &quot;mottled flowers&quot; appear on other plants</td>
</tr>
<tr>
<td>007</td>
<td>76</td>
<td>F</td>
<td>gargoyle-like faces started 3 years ago, stopped as vision declined 2 years ago; also saw &quot;midgets&quot; at that time. From 12 months ago, several times has seen cat in house, even went to get tin of salmon for &quot;it&quot;. Sees copper band around neighbour's chimney, lasted one week, totally convinced it was really there. Sees &quot;shapes&quot; of animals in trees, branching patterns on walls, lifelike. At night when looks out, streetlights look like Christmas trees, thought they had put decorations up early. On waking, sees &quot;mountains and valleys&quot;, these disappear when sits up</td>
</tr>
<tr>
<td>008</td>
<td>81</td>
<td>F</td>
<td>faces become distorted, like wolves- only on TV. Black and red zigzags on TV. Lines appear on wallpaper, toilet, as if has been drawn on. Often sees little girl by bed, looks like young version of her; looks sad, &quot;a poor little thing&quot;- never moves or speaks, sometimes only head there. Often thinks she is real. Saw a number of youths at neighbour's door, trying to pick neighbour up, but no one else saw this. Sees white bollards, on grass, but not actually there. Also seen daughter outside her flat when she is not there</td>
</tr>
<tr>
<td>009</td>
<td>92</td>
<td>F</td>
<td>last 2 years, saw &quot;ET&quot;- levitating cross legged alien figure. Looked threatening, ugly. Thought she was losing her mind. Repeated months later- friendly this time, aware of unreality. Sees assorted sized dogs around house e.g. rolling on carpet in living room. Also, rose stained glass window, can see grid/lattice support, very vivid colours, projected onto wall of bedroom. Few seconds at a time.</td>
</tr>
<tr>
<td>011</td>
<td>65</td>
<td>F</td>
<td>sees a patch of vivid, patterned colour like a skirt she wore many years ago projected over other parts of visual field. Can be on a daily basis, then not for weeks. Also sees ellipsoid vividly coloured shapes, brighter than surroundings</td>
</tr>
<tr>
<td>ID</td>
<td>Age</td>
<td>Sex</td>
<td>Symptoms</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>----------</td>
</tr>
<tr>
<td>012</td>
<td>79</td>
<td>F</td>
<td>Sees turquoise grid overlaid on what she is looking at, for 12 years, intensity varies, can have diamonds incorporated, or a honeycomb. Also, 2 episodes of seeing gnomes— for some hours, moved independently of each other on first occasion, then <em>en bloc</em>; after sudden onset of severe unilateral headache, in resolution phase of these— investigated but no cause found. First episode 6/12 before recruitment, 2nd 3 weeks before.</td>
</tr>
<tr>
<td>013</td>
<td>91</td>
<td>F</td>
<td>Over last 2 months, since intraocular injection, has seen &quot;teddy bear&quot;, then changed to &quot;poodle&quot;; also sees tree pattern; as long as 10 years ago, at times saw people &quot;walking crooked&quot;, distorted. Also has seen bricks in front of her house look larger, and seen small golden &quot;orbs&quot;.</td>
</tr>
<tr>
<td>014</td>
<td>72</td>
<td>F</td>
<td>Has seen sheep dog running past, and a face looking at her from behind doors. Has seen an armoured soldier on a chariot, the wheels of which were moving. Has seen &quot;wriggly&quot; patterns on walls, rabbits jumping about, horses, and the floor &quot;coming up&quot; with a person on it. Has seen field with grain and trees.</td>
</tr>
<tr>
<td>015</td>
<td>85</td>
<td>F</td>
<td>Has seen 2 men with ladder, friend said they were not there; queue of people to cross road, others walking through them; little girls with blue jackets and trousers, red hair, identical but not like any real person she has known. Sometime on bikes, or in air. If looks away, stop. Always silent. Always outside, except has seen the girls on TV a few times. Sees every day for few days, then not for a week. Sometimes on TV people have enlarged misshapen nose; also sees geometric patterns, flowers.</td>
</tr>
<tr>
<td>018</td>
<td>85</td>
<td>F</td>
<td>Sees ladies in 18th century dress, at a banquet. Also, small men in patterned suits. Will see children, who look familiar, like her own children— can be deceived and will talk to them. When she looks at trees, a brickwork pattern spreads over them.</td>
</tr>
<tr>
<td>020</td>
<td>90</td>
<td>M</td>
<td>Problems over last 5 years. Approached by hand sized, copper coloured, multi-legged spider, disappeared into door, caused &quot;concern&quot;. Saw again, tried to hit it. With repeated appearance, realised was unreal. Over last 3 years, sees people who disappear when they approach—men in suits, ladies carrying children. Over last year, wall is thousands of sparkling orange lights, form a ring, continuous; and blue points of light appear. Once saw his deceased wife sat in a chair. When looks in garden, a blood red bar shape appears and tracks from left to right, on a number of occasions. also, a cloud of pink steam came down corridor towards him, then disappeared as if sucked up by vacuum.</td>
</tr>
</tbody>
</table>
These results indicate that the overall emotional reaction to the hallucinations was generally mild, and where a strong reaction did take place, it was usually positive. No participant was significantly distressed by the experiences, while three participants frequently found them pleasurable. Participants had a good awareness that the experiences were unreal, only rarely being fooled into believing that this was a genuine percept, or into reacting to them. However, despite being aware of their unreality, participants had very little control over their onset, cessation or content.

Table 11: factor scores from NEVHI

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Mean Score</th>
<th>Score as percentage of maximum possible score</th>
<th>Number of participants with score of 5 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleasantness</td>
<td>2.33</td>
<td>29%</td>
<td>3</td>
</tr>
<tr>
<td>Distress</td>
<td>1.83</td>
<td>23%</td>
<td>0</td>
</tr>
<tr>
<td>Awareness</td>
<td>6.58</td>
<td>82%</td>
<td>11</td>
</tr>
<tr>
<td>Control</td>
<td>1.17</td>
<td>10%</td>
<td>0</td>
</tr>
</tbody>
</table>

ffytche and Howard (1999) set out a framework to describe the phenomenology of visual hallucinations, which ffytche subsequently developed further (ffytche 2007). This framework set out 16 categories of experience, and the definitions of these are set out in Appendix 7. ffytche grouped the experiences into three types: those which were hypothesised to be more likely to be associated with Charles Bonnet syndrome, those that were more likely to be associated with dementia, and those which carried no significance in either regard. The categories of hallucination, and their frequency at the initial and follow up assessment are shown in table 12. Using the ffytche framework, it is clear that a broad range of types of hallucinations occur in CBS, and that most participants have experiences in more than one category; indeed, the mean number of categories of experience was 4.2 per participant at the
initial assessment, and 2.6 at the follow up. The commonest types of experience was tesselopsia (seeing grid like patterns), experienced by 7/12 (58%) participants. Hallucinations of people could be classified in a number of different categories, but when these were combined, 6/12 participants had such an experience.

Table 12: Content of visual hallucinations by category

<table>
<thead>
<tr>
<th>Category A</th>
<th>Number of participants at initial assessment (N=12)</th>
<th>Number of participants at follow up (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual perseveration</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Illusory visual spread</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Micropsia/macropsia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hyperchromatopsia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Category B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosopometamorphosis</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Polypia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tesselopsia</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Dendropsia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Unfamiliar figures in costumes</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Landscape scenes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Confinement to one part of visual field</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Category C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Familiar figures</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Extracampine hallucinations</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Absence of simple hallucinations</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Multimodal hallucinations</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Fewer participants reported visual hallucinations at follow up compared to at the initial assessment. In total, seven of the twelve participants continued to meet the
Teunisse criteria for Charles Bonnet syndrome after follow up for one year. Three participants no longer experienced visual hallucinations, while a further two participants continued to have hallucinations but did not meet the Teunisse criteria. Among the controls, none developed visual hallucinations over the course of the study.

The fytche (2007) framework attempted to cluster the types of visual experience into three higher-order categories, which were suggested may be more likely to be associated with Charles Bonnet syndrome, more likely to be associated with dementia, or have no predictive value. Part of this study investigated whether an operationalised version of this framework did have predictive value, with the development of a visual hallucinations index score. A score of above zero on this index would suggest that the hallucinations were more likely to be due to Charles Bonnet syndrome, while a score below zero would suggest they were more likely to be due to dementia. The range of scores obtained at the initial assessment with this index score was -2 to 2, with six of the cohort scoring below zero.

6.7 Visual assessment- Ophthalmological Diagnoses

Participants underwent an assessment by optometrists in the Low Vision Clinic at Manchester Royal Eye Hospital who were collaborating with the study. This established the nature of any diagnosed ophthalmological conditions in the CBS participants and controls. The assessment also set out to measure a number of parameters of visual functioning that were felt to be relevant to the development of Charles Bonnet syndrome. There has been a clear link established between visual
acuity and Charles Bonnet syndrome, though there is some debate over whether visual acuity in the better eye, or binocular visual acuity (ffytche 2009), is the better measure. Most authors have favoured the former, and that measure is adopted here. Other dimensions of visual functioning have also been suggested as being relevant to the development of CBS. These include contrast sensitivity and the presence of scotoma, so the optometry assessment was designed to incorporate testing of these, with the Pelli-Robson chart for contrast sensitivity, and the Amsler grid for scotoma. The results of this are set out in tables 13a and 13b.

The number of participants with a diagnosis of each of the main ophthalmological disorders in each of the groups is shown in table 14 below. The total number of diagnoses adds up to more than the number of participants, as some participants had two, or even three diagnoses. The commonest disorder among participants with CBS was age related macular degeneration, followed by cataracts. These were also the two commonest diagnoses in the control group, though the order was reversed. Glaucoma was equally common amongst CBS participants and controls, and there were a few less common conditions also seen.
Table 13a: Visual assessment results for CBS participants

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>Age</th>
<th>Gender</th>
<th>Ophthalmic diagnoses</th>
<th>Visual acuity R eye</th>
<th>Visual acuity L eye</th>
<th>Binocular visual acuity</th>
<th>Contrast sensitivity</th>
<th>Scotoma?</th>
</tr>
</thead>
<tbody>
<tr>
<td>002</td>
<td>83</td>
<td>F</td>
<td>Age related macular degeneration (AMD)</td>
<td>&gt;1.00</td>
<td>0.82</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>005</td>
<td>81</td>
<td>M</td>
<td>AMD 2007</td>
<td>0.9</td>
<td>0.5</td>
<td>0.44</td>
<td>1.2</td>
<td>Yes</td>
</tr>
<tr>
<td>007</td>
<td>76</td>
<td>F</td>
<td>bilateral wet AMD, R disciform scar, L pigment epithelial detachment</td>
<td>1.52</td>
<td>0.3</td>
<td>0.22</td>
<td>1.05</td>
<td>Distortion</td>
</tr>
<tr>
<td>008</td>
<td>81</td>
<td>F</td>
<td>bilateral macular scars, R AMD</td>
<td>1.54</td>
<td>1.2</td>
<td>1.2</td>
<td>0.75</td>
<td>Yes</td>
</tr>
<tr>
<td>009</td>
<td>92</td>
<td>F</td>
<td>bilateral AMD, glaucoma</td>
<td>0.84</td>
<td>1.68</td>
<td>1.2</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>011</td>
<td>65</td>
<td>F</td>
<td>bilateral proliferative diabetic retinopathy (PDR), bilateral cataracts</td>
<td>1.5</td>
<td>0.22</td>
<td>0.22</td>
<td>1.05</td>
<td>Distortion</td>
</tr>
<tr>
<td>012</td>
<td>79</td>
<td>F</td>
<td>bilateral wet AMD, L PDR 1999, L pseudophakia and YAG 2011, R longstanding subretinal neovascular membrane</td>
<td>2</td>
<td>0.4</td>
<td>0.4</td>
<td>1.35</td>
<td>Yes</td>
</tr>
<tr>
<td>013</td>
<td>91</td>
<td>F</td>
<td>R wet AMD, L end stage AMD- AMD since 2006</td>
<td>0.96</td>
<td>2</td>
<td>0.96</td>
<td>1.05</td>
<td>Distortion</td>
</tr>
<tr>
<td>014</td>
<td>72</td>
<td>F</td>
<td>L cataract, bilateral glaucoma, anterior ischaemic optic neuropathy</td>
<td>1.06</td>
<td>1.08</td>
<td>1.06</td>
<td>0.45</td>
<td>Yes</td>
</tr>
<tr>
<td>015</td>
<td>85</td>
<td>F</td>
<td>dry AMD 2007, bilateral pseudophakia 2005</td>
<td>1.06</td>
<td>1.26</td>
<td>1.08</td>
<td>1.05</td>
<td>Yes</td>
</tr>
<tr>
<td>018</td>
<td>85</td>
<td>F</td>
<td>bilateral macular degeneration; bilateral cataract surgery; bilateral pseudo-exfoliation</td>
<td>1.48</td>
<td>1.22</td>
<td>1.2</td>
<td>0.33</td>
<td>Yes</td>
</tr>
<tr>
<td>020</td>
<td>90</td>
<td>M</td>
<td>AMD with macular hole surgery, L cataract surgery</td>
<td>2.00</td>
<td>0.1</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Table 13b: Visual assessment results for controls

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Description</th>
<th>Distortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>76</td>
<td>2</td>
<td>R cataract surgery, now aphakic; L cataract and dry AMD</td>
<td>Distortion</td>
</tr>
<tr>
<td>106</td>
<td>72</td>
<td>1</td>
<td>bilateral myopic maculopathy, bilateral pseudophakia</td>
<td>No</td>
</tr>
<tr>
<td>107</td>
<td>87</td>
<td>1</td>
<td>bilateral AMD, L previous cataract surgery</td>
<td>No</td>
</tr>
<tr>
<td>110</td>
<td>91</td>
<td>1</td>
<td>bilateral AMD, bilateral amblyopia</td>
<td>Yes</td>
</tr>
<tr>
<td>111</td>
<td>86</td>
<td>1</td>
<td>bilateral cataracts</td>
<td>Yes</td>
</tr>
<tr>
<td>112</td>
<td>76</td>
<td>1</td>
<td>bilateral glaucoma, dry AMD, L cataract</td>
<td>Yes</td>
</tr>
<tr>
<td>113</td>
<td>82</td>
<td>2</td>
<td>glaucoma, bilateral cataracts, R lower trabeculotomy</td>
<td>Yes</td>
</tr>
<tr>
<td>114</td>
<td>79</td>
<td>1</td>
<td>bilateral cataracts</td>
<td>Yes</td>
</tr>
<tr>
<td>115</td>
<td>75</td>
<td>1</td>
<td>glaucoma</td>
<td>Distortion</td>
</tr>
<tr>
<td>116</td>
<td>89</td>
<td>1</td>
<td>R wet AMD, disciform scar; L dry AMD; L cataract</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 14: Frequency of Ophthalmological Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number (CBS)</th>
<th>Number (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Related Macular Degeneration</td>
<td>9/12</td>
<td>5/10</td>
</tr>
<tr>
<td>Cataract</td>
<td>6/12</td>
<td>8/10</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>3/12</td>
<td>3/10</td>
</tr>
<tr>
<td>Diabetic Retinopathy</td>
<td>1/12</td>
<td>0/10</td>
</tr>
<tr>
<td>Ischaemic Optic Neuropathy</td>
<td>1/12</td>
<td>0/10</td>
</tr>
<tr>
<td>Myopic Maculopathy</td>
<td>0/12</td>
<td>1/10</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>0/12</td>
<td>1/10</td>
</tr>
</tbody>
</table>
6.8 Visual assessment - Acuity, Contrast Sensitivity and Scotoma Testing

The descriptive statistics for the visual acuity (better eye) and contrast sensitivity of the two groups are shown in tables 15 and 16 below.

Table 15: Comparison of visual acuity results

<table>
<thead>
<tr>
<th>Participant Type</th>
<th>Mean visual acuity best eye (logMAR)</th>
<th>Range of visual acuity best eye</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS</td>
<td>0.72</td>
<td>0.10 to 1.22</td>
<td>0.40</td>
</tr>
<tr>
<td>Control</td>
<td>0.32</td>
<td>-0.10 to 1.20</td>
<td>0.38</td>
</tr>
</tbody>
</table>

The scores for Visual acuity are shown in logMAR units, where 0.0 is equivalent to a score of 6/6 measured with a Snellen chart. A higher logMAR score indicates a poorer visual acuity, with a score of 1.0 on logMAR being equivalent to 6/60 with Snellen. The mean visual acuity in the CBS group was logMAR 0.72, which approximates to a Snellen acuity score of 6/30. This compared to a logMAR score of 0.32 in the control group, approximately Snellen 6/12. This difference was explored using a t test to determine if the mean scores in the two groups were significantly different. This was done with SPSS version 20. Levene's test for equality of variance was applied, and generated an F value of 0.61, giving a p value of 0.44, indicating that the variances of the samples were not significantly different. A t-test was conducted. This gave a t value of 2.39, with a p value of 0.027 (degrees of freedom 20). Thus, the visual acuity of the better eye was statistically, and clinically, worse in the CBS group than in the controls. Even in the control group however, there were clinically relevant levels of impaired visual acuity, and the mean visual acuity score was poorer than the threshold of logMAR 0.3 found by Teunisse et al. (1995) to confer a significantly raised risk of developing Charles Bonnet syndrome.
The mean value for binocular visual acuity was also calculated, for comparative purposes, given the lack of certainty over which measure is the most appropriate to use. A result for this was available for all 10 controls, but only 9 of the twelve CBS participants. The mean scores were very similar to those for visual acuity better eye, with a logMAR of 0.75 for CBS participants, and 0.32 for controls.

The results for contrast sensitivity testing are set out in table 16.

Table 16: Comparison of Contrast Sensitivity results

<table>
<thead>
<tr>
<th>Participant Type</th>
<th>Mean Contrast Sensitivity</th>
<th>Range of contrast sensitivity</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS</td>
<td>0.95</td>
<td>0.33 to 1.35</td>
<td>0.33</td>
</tr>
<tr>
<td>Control</td>
<td>1.09</td>
<td>0.15 to 1.95</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Contrast sensitivity is tested using the Pelli-Robson chart and gives a value of between zero and 2.00. Unlike visual acuity, a higher score indicated better contrast sensitivity, with a score of 2.00 indicating ‘perfect’ contrast sensitivity. The mean score of 0.95 in the CBS group indicates severely impaired contrast sensitivity, though the controls, with a mean of 1.09 also had clinically significant impairment in this measure. I carried out a t-test to see if these differences were statistically significant. Levene’s test of equality of variance did not indicate significant difference in the variance (F=0.53, p=0.48), and the t-test also did not reach statistical significance (t= -0.79, d.f. 18, p=0.44). This shows participants with CBS and controls did not differ significantly in contrast sensitivity scores.
With regard to the Amsler testing for scotoma, this was almost universally positive. All the CBS participants where this testing was undertaken had either a scotoma or distortion of the image evident, and all but two of the controls also did.

Overall, all the participants, both those with CBS and the controls, had some impairment of vision evident on the optometry assessment. The visual acuity was significantly better among the controls, and indeed, there were three of the controls whose visual acuity was essentially normal. However, two of these had clinically significant abnormalities in contrast sensitivity, and all three had abnormalities in Amsler testing, with either a scotoma or distortion present.

6.9 Neuroimaging

Participants were offered an MRI scan as part of the protocol, though this was made optional due to concerns over acceptability. In the end, all ten controls underwent a scan, along with ten of the twelve participants with CBS. The findings of the scans are set out in tables 17a and 17b below.
The scans showed very high levels of small vessel ischaemic changes in both groups, and high rates of atrophy. Some degree of involutional change or cerebrovascular disease was not unexpected given the high mean age of the sample, but the extent of the abnormalities in both the CBS participants and the controls did seem greater than would be predicted by their age alone. The scans were reviewed by Professor Alan Jackson of the Wellcome Trust Clinical Research Facility to produce the reports summarised above, and in Professor Jackson’s opinion the degree of vascular change was greater overall in the Charles Bonnet group than in the controls. In conducting this analysis, Professor Jackson was blind as to group membership of the images reviewed.
Table 17b: MRI Scan results (controls)

<table>
<thead>
<tr>
<th>Participant number</th>
<th>Scan Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>Minimal microvascular disease, otherwise normal</td>
</tr>
<tr>
<td>106</td>
<td>No significant structural abnormalities</td>
</tr>
<tr>
<td>107</td>
<td>Mild microvascular disease</td>
</tr>
<tr>
<td>110</td>
<td>Moderate cerebral atrophy, marked cerebellar atrophy. Severe microvascular disease.</td>
</tr>
<tr>
<td>111</td>
<td>Moderate to severe microvascular disease</td>
</tr>
<tr>
<td>112</td>
<td>Mild communicating hydrocephalus of vascular origin, minimal evidence of ischaemic change</td>
</tr>
<tr>
<td>113</td>
<td>Very severe microvascular disease</td>
</tr>
<tr>
<td>114</td>
<td>Moderate cerebral atrophy with some prominence of medial temporal lobe structures</td>
</tr>
<tr>
<td>115</td>
<td>Evidence of microvascular disease</td>
</tr>
<tr>
<td>116</td>
<td>Severe bilateral atrophy with marked involvement of medial temporal lobes. Marked microvascular ischaemic changes and small lacunar infarct</td>
</tr>
</tbody>
</table>
6.10 Cognitive Examination- Development of Dementia

Over the course of the study, two of the participants in the Charles Bonnet syndrome developed dementia. In comparison, none of the controls developed dementia. Thus, 17% of the CBS group developed dementia during the year of follow-up, compared to 0% of the controls. I tested the significance of this finding using Fisher’s exact test in SPSS version 20. The test generated a p value of 0.481 on two-sided testing, meaning that this result was not statistically significant. Of the two participants who developed dementia, one met consensus criteria (McKeith et al. 1996) for the diagnosis of Lewy body dementia, and the other met NINCDS-ADRDA criteria (McKhann et al. 1984) for probable Alzheimer’s disease.

6.11 Cognitive Examination- Scoring Below Cut-off on ACE-R

I measured the change in scores in cognitive testing over the course of the study using the Addenbrookes Cognitive Examination (Revised) (ACE-R) (Mioshi et al. 2006), which had been adapted for a low vision population. This also generates a score on the Mini-Mental State Examination (MMSE). The results of these assessments are shown in tables 18a and 18b, below.

One of the aims of this study, as set out in Chapter 4.2, was to determine what proportion of participants demonstrated abnormalities in cognitive functioning at diagnosis of Charles Bonnet syndrome which were not severe enough to warrant a diagnosis of dementia. Excluding dementia was done on the basis of the clinical
interview and accepted diagnostic criteria, but I required a definition of what to include as cognitive impairment. For the purpose of the study, I defined this as having a score on the ACE-R that fell below an accepted cut point. Mioshi et al. (2006) undertook validation work for the ACE-R, and defined a cut-off for the lower limit of normal on the test as being two standard deviations below the mean score for healthy controls in their study. This cut point was stratified by age. While the oldest cohort in their study was aged 70-75, and thus younger than the participants in this study, they conducted ANOVA testing on the results and found no significant effect of age on the scores across the age range they studied. Thus I have taken the cut off for the lower limit of normal to be the same as they suggested for the 70-75 cohort, at 84/100.

Table 18a: ACE-R scores (CBS participants)

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>Initial ACE-R Score</th>
<th>Follow-up ACE-R Score</th>
<th>Change in ACE-R score</th>
</tr>
</thead>
<tbody>
<tr>
<td>002*</td>
<td>97</td>
<td>83</td>
<td>-14</td>
</tr>
<tr>
<td>005</td>
<td>90</td>
<td>94</td>
<td>+4</td>
</tr>
<tr>
<td>007</td>
<td>88</td>
<td>89</td>
<td>+1</td>
</tr>
<tr>
<td>008</td>
<td>75</td>
<td>69</td>
<td>-6</td>
</tr>
<tr>
<td>009</td>
<td>88</td>
<td>93</td>
<td>+5</td>
</tr>
<tr>
<td>011</td>
<td>86</td>
<td>83</td>
<td>-3</td>
</tr>
<tr>
<td>012</td>
<td>94</td>
<td>96</td>
<td>+2</td>
</tr>
<tr>
<td>013</td>
<td>74</td>
<td>74</td>
<td>+0</td>
</tr>
<tr>
<td>014</td>
<td>94</td>
<td>89</td>
<td>-5</td>
</tr>
<tr>
<td>015</td>
<td>90</td>
<td>89</td>
<td>-2</td>
</tr>
<tr>
<td>018*</td>
<td>79</td>
<td>64</td>
<td>-15</td>
</tr>
<tr>
<td>020</td>
<td>91</td>
<td>80</td>
<td>-11</td>
</tr>
</tbody>
</table>

* indicates that the participant was found to have developed dementia at follow-up
Using this cut off, at the initial assessment, 3/12 of the CBS participants fell below the normal range for the ACE-R, compared to none of the controls. Thus 25% of the CBS group showed abnormal cognitive functioning at the point of diagnosis with Charles Bonnet syndrome, which fell short of a diagnosis of dementia. At the follow up assessment, this had increased to 6/12 (50%) of the CBS cohort who were found to have scores on the ACE-R which fell below the adopted normal range. This compared to only 1/10 controls. The results of this follow up assessment were subjected to testing using Fisher’s exact test; the result fell short of being statistically significant on two sided testing (p=0.074).

A further aim of the study, as set out in chapter 4.2, was to determine if there was correlation between those with abnormal cognitive functioning at diagnosis of Charles Bonnet syndrome, and those who later developed dementia, or progressive cognitive impairment falling short of dementia. The number of participants who developed
dementia was too few to allow a meaningful analysis, but it is worth noting that one of the dementia cases actually had the highest initial score on the ACE-R among the CBS group.

However, abnormal cognitive status at baseline may have had some utility in identifying which participants would show the largest declines in cognitive functioning over the study. Of the six participants who demonstrated falls on the ACE-R of five points or more, two were in the group identified as abnormal at the initial assessment. This means that 2/3 participants identified as having abnormal cognition at baseline went on to show progression of their cognitive impairment, compared to only 4/19 that had normal cognitive functioning at the initial assessment. I conducted significance testing using Fisher’s exact test, but this result failed to reach statistical significance (p=0.17). It was thus not possible to demonstrate a relationship between abnormal cognitive functioning at baseline, and the subsequent development of dementia, or milder degrees of progressive loss of cognitive functioning, though this is an area which may be worth further investigation.

There are potential doubts over the validity of using a cut-off point on test scores to define abnormal cognitive functioning, however. This is because the cut-off point that the analysis relies upon was not validated in a population of this advanced age, and more importantly, which had the level of visual impairment seen in this study. The differences in visual acuity between the groups could potentially act as a confounder, as poorer vision may independently be associated with poorer scores on the assessment. An alternative approach which may avoid these concerns is to look directly at the changes in the raw scores obtained on the ACE-R.
6.12 Cognitive Examination- Analysis of Changes in Raw Scores

I calculated the mean scores on the ACE-R at initial and follow-up assessments, and the change over time; these are shown in table 19 below. They show that among the CBS participants, there was a mean fall in the ACE-R score over the period of the study of 3.7 points, compared to an increase of 1.4 points among the controls.

Table 19: Mean ACE-R scores including change over study

<table>
<thead>
<tr>
<th>Participant Group</th>
<th>Mean initial ACE-R (range)</th>
<th>Mean follow-up ACE-R (range)</th>
<th>Mean change in ACE-R (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS</td>
<td>87.2 (74 to 97)</td>
<td>83.5 (64 to 96)</td>
<td>-3.7 (-15 to +5)</td>
</tr>
<tr>
<td>Controls</td>
<td>90.6 (85 to 97)</td>
<td>92.0 (82 to 100)</td>
<td>+1.4 (-5 to +6)</td>
</tr>
</tbody>
</table>

Thus the mean scores in the two groups diverged by five points over the course of the study, a difference that would be of clinical significance. The ACE-R allows scores on the mini-mental state (MMSE) examination to be derived. These showed a mean score of 28.6 (range 27-30) in the CBS group, which fell to 27.5 (range 25-30) at follow-up; and 28.9 (range 27-30) in the control group, rising to 29.0 (range 27-30) at follow-up.

However, given the small sample size and the concerns set out in detail in chapter 4.3, it was possible that these findings could have arisen by chance. As a result, I set out to undertake statistical testing to determine if this difference reached statistical significance.
I conducted a t-test using SPSS version 20, comparing the mean change in ACE-R score in the CBS group with the control group. Levene’s test of equality of variance was initially applied, and gave a result of F=5.20, p=0.034. This indicated the variances in the CBS group and control group were significantly different. As a result I used the t-test results where equal variances were not assumed. The t-test gave a t value of -2.23, degrees of freedom 16.8, 2-sided significance p=0.039.

The analysis seemed to indicate the change in cognitive functioning in the groups over the course of the study was both clinically and statistically significant. This was despite the small sample size, suggesting a large effect size for a diagnosis of Charles Bonnet syndrome. However, differences between the Charles Bonnet participants and the control group had the potential to be confounding factors. The differences have been described above in chapters 6.3 and 6.8, and included differences in the gender balance of the two groups, and differences in visual performance. I again took advice from Julie Morris, who suggested that an analysis of covariance (ANCOVA) would be a better test to use to investigate the statistical significance of this finding, as this would allow the effect of these potential confounding variables to be taking into account. She also advised that instead of using the change in the ACE-R score over time, a more statistically robust method would be to use the ACE-R score at follow-up as the dependent variable, and include the initial ACE-R score as a covariate in the analysis.

I therefore set out to conduct an ANCOVA using SPSS version 20. In the ANCOVA, the dependent variable was the score on the ACE-R at follow up, and the independent variable was the group the participant belongs to (CBS or control group). The first covariate was the initial ACE-R score. I considered whether to
include gender as a covariate; however, I was unable to find any evidence of gender differences in performance in this assessment, so took the decision not to. The differences in visual functioning were clearly important however, particularly those in visual acuity. I had produced large scale versions of the vision dependent items of the test, and these proved to be readable by all but one participant. However, formal validation work to determine the effect of vision impairment on this assessment, and whether my measures did mitigate any negative effects on performance, was beyond the scope of this work. It was clearly possible that difficulties in seeing some of the items could have led those with worse visual acuity to perform more poorly for reasons that were nothing to do with cognitive functioning. Visual acuity was therefore included as a covariate, and the acuity of the better eye was chosen as the relevant measure as this has been used in previous studies.

I also considered whether to include contrast sensitivity in the analysis. There were difficulties in this, as this data was not collected on three subjects, so inclusion of this measure would reduce the sample size in the analysis. I was also concerned over the power of the analysis being undermined by too many covariates, given the very small sample size. I felt that, given the nature of the stimuli being tested—black large scale type, or black drawings on a white background—loss of contrast sensitivity was less likely to influence performance than low visual acuity. Moreover, there was no statistically significant difference in contrast sensitivity between the groups. As a result, I decided not to include contrast sensitivity as a covariate.

The model for the ANCOVA therefore included initial ACE-R score and visual acuity of the better eye as covariates. In order for the ANCOVA to be valid, nine
assumptions regarding the data to be analysed must be met. I deal with each of these below.

6.13 Assumptions of ANCOVA Testing

Assumption 1. The dependent variable and covariate variable should be measured at the interval or ratio level. This assumption is met.

Assumption 2. The independent variable should consist of two or more categorical, independent groups. This assumption is met.

Assumption 3. There should be independence of observations, i.e. there must be no relationship between the observations within each group or between the groups. This assumption is met.

Assumption 4. There should be no significant outliers. I tested this using the outlier labelling rule (Hoaglin et al. 1986). This confirmed that there were no outliers in the ACE-R scores, and so this assumption is met.

Assumption 5. The dependent variable should be approximately normally distributed for each category of the independent variable. This was tested using the Shapiro-Wilkes test in SPSS version 20, and the p values for both groups were non-significant (CBS group p=0.31, control group p=0.81), lending support to the contention that the data were normally distributed. Also, Q-Q plots were created, and are shown in Appendix 8.1. These further support this contention, and so assumption five is met.

Assumption 6. There needs to be homogeneity of variances. This was tested using Levene’s test of equality of error variances on SPSS version 20. This generated an
F=3.57 (df 1=1, df2=20), p=0.073. Thus the null hypothesis- that there is no difference in the variances- is not rejected, and this assumption is met.

Assumption 7. The covariate is linearly related to the dependent variable at each level of the independent variable. I examined this using scatter plots, which are shown in Appendix 8.2. These show a reasonable linear relationship between the covariates and the dependent variable, and so suggest that this assumption is met.

Assumption 8. There needs to be homoscedasticity. This is a measure of homogeneity of variance across the range of variables in the sample. A plot of the standardised residuals is shown in appendix 8.3. These show similar variability along the range of predicted values. This assumption is therefore met.

Assumption 9. There needs to be homogeneity of regression slopes. This means that there is no interaction between the covariates and the independent variable. This was tested by creating a custom model in the ANCOVA and looking at the interaction between the independent variable and covariates. I did this for the interaction term participant group*visual acuity*initial ACE-R, which generated p= 0.459. This suggests that the regression slopes are not significantly different, and assumption 9 is met.

6.14 Cognitive Examination- Results of the ANCOVA

Having demonstrated that the data do not violate the assumptions inherent in ANCOVA, I proceeded to carry out this analysis, using the general linear model function in SPSS version 20. This generated the results shown in table 20.

The results show that the positive findings of the t-test on change in ACE-R scores over the course of the study do not persist when the effects of potentially confounding variables are taken into account. There was no statistically significant
relationship between participant group and ACE-R score at follow-up, once the effects of the initial ACE-R score and visual acuity had been controlled for, $F(1, 18) = 2.232, p = 0.153$. The ANCOVA gave an effect size for the diagnosis of Charles Bonnet syndrome, as measured by the partial eta squared result, of 0.11. This suggests that 11% of the variance in ACE-R scores at follow-up could be explained by the diagnosis of CBS.

Table 20: results of ANCOVA

<table>
<thead>
<tr>
<th>Source</th>
<th>Type III Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
<th>Partial Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Model</td>
<td>1230.814*</td>
<td>3</td>
<td>410.271</td>
<td>13.366</td>
<td>.000</td>
<td>.690</td>
</tr>
<tr>
<td>Intercept</td>
<td>4.613</td>
<td>1</td>
<td>4.613</td>
<td>.150</td>
<td>.703</td>
<td>.008</td>
</tr>
<tr>
<td>ACER</td>
<td>569.570</td>
<td>1</td>
<td>569.570</td>
<td>18.556</td>
<td>.000</td>
<td>.508</td>
</tr>
<tr>
<td>VAbest</td>
<td>56.343</td>
<td>1</td>
<td>56.343</td>
<td>1.836</td>
<td>.192</td>
<td>.093</td>
</tr>
<tr>
<td>CBSorCTL</td>
<td>68.496</td>
<td>1</td>
<td>68.496</td>
<td>2.232</td>
<td>.153</td>
<td>.110</td>
</tr>
<tr>
<td>Error</td>
<td>552.504</td>
<td>18</td>
<td>30.695</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>169871.000</td>
<td>22</td>
<td>30.695</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected Total</td>
<td>1783.318</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. R Squared = .690 (Adjusted R Squared = .639)

6.15 Cognitive Examination - ACE-R subscale scores

The Addenbrooke’s cognitive examination, in addition to providing an overall score of global cognitive functioning, also provides scores on five sub-scales relating to specific domains of cognition. These are attention and orientation, memory, verbal fluency (taken as a measure of frontal lobe/executive function), language and
visuospatial functioning. This is useful, as different dementias will characteristically display different patterns of cognitive decline early in their course, and so the subscales can provide some indication of the type of dementia that may be present. Serial measurements with the ACE-R also offer the potential to track differences in the trajectories of decline across a range of domains of cognitive functioning as a dementia progresses.

In this study, the subscales also allow the opportunity to make some assessment of whether the differences in visual acuity between the groups impacted on participants' performance on cognitive testing. Some of the items of the test are likely to be affected by visual functioning, whereas for others a connection to visual performance is unlikely. Comparing the participants' results across the subscales offers a potential way to examine whether the differences in visual acuity did affect the findings. The results obtained are shown in tables 21a and 21b below.

Table 21a: ACE-R subscale scores for CBS participants

<table>
<thead>
<tr>
<th>Subscale (Maximum Score)</th>
<th>Initial Score (% of max possible score)</th>
<th>Score at Follow-Up (% of max possible score)</th>
<th>Change in Score (% of max possible score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/Concentration (18)</td>
<td>17.8 (98.9)</td>
<td>17.1 (95.0)</td>
<td>-0.7 (-3.9)</td>
</tr>
<tr>
<td>Memory (26)</td>
<td>21.8 (83.8)</td>
<td>20.7 (79.6)</td>
<td>-1.1 (-4.2)</td>
</tr>
<tr>
<td>Verbal Fluency (14)</td>
<td>9.7 (69.3)</td>
<td>9.3 (66.4)</td>
<td>-0.4 (-2.9)</td>
</tr>
<tr>
<td>Language (26)</td>
<td>23.6 (90.8)</td>
<td>22.2 (85.4)</td>
<td>-1.4 (-5.4)</td>
</tr>
<tr>
<td>Visuospatial (16)</td>
<td>14.3 (89.4)</td>
<td>14.3 (89.4)</td>
<td>+0.0 (+0.0)</td>
</tr>
</tbody>
</table>
Table 21b: ACE-R subscale scores for controls

<table>
<thead>
<tr>
<th>Subscale (Maximum Score)</th>
<th>Initial Score (% of max possible score)</th>
<th>Score at Follow-Up (% of max possible score)</th>
<th>Change in Score (% of max possible score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/Concentration (18)</td>
<td>17.9 (99.4)</td>
<td>17.8 (98.9)</td>
<td>-0.1 (-0.5)</td>
</tr>
<tr>
<td>Memory (26)</td>
<td>22.1 (85.0)</td>
<td>22.4 (86.2)</td>
<td>+0.3 (+1.2)</td>
</tr>
<tr>
<td>Verbal Fluency (14)</td>
<td>11.3 (80.7)</td>
<td>11.7 (83.6)</td>
<td>+0.4 (+2.9)</td>
</tr>
<tr>
<td>Language (26)</td>
<td>24.4 (93.8)</td>
<td>25.1 (96.6)</td>
<td>+0.7 (+2.7)</td>
</tr>
<tr>
<td>Visuospatial (16)</td>
<td>14.9 (93.1)</td>
<td>14.8 (92.5)</td>
<td>-0.1 (-0.6)</td>
</tr>
</tbody>
</table>

The results are of some interest. The scores of participants with CBS in the visuospatial subscale were a mean of 0.6 points lower on a 16 point scale at baseline. This represented the second largest difference between groups among the five subscales as a percentage of the maximum available score. However, by the follow-up point, this difference was largely unchanged, while the differences between the groups on all the other subscales increased, largely due to deterioration in the performance of the CBS participants across the other domains. As a result, visuospatial functioning was the domain with the smallest difference between the two groups at follow up.

The differences between the groups were most striking in the verbal fluency subscale, with a difference of 2.4 points on a 14 point scale at the follow up point. This difference was statistically significant on t-testing (p=0.025). This was one of only two subscales at either time point where a statistically significant difference was found between the scores of the CBS participants and controls (though the difference on the verbal fluency subscale at the initial time point approached significance, with
p=0.10 on a t-test); and as it consists of generating lists of exemplars of specified categories, it is unlikely to have been influenced by visual functioning.

The other subscale where there was a statistically significant difference between the groups at follow-up was language; the difference was substantial, at 11.2% of the available points on the subscale, and reached statistical significance (p=0.011) when a t-test was conducted. The language subscale is made up of a composite of both visually dependent and independent items, so it is less certain how to interpret this finding.

6.16 Cognitive Examination- Comparing Performance on Vision-Dependent and Vision-Independent Items of the ACE-R

A further way of examining the effect of visual functioning on performance on the ACE-R is to look at the global scores attained by participants, but only to include items which are not likely to be affected by vision. This is a similar approach to the subscale analysis shown above, but slightly broader in scope. While the items of the visuospatial subscale are all potentially vision-dependent, there are also vision-dependent items in the language subscale, and so poor visual acuity also has the potential to affect this part of the test. The vision-dependent items in the language subscale include reading a sentence, identifying the objects and answering questions about them, and reading aloud a list of words. In total, all 16 items on the visuospatial subscale, and 18/26 of the items on the language subscale could potentially be affected by poor visual performance. Extracting the results relating to these items
gives a remaining ACE-R score out of 66, and the performance of CBS participants
and controls at the two assessment points are shown on table 22 below

Table 22: Scores on ACE-R after vision-dependent items removed

<table>
<thead>
<tr>
<th>Participant Group</th>
<th>Mean initial ACE-R (range)</th>
<th>Mean follow-up ACE-R (range)</th>
<th>Mean change in ACE-R (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS</td>
<td>56.7 (49 to 63)</td>
<td>54.1 (39 to 64)</td>
<td>-2.6 (-12 to +4)</td>
</tr>
<tr>
<td>Controls</td>
<td>59.0 (51 to 64)</td>
<td>59.5 (52 to 66)</td>
<td>+0.5 (-5 to +5)</td>
</tr>
</tbody>
</table>

The results are similar to those obtained from the analysis of the overall ACE-R score
changes set out in Table 19 above. There is a small difference between the groups’
scores at the initial time point, which has become larger at the follow up assessment
point. This divergence in scores has occurred due to a fall in the CBS participants’
scores, and a smaller rise in the controls’ scores. Overall, the mean scores of CBS
participants and controls on the 66-point ACE-R, with vision dependent items
excluded, diverged by 3.1 points over the course of the study. This is a smaller
amount than the divergence on the full ACE-R, which was 5.0 points; however, it is in
line with what would be expected given the smaller total score achievable.

The difference in the ACE-R scores, excluding vision-dependent items, was not
statistically significant at baseline, when a t-test was conducted (p=0.23). However,
the difference in the results at the follow-up assessment did achieve statistical
significance when a t-test was carried out (p=0.04).

A final way of analysing the data is to compare the performance on the vision
dependent and vision independent items of the ACE-R. Table 23a shows the mean
scores for CBS participants, at initial assessment and follow up, on the 66-point
vision-independent subscale of the ACE-R, and also the scores on the 34-point vision-dependent subscale. It also expresses these scores as a percentage of the maximum possible score in that subscale of the test. Table 23b displays the same information for the control group.

Table 23a: Comparision of vision dependent/independent items for CBS participants

<table>
<thead>
<tr>
<th>Time Point</th>
<th>ACE-R 66 item raw scores</th>
<th>ACE-R 66 item as percentage</th>
<th>ACE-R 34 item raw scores</th>
<th>ACE-R 34 item as percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial assessment</td>
<td>56.7</td>
<td>85.9%</td>
<td>30.5</td>
<td>89.7%</td>
</tr>
<tr>
<td>Follow-up assessment</td>
<td>54.1</td>
<td>81.9%</td>
<td>29.4</td>
<td>86.5%</td>
</tr>
<tr>
<td>Change in score/percentage</td>
<td>-2.6</td>
<td>-4.0%</td>
<td>-1.1</td>
<td>-3.2%</td>
</tr>
</tbody>
</table>

Table 23b: Comparision of vision dependent/independent items for controls

<table>
<thead>
<tr>
<th>Time Point</th>
<th>ACE-R 66 item raw scores</th>
<th>ACE-R 66 item as percentage</th>
<th>ACE-R 34 item raw scores</th>
<th>ACE-R 34 item as percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial assessment</td>
<td>59.0</td>
<td>89.4%</td>
<td>31.6</td>
<td>92.9%</td>
</tr>
<tr>
<td>Follow-up assessment</td>
<td>59.5</td>
<td>90.2%</td>
<td>32.5</td>
<td>95.6%</td>
</tr>
<tr>
<td>Change in score/percentage</td>
<td>+0.5</td>
<td>+0.8%</td>
<td>+0.9</td>
<td>+2.7%</td>
</tr>
</tbody>
</table>

These results show evidence that the performance on vision-independent items in both groups was worse than on the vision-dependent items; and that the deterioration in performance on the ACE-R in the CBS participants was seen equally across both vision-dependent and vision-independent items. At the follow up point,
the magnitude of the differences between the CBS participants and controls across both vision-dependent and vision-independent subscales was very similar, with the controls performing around 9% better on both.

6.17 Cognitive Examination- IQCODE scores

In addition to the ACE-R, an informant was requested to carry out the Informant Questionnaire on Cognitive Decline in the Elderly- Short Form (IQCODE), which rates performance a range of daily living skills and compares this to the person’s performance 10 years previously. There are 16 items, rated on a five point scale, with ‘3’ indicating no change, scores higher than this indicating decline, and scores lower an improvement. The sum score for all items is divided by the total number of items, to give a score between 1 and 5. Scores of above 3.40 are taken to indicate the presence of dementia. However, this threshold was not established in a low vision population, and many of the items could be influenced by visual functioning.

Data for this measure was not collected in three cases, two with Charles Bonnet syndrome, and one control. The results for those where it was collected are shown in table 24.

The Charles Bonnet group have higher scores on the IQCODE at both time points, indicating greater difficulties with daily living skills. The mean score for the Charles Bonnet syndrome group was above the accepted cut-off point for dementia (3.40) at both time points. With regard to individual participants, 6/12 in the CBS group and
3/10 of the control group were above the cut-off point at baseline. At the follow-up assessment this had fallen to 4/12 of the CBS group, and 3/10 of the control group.

Table 24: Scores on the IQCODE

<table>
<thead>
<tr>
<th>Participant Group</th>
<th>Mean Initial Score (Range)</th>
<th>Mean Follow-up Score (Range)</th>
<th>Change in Mean Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS group</td>
<td>3.57 (3.00-4.69)</td>
<td>3.53 (3.00-4.63)</td>
<td>-0.04</td>
</tr>
<tr>
<td>Controls</td>
<td>3.31 (3.00-3.94)</td>
<td>3.10 (2.50-3.69)</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

However, the high scores on this measure could potentially be accounted for by the poorer visual acuity in the CBS group. The IQCODE is not validated for use in a population with such significant levels of visual impairment, and so the established cut-off point suggesting the presence of dementia is unlikely to have the same significance in the study population. It is also of note that there was little change in the IQCODE scores between the initial and follow up assessments for the CBS group, despite deterioration in their cognitive functioning as assessed by the ACE-R, and an improvement in the scores in the control group.

Of perhaps more interest, the two highest scores on the IQCODE at baseline across both groups (4.69 and 4.12) were in the two participants who developed dementia, and the participant with the third highest score, of 4.10, had evidence of mild cognitive impairment at follow-up, and a fall of 6 points on the ACE-R score over the course of the study. The potential significance of these findings will be discussed further in chapter 7 below.
7. Clinical Study- Discussion

7.1 Introduction and Summary

In chapter 7, the findings of the study, and their significance in relation to the existing literature on Charles Bonnet syndrome, are discussed. Chapter 7.2 reviews the findings in relation to its role as pilot study. The main findings in this regard were that, despite the advanced age of participants, the protocol was acceptable, and when delivered efficiently and modified to remove the requirement for an MRI scan, resulted in the retention of all participants who were recruited. Another measure of acceptability, the proportion of patients screening positive who were actually recruited, was around the level predicted at the outset of the study, at either 20% or 34% depending on how this value was calculated. The other positive finding was that it was possible to establish effective working relationships between the different specialities involved, and sustain these over a longer period than was anticipated.

Set against this, the rate of positive screening was lower than expected, with only 70 people screening positive in 26 months, when around 170 could have been expected in that time. If this reflects a lower prevalence of CBS in the target population than was predicted by existing literature, and if inferences about the increase of relative risk of dementia in the CBS cohort are correct, it would mean that a definitive study would have to recruit from a very large population, and so would need to be conducted on a multi-site basis. This would clearly have implications for the scale of funding and study infrastructure that would be needed to conduct a full-scale study.
Chapter 7.2 also discusses estimates of the number of participants that a future study would need to recruit in order to be adequately powered. These suggest that a study with 100 participants in both the CBS cohort and control group may be needed. Given the amount of face-to-face contact with senior medical clinical personnel that would be needed in order to assess this number of participants, this is further evidence that such a study would need to be conducted on a multi-site basis. Amendments to the protocol to delegate some of the assessment work to Clinical Studies Officers may reduce some of the need for senior medical input, but as discussed below, their involvement would bring additional complications.

Nonetheless, this pilot study establishes that a study powered to address the hypotheses set out in chapter 4.2 is feasible, and would be acceptable to participants, though it would be a large-scale undertaking which would have considerable resource implications. Given the clinical relevance of the study aims, and the potential to support current Department of Health priorities regarding the timely diagnosis of dementia, such a study still could be seen as a priority for the NHS.

The remainder of chapter 7 discusses the findings of the study in relation to the experimental hypotheses set out in chapter 4.2. Chapter 7.3 discusses the striking differences in the gender balance between the cohort with CBS and the control group, and chapter 7.4 comments on the findings of the clinical assessment of participants, noting that this thorough assessment was a methodological strength of the study and represents a development from previous work in the area. The detection of subtle but potentially relevant changes on examination by experienced
clinicians among the participants who went on to develop dementia was also noted.

Chapter 7.5 discusses the data relating to the BPRS, which supports the clinical impression that participants' visual experiences were not due to coexisting mental disorder.

In chapter 7.6, findings relating to visual hallucinations are discussed. The robust validation of diagnosis against recognised diagnostic criteria for Charles Bonnet syndrome is noted as a strength of this study, as this has been absent from previous work in the area. The persistence of symptoms, with over half of participants still meeting diagnostic criteria after a year, is commented on, along with the broadly neutral response to the experiences, and absence of control over them; all these findings are noted to be in keeping with the existing literature. One area where the findings of this study appear to deviate from the established literature is in the content of the hallucinations reported. The figures in unusual costumes, or landscape scenes, which are so closely associated with the condition, were uncommonly seen, with geometric patterns and animals being the commonest experiences. The limited utility of the visual hallucination index, derived from the classification framework of ffytche, is also discussed.

Chapter 7.7 considers the findings relating to the optometric assessment carried out with participants. As with many previous studies, age related macular degeneration was the commonest diagnosis in the cohort with CBS. This may however be an artefact reflecting the nature of the clinical setting where recruitment was conducted. The poor visual acuity of the CBS group is discussed, noting that this is in keeping with existing literature. This offers support to the de-afferentation hypothesis of the causation of CBS. Chapter 7.7 also discusses the findings relating to the other
measures of visual functioning that were undertaken, contrast sensitivity testing and scotoma testing, and notes the significant abnormalities found on these measures in this work. This is the first study which has set out to carry out three different measures of visual functioning in patients with CBS, which represents another methodological strength. It raises the possibility that the focus on visual acuity in previous studies may have been too narrow, and suggests that future work which more fully explores the relationship of multiple coexisting deficits in visual functioning would be a valuable addition to the literature.

Chapter 7.7 also notes the presence of multiple and significant abnormalities in visual functioning in the control group, further weakening the position that Charles Bonnet syndrome is caused by eye disease alone. This is in keeping with existing literature which suggests that visual impairment is neither necessary nor sufficient to explain the development of CBS, and lends support to de Morsier’s hypothesis that Charles Bonnet syndrome reflects an underlying brain abnormality.

Chapter 7.8 discusses the neuroimaging findings, mainly to note that clinical interpretation of the scans seemed to be of no value in determining which participants with CBS would go on to develop dementia. This was largely due to the very high levels of atrophy and cerebrovascular disease which was present across both the CBS and control cohorts. Neuroimaging will be considered in much greater depth in part III of the thesis, and so will not be further expanded on here.

The findings in relation to the development of dementia and cognitive impairment are discussed in chapters 7.9 through 7.17. Chapter 7.9 discusses the strengths of this
study design, with the inclusion of a control group, a longitudinal component, and the clinically important outcome measure of diagnosis of dementia, all representing improvements in methodology over previous work in the field. It also discusses the development of dementia in two of the participants with Charles Bonnet syndrome; this finding adds to the existing literature, which documents 16 other cases of this outcome. The failure of the difference in incidence of dementia between the CBS and control cohorts to reach statistical significance is acknowledged; this was anticipated, given the underpowered nature of the study, but this is a shortcoming shared by all previous studies. In chapter 7.10 the findings of the ACE-R analysis are discussed in relation to the study aims, which overall are found not to be met. The unanticipated finding that the CBS participants had poorer visual acuity than the controls opens up the possibility that the difference in cognitive testing observed between the groups could be due to confounding, and this difference did not reach significance on ANCOVA. Chapter 7.11 deals with the ACE-R subscale analysis, which does however offer some evidence that the between-group differences in visual acuity are unlikely to fully account for the differences seen in cognitive functioning.

In chapter 7.12 the implications of the finding of Mild Cognitive Impairment in a number of the CBS participants are discussed. These include a tentative suggestion that the presence of MCI and impaired insight at diagnosis of CBS potentially place the patient at a higher risk of developing dementia subsequently. Chapter 7.13 looks at the performance of the IQCODE, which appeared to have some potential utility in predicting which participants would go on to develop dementia. A further notable finding is discussed in chapter 7.14: the inadequacy of the mini-mental state examination to detect significant cognitive impairment, or even frank dementia. Both participants who developed dementia had MMSE scores which could be interpreted as being in the ‘normal’ range. This should be borne in mind when interpreting
studies that have made use of this measure to exclude cognitive impairment in populations with CBS, and its use in studies of this condition should be avoided in future.

In chapter 7.15, a number of limitations in the design of this word are acknowledged and discussed. These include the reliance on the unvalidated assessment of a single investigator in making the diagnosis of dementia, the potential confounding effects of poor vision on both clinical and instrument-based assessments of cognitive functioning, the lack of a measure of premorbid intellectual functioning, and the short period of follow-up in the study.

The final aspect of the discussion, set out in chapter 7.16, concerned the utility of the study instruments as predictors of which participants would go on to develop dementia. Of course, with the small numbers of participants, only two of whom developed this outcome, these results are not statistically significant. Nonetheless, it was notable that a combination of the Addenbrooke’s Cognitive Examination (Revised), the Brief Psychiatric Rating Scale and the Informant Questionnaire on Cognitive Decline in the Elderly did seem to have some value in identifying the participants who developed dementia, or had a fall in their ACE-R score of 5 points or more from baseline, in a post hoc analysis. Taken along with the earlier finding that examination of neurological system and mental state by an experienced clinician also seemed to pick out the participants who developed dementia, this is an area that would be worth further research in any larger scale study of the subject.
A summary of the discussions around the findings in relation to cognitive impairment is presented in chapter 7.17. Overall, taking into account the findings of the cognitive testing presented here, and given the accumulation of cases of CBS where dementia has been observed to develop, caution should be exercised before reassuring people with CBS that their experiences are always necessarily benign.

7.2 Pilot aspects

The principal findings of this study relate to its status as a pilot. As set out in chapter 4.7, there were many aspects of this study, principally around the acceptability of the protocol to the target population, and the need for interdisciplinary working, whose practical application was uncertain.

Concerns over the first of these, acceptability of the protocol, related to the need for participants, who were of advanced age and significant disability, and who often lived alone, having to undergo up to five contacts of 1-2 hours each, including two which involved travelling to hospital. This was important, as it would contribute to estimating the population of clinic attenders who would need to be screened to recruit enough participants to ensure any future study was adequately powered. In chapter 4.5 I discussed how the assumptions used in this study relating to the proportions of clinic attenders who would meet eligibility criteria, and who would agree to participate, were arrived at. In the absence of evidence in the literature from the methodology of similar studies, I had to rely upon the clinical judgement of myself and a senior colleague in the department where recruitment was carried out. The data generated
in this study allowed the accuracy of these assumptions to be gauged, and the implications for future research to be assessed.

My estimate in chapter 4.5 had been that 30% of those eligible to be recruited would agree to take part. Given this, the finding that only 12 out of a total of 70 screening positive completed the study is important. Nine of those screening positive were judged not suitable for participating in the study, but even taking that into account, this suggests that only 20% of eligible people find the concept of the study acceptable. This is lower than the 30% predicted. However, there were four participants who may have been retained in the trial had the protocol been delivered more efficiently, especially in the early stages; and a further five who may have been willing to either participate, or remain in the trial rather than withdrawing, had the requirement for the MR scan been relaxed sooner. This gives 21/61 (34%) who could potentially have been recruited, and so possibly indicates a higher degree of acceptability than was first suggested, and in line with predicted rates.

The total number of patients who screened positive for the presence of complex visual hallucinations was lower than anticipated, at 70. This was despite recruitment being extended to just over two years, rather than the one year that was planned. Based on the estimates made before the study, I had predicted around 80 patients per year would screen positive, so the actual number was less than half the predicted number. There are two possible reasons for this: either the actual prevalence of CBS in the target population was lower than predicted from the literature, or the proportion of potentially eligible people screened was less than the 1/3 that was predicted. If it was the latter, then there is the potential for improved screening processes, delivered by research staff allocated to a study rather than clinicians in the department, to
improve the detection rate. If it was due to the former reason, then the target population would need to be considerably larger than predicted in order for any definitive study to reach its necessary recruitment targets.

Recruitment of controls proved to be, if anything, more of a challenge. There are no accurate figures for the number of people approached to take part, but until the introduction of support for recruitment by Dendron, very few potential controls were identified. This is possibly due to there being less personal involvement in the study for controls; not having the condition being studied, they may not have identified with the aims of the study as closely as those with Charles Bonnet syndrome. Another possibility is that eye hospital staff, for whom recruitment for the study was taking place alongside running a busy clinical department, may have been less active in promoting the study to controls as there was no specific positive trigger to do so. The improvement in control recruitment after specific support to recruit was introduced lends weight to the latter suggestion.

Of those that did complete the initial data collection, across CBS participants and controls 23/28 completed the follow-up. Of those that did not, one sadly died, two did not wish to undergo MR, and two were unable to be assessed before the closing date of the study, but were willing to be seen. This means that there were no participants who underwent data collection who withdrew for reasons other than a requirement to participate in the MRI scan. This suggests that the protocol, when delivered efficiency and sympathetically, is in fact highly acceptable to the study population, despite their high levels of disability and advanced age.
The second aspect that this pilot study set out to test was to evaluate the effectiveness of joint working between ophthalmology staff and old age psychiatry, two specialities which would not come into regular contact in normal clinical practice. Each of these specialities has its own technical language, forms of assessment and range of presenting conditions - for example logMAR scores and visual fields testing in ophthalmology and phenomenology and the mental state examination in psychiatry - which would be unfamiliar to those from the other speciality. It was possible that the lack of a shared language and understanding of the nature of each speciality would prove a barrier to effective communication and co-working. However, this did not prove to be a significant problem in practice. This was in part due to a lot of time spent by me in the eye hospital, explaining the rationale for the study, and getting senior members of the department to act as champions for the study. By regularly visiting the department throughout the course of the study, and becoming known to the optometrists who would be responsible for carrying out the recruitment, I hoped to foster a sense of there being a team working on the project, of which they were a key part. Having a personal investment in the success of the study helped keep interest in it sustained over the recruitment period, and helped staff there to understand the nature and significance of the psychiatric conditions for which we were looking for evidence.

During the study, recruitment opened in a second clinic in the eye hospital. This formed a useful contrast, being a clinic staffed by medical staff rather than optometrists. Due to the rotational nature of medical training, the junior doctors working in the clinic changed during the study, while the optometry staff remained more stable. This meant that I had much closer working relationships with the optometry staff, and this translated into much better recruitment from the optometry led clinic. Indeed, until staff from Dendron began to attend the medical-led clinic,
there was no recruitment from the glaucoma assessment clinic at all. The level of personal input into the clinic needed to sustain recruitment would be hard to sustain in any full scale version of this study, suggesting that designated recruitment support from clinical studies officers would be necessary for successful progress.

The final, and more contentious, role of pilot studies, can be to help inform calculations as to the number of participants that would be needed to adequately power a subsequent definitive study. The limitations of this, particularly those set out by Kraemer et al. (2006) are dealt with in detail in chapter 4.6. The mean age of the study population settled at 81, which places this population in a cohort where the expected incidence of dementia would be 60/1000 per year (Jorm and Jolley, 1998). This would equate to an expected 0.7 cases in each group over the course of the study. The actual incidence in the CBS group was three times this, suggesting a relative risk of three in the CBS group for the development of dementia; of course, given the very small numbers, this estimate is likely to have a low precision. A power calculation, in order to generate alpha= 0.05 and beta = 0.80, using this information about likely underlying incidence and relative risk in controls, gives a sample size of 151 to achieve the necessary power.

Putting this information together allows some recommendations to be made to inform the possibility of a full scale study to investigate the hypothesis this pilot work deals with. Given the lack of precision in the predicted sample size, it would be prudent to try to recruit a larger number of participants to allow for the possibility that the relative risk was less than three. Aiming to recruit a total of 200 participants, with 100 in each group, should enable the study to be adequately powered. While neuroimaging would be useful, it is not a necessary requirement of the study, and by discarding this
element, an increase in the acceptability of the study to potential recruits could be achieved. Based on this pilot work, the proportion of people screening positive who would potentially agree to be recruited was either 20% or 34%, depending on how this was defined; taking a conservative estimate of 20% of eligible candidates with Charles Bonnet syndrome being recruited into the study, this would mean finding 500 people who screening positive as being probable cases of Charles Bonnet syndrome. Charles Bonnet syndrome is a common condition among low vision populations; the literature review in chapter two sets out the epidemiological evidence that between 12-63% of people with significantly reduced vision will experience this condition. Again, taking a conservative estimate, of 15% in a population attending a low vision clinic, this would mean screening a total of 3300 people over the age of 65, and with an informant able to support them. This assumes that screening processes are sensitive and detect all cases of CBS that are present; given the concerns noted above, that in this study the number of people screened may have been less than anticipated, the total number of people requiring screening may need to be even higher.

By the same token, if the proportion of eligible participants agreeing to take part was around the higher of the two estimated values, at 34%, and the proportion of those attending low vision clinics who had CBS was towards the higher end of prevalence estimates, at 25%, the number of over-65s needing to be screened could be as low as 1200.

These are clearly a very large numbers, and more than one centre is likely to be able to provide. If a clinic-based model was followed, then it would need to be multi-centre, with the additional complexities this entails, including recruiting sites and
ensuring the staff are trained to the necessary degree to reliably deliver the protocol. With multiple sites, having one small, highly motivated team of clinical staff already in the department supporting recruitment would not be possible; it would unquestionably need to be supported by professional research staff, in order that sufficient focus was maintained on the process of recruitment. Given the scale of the task, consideration might be given to opening recruitment in other, non-clinical, areas, such as voluntary sector agencies and support groups for vision impaired people.

The required scale of the project would pose a challenge for the piloted means of delivering the assessments in the protocol. All these were carried out by old age psychiatrists of higher specialist trainee or consultant level, allowing a diagnosis of dementia, the primary outcome, to be made by researchers highly skilled in this task. This also addressed concerns over capacity to consent, as this is another area of expertise of senior clinicians working in the field of old age psychiatry. However, for senior medical staff to carry out all the assessments in a large scale version of this research would be difficult. Even excluding an MRI scan, there would still be at least three contacts, with a total time of 4-5 hours per participant; across all participants, this would amount to 900 hours of senior medical time, not including travelling. I found that I could make three contacts per day when working on the study, allowing time for record keeping and travel; this would amount to 300 days of medical time for data collection alone, over a year of a whole time equivalent senior doctor. In a multi-centre trial, this would need a senior old age psychiatrist at each site potentially working for a considerable part of each week on the project; this would be logistically challenging to deliver.
It may be possible to delegate some of the tasks to clinical studies officers, and so reduce the medical input. The administration of the study measures at baseline and follow up could be a task undertaken by CSOs, as could consenting with sufficient training. However, the diagnostic aspect of the study would require input from a doctor for each participant, so the demands on medical time could not be entirely removed. Moreover, introducing CSOs potentially increases the total number of contacts over the study, and so could reduce its acceptability.

Finally, if such a large scale study were to be undertaken, it may wish to look at a longer follow-up period than I did. My literature review, set out in chapter two, describes the cases of Charles Bonnet syndrome reported where dementia did develop. The delay from diagnosis of CBS to dementia diagnosis was up to five years in some cases; so a longer time period would potentially increase the power of the study, as the proportion of people in both the control and CBS groups who developed dementia would potentially be considerably higher. This could reduce the overall size of the population needed, and so make the practical administration of the study easier.

Given the discussion above, carrying out a sufficiently powered full scale study to investigate this area is certainly possible; the protocol was largely acceptable to participants, who were mostly very interested in the study and keen to be told its findings. Estimates made in chapter 4.5 regarding the proportion of eligible candidates who would agree to be recruited proved to be reasonably accurate; however, estimates of the total number of people meeting the eligibility criteria who would be identified by screening were lower than expected. Further piloting work to better understand this could have a place before a full scale study was undertaken, if
recruitment from low vision clinics was adopted as the preferred strategy, in order to optimise the screening process and minimise the number of sites that would be needed to screen the required numbers.

In the event of a large scale study proceeding, due to its scale, its multi-centre nature, the need for professional recruitment support, and demands on both CSO and medical staff time, this would need to be supported by substantial funding, and undertaken by a team with experience of coordinating multi-site studies. Given the potential significance of the findings were a clinically important link between CBS and dementia confirmed, then it would be a potentially good candidate for such funding, fitting as it does into the current national priority for research into the early detection of dementia.

7.3 Demographics

The striking difference in the gender balance of the CBS and control groups was an unexpected and troubling finding. The observed excess of females in the CBS group was anticipated, given the age of the study population and the higher proportion of females in that age range. There is also some suggestion in the literature that CBS may be more common in females (Holroyd et al. 1994, Scott et al. 2001), though Teunisse et al. (1995) reported no such association when age was controlled for. The excess of men in the control group was not expected, however. As noted, the controls had less personal investment in the trial, as they did not have the condition being investigated. It may be that the protocol felt more acceptable to males than females who were not experiencing symptoms, though why this should be the case is
unclear. It may also be a chance finding, though the difference was statistically significant on Fisher's exact test (p=0.008), so attributing it to chance is rather unsatisfactory. Further pilot work, using qualitative methodology, could potentially investigate this, and so try to avoid a similar problem affecting any large scale version of the study in future.

7.4 Findings of history taking and examination

The thorough assessment by a clinician experienced in diagnosing dementia and delirium, including taking an informant history, obtaining a summary medical history and medication list from the GP, and conducting a mental state examination and neurological examination, should provide assurance that the participants did not have dementia at the point of entry to the study, or any other potential causes of visual hallucinations. This is a methodological strength of this study, as many of the existing studies in the literature which comment on cognition, such as Menon (2005), Crumbliss et al. (2008), and Gilmour et al. (2009), did not feature any such assessment.

The elderly population experiencing the combination of visual and cognitive impairment, and visual hallucinations, are at a higher risk of experiencing a depressive disorder, which could in turn account for the presence of the psychiatric symptoms observed. It could be argued that a specific instrument to detect and quantify the severity of depression should have been included in the protocol. An example of such an instrument is the Geriatric Depression Scale, a 30-item self-reported measure of the presence and severity of depressive symptoms (Yesavage
et al. 1983). However, this would have added to the burden placed on participants, who were already being asked to undergo a clinical evaluation, and complete three psychometric tests. Moreover, while the GDS would allow for the detection of depression, other mental disorders such as chronic delirium or late onset schizophrenia could also potentially account for the CBS participants’ presentations, and could arguably warrant independent evaluation by a specific psychometric tool. This would then further increase the burden on participants, and risked the protocol becoming unacceptable. In the end, I took the decision to rely on a combination of clinical assessment by an experienced old age psychiatrist, supplemented by the Brief Psychiatric Rating Scale, to detect and categorise any coexisting mental disorders, viewing this as an acceptable compromise between comprehensiveness and acceptability to participants. As noted above, this is still a substantial improvement in methodological robustness compared to previous work in the area.

In relation to the clinical assessment, it is interesting to note that in both participants who did develop dementia, there were minor abnormalities present and detected at the initial assessment. These included a tremor and reduced arm swing, and some mild cognitive impairment, in the participant who subsequently developed Lewy body dementia; and mild word finding difficulties and a flattened affect in the participant who developed Alzheimer’s disease. While there were other participants with similar abnormalities identified who did not go on to develop dementia, this finding offers some support for role of the experienced clinician in being able to detect subtle abnormalities present in physical and mental state examinations which may have important prognostic implications.
7.5 BPRS scores

The inclusion of the BPRS was an additional measure to address any concerns that the study may have recruited participants who were experiencing visual hallucinations due to causes related to significant underlying mental disorder, and that the clinical assessment described above may have failed to recognise this. The low scores in both the CBS and control groups support the findings of the clinical assessment, and add further weight to the assertion that there were no medical or psychiatric reasons for the participants to experience visual hallucinations other than Charles Bonnet syndrome.

Looking at the individual scores, the two highest scores across both groups at the baseline assessment were in the CBS group, and were in a participant who developed mild cognitive impairment (29), and one who developed Alzheimer’s disease (28). The highest score at follow-up (42) was in the participant who developed Lewy body dementia, and reflected the distress she was experiencing due to the symptoms of this condition. This was the only person who scored over 30 at either time point. Thus, where there were raised scores found on the BPRS at either time point, this seemed to be more related to an emerging cognitive disorder than to any other mental health problems.

7.6 Characteristics of visual hallucinations

The specific findings of the study, while of lesser importance due to the small sample size, were nonetheless interesting. This study made use of the Teunisse criteria, whose strict operationalized nature allows clarity in the nature of the participants
recruited to be achieved. The failure of many other studies to make use of well-defined criteria is a significant criticism, given the evidence in chapter 1.3 describing how the types of patient given the label of Charles Bonnet syndrome has changed over time. Of the eleven studies my literature review identified which made reference to the cognitive functioning of participants, only four (Pliskin et al. 1996, and three by Teunisse and colleagues) established the CBS diagnosis with reference to recognised criteria. For those that did not, there is a risk that they may have included people who may have other reasons for visual hallucinations and so who many would not consider to have CBS at all; and indeed Gilmour et al. (2009) record that they included participants on acetylcholinesterase inhibitors, who are likely to have had diagnosis of dementia.

Of the 12 participants in this study confirmed as having Charles Bonnet syndrome, 7 (58%) still met the Teunisse criteria one year later. Taken together with the finding that two thirds of participants had already experienced symptoms for over a year at the point of entry into the study, this supports the existing literature which suggests that, for many, CBS is a chronic condition (Menon 2003).

The phenomenology of the visual experiences seen in participants was typically diverse, both across the group and within each individual. The descriptions in table 10, while highly varied in their content, share a common theme of vividness and complexity which is central to the Charles Bonnet syndrome diagnosis. A number of participants experienced initial lack of insight, which is seen in 20% (Gimour et al. 2009) to 60% (Menon 2005) of cases in the literature, but overall the awareness of the unreal nature of the experiences was well preserved among participants, thus satisfying the Teunisse criterion of full or partial insight.
The psychological responses to the visual experiences among participants, as measured by the NEVHI, were on the whole mild, and more often positive than negative. None of those with CBS was significantly distressed, a finding that is supported by the scores on the BPRS, as psychological morbidity in response to the hallucinations would be identified by this. This neutral response was broadly in keeping with the existing literature. In studies where the emotional response of participants to the experiences was sought, the commonest response was one of tolerance or neutrality in five (Norton-Willson and Munir 1987, Teunisse et al. 1994, Teunisse et al. 1996, Khan et al. 2008, and Gilmour et al. 2009). In all of these, while fewer participants reported a strong emotional response, where they did it was more often negative than positive. In two further studies (Menon et al. 2005, and Vukicevic and Fitzmaurice 2008), the hallucinations were experienced as more clearly negative or stressful, with fears expressed that they would be labelled insane. Only one study, Plisken et al. (1996) found more participants describing the hallucinations as benign rather than unpleasant. In this regard, this study, which also reports positive responses more often than negative, is in the minority. The small sample size again reduces the strength of any conclusions, though it is possible that the assessment in clinic by optometry staff with a good understanding of CBS prior to their being assessed as part of the study had gone some way to alleviating any anxieties that may have existed.

The final aspect of the NEVHI factors scores was control over the images content and timing. This study found the level of control that people were able to exert was very low. The literature on this is split, with three studies (Teunisse et al. 1996, Khan et al. 2008 and Vukicevic and Fitzmaurice 2008) reporting that subjects frequently
were able to control some aspects of the hallucinations, but Teunisse et al. (1994) and Menon (2005) reporting that this ability was uncommon, or entirely absent.

Relating the content of the hallucinations described to the literature on the subject is hampered by the lack of a widely accepted framework for reporting results. The framework chosen here, that of ffytche, has the advantage of being grounded in research to establish the validity of the categories, and being related to underlying brain neuronal architecture (ffyche 2007). Direct comparison with the existing literature on content of experiences is made more difficult due to this issue. However, when the content of the hallucinations has been commented on, the commonest experience is people in four studies (Lepore 1990, Schultz 1996, Teunisse et al. 1996, Khan et al. 2008) and complex patterns in one (Vukicevic and Fitzmaurice, 2008). Animals and geometric patterns, each seen by over 50% of participants in this study, were less common in the literature. In addition to Vukicevic and Fitzmaurice (2008), geometric patterns were recorded commonly in Lepore (1990), and Schultz (1996). Animals were less common again, with only Teunisse et al. (1996) reporting them in over 20% of cases.

The more memorable complex hallucinations often associated with Charles Bonnet syndrome, of unfamiliar figures in costumes, or landscape scenes, were uncommon in this study, with only three reports of these across both assessment points. Interpreting the literature on this matter is made more difficult by a lack of detail in reports; while visions of people appear to be the most commonly reported experience, this could be classified in four different ffytche categories, with potentially different prognostic significance. Determining how often the experience was of unfamiliar costumed figures is often not possible from the reports, so it is unclear how
frequently this symptom, which is possibly the best known aspect of the condition, actually occurs in practice.

The performance of the visual hallucination index, derived from ffytche (2007), was disappointing. The numbers of people developing dementia (two) were too small to meaningfully test this measure. One of these participants did have the lowest score in the cohort (-2), and so could be argued to have had the highest likelihood of going on to develop dementia. However, the other was one of only two that had a positive score on the index, and given nearly half the sample had a negative score, but did not go on to develop dementia, this appears to reduce the likely utility of the index as a predictive tool. The spread of results obtained across the sample was also very small, making it less likely that a ‘cut-off point’ with acceptable sensitivity and specificity could be developed. One possible counter argument to this, and in favour of the index, is that the follow up period of this study was too short, and that it is possible that more of those with negative scores may develop dementia in time.

Overall, the ffytche classification, being grounded in insights from neuroscience, appears to be a useful way of describing the phenomenology of visual hallucinations in a reliable way, and its wider use may help bring greater clarity to descriptive studies in this area. The operationalising of the classification into an index to try to predict the development of dementia in the Charles Bonnet population looks less likely to be useful, but may be worthy of further research, as part of larger, well conducted studies of the condition.
With regard to persistence of the symptoms, in this study, 7/12 participants with CBS continued to experience symptoms after one year. There are numerous case reports in the literature describing symptoms of CBS continuing over time, but resolving as vision deteriorates toward blindness; indeed this pattern was documented in Charles Bonnet’s original account of his grandfather’s experiences. There is even a classification of the condition into episodic, periodic and continuous forms (Menon 2003), with the episodic variant held to be least common. However, there have been few recent, properly constructed longitudinal studies which have investigated this matter, and those that do exist have been small in size. The finding of this study, of continuing visual hallucinations meeting criteria for Charles Bonnet syndrome in 7/12 participants (58%) is similar to the rates recorded in these studies: Holroyd and Rabins (1996) found 4/10 continued to have visual hallucinations after one year, while in Eagan and Williams (2000), 6/7 continued to have symptoms after 2 years. Two other studies report on the proportion of participants remaining symptomatic, but after a shorter period of follow up: Jackson et al. (2005) reported that 23/33 were symptomatic after 6 months, and in Crumbliss et al. (2008), all 11 participants followed up continued to experience hallucinations at follow up, though after a mean duration of only 35 days. This study, although small, does therefore provide a useful addition to the understanding of progress of Charles Bonnet syndrome over time.

7.7 Visual assessment

The results relating to ophthalmological diagnoses were also of interest. Epidemiological work has established that CBS is relatively common in age related macular degeneration and glaucoma, with substantial cross sectional studies conducted in both groups (Abbott et al. 2007 and Khan et al. 2008 for AMD, Nesher
et al. 2001 for glaucoma). Most studies, however, have been done on populations with mixed ocular pathology. The findings in relation to ophthalmic diagnosis in four of these are shown in table 25.

Table 25: Ophthalmic diagnoses in Charles Bonnet syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>AMD</th>
<th>Glaucoma</th>
<th>Diabetic retinopathy</th>
<th>Cataract</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pliskin et al. 1996</td>
<td>1/15</td>
<td>5/15</td>
<td>0/15</td>
<td>4/15</td>
<td>5/15</td>
</tr>
<tr>
<td>Tatlipinar et al. 2001</td>
<td>5/12</td>
<td>1/12</td>
<td>2/12</td>
<td>0/12</td>
<td>4/12</td>
</tr>
<tr>
<td>Scott et al. 2001</td>
<td>4/13</td>
<td>0/13</td>
<td>8/13</td>
<td>0/13</td>
<td>1/13</td>
</tr>
<tr>
<td>Gilmour et al. 2009</td>
<td>75%</td>
<td>5%</td>
<td>7%</td>
<td>2%</td>
<td>10%</td>
</tr>
</tbody>
</table>

The results for Gilmour et al. (2009) are expressed as percentages, as the actual values were not given. These show a wide variety of diagnoses, with little consistency over which condition is most frequently found in association with CBS. This can probably be accounted for by specific local factors relating to the clinical environment where the participants were recruited from. In this study, as with those cited above, there was a wide range of diagnoses (seven across only 22 participants). As with Tatlipinar et al. (2001) and Gilmour et al. (2009), age related macular degeneration was the commonest diagnosis found. This probably reflects the fact that most of the participants were recruited from a low vision assessment clinic, where advanced AMD was the commonest reason for attending, rather than allowing any broader interpretation of the relative frequencies of ophthalmic diagnoses in CBS.
The data on visual acuity in the participants with Charles Bonnet syndrome in this study showed a mean acuity of logMAR 0.72 (equivalent to around a Snellen acuity score of 6/30). Visual acuity is very frequently described in published studies on CBS, and is usually the only measure of visual functioning given. Two significant studies have investigated the link between visual acuity, and were described above in chapter 1.4. Briefly, Teunisse et al. (1995) found a significant association between CBS and acuity of logMAR 0.3 or worse in the better eye, while Khan et al. (2008) found that found that worse visual acuity was strongly related to CBS. They reported with an odds ratio of 3.5 (1.6-7.5) for being given a diagnosis of CBS in those with a visual acuity in the better eye of worse than 6/36 (approximate logMAR 0.77), compared to those with a visual acuity of better than 6/12 (logMAR 0.3).

The original study protocol had an inclusion criterion drawn from the Teunisse study, of a visual acuity in the better eye of worse than logMAR 0.3. This was relaxed to include participants with better acuity, but even with this only 1/12 participants with CBS had acuity of better than this value. Relating this finding to the Khan et al. (2008) high risk criteria, 7/12 participants had a visual acuity value in the better eye that would place them at high risk of developing CBS. The findings of this study are in keeping with the literature which notes the clear relationship between poorer visual acuity and CBS, but limitations of the study design prevent any wider conclusion being drawn. As with the underlying ophthalmic diagnosis, the poor visual acuity scores may simply be a reflection of the study population, most of whom were drawn from a clinic where the very fact they were attending it meant they had very significant impairment in this area.
This study collected data on two other dimensions of visual functioning, the presence of a scotoma and contrast sensitivity. A study by Abbott et al. (2007) did look at binocular field loss using Bjerrum plots, and while the result was not statistically significant (p=0.061), this may have been a type II error due to limited study power, as the mean value for the CBS group was four times higher than the controls. The data on scotoma in this study were collected using an Amsler grid, which does not allow for quantitative analysis of the extent of the scotoma. However, among the 11 participants with CBS where visual field testing was conducted, 9 had a confirmed scotoma, and the remaining two showed evidence of significant distortion of the Amsler grid on testing, indicating abnormality of the retina was present. Thus, all 11 participants with CBS had significant retinal abnormalities, in line with the findings of Abbott et al. (2007) and suggesting that scotoma presence as well as impaired visual acuity may play an important role in the development of CBS.

The final dimension of visual functioning measured as part of the study was contrast sensitivity. This is only the second study which has looked at this measure of visual functioning in relation to the development of visual hallucinations. The first, Jackson et al. (2007), reported that contrast sensitivity may be a better predictor of hallucination risk than visual acuity. Moreover, contrast sensitivity has been reported to be strongly associated with face recognition and performance on tasks of daily living (West et al. 2002), and has been suggested as being useful in determining disability due to visual impairment. It thus has the potential to be a particularly relevant measure. In contrast to visual acuity, a lower score on Pelli-Robson contrast sensitivity testing indicates poorer contrast sensitivity, with scores of 1.5 or less indicating impairment on this measure, and scores of less than one being consistent with significant disability. The mean scores on contrast sensitivity in both the CBS and control groups were significantly impaired, with the mean in the CBS group, at
0.95, falling into the range likely to lead to disability. The control group were only a little better, with a mean score of 1.09. Among the CBS group, none of the participants had a contrast sensitivity of better than 1.5, and only one of the controls did.

This result is of some interest, as it is only the second study to demonstrate serious deficits in contrast sensitivity in people with Charles Bonnet syndrome. While the link between visual acuity and CBS is well established, it is possible that contrast sensitivity could play a significant role in the development of the condition; the link described between contrast sensitivity and face recognition may be of relevance here, given that prosopometamorphopsia, seeing faces as distorted and misshapen, is one of ffytche’s categories of abnormal visual experience. Further work investigating this possible link would certainly be worthwhile.

Taken together, the data for the participants with CBS show severe abnormalities in all three dimensions of visual functioning. This lends some weight to theories about the origin of Charles Bonnet syndrome that stress a role for de-afferentation (Collerton et al. 2005, ffytche 2007). This can only be a partial explanation, however, as there were also high levels of visual pathology and impairment across all three dimensions of visual functioning in the control group. While there was a statistically significant difference in visual acuity between the groups, the control group still had a mean visual acuity (logMAR 0.34) which was above the threshold demonstrated by Teunisse et al. (1995) to be associated with the development of CBS. Moreover, other measures of visual functioning, including the prevalence of scotoma and the score on contrast sensitivity, were not significantly different between the groups. So, visual functioning alone cannot explain why the CBS group developed the condition,
and another factor must also be necessary for its emergence. Georges de Morsier’s contention, that CBS is not related to eye disease, but instead reflects underlying brain pathology (de Morsier 1967), seems to be at least partially correct.

7.8 Neuroimaging

While patients with Charles Bonnet syndrome in many of the case reports in the literature have undergone a range of neuroimaging, this only the third observational study to attempt to routinely offer a structural imaging procedure as part of the protocol. The only other studies, Shedlack et al. (1994), and Adachi et al. (2000), were very small, with only five CBS participants in each. In Shedlack et al., participants also underwent MRI scanning, and the study claimed to find increased hyperintensities in posterior white matter when compared to a control group. In the light of this, the findings of this study, of very high levels of deep white matter ischaemic change suggestive of advanced microvascular disease, are of great interest. As discussed above, the presence of significant eye disease alone does not seem to be a sufficient explanation as to why some people develop CBS and others with similar visual impairment do not. Many authors, from de Morsier onwards, have made the case that there must be some degree of underlying brain dysfunction in order for the symptoms to emerge. The possibility of a link between cerebral small vessel ischaemic disease and Charles Bonnet syndrome, with disruption to the connectivity between parts of the brain involved in visual processing, is an interesting one, which will be explored further in Part III of this thesis.
A number of participants also had atrophy affecting the medial temporal lobes, suggestive of Alzheimer’s disease. These included participant 018, who did go on to develop Alzheimer’s disease at follow up. However of the five other participants with medial temporal lobe atrophy, none recorded a fall in their ACE-R, and indeed in some cases the score improved. Only one showed an increase in the IQCODE score, signifying a loss of daily living skills, and this was by a small amount (0.25 points). This highlights the weakness of neuroimaging in diagnosing dementia, especially in more elderly cohorts (Sulliven et al. 2012).

The aim of this study, as set out in chapter 4.2, to determine if there are abnormalities detectable on MRI scanning present at diagnosis of Charles Bonnet syndrome that predict the subsequent development of dementia, or progressive cognitive impairment falling short of dementia, has not been realised. However, more detailed examination of the T2-weighted scans using a semi-quantitative method of determining the extent of microvascular ischaemic changes, such as that of Scheltens et al. (1993), is an approach that I intend to take forward, to determine if Professor Jackson’s impression of a greater burden of cerebrovascular disease in the Charles Bonnet group is supported by an objective scoring system.

**7.9 Cognitive Testing: Development of Dementia**

Beyond its role as a pilot study, the main aim of this work was to define the proportion of a cohort diagnosed with Charles Bonnet syndrome who go on to develop dementia in the following year. This proportion was 2/12 (17%). This compared to no cases of dementia emerging in the control group over the same
period. When subjected to statistical testing using analysis of covariance, this finding did not reach statistical significance. The study did not have sufficient power to have a realistic expectation of making a positive finding in this outcome, as discussed in chapter 4.3.

Nonetheless, this is the first study that has attempted to follow up a cohort of people with Charles Bonnet syndrome for the purpose of detecting a clinically significant outcome, that of a diagnosis of dementia. None of the three other studies in the literature which explicitly set out to examine the relationship of cognitive functioning with CBS (Schultz and Melzack 1993, Holroyd and Rabins 1996, and Pliskin et al. 1996) had dementia as a study outcome, reporting instead on the results of cognitive testing. While of interest in helping to understand the biological basis of the condition, and clearly having a relationship to dementia, cognitive test scores alone are of less direct significance than a diagnosis of dementia, and are likely to be held as being of less importance by clinicians and patients. Moreover, only one of the three studies (Holroyd and Rabins, 1996), included a longitudinal component, the others only conducting cognitive testing at one time point.

The finding that two patients diagnosed with Charles Bonnet syndrome went on to develop dementia therefore adds to the existing literature in the area, which is mostly in the form of case reports. These are set out in the review in chapter 2.7, and include 15 cases described in 11 publications. Moreover, these 15 cases account for nearly two thirds of the 22 cases reported in the literature where cognitive functioning was assessed at baseline and again after a period of follow up. Of course, this is not a representative sample of the population with CBS, and the greater emphasis on cognitive testing in these cases is possibly because they developed dementia.
Nevertheless, this study, while failing to derive a statistically robust measurement of the increased risk of developing dementia that a diagnosis of Charles Bonnet syndrome confers, still adds weight to the theory that there is a clinically important overlap between the conditions, and that this is not simply down to misdiagnosis or coincidence.

7.10 Cognitive Testing: Discussion of ACE-R findings

A second aim, to determine the proportion of participants who demonstrated abnormalities in cognitive functioning at diagnosis of Charles Bonnet syndrome that were not severe enough to warrant a diagnosis of dementia, was also not met. A higher proportion of participants with CBS were found to have abnormal scores on the ACE-R at both the initial and follow-up assessment, and at the follow up point 50% of the CBS cohort scored below the cut-off point which suggested significantly abnormal cognitive functioning.

Overall, the findings of the analysis of ACE-R scores relating to cut-off points for dementia is largely supportive of the conclusion of Pliskin et al. (1996). Pliskin et al. (1996) found even higher rates of abnormalities in their population, with 14/15 reported as having abnormal cognitive functioning. They made use of a wider range of measures to assess cognitive functioning than were used in this study, including the Wechsler Adult Intelligence Scale-Revised, the Dementia Rating Scale, the MMSE and the Wechsler Memory Scale. However, they did not however include a control group, raising concerns over how to interpret the results, given the potential confounding effects of poor visual functioning on the outcomes of these
assessments. More seriously, more than half their population failed to have insight in the unreal nature of the experiences, meaning that they would not have met the criteria for Charles Bonnet syndrome used in this study.

Both Schultz and Melzack (1993) and Holroyd and Rabins (1996) reported normal cognitive functioning in their participants, but the testing they did was much more limited, and restricted to instruments which are poor at detecting milder degrees of cognitive impairment, especially when it affects the domains of frontal/executive functioning and visuo-spatial functioning, which are of particular relevance in Lewy body dementia (McKeith et al. 1996). Neither study made use of accepted diagnostic criteria to select participants, neither included a control group, and both were small and underpowered (14 participants in Schultz and Melzack, and 10 in Holroyd and Rabins). Given this, their conclusions, that they had ‘ruled out the hypothesis that the hallucinations were caused by dementia’ (Schultz and Melzack), and that patients with CBS could be reassured (Holroyd and Rabins), appear overstated.

A third study aim was to establish whether there was a correlation between those who show abnormalities in cognitive functioning at diagnosis of Charles Bonnet syndrome, and those who later developed dementia, or progressive cognitive impairment falling short of dementia. The small sample, of which only two developed dementia, meant that this would not be possible to establish to a level of statistical significance. However, it was notable that of the three participants who scored below the normal range on the ACE-R at baseline assessment, one went on to develop dementia, and a second had mild cognitive impairment and a fall of 6 points on the ACE-R score at the follow up point. This suggests that further study, looking at the
establishment of a validated normal range for ACE-R scores in a low vision population may be worthwhile.

The further analysis by examining the change in the raw ACE-R scores over the course of the study using ANCOVA was a more powerful way of investigating the cognitive functioning of participants, as it was able to control for the effect of differences in visual acuity. This did not support a significant relationship between diagnosis of CBS and cognitive functioning. The effect size for this relationship was small, with a partial eta squared result of 0.11 suggesting that only 11% of the variance in scores on the ACE-R at follow up was explained by the diagnosis of CBS. This was, however, a larger effect size than for visual acuity (partial eta square 0.09). The majority of the variance was accounted for by the initial ACE-R score; but this value is not entirely independent, as it is likely to be influenced by both visual acuity and any emerging dementia at the time of testing.

7.11 Cognitive Impairment: ACE-R subscale analysis

The ACE-R subscale analysis generated some interesting observations, which suggested the confounding effect of differences in visual acuity between the groups may have been small. There was a small difference in performance on the visuospatial subscale between the CBS participants and controls at baseline, though this was not statistically significant. Taken alongside the difference in performance at follow-up in the language domain, two-thirds of the items of which have a dependency on visual functioning to complete, this lends some support to the
contention that there may have been a visual performance effect despite the large-format adaptations.

However, the initial differences in verbal fluency scores were larger than those in either of the two visually-dependent domains, and verbal fluency is a domain where visual acuity is unlikely to have played a part in influencing the outcome. Moreover, the follow-up data were also less supportive of differences in visual performance having a substantial impact on the findings. Over the course of the study, the visuospatial subscale was the only one which did not show deterioration in performance in CBS participants, or a widening of the difference in performance between CBS participants and controls. The differences in scores in the verbal fluency subscale at follow-up were statistically significant, and showed the largest overall magnitude, at 17.2% of the maximum score in this subscale. In summary, while there may have been some effect of visual functioning on performance of the ACE-R, this does not seem to be able to fully account for the pattern of change on test results seen, and so offers some support to the contention that the differences observed may arise from real differences in cognitive functioning between the groups.

The finding that verbal fluency appeared to show the biggest magnitude of change is of particular interest in light of Collerton et al. (2005), who advanced the perception/attention deficit model of recurrent complex visual hallucinations. Verbal fluency is a measure of frontal lobe functioning, and Collerton et al. (2005) suggest that the lateral frontal cortex may be a key location for the generation of visual hallucinations, with roles including attentional binding of objects in the field of view. Abnormalities in frontal lobe functioning could potentially lead to impaired attentional
binding of objects, which along with the impaired afferent information from the retina, could be offer a mechanism as to why the CBS group develop visual hallucinations when most people with impaired vision do not experience these phenomena.

The possible link to frontal/executive functioning is also of interest in relation to the hypothesised link with Lewy body dementia. In Lewy body dementia, there is often less memory loss evident early in the condition, with more significant impairment in other domains, including frontal/executive functioning. The finding of particularly poor performance on this part of the ACE-R among the CBS participants, and the emergence of one manifest case of Lewy body dementia in a participant with CBS, raises the possibility that there may be other participants on the pathway to developing Lewy body dementia, who would have become apparent with a longer period of follow-up.

Further evidence against differences in visual functioning being responsible for the differences in performance on cognitive testing comes from the analysis of the ACE-R scores with vision-dependent items extracted, and the comparison of deficits across the vision-dependent and vision-independent parts of the test. The pattern of deficits on testing, and the change over time, was similar whether the vision dependent items were included or excluded. Furthermore, when the magnitude of the change in scores between the groups in the 66-point ACE-R without vision-dependent items was looked at, it also did not provide support for there being an effect on scores from group differences in visual functioning. The performance on vision-independent items was worse than for vision-dependent items at both time points and in both groups, and the deterioration in performance on the ACE-R showed a similar magnitude for vision-dependent and vision-independent items. This
suggests that the change in scores over the study period did not arise disproportionately from the vision-dependent part of the examination, but instead occurred equally across both vision-dependent and vision-independent items. It is thus not supportive of the ACE-R findings being confounded by the poorer visual acuity in the CBS group. Moreover, the difference in scores on the ACE-R remained statistically significant at follow up, even when the vision-dependent items were excluded, further undermining the argument that the cognitive test findings represent the effect of confounding.

7.12 Cognitive Testing: Mild Cognitive Impairment

The finding of mild cognitive impairment in a number of the CBS participants is also worthy of note in relation to the subsequent development of dementia in two cases. At baseline there were three of the CBS cohort who scored below the cut off point for dementia on the ACE-R, but who did not have dementia when assessed clinically and when an informant history was taken. There was a further participant with CBS who reported subjective increased forgetfulness, but who had no decline in performance of daily living tasks, and who performed well on the ACE-R. Nonetheless, this participant could also be described has having mild cognitive impairment.

One of these four participants with mild cognitive impairment went on to subsequently develop dementia, and two of the other three experienced a deterioration in their scores on the ACE-R over the course of the study, of 6 points and 11 points. This raises a suspicion that they may have been on a pathway to
developing dementia. The fourth participant with mild cognitive impairment showed no change in their score on the ACE-R between the baseline assessment and follow up.

The significance of the higher rate of mild cognitive impairment among the CBS participants is unclear. It could be unrelated to the CBS diagnosis, and represent another dimension on which the CBS and control cohorts were dissimilar. However, it is also possible that the higher rates of mild cognitive impairment observed relate directly to the matter that the study is investigating. The systematic review set out in chapter 2 suggested that there were high rates of partial insight at diagnosis of CBS in patients who subsequently developed dementia. If CBS was to be a pre-dementia state for some people, then it would not be surprising to find evidence of mild cognitive impairment in this cohort, and this could be the factor underlying the frequent finding of impaired insight seen in the literature. The finding of a degree of partially impaired insight in three of the four participants with mild cognitive impairment at baseline assessment in this study adds some further weight to this finding.

An extended period of follow up, greater than the one year allowed for in this work, would have been interesting, and would have enabled the determination of whether the two participants with apparent progression of their cognitive impairment were in fact in the early stages of a dementia. Overall, these findings allow no definitive statement to be made in relation to the significance of the high rates of mild cognitive impairment in the CBS cohort; but taken together with what is already known from the literature, there is a suggestion that the combination of partial insight and MCI at diagnosis of CBS places the patient in a category that is at higher risk of the
development of dementia, and so may warrant closer follow up to be alert for this outcome emerging.

7.13 Cognitive Impairment: Discussion of IQCODE results

Another area that may be worthy of further study is the use of the IQCODE. This was included as a way of gathering informant information on performance on tasks of daily living in a structured manner, in order to supplement the unstructured account elicited during the history taking assessment. While there is a cut-off point taken to signify the likely presence of dementia (Jorm et al. 1996), this was not derived in a low vision population and so is unlikely to be valid in the cohorts in this study. The finding of higher scores on the IQCODE among CBS participants than controls could just be a reflection of this group’s poorer visual acuity, and so is hard to interpret. It was interesting that, of the three participants with scores above 4.00 on the IQCODE at the baseline assessment, all had CBS, and two also fell below the cut-off point for abnormal functioning on the ACE-R. All three of these participants went on to have abnormal cognitive testing at the follow-up assessment. They included both participants who developed dementia, and one of the two who had mild cognitive impairment and a large fall on their ACE-R score. This suggestion that the IQCODE may be of predictive value in the CBS population could be worthy of further investigation.
7.14 Cognitive Impairment: Discussion of MMSE results

A final interesting finding of this study was confirmation that the mini-mental state examination (MMSE) is poor at detecting clinically relevant cognitive impairment in a cohort diagnosed with Charles Bonnet syndrome. No participant with CBS scored lower than 25/30 on the MMSE at the follow-up assessment, despite two participants being diagnosed with dementia, and a further three showing clinically relevant falls on their score on the ACE-R. As noted in chapter 2, most previous studies which have considered the issue of cognitive impairment in Charles Bonnet syndrome have relied on the MMSE as their assessment of cognition. This study demonstrates that the ‘normal’ scores that these studies reported cannot be relied upon to exclude the development of serious cognitive impairment among their participants, up to and including frank dementia.

7.15 Cognitive Impairment: Limitations of this Study

There were some limitations to this work that warrant discussion. As noted in chapter 5.4, diagnosis of dementia relies on demonstrating the presence of an impairment in social or occupational functioning which is a consequence of the cognitive impairment the condition causes. The low vision population that this study investigated often had impaired functional ability due to their visual impairment, and this added a degree of complexity to the diagnostic process. Moreover, dementia diagnosis in a study such as this should ideally be done by two or more experts, examining the clinical material obtained during the assessment, while being blinded to which group the participant belongs to.
There were no easy solutions to these problems. It was beyond the resources available to the study to set up a panel of experts to conduct blinded diagnosis; and there are no validated instruments to carry out cognitive testing in a low vision population, or to assess the relative contributions of cognitive impairment and visual impairment to a loss of functional ability. This places some limitation to the confidence with which the findings can be reported.

However, as commented on in chapter 5.4, making diagnosis of dementia in patients who have multiple coexisting sensory or mobility impairments is part of the everyday work of old age psychiatrists, and both investigators were experienced senior practitioners in this field. Also, in both cases where dementia was diagnosed, this was done by me, as Chief Investigator. In these two participants, there was no doubt at all that the person had developed dementia at the follow up assessment, with obvious and severe impairments in cognitive functioning being clearly evident.

This should go some way to addressing the concerns over assessing the contribution of visual impairment to the observed functional decline; though it is not possible to rule out the possibility that this may have confounded the assessment in less clear cases, and could potentially have led to under-diagnosis of dementia. The issue of diagnosis being made on the judgement of a single assessor remains an issue, though one it shares with previous work in the field, all of which included assessments of cognitive functioning carried out by one person.
A further limitation is the short period of follow up allowed for in the study. This was in part driven by necessity, as the study had to be possible to be completed within the timescale allowed by the degree programme. As shown in the systematic review in chapter 2.7, where case reports document the emergence of dementia in CBS, there has often been a delay, of up to five years in some cases. In only 3/12 cases was the dementia manifest within a year, the time for follow up allowed in this work. However, it is certainly arguable that the closer the temporal relationship between the diagnosis of CBS and the emergence of dementia, the more likely it is to represent a genuine link between the two conditions. The age group of the cohort who are at higher risk of CBS are also at a significant risk of developing dementia, and it is inevitable that in some cases, the emergence of both conditions its coincidental and the linkage spurious. This is more likely when there are an number of years between the CBS diagnosis and dementia becoming apparent.

So by having a shorter period of follow up, it increases the likelihood that any cases of dementia that emerge have a causal link to the presence of CBS. This greater confidence in the observed effect being of clinical relevance comes at the price of failing to detect cases of dementia that are genuinely linked to the presence of CBS but which emerge after the year’s follow up. The two cases of mild cognitive impairment where there seemed to be progressive deterioration in cognitive functioning over the course of the study, discussed above, are of particular relevance in this regard. A longer period of follow up, of 2-3 years, would be useful in any large scale replication of this work.

There are some limitations in relation to the use of the ACE-R as a measure of cognitive impairment which are worth noting here. The ACE-R is not validated for use
in a low vision population, as noted in chapters 5.4 and 6.11. As a consequence, cut-off points for the diagnosis of dementia, which have not been derived from this population, are of questionable relevance. This is a difficult issue to deal with, as measurement of cognitive functioning is at the core of this work, and the poor vision of the participants was therefore a potentially serious confounder - more so given the differences in visual acuity between CBS participants and controls discussed in chapters 6.8 and 7.7. However, there were no other instruments to test cognitive functioning available which were validated in the low vision population which could be used in stead of the ACE-R; and indeed, such a tool may not be possible, as aspects of cognitive functioning such as comprehension of written language, and visuospatial ability, are necessarily dependent on visual performance.

Given that no ready alternative to the ACE-R was available, a number of steps were taken to mitigate any effect of visual performance on the results obtained. Very large format versions of the visually dependent items were developed and piloted in the target population, with a good degree of acceptability achieved. A participant whose visual acuity was very significantly worse than the other study participants, and whose score on the ACE-R was an outlier which did not seem to be explained by cognitive impairment on clinical assessment, was excluded from the analysis. And finally, further analysis of the ACE-R data, looking at subscale results, and comparing the scores on visually dependent and visually independent items of the test (as set out in chapters 6.15 and 6.16), was conducted.

Taken together, these measures should provide some assurance that this limitation has been accounted for; and while some confounding from impaired visual performance cannot be entirely excluded, the subscale analyses suggest that this did not account for the findings presented.
A further limitation in the results relating to the ACE-R is the lack of a measure of premorbid intellectual ability. It is known that this factor, and educational attainment, can influence the results of cognitive testing, and so this is another potential source of confounding. One measure of premorbid intellectual ability is the National Adult Reading Test (NART) (Nelson 1982). This instrument is based on the observation that recognition and ability to read out words is preserved during the development of dementia, and so offers a way of estimating premorbid intellectual abilities when direct data relating to this is not available. There has been work showing it to be superior to the use of demographic variables to estimate premorbid intelligence (Bright et al. 2002), and showing a moderate high correlation with IQ measured at age 11 (McGurn et al. 2004). However, this instrument was not used in the work reported on in this thesis.

There are other, less robust ways of attempting to capture information about premorbid intellectual ability as part of testing cognitive functioning. As an example, another bedside cognitive test, the Montreal Cognitive Assessment, makes an adjustment to the result obtained based on the duration of time the subject spent in formal education (Nazreddine et al. 2005). The ACE-R does prompt for age at which formal education ended, but this information was not reliably completed, and the ACE-R has no formula for adjusting the results obtained to take differences in duration into account. In summary, the lack of a measure of this factor is a limitation of the study, and increases the caution with which the results should be interpreted.
7.16 Cognitive Impairment: Predicting Dementia

One of the most interesting aspects of this study was an attempt to identify markers that could be administered at the time of diagnosis of Charles Bonnet syndrome that could predict the likelihood of subsequently developing dementia. Given that CBS diagnosis will often be in ophthalmology departments, the staff there are unlikely to be familiar with early presentations of dementia, or detailed psychometric tests. CBS is a common condition, and it is unlikely to be practical, necessary, or acceptable to patients to refer all new diagnoses of CBS to a memory clinic for assessment. Hence a screening test, or battery of tests, that could be administered in non-psychiatric settings by non-mental health professionals, and which would identify those at higher risk of developing dementia, would have considerable utility, as it could identify those where a memory clinic referral would be of value.

There were four instruments administered as part of the protocol which could potentially serve this purpose. These were the ACE-R, the IQCODE, the BPRS and the VH index score (VHIS). With only two participants developing dementia, none of these could be subject to meaningful statistical testing. However, when the performance on the initial assessments of each of these parameters in the two participants who developed dementia, and the two who showed evidence of MCI and falls of over 5 points on the ACE-R score, is examined, an interesting pattern emerges. This is shown in table 26, with the participants' scores expressed as a ranking among all 22 participants across both groups.
Table 26: Predictive value of study instruments

<table>
<thead>
<tr>
<th>Participant</th>
<th>Condition</th>
<th>ACE-R (lower scores rank higher)</th>
<th>IQCODE</th>
<th>Modified BPRS</th>
<th>VHIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>002</td>
<td>Lewy body dementia</td>
<td>21=</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>008</td>
<td>MCI</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2=</td>
</tr>
<tr>
<td>018</td>
<td>Alzheimer’s disease</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>20=</td>
</tr>
<tr>
<td>020</td>
<td>MCI</td>
<td>15=</td>
<td>14</td>
<td>13=</td>
<td>16=</td>
</tr>
</tbody>
</table>

These tests did appear to have some success in predicting those who would go on to develop dementia, or MCI. Only participant 020 did not appear to be identified as potentially abnormal by this post-hoc exercise. Of the four measures, the two which appeared to have the greatest success were the IQCODE and the modified BPRS. The VHIS is limited by its lack of granularity, with all participants grouped very closely together, and the BPRS is limited by requiring more training and understanding of mental health issues to administer. It may not be suitable for use by staff in an ophthalmology department. However, this finding tentatively suggests that a combination of the ACE-R and the IQCODE, which could be administered speedily and with minimal training, may be worth investigating further as a screening package to identify patients with CBS who should be referred to memory clinics for more thorough assessment.

In psychiatric settings, the addition of the BPRS could potentially strengthen any predictive assessment. Also, as noted in chapter 6.3, the mental state examination was mildly abnormal in both patients who developed dementia, and in no other participants; and one of the participants who developed dementia was among those with soft signs on neurological examination. Taken together, while this study is not powered to accurately investigate the predictive performance of these instruments,
there seems to be a combination of abnormalities on examination, and on structured psychometric instruments, that offer some promise in assessing the risk of patients with Charles Bonnet syndrome going on to develop dementia. This may offer some support to clinicians in old age psychiatry who not infrequently come across patients with Charles Bonnet in clinic, and currently have to make a judgement on which ones to follow up, and which can be reassured and discharged, on the basis of very little evidence. Further work could potentially refine this advice, and determine which measures are of the greatest value in predicting this important clinical outcome.

7.17 Cognitive Impairment: Summary of Discussion

In summary, given the underpowered nature of the study, and the failure of the differences in ACE-R scores to achieve statistical significance once confounders were including in the ANCOVA analysis, it is impossible to draw any definite conclusions from these results. However, a number of tentative findings of interest did emerge. There did seem to be evidence of mild cognitive impairment in the CBS participants. Although none of these participants satisfied diagnostic criteria for dementia at the initial clinical assessment, three had scores on cognitive testing which were below an established cut off point for dementia. There was evidence of greater impairment of frontal lobe functioning in the CBS group than the control group, and this difference was statistically significant at the follow up assessment; and there was evidence of deterioration in performance across a range of cognitive domains in a pattern which was not readily explicable by differences in visual functioning. A number of the participants had notably poor performances on other parts of the ACE-R, with three CBS participants and one control having scores on the memory subscale at follow-up suggesting amnestic mild cognitive impairment.
Finally, the differences in performance on cognitive testing which emerged between the groups continued to show statistical significance even after the vision dependent items in the test were excluded from the analysis.

So, it cannot be reliably ruled out that the trend towards the CBS group showing decline on measures of cognitive functioning, and an increased frequency of the development of dementia, occurred by chance. However, taking the evidence set out above together with the neuroimaging findings of high levels of ischaemic white matter changes and cerebral atrophy, a case can be made that the CBS population appears to include significant numbers of individuals who have neurocognitive abnormalities at the point of diagnosis. There is also some evidence that these abnormalities may progress with time, in a pattern that are unlikely to be completely accounted for by differences in visual acuity between the groups. Further more powerful studies would be needed to more precisely explore this relationship.
8. Clinical Study: Conclusion

In chapter 2 I set out the current evidence relating to Charles Bonnet syndrome and cognitive functioning, demonstrating that the literature in this area is very limited and has significant methodological shortcomings. I also set out why this is important, as this is not an uncommon condition; and if a substantial number of people thought to have it were actually in the early stages of dementia, then there is the potential to improve the early recognition of dementia, allowing treatment and support to be provided to people, and allowing them to make important decisions and choices in their lives while they retain the capacity to do so.

This study is therefore an important contribution to the literature on a number of grounds. It is the first longitudinal study of cognitive functioning in Charles Bonnet syndrome that has rigorously applied clear diagnostic criteria for the condition, that has used a control group, that has included an assessment by an experienced clinician to rule out other medical or psychiatric causes, that has made serial measurements using a test that is recognised to cover a broad range of domains of cognitive functioning, that has used the clinically relevant outcome of dementia, and that has attempted to relate this to characteristics of participants at baseline. In addition, it is the first to examine the visual functioning of participants using three different parameters, the first to make use of a neuroanatomically grounded system of classifying the phenomenology of visual experiences, and the first to offer neuroimaging as part of the study protocol to all participants.
As such, its findings are of some significance. The near-universal presence of scotoma and marked impairment on contrast sensitivity suggests the role of these attributes has been under-researched to date, and that there may have been an over-reliance on visual acuity alone to define the extent of visual impairment. The stability of the experiences over time suggests that Charles Bonnet syndrome is often a chronic condition, and advice to those experiencing it should reflect this. The very high levels of cerebrovascular disease found on neuroimaging may offer a potential aetiological mechanism to explain why some people with impaired vision develop the condition and others do not. This warrants further research, and is the focus of the linked study described in Part III of this thesis.

The finding that two of the Charles Bonnet group developed dementia, while falling short of statistical significance, joins the existing literature reports of this outcome, and lends weight to the clinical impression that this is not a rare occurrence, but instead is a clinically relevant pathway by which people developing dementia present to health services. The changes in the score on the Addenbrooke’s cognitive examination over the study also failed to reach statistical significance, and there were concerns over whether the poor matching between CBS participants and controls may have acted as a confounder. However, analysis of the patterns of cognitive impairment seen in the CBS group suggested that the differences in visual acuity had not influenced the result to a large degree, with the differences between the groups at follow-up achieving statistical significance when the visually-dependent items of the ACE-R were excluded from the analysis.

Frontal lobe/executive functioning emerged as the domain of cognitive functioning which showed the largest difference in performance between the groups. This
difference was of statistical significance, and was unlikely to have been influenced by between-group differences in visual acuity. This finding is of particular interest given the importance of the frontal lobe in one of the leading explanatory models of recurrent complex visual hallucinations (Collerton et al., 2005), and overall this area did look worthy of further research with better-powered studies. It is also potentially relevant in relation to the hypothesis that some cases of CBS may in fact be early presentations of Lewy body dementia, as frontal/executive dysfunction is known to be present in this condition.

Finally, some of the study measures appeared to have potential utility in helping identify those with Charles Bonnet syndrome who are at higher risk of going on to develop dementia, though much more work would be needed to explore this more fully to see if they could be useful in a clinical setting.

There were some shortcoming of this work. The principal of these was the small sample size and consequent lack of power to adequately test the study hypotheses. This has been a longstanding problem in this field, and although this study is small, it is of a similar scale to all previous published work in the area. As a result, this study shares a flaw with all the previous research; that it is unable to say conclusively whether the observed differences between the groups occurred purely through chance, or reflects a real difference. Another shortcoming was that assessment of visual functioning took place only at one time point; had there been a repeat of this assessment at the follow-up after one year, it would have been possible to more robustly control for the effect of visual impairment on the results. The third significant shortcoming was the failure to recruit a control group that more closely resembled the study cohort, and that in particular was more similar in gender and visual acuity. This
problem arose in part due to the change in the protocol to remove the minimum level of impairment on acuity from the inclusion criteria, but that alone does not explain the markedly smaller number of women willing to be controls compared to participants with the condition. This shortcoming significantly complicated the analysis and interpretation of the findings. A final shortcoming was the lack of a measure of pre-morbid intellectual ability; this is an omission that any subsequent work should seek to rectify.

Overall, the most significant finding of this work is that it is possible to carry out a methodologically robust study in this population. The barriers to recruitment can be overcome, and the protocol was acceptable; indeed participants were interested and keen to help, despite their often advanced years. It was possible to build an effective study team despite working across specialities and trusts.

This suggests that a larger scale study, powered to be able to properly test the study hypotheses, would be viable; and given the clinical significance were an increased incidence of dementia in people with Charles Bonnet syndrome to be confirmed, it would also be desirable. The clinical implications would be important. These could include revising commonly-stated guidance to those diagnosed with Charles Bonnet syndrome that it is a benign condition, and does not indicate the presence of a psychiatric disorder; and setting up pathways for referral of patients to memory clinics from ophthalmology settings. Any such work is likely to need to be multi-centre, to ensure that the criticism of most previous studies, that they are underpowered and unable to meet their study aims, does not end up being repeated.
Other related areas that would justify further research are the phenomenology of visual hallucinations in Charles Bonnet syndrome, and the nature and extent of visual impairments that predispose to the development of this condition, including the role of contrast sensitivity. A final area that should be studied more is the relationship of brain disease to Charles Bonnet syndrome. The neuroimaging findings in this study raise the possibility of there being a relationship to cerebrovascular disease; and if this was confirmed, de Morsier’s belief that Charles Bonnet syndrome had its origins in the brain, and not the eye, would find further support. I will consider this matter in more detail in part III of this thesis.
Part III

Voxel-Based Morphometry Imaging Study
9. Imaging Study: Introduction

9.1 Introduction

Part III of this thesis describes the development, execution and results of a study using voxel-based morphometry analysis (VBM) of magnetic resonance imaging scans (MRI) to investigate whether there are structural differences between the brains of people with a diagnosis of Charles Bonnet syndrome and controls matched for age and visual impairment. This chapter explores the existing literature on the relationship between Charles Bonnet syndrome and abnormal neurology, and establishes the case for conducting the study that the remainder of this thesis describes.

In chapter 9.2, I set out the existing literature, mostly in the form of case reports, which links CBS to a range of neurological disorders. Chapter 9.3 summarises the current literature on neuroimaging studies in CBS, which is again mostly in the form of case reports, but does include three small studies. These made use of structural MRI, functional MRI and SPECT, but taken along with the case reports, do not establish a consistent pattern of abnormal findings; while the occipital cortex is often found to be abnormal, a range of other areas including the thalamus, basal ganglia, cerebellum, temporal lobe, and parietal lobe, have been found to be abnormal in some studies.

Given the lack of clarity around the interrelationships between disorders where visual hallucinations occur, and the suspicions described in part II of this thesis, that in
some cases CBS may represent the onset of dementia, the literature relating to neuroimaging in other visual hallucinatory disorders is reviewed in chapter 9.4. The findings from these studies are again rather heterogeneous, with abnormalities demonstrated in a range of locations. These include the sites already noted in chapter 9.3, with the addition of the frontal lobe.

Chapter 9.5 explores a number of theories which attempt to set visual hallucinations caused by a range of conditions within a single, overarching framework. Differences between these frameworks over how they would classify Charles Bonnet syndrome, and the implications for the potential presence of an underlying brain abnormality in the condition, are discussed in this section.

In section 9.6, the technique of voxel-based morphometry is introduced, and its capabilities and limitations are discussed. Chapter 9.7 acts a summary, and sets out the grounds for applying the VBM technique to Charles Bonnet syndrome.

9.2 Underlying brain abnormalities and Charles Bonnet syndrome

In 1967, the originator of the diagnosis of Charles Bonnet syndrome, Georges de Morsier, published a paper on the subject (de Morsier 1967), in which he restated his position on the aetiology of the condition he first described 31 years earlier. In the intervening years, the condition he first described had been redefined from indicating visual hallucinations in elderly people with intact cognition, to visual hallucinations in eye disease (Hecaen and Badaracco, 1956; Burgermeister et al. 1965). Far from
being related to eye disease, de Morsier contended that Charles Bonnet syndrome always had as its cause underlying disease of the brain. He based that view on a case series where 5/18 patients with the condition had normal visual functioning. While subsequent research (Teunisse et al. 1995, Khan et al. 2008) has confirmed that there is a relationship between impaired visual acuity and Charles Bonnet syndrome, it remains the case that the majority of people with significant visual impairment will not develop symptoms of the condition. This objection to the primacy of eye disease in the aetiology of visual hallucinations was raised by Terson (1930). If the underlying abnormality causing Charles Bonnet syndrome is not to be found in the eye, then de Morsier may be correct, and the brain is its likely location. This possibility has been investigated by a number of authors, using a range of investigative techniques, and the findings of their work are described below.

There are many case reports in the literature where the development of visual hallucinations suggestive of Charles Bonnet syndrome has been associated with a specific brain abnormality. Most of these did not make use of recognised diagnostic criteria, and many did not mention the term “Charles Bonnet syndrome”, but all made reference to formed, complex visual hallucinations developing in the absence of a clear mental or cognitive disorder. These have included occipital infarction (Brust and Behrens 1977, Benson and Rennie 1989, Ashwin and Tsaloumas 2007, Chen and Liu 2011), cerebellar infarction (Nguyen et al. 2011), occipital resection (Choi et al. 2005), cardiac arrest leading to cortical blindness (Wunderlich et al. 2009), multiple sclerosis (Chen et al. 2001, Alao and Hanrahan 2003, Komeima et al. 2005), temperoparietal trauma (Rousseaux et al. 1994), and pituitary adenoma (Ram et al. 1987).
There is also one cross sectional study (Vaphiaides et al. 1996) which looked at 32 patients with ischaemic infarction of retrochiasmatic pathways, and found complex visual hallucinations in 9 of them. The study included brain CT or MRI for all participants, and found that positive spontaneous visual phenomena did not occur when the infarct destroyed the visual association areas. This suggests two components to the development of the experiences, with both damage to the afferent tracts or visual cortex and adequate functioning visual accessory cortex being required to generate symptoms.

9.3 Neuroimaging in Charles Bonnet syndrome

Many case reports have also commented on the findings of neuroimaging tests, and findings of atrophy or small vessel cerebrovascular disease are common. However, the significance of these findings is difficult to interpret, as they were largely carried out to clinical protocols, and interpreted as part of the clinical management of the patient, rather than with reference to research criteria. Moreover, given the advanced age of very many of the cases, involutional change from normal aging, or clinically non-significant minor ischaemic changes will be very common. As a result, for the most part they are not described further here, with a few exceptions which are set out in more detail below.

Ball (1991) described three cases of CBS where CT scanning was undertaken. In one case, there was only the evidence of a previous operation on the pituitary gland, and some mild atrophy. The other two cases had significant amounts of cerebrovascular disease, particularly affecting the cerebellum. Teunisse et al. (1994)
set out to evaluate the characteristics of people presenting with Charles Bonnet syndrome. They did not carry out imaging as part of the study protocol, but did seek to obtain the clinical report of any scan which had been done as part of the patient’s routine care. Of the 14 participants, nine did undergo CT scanning, and this was reported as abnormal in eight cases. The nature of these abnormalities was not further described.

A further six studies have used Single Photon Emission Computed Tomography (SPECT) in addition to structural imaging to investigate the nature of any underlying brain disease in patients with Charles Bonnet syndrome. Adachi et al. (1994) reported the case of an 86 year old lady who underwent MRI, showing temporal lobe atrophy, in addition to SPECT. The SPECT showed hyperperfusion in the left temporal region and basal ganglia, and hypoperfusion in the right temporal region. Guerra-Garcia (1997) described an 83 year old patient with CBS, who had a normal CT head, but a SPECT which demonstrated decreased perfusion in the left mid parietal region and in the occipital lobe. Kishi et al. (2000) report the case of a 73 year old woman who had mild occipital atrophy on MRI scanning of her brain, but marked occipital hypoperfusion on SPECT. Saiz and Diaz (2003), describe an 81 year old lady, who had symptoms consistent with Charles Bonnet syndrome, and who underwent SPECT; this was reported as being within normal limits. Kazui et al. (2009) present two cases, a 76 year old woman and a 65 year old man; the second of these had a normal MRI brain. Both patients showed reduced perfusion of the occipital cortex, in Brodmann's areas 17 and 18. Finally Gil Navarro et al. (2011) report a case of a patient diagnosed with CBS who went on to develop Lewy body dementia after two years. The patient was a 78 year old male, who underwent SPECT at time of CBS diagnosis, which demonstrated severely reduced perfusion in the posterior cortex.
In addition to these six papers, Kazui et al. (2009) also report the findings of two papers from outside the English or Spanish language literature. Sichart and Fuchs (1992) reported on an 81 year old woman with Charles Bonnet syndrome who underwent SPECT which showed reduced cortical blood flow in the left occipital lobe. Kanzaki (1998) described the case of a 71 year old patient who had a normal MRI brain, but reduced cerebral blood flow bilaterally in Brodmann's areas 17 and 18.

In addition to these case reports reporting SPECT findings, there is one report of the use of positron emission tomography in association with statistical parametric mapping (PET-SPM) to investigate Charles Bonnet syndrome (Jang et al. 2011). The authors carried out PET scanning on a 69 year old man with CBS, and compared the findings to 19 controls. Previous MRI brain had shown lacunar infarcts in both basal ganglia, and the PET-SPM found hypermetabolism in the right inferior temporal area and left thalamus. Interestingly, the patient was treated with valproic acid, and following this the areas of hypermetabolism returned to normal in a subsequent scan.

In addition to the case reports described above, there are three studies in the literature which made use neuroimaging to investigate the potential underlying neurological correlates of Charles Bonnet syndrome. The first of these was Shedlack et al. (1994), which used MRI scanning and a case/control methodology. Five participants with CBS and 12 healthy controls underwent MRI scanning, and the presence and severity of small vessel cerebrovascular disease, as inferred by the presence of periventricular and deep white matter hyperintensities on T2-weighted images, was quantified using a version of the Fazekas scale (Fazekas et al. 1987). While total number of white matter hyperintensities was not significantly different
across the groups, the difference total lesion size posteriorly was highly significant (p=0.004). The authors concluded that structural abnormalities in the area of the primary visual pathways may disrupt these pathways and lead to the development of the symptoms seen in Charles Bonnet syndrome.

The second study made use of fMRI to investigate Charles Bonnet syndrome (ffytche et al. 1998). In this study, conducted on six participants with a diagnosis of Charles Bonnet syndrome, patient underwent fMRI and indicated when visual hallucinations occurred during the scanning procedure. Four participants actually experienced hallucinations during scanning, and these participants showed fMRI activity in the ventral occipital lobe (Brodmann area 37, the fusiform gyrus- part of the visual accessory cortex). Moreover, the precise location of the activity in BA37 was found to correlate well with nature of the hallucinations described, and to be consistent with the known functional organisation of this region.

The third study used both MRI and SPECT to investigate the brains of five participants who were diagnosed as having Charles Bonnet syndrome (Adachi et al. 2000). The authors reported increased perfusion in the temporal lobe, striatum and thalamus of all five participants on SPECT. There was also evidence of atrophy in 3/5 participants, occipitally in all three, and in the temporal and parietal lobes in two of the three.

Thus there have been a number of published papers reporting the results of neuroimaging investigations conducted on participants experiencing Charles Bonnet syndrome. However, with the exception of Shedlack et al. (1994), ffytche et al.
(1998), and Adachi et al. (2000) these have consisted only of case reports, and their findings have been inconsistent. The commonest finding in these case reports is occipital hypoperfusion, sometimes unilateral, more often bilateral. However, normal occipital perfusion, but with reduced parietal or temporal, or even increased temporal perfusion has also been seen. In total these represent only eight case reports, in a 20 year period. None of these findings are in alignment with the studies that exist in this field; neither ffyche et al. (1998), where increased activity of the fusiform gyrus was reported as potentially important in generating the hallucinations, nor Shedlack et al. (1994), which focussed on white matter changes rather than grey matter, nor Adachi et al. (2000) where there was normal occipital perfusion but increased perfusion in the temporal lobe, striatum and thalamus. Even the three studies have methodological shortcomings, all having small sample sizes, and over 13 years later all await repetition to see if the findings are confirmed by other authors.

9.4 Imaging in other conditions associated with visual hallucinations

There are some other studies which have investigated the underlying neurological basis of visual hallucinations, though not specifically in a Charles Bonnet population. Shin et al. (2012) carried out a voxel-based morphometry analysis using MRI scans on 110 patients with Parkinson’s disease, but without dementia. They found that PD patients with visual hallucinations had significantly lower grey matter volume in the frontal, temporal, cerebellar and thalamic areas, and in the substantia innominata compared to those without. Sanchez-Castaneda et al. (2010) used MRI-VBM to investigate patients with Lewy body dementia and Parkinson’s disease dementia. They found visual hallucinations in 6/12 participants with LBD, and in 7/15 patients with PDD. There was more frontal grey matter atrophy in participants with visual
hallucinations, and this grey matter loss was more evident in the LBD group. Lin et al. (2006) investigated patients with Alzheimer’s disease both with and without visual hallucinations. They found that those with VH has more occipital periventricular white matter hyperintensities, suggestive of ischaemic change, but that occipital deep white matter hyperintensities were absent in both groups. These findings echo those of Shedlack et al. (1994) above, from a cohort with Charles Bonnet syndrome.

Holroyd and Wooten (2006) made use of fMRI to investigate patients with Parkinson’s disease, some of whom experienced visual hallucinations. Participants with visual hallucinations showed decreased activation in the primary visual cortex and increased activation in the visual association cortex when compared to those who did not hallucinate.

Finally, Miyazawa et al. (2010) used positron emission tomography (PET) to investigate Lewy body dementia. They found evidence of hypermetabolism in the cerebellum, peri-motor area and basal ganglia, in a cohort of 22 participants with the condition. Hypermetabolism was most common in the cerebellum, seen in 18/22 participants, and in 11/22 hypermetabolism was seen in all three areas. Among those with increased metabolism in all three areas, visual hallucinations were very significantly more frequently observed (p=0.0018).
9.5 Theories of the Neuroanatomy of Visual Hallucinations

In psychiatry, phenomenology stresses the differences in the nature of perceptual experiences such as illusions, hallucinations, pseudohallucinations, and true percepts. However, the work of ffytche et al. (1998) challenged these demarcations, by demonstrating that activation of the brain during hallucinations took place in the same brain regions that were activated by similar true perceptions. Similarly, activation of visual area of the brain has been detected in REM sleep (Braun et al. 1997). These perceptual experiences, along with illusions, are held by ffytche (2007) to be neurophenomenologically related, and separate from visual imagery, where the activations have been found in the frontal and parietal lobes (Ganis et al. 2004).

ffytche (2007) developed a framework to classify visual perceptual experiences using a three dimensional framework, where the sense of agency, the vividness of the percept, and its locus were the dimensions against which the percept was assessed. This placed true percepts and hallucinations, with or without insight, in the same class, related not only by their place in this dimensional approach, but also by the underlying brain activity.

ffytche (2007) went on to distinguish between different hallucinatory syndromes which he argued had different underlying causes. He theorised that they could be distinguished by an assessment of the content of the hallucinations, and divided into three categories. These were hallucinations due to de-afferentation, leading to ‘true’ Charles Bonnet syndrome; due to dysfunction in cholinergic transmission systems, as a result of Lewy body diseases, Alzheimer’s disease or peduncular lesions (Perry...
and Perry 1995); and related to the serotonergic system, for example in LSD flashbacks. ffytche acknowledged that the deafferentation hypothesis alone is not sufficient to account for the emergence of Charles Bonnet syndrome-type hallucinations, as the majority of people with significantly impaired vision do not suffer from this condition; and that these ‘prototypical’ and distinct syndromes are often not as clear-cut in reality, with Lilliputian figures and metamorphopsia, classically part of the deafferentation syndrome, also occurring in visual hallucinations in dementia.

Manford and Andermann (1998), in their review of visual hallucinatory disorders discussed in more detail the potential role of the thalamus, and also the role of ascending cholinergic and serotonergic pathways from midbrain structures in generating these experiences. This role for ascending pathways to modulate activity in the retinogeniculocalcarine tract was also discussed by Mocellin et al. (2006) in their paper on the neuropsychiatric basis of complex visual hallucinations. In this work they set out details of three cases who experienced visual hallucinations which were phenomenologically similar, but had different underlying causes, namely deafferentation and diffuse cerebrovascular disease, a thalamic infarct, and temporal lobe epilepsy.

Collerton et al. (2005) presented a model of visual hallucinations which they called the perception and attention deficit model. In this model, afferent information from the eye is relayed via the retinogeniculocalcarine tracts, with inputs in the thalamus from ascending fibres from the midbrain, and the brain looks for a ‘best fit’ with prototypical objects stored in the visual accessory cortex. If the afferent information is of low quality, or the brain’s level of arousal or ability to sustain attention are reduced, then
a mismatch between the afferent input and the proto-object is more likely to take place and is experienced as an abnormal percept. The greater the difference between the percept seen and what would be expected given the context, the more likely it will be experienced as a hallucination. In this model, both visual and brain abnormalities have a role to play in the development of hallucinations, with the balance between the two factors being different in different conditions; the underlying processes by which the hallucinations emerge is common to all conditions.

ffytche (2005, in reply to Collerton et al.) criticised this model as failing to account for the difference in content of hallucinations that his work suggested, using the vivid metaphor of a ‘Procrustean bed’ to convey his belief that the model of Collerton et al. forced together phenomenologically distinct experiences. Collerton et al. responded by suggesting that there is a distinction between simple hallucinations in eye disease, which may be due purely to deficits in afferent information, and complex hallucinations which they argued must have some degree of brain abnormality, even if deafferentation has a role to play. Echoing ffytche’s evocative language, they described themselves as ‘parsimonious lumpers’, believing that all recurrent, complex visual hallucinations have a common cause.

The evidence presented that suggests that there are likely to be different causes of complex visual hallucinations, even within one person, with combinations of abnormalities in the eye, visual afferent tracts, ascending midbrain tracts, the primary visual cortex and accessory visual cortex all playing a role. While there may theoretically be differences in the content of visual hallucinations depending on where the most important abnormality is found, this is not always the case in practice, with different causes sharing similar clinical presentations. The work of
ffychte suggests that whatever the underlying cause of the abnormal perception, there may be a final common pathway, which is activation of the specialist visual cortex related to the nature of the percept being experienced; and that of Collerton et al. raises the possibility that all conditions that cause complex visual hallucinations share a common explanatory framework.

Given that Charles Bonnet syndrome, as defined by Teunisse et al. (1996) makes no reference to aetiology, it is likely that this diagnostic group will include cases where there are underlying abnormalities in a wide range of brain regions across the system of visual tracts and ascending inputs described above, and potentially beyond. This is supported by the imaging studies described in 9.3 above. Moreover, since a person developing dementia who presented with complex visual hallucinations in advance of clinically significant cognitive impairment would be likely to attract a diagnosis of Charles Bonnet syndrome in the first instance, the location of the abnormalities seen in the studies described in 9.4 are of interest to this work too. Overall, a wide range of possible locations of an underlying brain abnormality in Charles Bonnet syndrome would need to be borne in mind when designing any study to investigate this condition with neuroimaging techniques.

9.6 Voxel Based Morphometry

There have been attempts to quantify differences between structuring imaging scans using volumetric methods for many years. These were initially done by identifying regions of interest (ROIs) from the existing literature, and which were delineated by hand from scans by the operator. However, this process was imprecise, of uncertain
anatomic validity, and limited in power. The process of statistical parametric mapping (SPM) was developed in the late 1980s, with key aspects of the methodology and conceptual underpinning being set out by Friston et al. (1990), and Friston et al. (1991). SPM relies on making voxel-based statistical inferences across the volume of the brain, and opened up the possibility of making inferences about structural differences between groups without knowing in advance where there differences would be found. This was initially applied to positron emission tomography, with the methodology being subsequently adapted for use in structural MRI imaging modalities (Wright et al. 1995), and then further developed by Ashburner and Friston (2000). There have been criticisms of this approach (Bookstein, 2001), that findings of the technique may be simply down to imperfect registration of images. These were responded to by the team developing the technique (Asburner and Friston 2001), with subsequent developments and refinements set out by Mechelli et al. (2005) and summarised by Whitwell (2009).

In essence, the VBM technique sets out to detect differences in brain tissue composition on a small scale, while controlling for larger scale differences resulting from gross anatomy or positioning. The process involves a number of steps of pre-processing of the images. These are, in sequence, registering structural MR images to a standard template; segmenting the images into grey matter, white matter and cerebrospinal fluid; modulating the images so that the relationship between the volume of grey matter represented by any given voxel is maintained after the registration step; and then smoothing the images to compensate for any inaccuracies in the registration process and render the data more normally distributed. Statistical testing is then done, carrying out a series of t-tests at the level of every voxel to see if it meets the chosen threshold for significance. Statistical testing can also be performed at the level of clusters of voxels identified as significant, though this testing
needs to have a statistical correction applied to avoid detecting false positives due to multiple comparisons.

VBM techniques have been used widely to detect structural changes in the brains of people suffering from a range of conditions, including Parkinson’s disease (Price et al. 2004), Huntington’s disease (Thieben et al. 2002), Alzheimer’s disease (Karas et al. 2004), and frontotemporal dementia (Gorno-Tempini et al. 2004). While comparing results of different VBM studies is difficult due to a lack of methodological standardisation, there have been studies which have compared findings of VBM analysis with results obtained by manual volumetric analysis of structures in dementia (Good et al. 2002, Whitwell et al. 2005). These have shown relatively good correspondence suggesting that there is an underlying biological validity to the technique.

9.7 Summary

There appears to be a significant body of evidence that supports in part de Morsier’s contention that the primary abnormality in Charles Bonnet syndrome is in the brain. There are a substantial number of case reports and one study where a relationship to underlying brain disease is suggested. There are also a number of imaging studies suggesting links to posterior periventricular white matter ischaemic change, to reduced activity in the occipital and temporal cortex, and to increased activity in the fusiform gyrus, temporal lobe and thalamus. Further imaging studies, with larger numbers of participants, and using more powerful analytic techniques, have been carried out in Parkinson’s disease, Lewy body dementia and Alzheimer’s disease.
These have found associations between visual hallucinations and abnormalities in a number of brain areas, including the frontal, temporal, occipital lobes, and the cerebellum.

There would therefore seem to be potential in applying these more powerful techniques, such as MRI-VBM, to Charles Bonnet syndrome, in a study that recruits sufficient numbers of participants, to try to determine whether the abnormalities suggested by the case report literature can be confirmed and more precisely defined. This is the goal of the work described in chapters 10-13 below.
10. Imaging Study: Methods

10.1 Introduction and summary

In this chapter the design and methods of the neuroimaging study are set out. Chapter 10.2 describes the arrangements for participant recruitment, and chapter 10.3 set out the technical data related to the MRI scan acquisition. Chapter 10.4 details the protocol followed to conduct the VBM analysis, and chapter 10.5 describes the arrangements for statistical testing, including setting up regions of interest in case region of interest analysis was to be undertaken. Finally, chapter 10.6 describes the processes to be applied in order to display any results obtained.

10.2 Recruitment of participants

Participants were recruited from the low vision clinic and glaucoma assessment clinic at the Manchester Royal Eye hospital between April 2010 and June 2012. The details of the recruitment process are set out in chapter five, and included the administration of the four-point screening section of the North East Visual Hallucination Interview (Mosimann et al. 2008). Participants screening positive were invited to an interview with a member of the study team, and informed consent was sought. If they agreed to participate in the study, the remainder of the NEVHI was administered and clinical history was taken, in order to confirm the diagnosis of Charles Bonnet syndrome, in reference to the Teunisse criteria. A control group of attenders at the same clinics was also recruited.
Participants were seen by an experienced old age psychiatrist, and the protocol of assessments described in the clinical cohort study in chapters 5.3 and 5.4 was carried out. This included the NEVHI, a clinical assessment including neurological and mental state examinations, the Addenbrooke’s cognitive assessment (ACE-R), the 18 item brief psychiatric rating scale (BPRS), and the short form of the informant questionnaire for cognitive decline in the elderly (IQCQDE). In addition participants were invited to attend an assessment at the Manchester Royal eye hospital (MREH), where an optometrist examined them to determine a range of visual parameters including ophthalmological diagnosis, visual acuity, contrast sensitivity and scotoma presence, as described in chapter 5.5 in part II.

10.3 MRI Scan Acquisition

Participants were invited to attend the Wellcome Trust Clinical Research Facility to undergo an MRI brain scan. Scanning took place using a Philips Achieva 1.5T MR scanner (Philips Healthcare, Best, The Netherlands). The pulse sequence was a T1-weighted Inversion-Recovery 3D TFE (Turbo Field Echo) sequence, TR = 9 ms, TE = 4.2 ms, and inversion delay = 858 ms. Field of View was 224x224x160 mm, giving 160 slices of thickness 1 mm; acquired in-plane resolution was 1x1 mm, which was then interpolated to 0.88x0.88 mm. The same standard head positioning was used throughout all scans, with participants aligned parallel to the ac-pc line.
The images obtained from the scanner were in PAR/REC format. MRicro
(http://www.mccauslandcenter.sc.edu/micro/micro/micro.html) was used to convert
these into hdr/img format. Data was analysed with Matlab, using the VBM8 toolbox
(http://dbm.neuro.uni-jena.de/vbm) in SPM8 and applying the optimised VBM
The VBM8 manual developed by the Structural Brain Mapping Group of the
Departments of Psychiatry and Neurology at the University of Jena
(http://dbm.neuro.uni-jena.de/vbm8/VBM8-Manual.pdf) was used as a reference to
inform the process.

Images were visually inspected for artefacts, including motion and high levels of
inhomogeneities, and to ensure they were in the correct orientation. Images were
then processed using the ‘estimate and write’ function of the VBM8 toolbox. In this
function, images were normalised to the MNI template space using the diffeomorphic
anatomical registration using exponentiated lie algebra (DARTEL) technique
developed by Ashburner (2007). The images were also segmented into grey matter,
white matter and cerebrospinal fluid. The VBM8 toolbox is able to carry out this
segmentation making reference to the ICBM tissue probabilistic atlases (Mazziotta
and Toga, http://www.loni.ucla.edu/ICBM/ICBM_TissueProb.html). The images were
then subject to modulation using the Jacobian determinants of the spatial
normalisation step, in order to preserve the relationship between the amount of grey
matter in each brain region after the distortion applied by normalisation. Modulation
was conducted for non-linear effects only, correcting for global brain size and
removing the need to calculate total intracranial volume. VBM8 uses a generative
model, where the steps of segmentation and normalisation are cycled through repeatedly until optimal criteria for these functions are met.

After applying these processes to original, non-segmented T1-weighted images, the spatially normalized images were resampled with a cubic voxel size of 1 by 1 by 1 mm$^3$, with an extended bounding box, which included the whole cerebellum and lower parts of the brainstem. The images were then segmented into grey matter and white matter for a second time, with the grey matter tissue probability maps being taken forward to the next stage of the analysis.

A quality check was performed, both by visually inspecting the output from these steps, and checking sample homogeneity using covariance.

Images were then smoothed using a full width at half maximum (FWHM) = 12mm isotropic Gaussian kernel, and a further image quality check was applied. In this step, each voxel becomes a weighted average of the surrounding ones. The visual effect of the step is that the images become ‘blurred’. By applying this step, the data become more normally distributed, making subsequent statistical analysis more powerful, and inaccuracies in the normalisation step are reduced.

The processes described were applied to the T1-weighted images to analyse grey matter. Following this, the same processes were then conducted to analyse white matter.
10.5 VBM Analysis: Statistical Testing

Statistical analysis was carried out using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/), defining a model comparing the Charles Bonnet group and the control group and carrying out t tests using the following comparisons, for both grey and white matter:

- ‘Charles Bonnet group minus control group’ (CBS minus CTL): tests for there being an increase in volume of grey/white matter in the Charles Bonnet group
- ‘Control group minus Charles Bonnet group’ (CTL minus CBS): tests for there being reduced grey/white matter in the Charles Bonnet group.

A threshold p value of 0.005 was set, with a voxel extent threshold of 10. Clusters identified where there were differences between the groups were examined to see if they met the criteria for statistical significance after false discovery rate correction (FDR) (q <0.05) at cluster level (Genovese et al. 2001). This is a way of dealing with the multiple comparison problem; the VBM analysis carries out tens of thousands of comparisons, so with a p=0.05, there may be thousands of voxels that give a false positive result. There are two widely used methods to control for this. The Bonferroni method involves a family-wise error correction (FWE), but this has been criticised for being overly strict and having a high false negative rate. The false discovery rate (FDR) developed by Genovese et al. (2001), and further developed by Chumbley and Friston (2009), is reported to be a more sensitive method of carrying out multiple comparison correction, as it includes a further correction for the expected number of true positive voxels that are falsely rejected, and so is preferred to the FWE correction in this work.
In the event of no clusters reaching statistical significance, region of interest analysis would be applied. Regions of interest were created using the automated anatomic labelling (AAL) atlas (Tzourio-Mazoyer et al. 2002) of the wfu_pickatlas toolbox (Maldjian et al. 2003, Maldjian et al. 2004). This included regions and structures previously associated with visual hallucinations in the literature. In total, seven regions of interest were identified from the review of the literature described in chapter 9.

Regions were identified as brain structures or regions which had been associated with abnormal findings on neuroimaging in at least one case report or study. Articles where neuroimaging in Charles Bonnet syndrome was conducted were included, but as described above, there were only three relevant studies in this group of patients, with the other papers reporting only 1-2 cases each. As a result, papers where abnormal findings on neuroimaging associated with visual hallucinations in other conditions were also included in defining the regions of interest. Papers reporting work carried out in Lewy body dementia were felt to be particularly relevant, given the hypothesis tested in part II of this thesis, that a proportion of those diagnosed with CBS may actually be in the early stages of this condition. The work of Collerton et al. (2005) and ffytche (2007) was also relevant to this decision, suggesting, respectively, a possible common cause for all recurrent complex visual hallucination syndromes, and a common process in the visual accessory cortex by which the precepts were generated.

In general, these regions of interest include structures and regions known to be involved in visual processing, including the primary visual cortex, the accessory
visual cortex in the temporal and parietal lobes, the visual white matter tracts, and the lateral geniculate nucleus of the thalamus. They also include some regions not obviously connected to visual functioning, but nonetheless implicated by previous research. The regions of interest and the evidence that supports their inclusion are set out below in table 27.

Table 27: Regions of interest for MRI analysis

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>References</th>
<th>AAL atlas regions used to define ROI (all bilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Occipital</td>
<td>Sichert and Fuchs (1992); Shedlack et al. (1994); Guerra-Garcia (1997); Kanzaki et al. (1998); Adachi et al. (2000); Kishi et al. (2000); Holroyd and Wooten (2006); Kazui et al. (2009); Gil Navarro et al. (2011)</td>
<td>Superior, middle, inferior occipital</td>
</tr>
<tr>
<td>2. Fusiform gyrus</td>
<td>ffytcche et al. 1998</td>
<td>Fusiform</td>
</tr>
<tr>
<td>3. Basal ganglia and thalamus</td>
<td>Adachi et al. (1994); Adachi et al. (2000); Miyazawa et al. (2010); Jang et al. 2011; Shin et al. (2012)</td>
<td>Caudate, putamen, pallidum, thalamus</td>
</tr>
<tr>
<td>4. Cerebellum</td>
<td>Ball (1991); Miyazawa et al. (2010); Shin et al. (2012)</td>
<td>All cerebellar regions (26 in total)</td>
</tr>
<tr>
<td>5. Orbital frontal lobe</td>
<td>Sanchez-Castaneda et al. (2010); Shin et al. (2012)</td>
<td>Frontal superior, middle and inferior orbital</td>
</tr>
<tr>
<td>6. Inferior temporal lobe</td>
<td>Adachi et al. (1994); Adachi et al. (2000); Jang et al. 2011; Shin et al. (2012)</td>
<td>Middle and inferior temporal</td>
</tr>
</tbody>
</table>
In the ROI analysis, statistical testing was carried out using t test as before, and clusters examined to see if any achieved statistical significance after FDR correction at cluster level had been applied.

A non-stationary correction was applied to any clusters from the whole-brain or region of interest analysis which were demonstrated to be statistically significant. This was carried out using the ns toolbox version 0.76 beta for spm8 (Worsley et al. 1999, Hayasaka et al. 2004). This analysis addresses methodological concerns over cluster size analysis. The concerns are that cluster sizes tend to be large in ‘smooth’ areas of the brain, which can result in false positive results being generated.

10.6 VBM Analysis: Displaying Results

Data for any clusters that survived the non-stationary correction, either at whole-brain or region of interest analysis, were reported on. Copies of the output images from the t-tests, and the tabulated statistical output that accompanies this, were saved and exported. Coordinates of clusters were reported in Montreal Neurological Institute (MNI) standard space. A copy of the thresholded t-map was also saved in hdr format and exported. MRICron (http://www.mccauslandcenter.sc.edu/mricro/mricron/, Rorden and Brett, 2000) was used to display the thresholded t-map mask overlaid on the ch2.bet template, to display any significant clusters.
11. Imaging Study: Results

11.1 Introduction and Summary

The findings of the study are set out in this chapter. Sections 11.2 to 11.7 describe the findings in relation to a range of aspects of the participants, including their demographics, visual functioning and cognitive assessments. Sections 11.8 and 11.9 then set out the findings of the voxel-based morphometry (VBM) analysis.

In section 11.2, the demographic characteristics of the 11 participants and 11 controls are described. The imbalance in gender seen in part II persisted, but again the ages were comparable. This was unsurprising as all but three of the participants in this study were also in the clinical cohort study described in part II of this thesis. Sections 11.3 and 11.4 detail the findings of the clinical assessment and brief psychiatric rating scale (BPRS) that all participants underwent; these assessments confirmed the diagnosis of Charles Bonnet syndrome using the Teunisse et al. (1996) criteria, and excluded the presence of any relevant medical or psychiatric conditions.

Section 11.5 provides details of the content of the visual hallucinations experienced, and again notes the frequency and persistence of these phenomena, with 8/11 participants reporting the hallucinations had been present for over a year, and all reporting that they occurred at least weekly. Section 11.6 describes the performance of participants on the visual assessments, and as in the cohort study in part II, finds a significant difference in the visual acuity of CBS participants and controls. However,
even the controls had clinically relevant deficits in visual acuity, and both groups had severe impairments in contrast sensitivity, and almost universal presence of retinal abnormalities as evidenced by scotoma or image distortion. When all three dimensions of visual functioning were considered, all participants showed clinically relevant impairments.

Chapter 11.7 presents the findings relating to cognitive impairment. No participant was found to have dementia, and the performance on the ACE-R and IQCODE was comparable in both participants with CBS and controls.

Chapter 11.8 presents the findings of the VBM analysis of grey matter. This did not find evidence of atrophy in any brain region, which was somewhat unexpected given the frequent reports of occipital hypoperfusion in functioning imaging studies. However, there was evidence of increased grey matter volume in the right posterior parietal lobe and in the cerebellum, though these findings did not retain statistical significance when whole brain comparison corrections were applied. Region of interest analysis was performed using the regions of interest defined in chapter 10.4, and the cerebellar clusters were found to be statistically significant even when corrections for multiple analyses were applied. In order to control for the effects of potential confounders, data relating to the cerebellar clusters from each individual scan was extracted and analysis of covariance (ANCOVA) was conducted. One of the clusters retained statistical significance even after this more stringent analysis, and so this study provides robust evidence for an increase in grey matter volume in the posterior lobe of the right cerebellar hemisphere in people with Charles Bonnet syndrome.
Chapter 11.9 presents the findings of the VBM analysis of white matter. This was less conclusive, with evidence of clusters of voxels suggesting reduced white matter volume in the posterior parietal and temporal lobes. However, these did not achieve statistical significance on whole brain analysis, or on region of interest analysis, when corrections for multiple comparisons were applied.

11.2 Demographics

A total of 11 participants with Charles Bonnet syndrome, and 11 controls, were recruited and successfully underwent MRI scanning. The 11 controls included the 10 who participated in the study of cognitive functioning described previously, and one more person who died before the follow up assessment was carried out and was therefore not included in that part of the study. The Charles Bonnet syndrome participants included nine who took part in the cognitive assessment component of the study, and two others who completed the first part of this but did not undergo the follow up assessment.

The mean age of Charles Bonnet syndrome participants was 78.8 (range 65-90). The mean age of controls was 81.7 (range 72-91). The gender distribution was unequal, with 2/11 of the CBS participants being male, while 9/11 controls were male. Ethnicity was similar, with 10/11 CBS participants having white British ethnicity compared to 10/11 controls.
11.3 Findings of history taking and examination

All participants underwent an interview with an experienced old age psychiatrist as part of the protocol. All participants had a range of medical diagnoses, as would be expected for a cohort of this age. No participants were felt to be medically unstable, nor were their diagnoses felt to be responsible for the presence of hallucinations. As set out in chapter 6.4, five of those with Charles Bonnet syndrome had a positive psychiatric history, three with depression, one with an anxiety disorder and one with an adjustment reaction. However, none felt that they were experiencing current symptoms related to these conditions, and none had ever been referred to secondary care mental health services. None were on medication that was felt could be contributing to the hallucinations, such as dopamine agonists or narcotic analgesics. As previously described, four CBS participants had minor abnormalities on neurological examination: in three cases a tremor, one accompanied by reduced arm swing when walking, and in one, peripheral neuropathy.

The mental state examinations of the three additional participants were unremarkable. None of the additional participants reported increased forgetfulness, and none of the informants raised concerns over significant problems with cognitive functioning. None of the participants met diagnostic criteria for dementia during the initial interview, nor were any diagnosed with other exclusion conditions, such as Parkinson’s disease, alcohol dependency, delirium, psychosis or significant depression.
11.4 Brief psychiatric rating scale (BPRS) scores

The participants also underwent the BPRS as a means of objectively quantifying their level of psychiatric morbidity, and so help provide evidence that the hallucinations the Charles Bonnet syndrome participants experienced were not due to a psychiatric disorder. As noted in chapter 5.4, a modified version of the 18 item BPRS was used, with the item relating to hallucinations excluded. The results of this, for the 22 participants included in the MRI scanning component of the study are set out in table 28.

Table 28: BPRS scores in VBM study

<table>
<thead>
<tr>
<th></th>
<th>Minimum BPRS score</th>
<th>Maximum BPRS score</th>
<th>Mean BPRS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS Participants</td>
<td>18</td>
<td>29</td>
<td>22.4</td>
</tr>
<tr>
<td>Controls</td>
<td>17</td>
<td>27</td>
<td>19.6</td>
</tr>
</tbody>
</table>

The mean score on the modified BPRS was a little higher in the CBS participants. However, the difference between the groups, of around 3 points on a scale scored out of 119, is unlikely to be clinically significant, and overall these generally low scores on the BPRS support the evidence from history taking and mental state examination that none of the participants had a recognisable mental disorder which was relevant to their presentation.
11.5 Characteristics of Visual hallucinations

The visual hallucinations experienced by the Charles Bonnet syndrome participants were characterised in detail, and the participants descriptions of their experiences were set out in table 10 in chapter 6.6. The details of the experiences of the two CBS participants who did not take part in the longitudinal part of the study are shown in table 29 below.

Table 29: Content of visual hallucinations in VBM study

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>017</td>
<td>77, F</td>
<td>Sees small people, with egg shaped faces, with the left hand side of their face “ripped away”. Saw a dog running away over her sofa and TV. Saw birds and other animals, a leather mantelpiece on the side of the room, and a door with a lady behind it</td>
</tr>
<tr>
<td>019</td>
<td>70, F</td>
<td>Has seen people in her garden with dark clothing; when she has gone out to look, there is no-one present. She never sees their faces. ‘Shadows’ of people walk past her when she is sat in the living room. At times everything is ‘foggy’ as if the room is full of smoke. Once when watching television, a figure on the screen stopped, turned his head and waved directly to her. Has seen cats and birds in her garden which she was aware were not really present. Sees her wallpaper replaced by bright red or dark yellow brick patterns. Colours seen can change in intensity, and her furniture at times looks ‘filthy’.</td>
</tr>
</tbody>
</table>

The data generated by the NEVHI included information on the duration and frequency of the visual hallucinations. Of the 11 participants who experienced these, 8 had done so for over one year by the point of recruitment. Among the remaining three, two had experienced them for less than 6 months. Five participants
experienced hallucinations daily, while six experienced them less frequently, but at least once every week.

11.6 Visual assessment

Participants underwent an assessment by optometrists in the Low Vision Clinic at Manchester Royal eye hospital who were collaborating with the study. This established the nature of any ophthalmological diagnoses that the CBS participants and controls had been diagnosed with. The assessment also set out to measure a number of parameters of visual functioning that were felt to be relevant to the development of Charles Bonnet syndrome. These were visual acuity of the better eye, contrast sensitivity and presence of scotoma, and are discussed at greater length in chapter six. The results of this are set out in tables 13a and 13b in chapter 6.7, and in table 30 below for the three additional participants.

Table 30: Visual assessment results in VBM study

<table>
<thead>
<tr>
<th>Participant code</th>
<th>Age</th>
<th>Gender</th>
<th>Ophthalmic diagnoses</th>
<th>Visual acuity R eye</th>
<th>Visual acuity L eye</th>
<th>Binocular visual acuity</th>
<th>Contrast sensitivity</th>
<th>Scotoma presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>017</td>
<td>77</td>
<td>F</td>
<td>Severe glaucoma R eye, optic disc atrophy L eye</td>
<td>1.26</td>
<td>2.00</td>
<td>1.26</td>
<td>0.15</td>
<td>n/a</td>
</tr>
<tr>
<td>019</td>
<td>70</td>
<td>F</td>
<td>Retinal detachment bilaterally, secondary to neovascular AMD</td>
<td>1.50</td>
<td>1.44</td>
<td>1.40</td>
<td>0.60</td>
<td>n/a</td>
</tr>
<tr>
<td>109</td>
<td>86</td>
<td>M</td>
<td>Diabetic macular oedema, previous cataract surgery</td>
<td>1.6</td>
<td>0.6</td>
<td>0.52</td>
<td>1.15</td>
<td>No</td>
</tr>
</tbody>
</table>
Overall, all the participants, both those with CBS and the controls, had some impairment of vision evident on the optometry assessment. As was the case with the longitudinal component of the study, the visual acuity was significantly better among the controls. The mean visual acuity for the CBS participants was logMAR 0.79 (approximately Snellen acuity 6/36), and for the controls was logMAR 0.35 (approximately Snellen 6/14). This difference was statistically significant on conducting a t-test on SPSS version 20 ($t = 2.38$ d.f. = 20 $p = 0.027$). There was a smaller difference in contrast sensitivity between the groups, with a mean score in the CBS group of 0.80, and in the controls of 1.00. This was not statistically significant on a t-test ($t = -1.006$ d.f. = 19, $p = 0.33$), and in both groups the mean contrast sensitivity indicated severe impairment.

As with the longitudinal study described in Part II, there were three controls whose visual acuity was essentially normal. However, two of these had clinically significant abnormalities in contrast sensitivity, and all three had abnormalities in visual fields testing, with either a scotoma or distortion present. Moreover, the mean visual acuity in both groups was impaired beyond the threshold identified in Teunisse et al. (1995) as being associated with an increased risk of developing visual hallucinations.

### 11.7 Cognitive testing

The participants underwent testing with the Addenbrooke’s cognitive examination (revised) (ACE-R). The mean score for participants with CBS was 86.7/100 (range 74-94), while the score for controls was 90.7/100 (range 85-97). The ACE-R allows a score on the mini-mental state examination to be derived, and these were a mean
score of 28.3/30 (range 27-30) in the CBS group, and 28.8 (27-30) in the control group. A further measure was administered, the IQCODE. This is an informant assessed scale measuring activities of daily living. A score between 1 and 5 is generated, with a score of 3 indicating no change from the previous level, and scores above 3 suggestive of deterioration. The mean scores on the IQCODE in the CBS group were 3.36 (range 1.40-4.69), which was the same as the mean for the control group (3.36, range 3.00-3.94).

11.8 Voxel-based morphometry analysis: grey matter

The VBM analysis protocol described in chapter 10.3 was followed. The image homogeneity check showed that the median covariance of the grey matter segments was 0.615, with a minimum of 0.555 and a maximum of 0.640. Five of the 22 scans had covariances which fell out with the interquartile range, and one scan (a control) was more than 2 standard deviations below the median. Following advice in the VBM-toolbox manual, this scan was visual inspected, and no obvious artefacts were found to explain the lower covariance, although the scan did look notably atrophic. Figure 2 shows one slice of the grey matter segment for each of the scans after the normalisation and segmentation process has been applied, and figure 3 shows the output of the homogeneity analysis.
Figure 2: Quality Check, one slice of each scan showing grey matter
Figure 3: Quality check, displaying covariance for each scan, white matter
T-tests were conducted using the comparisons ‘CBS minus CTL’ and ‘CTL minus CBS’, using comparisons across the whole brain. The outputs of these t tests, in the form of maximum intensity projections (also known as ‘glass brain’ figures), are shown in figure 4 below. The ‘glass brain’ figures show three projections of the brain, viewed laterally, from above, and from the front. Clusters of 10 or more voxels where a result significant to 0.005, uncorrected for multiple comparisons, was obtained on t-testing are shown as shaded areas. These clusters are located at the point where the maximum level of statistical significance was attained. The coordinates of clusters are given in MNI space. Figure 4A is the ‘glass brain’ output for the comparison ‘CBS participants minus controls’, and so indicates areas where the analysis suggests an increase in grey matter volume. Figure 4B shows the results for the opposite comparison, and so the presence of clusters of significant voxels would indicate the probability of reduced grey matter volume.

As can be seen, in 4A there are multiple clusters of voxels that attain significant on t-testing, uncorrected for multiple comparisons. These are predominantly posterior in location, in the posterior parietal/anterior occipital lobe, and in the cerebellum. This is suggestive of increased grey matter volume in these regions, but needs further analysis to correct for multiple comparisons. Figure 4B, showing the results of the comparison ‘Controls minus CBS participants’, showed no clusters of 10 or more voxels which attained statistical significance on t-testing. This means that there was no evidence of loss of grey matter volume in the CBS participants at any site in the brain.

In addition to the ‘glass brain’ projections, table 31 shows the output of statistical testing for the comparison ‘CBS participants minus controls’. It gives the results from
the cluster-level analysis, and shows data relating to 14 clusters that exceeded the minimum threshold of 10 voxels. The total number of voxels in the cluster is shown, alongside the uncorrected p-value derived from t-testing. In addition, two corrections for multiple comparisons are shown: these are the family-wise error (FWE) correction, and the false discovery rate (FDR) correction. These are discussed in chapter 10.5 above. Table 31 shows that two cerebellar clusters (cluster 42, -50, -32 and cluster -15, -60, -42) were much larger than any of the other clusters identified, and had uncorrected p values of less than 0.05. However, after either correction for multiple comparisons was applied, both clusters failed to retain statistical significance, when subject to whole-brain comparison.

As a result, region of interest analysis was carried out using the seven ROIs creating using the wfu_pickatlas and described in chapter 10. The cluster in the right parietal/occipital region failed to show significance on the ROI analysis, but the cerebellar clusters were more interesting. In this analysis, there were two clusters in the cerebellum that survived false discovery rate (FDR) correction, and remained statistically significant. Cluster (42, -50, -32) had an extent of 3059 voxels and a corrected q=0.026; and cluster (-15, -60, -42) had an extent of 1780 voxels and a corrected q=0.049. Non-stationary correction was applied to these data, and the extent and q values remained unchanged.
Figure 4: Maximum intensity projections ('glass brain' figures), thresholded at \( p < 0.005 \), uncorrected for multiple comparisons, of grey matter analysis.
Table 31: Cluster-level statistical analysis of results of comparison ‘CBS minus controls’ for grey matter

<table>
<thead>
<tr>
<th>Cluster location (MNI coordinates)</th>
<th>Cluster extent (voxels)</th>
<th>Uncorrected t-test result (p value)</th>
<th>t-test result output after FWE correction (p value)</th>
<th>t-test result after FDR correction (q value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42, -50, -32</td>
<td>3226</td>
<td>0.011</td>
<td>0.244</td>
<td>0.156</td>
</tr>
<tr>
<td>-15, -60, -42</td>
<td>2232</td>
<td>0.020</td>
<td>0.525</td>
<td>0.208</td>
</tr>
<tr>
<td>36, -60, 39</td>
<td>801</td>
<td>0.169</td>
<td>0.986</td>
<td>0.790</td>
</tr>
<tr>
<td>-4, -15, 19</td>
<td>138</td>
<td>0.577</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>-18, 22, -11</td>
<td>79</td>
<td>0.684</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>-42, -26, -17</td>
<td>73</td>
<td>0.698</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>18, -69, 12</td>
<td>38</td>
<td>0.792</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>-18, -64, 30</td>
<td>121</td>
<td>0.604</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>-32, -61, 39</td>
<td>66</td>
<td>0.714</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>9, -4, -15</td>
<td>62</td>
<td>0.722</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>36, -22, 46</td>
<td>49</td>
<td>0.759</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>-28, -12, 31</td>
<td>20</td>
<td>0.859</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>45, -42, 3</td>
<td>22</td>
<td>0.847</td>
<td>1.000</td>
<td>0.892</td>
</tr>
<tr>
<td>-10, -54, 55</td>
<td>12</td>
<td>0.892</td>
<td>1.000</td>
<td>0.892</td>
</tr>
</tbody>
</table>

Given the differences in visual functioning and gender between the CBS participants and the control group, the possibility that the observed differences were due to one or more of these confounding variables needed to be explored. The significant clusters from the cerebellar ROI were defined as regions of interest in MarsBaR (Brett et al. 2002). The ‘extract data (full options)’ function of MarsBaR was used to
extract a value for beta weights (raw intensity value) of the cluster for each of the 22 MRI scans, scaling from raw data and setting ‘scale grand mean’ to zero. These data were exported to SPSS version 20. An ANCOVA was then conducted, to control for any effect of visual acuity on the results obtained, using the beta weights as the dependent variable, the group of participant (CBS/control) as the fixed factor, and visual acuity (best eye), contrast sensitivity and gender as covariates. Only 10 of the 11 CBS participants had contrast sensitivity measured, so the ANCOVA was restricted to these 10 and the 11 controls. The p value was examined to see if the effect remained significant after these potential confounders were controlled for, and the effect size (partial eta squared) was noted.

Before conducting the ANCOVA, the nine assumptions set out in chapter 6.12 were again tested. These are set out below.

1. The dependent variable and covariate variable should be measured at the interval or ratio level. This assumption is met

2. The independent variable should consist of two or more categorical, independent groups. This assumption is met

3. There should be independence of observations, i.e. there must be no relationship between the observations within each group or between the groups. This assumption is met.

4. There should be no significant outliers. I tested this using the outlier labelling rule (Hoaglin et al. 1986). This confirmed that there were no outliers in the beta weight scores for either cluster, and so this assumption is met.

5. The dependent variable should be approximately normally distributed for each category of the independent variable. This was tested using the Shapiro-Wilk test in...
SPSS version 20, for both clusters identified as significant. When this test was carried out, the p values for both groups for cluster 1 were non-significant (CBS group p=0.69, control group p=0.70), lending support to the contention that the data were normally distributed. For cluster two, the CBS group were normally distributed (p=0.54), but the Shapiro-Wilk test for the control group almost reached statistical significance (p=0.053), raising doubts over whether these data were normally distributed. However, ANCOVA is reported to be robust to milder degrees of non-normality, so this assumption was not held to be violated.

6. There should be homogeneity of variances. Levene’s test for equality of variances was conducted, and the results for the extracted beta weight data were not significant on this test (F=1.087, p=0.310 for the first cluster, and F=3.205, p=0.089 for the second cluster), indicating that the variances were not significantly different.

7. The covariate should be linearly related to the dependent variable at each level of the independent variable. I examined this using scatter plots of the dependent variable against each of the covariates for both clusters, and both participant types. These showed a reasonable linear relationship between the covariates and the dependent variable, and so suggest that this assumption is met.

8. There should be homoscedasticity. This is a measure of homogeneity of variance across the range of variables in the sample. In figure 5 below, the standardised residuals show similar variability along the range of predicted values for cluster 1, so this assumption holds. It is less clear that this is the case for cluster 2, the small
Figure 5: Plot of standardised residuals

Scatterplot
Dependent Variable: R0(outputcluster1)

Regression Standardized Residual

Regression Standardized Predicted Value

R² Linear = 0
Scatterplot

Dependent Variable: ROIoutputcluster2

R² Linear = -2.220E-16
sample size making it unclear if there is a change in the standardised residuals of variance across the range of predicted values; however, there is no clear evidence that this assumption has been violated.

9. The final assumption is that there is homogeneity of regression slopes. This means that there is no interaction between the covariates and the independent variable. This was tested by creating a custom model in the ANCOVA and looking at the interaction between the independent variable and covariates. I did this for both clusters, and generated $p=0.239$ for cluster 1, and $p=0.243$ for cluster 2 for the interaction term, results that were not statistically significant. This suggests that the regression slopes are not significantly different, and assumption 9 is met.

As the nine assumptions appear to hold, I continued with the ANCOVA. The result for the second cluster was no longer statistically significant following the ANCOVA analysis, $p=0.098$; though the participant group did have a larger partial eta squared than the covariates (0.162), and so explained more of the variance in the beta weight scores than any of the other factors.

The result for the first cluster did remain statistically significant in the ANCOVA analysis, with $p=0.038$. The partial eta squared score was 0.243, indicating that 24% of the variance in beta weight scores was explained by the group the participant belonged to. This compared to partial eta square result of 0.037 for visual acuity, 0.031 for contrast sensitivity and 0.041 for gender, indicating a large effect size for participant group in comparison to the potential confounding factors.
SPSS was used to carry out a correlation analysis on the beta weight scores obtained for the two clusters. The analysis was carried out separately on the CBS participants and the controls. For the controls, there was a statistically significant correlation between the beta weight scores for the two clusters within participants. The Pearson coefficient was 0.603, 2-tailed significance 0.05. For the CBS participants, the correlation was even stronger; the Pearson coefficient was 0.695, 2-tailed significance 0.018.

The VBM analysis thus found an increase in grey matter volume in the cerebellum of participants diagnosed with Charles Bonnet syndrome, which remained statistically significant after non-stationary correction and after taking into account potential confounders. Moreover, there was a strong correlation in the magnitude of the volume increase between the two clusters within individuals.

The clusters identified in the cerebellar region of interest are shown below in Figures 6-9. The images were generated using MRlcron. Figure 6 shows cluster 1 in the right cerebellar hemisphere, and figure 7 shows the right-sided cluster 2.
Figure 6: location and extent of cluster 1
Figure 7: location and extent of cluster 2
Figure 8 shows transverse slices through the cerebellum, with the areas where there was increased grey matter indicated. Figure 9 is a 3 dimensional reconstruction of the data, with the ‘any depth’ display format selected. This shows cluster 1 in the posterior lobe of the right cerebellar hemisphere, with an extension medially. Cluster 2 is shown in the medial aspect of the posterior lobe of the left cerebellar hemisphere.

Figure 8: Transverse slices through cerebellum showing regions of increased grey matter

The location of the clusters within the cerebellum was more precisely defined by using the aal atlas in the wfu_pickatlas to create a series of regions of interest, each made up of one cerebellar lobule, and repeating the t-test to see if the cluster fell within the defined area. By this process, cluster 1 was found to lie within cerebellar lobule VI and Crus 1; and cluster 2 was in cerebellar lobule VIII.
Figure 9: Ventrolateral view showing extent of clusters 1 and 2
11.9 Voxel-based morphometry analysis: white matter

Analysis of was carried out using SPM8 on Matlab using the protocol described in chapter 10. t-tests were conducted using the comparisons ‘CBS minus CTL’ and ‘CTL minus CBS’, using comparisons across the whole brain. The outputs of these t-tests, in the form of maximum intensity projections (also known as ‘glass brain’ figures), are shown in figure 10 below. As with figure 4 above, these ‘glass brain’ figures show three projections of the brain, viewed laterally, from above, and from the front. Clusters of 10 or more voxels where a result significant to p < 0.005, uncorrected for multiple comparisons, was obtained on t-testing are shown as shaded areas. These clusters are located at the point where the maximum level of statistical significance was attained. The coordinates of clusters are given in MNI space. Figure 10A is the ‘glass brain’ output for the comparison ‘CBS participants minus controls’, and so indicates areas where the analysis suggests an increase in white matter volume. Figure 10B shows the results for the opposite comparison, and so the presence of clusters of significant voxels would indicate the probability of reduced white matter volume.

The results shown appear to be a near mirror-image of the results of the grey matter analysis in chapter 11.8 above. In the case of the white matter, as can be seen in 10A, the comparison ‘CBS participants minus controls’ shows only a few small clusters of voxels where there were statistically significant differences on t-testing. None of these retain significance at cluster-level analysis. However, the comparison ‘controls minus CBS participants’, shown in figure 10B, which would indicated loss of white matter volume, did show 9 clusters of voxels where statistically significant
differences were found. These appeared to be situated in the posterior parietal and temporal lobes.

Table 32 reports data on cluster location, size in voxels, and results of cluster-level analysis to determine statistical significance. Two clusters (cluster 64, -37, -15 and cluster -8, -67, 27), found in the right posterior temporal lobe and left posterior parietal lobe, were close to attaining statistical significance on uncorrected testing; however, neither cluster was significant after the application of either the FWE or FDR correction for multiple comparisons.

As a result, region of interest analysis was conducted on the seven regions of interest set out in chapter 10.4, using the comparison ‘CTL minus CBS’. All except the temporal lobe region of interest showed no differences of any magnitude. However, the temporal lobe region of interest analysis was worthy of comment. There was a cluster of voxels identified in figure 10B at MNI coordinates 64, -37, -15, in the posterior inferior temporal lobe, suggesting an area of reduced white matter volume, which just failed to reach statistical significance after family wise error (FWE) correction (p=0.088), or after FDR correction (q=0.113).
Figure 10: Maximum intensity projections (‘glass brain’ figures), thresholded at $p < 0.005$, uncorrected for multiple comparisons, for white matter analysis.
Table 32: Cluster-level statistical analysis of results of comparison ‘controls minus CBS’ for white matter

<table>
<thead>
<tr>
<th>Cluster location (MNI coordinates)</th>
<th>Cluster extent (voxels)</th>
<th>Uncorrected t-test result (p value)</th>
<th>t-test result output after FWE correction (p value)</th>
<th>t-test result after FDR correction (q value)</th>
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</thead>
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<tr>
<td>64, -37, -15</td>
<td>1345</td>
<td>0.056</td>
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</tr>
<tr>
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<td>0.075</td>
<td>0.808</td>
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<tr>
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<td>0.678</td>
</tr>
<tr>
<td>6, -70, -42</td>
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<td>1.000</td>
<td>0.678</td>
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<tr>
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<td>41</td>
<td>0.757</td>
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<td>0.779</td>
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</tbody>
</table>
12. Imaging Study: Discussion

12.1 Introduction and Summary

In this chapter the findings of the VBM analysis are discussed and set in context of the existing literature. In chapter 12.2, some methodological strengths of this study are discussed, including the choice of study population, which was more representative of patients with Charles Bonnet syndrome who present to ophthalmological settings than those recruited in previous studies. The control group also appeared more relevant, and the measures taken to confirm the diagnosis of CBS were more robust. The analysis technique, voxel-based morphometry, is also more powerful than the techniques applied in previous studies.

However, there were some shortcomings present in this study, and these are discussed in chapter 12.3. Some of these relate to the less than ideal matching of CBS cases and controls with regard to gender and visual acuity. This opens up the possibility that the observed differences in grey matter volume in the cerebellum may not be due to the presence of CBS, but instead may arise from differences in these other parameters. Evidence is provided, both from the study methodology and from existing literature that this is unlikely to be the case, but the possibility cannot be entirely ruled out. Another potential shortcoming relates to the VBM technique itself, which has faced criticism over both its replicability and whether findings made using the technique may represent artefacts. These criticisms have been largely rebutted by the originators of the technique, and a summary of the concerns, and responses to them is set out in this section.
In chapter 12.4 the actual findings of the VBM analysis are discussed, and in particular the unexpected location of the differences between the groups, the cerebellum. Previous work has generally been suggestive of the posterior cerebral cortex or basal ganglia as the site of abnormalities in CBS. Chapter 12.5 explores the literature describing the role of the cerebellum in visual functioning, including evidence of connections between the cerebellum and the visual accessory cortex, and a role for the cerebellum in both the development of nystagmus and in the modulation of saccadic eye movements. Imaging studies showing changes in the cerebellum related to these issues are discussed, and the proximity of the region of increased grey matter volume found in this study to areas identified as relevant in the control of saccades is noted. Finally, these areas are considered in the context of overarching theories of visual hallucinations to offer a tentative model describing how CBS could theoretically lead to chronic overactivity of the cerebellum, and so to increased grey matter volume.

Chapter 12.6 takes the discussions set out in chapters 12.2-12.5 and applies them to the findings presented in chapter 11. Four possible interpretations of the findings of increased cerebellar grey matter are set out:

- that the findings are an artefact

- that they actually indicate the presence of significant numbers of cases of Lewy body dementia which were not yet clinically manifest

- that cerebellar cognitive affective syndrome (CCAS) may be responsible for the clinical presentation in the cohort with visual hallucinations, rather than CBS

- or that increased cerebellar grey matter is a genuine consequence of CBS.
Of these three options, the fourth is felt to be most plausible. A final possibility is also discussed: that instead of there being an increase in cerebellar grey matter, the results may instead show a reduced level of cerebellar grey matter atrophy when compared to controls. Given that there is some evidence linking vision loss to cerebellar atrophy, and that there was no control group with normal visual functioning in this study, this is a plausible explanation and one that would warrant further investigation.

The white matter findings are explored in chapter 12.7, and the observed cluster of voxels suggestive of white matter loss in the posterior tracts is noted to be in a biologically plausible location. Implication of this are discussed, including the weakness of T1-weighted images for visualising brain white matter; and the possibility that this may be a type II statistical error, due to underpowering of the study, is noted.

Finally, chapter 12.8 discusses the relationship between CBS and other conditions where visual hallucinations are commonly observed, including dementias and the peduncular hallucinosis of L’hermitte. The diagnostic independence of CBS and peduncular hallucinosis is challenged, as many of the participants in this study would seem to meet diagnostic criteria for both conditions. Progress towards de Morsier’s original goal in defining Charles Bonnet syndrome, that of developing a comprehensive descriptive framework for visual hallucinatory disorders, is reviewed in the light of the recent work of ffytche, and of Collerton et al.; and implications of the findings of this study for these overarching theories are discussed.
12.2 Study Design and Participant Characteristics- Strengths

This is only the fourth imaging study to be carried out in Charles Bonnet syndrome, and with 22 participants (11 with CBS), it is the largest. The other three, Shedlack et al. (1994), ffytche et al. (1998), and Adachi et al. (2000) are now over 13 years old, and smaller, with 17 (5 with CBS), 13 (8 with CBS), and 6 (5 with CBS) participants respectively. While there have been a number of publications which comment on imaging findings in Charles Bonnet syndrome since then, these have all been limited to reports of one or two cases.

The participants in this study were recruited from ophthalmological clinic settings, as opposed to an in-patient old age psychiatry unit (Shedlack et al. 1994), or from an existing psychiatry-based study (ffytche et al. 1998) and so are more likely to be representative of people attracting a diagnosis of Charles Bonnet syndrome in community settings. It is likely that people with CBS who get admitted to in-patient psychiatric care are unusual in some aspects, as this is not a common occurrence. Adachi et al. (2000) did not report any details of the setting from where their participants were recruited.

The diagnosis of Charles Bonnet syndrome was made by an experienced old age psychiatrist, using recognised diagnostic criteria (Teunisse et al. 1996), and supplementing this assessment with a quantitative measure of psychiatric morbidity, the Brief Psychiatric Rating Scale, in order to increase the reliability with which other conditions associated with visual hallucinations could be excluded. The control group was drawn from the same population of eye hospital clinic attenders as the CBS group, unlike those in Shedlack et al. (1994), which were taken from a previous
unrelated study into neuroendocrine conditions. This study also carried out detailed characterisation of the participants’ visual functioning by experienced optometrists, explored the content of the visual experiences, and measured participants’ cognitive functioning, none of which were undertaken by Shedlack et al. (1994). Adachi et al. (2000) did undertake some of these measures, but report that at least two participants had fluctuating levels of confusion, and one had secondary delusions, raising some doubts over the validity of the CBS diagnosis in a number of those included. Moreover, four of the five CBS participants in Adachi et al. (2000) had a diagnosis of leprosy, making them unrepresentative of those who generally attract this diagnosis in UK practice.

Finally, this current study makes use of voxel-based morphometry (Ashburner and Friston, 2000), a well-established and powerful technique for investigating differences in grey matter volume which does not rely on subjective rating scales or operator-dependent landmark definition. As discussed in chapter 9, this technique has been successfully applied to a wide range of conditions and has found volumetric differences which have contributed to their understanding (Whitwell, 2009). As such, this study is more rigorous in its design and potentially more powerful in identifying abnormalities in the Charles Bonnet group, than any previous work in this field.

12.3 Study Design and Participant Characteristics- Limitations

Although the source of the control group was from the same population as the CBS participants, and they were well matched in age and gender, they did differ significantly in two areas of potential relevance to the study. The gender balance of
the CBS group and the control group were very different, with 9/11 CBS participants being female, compared to 2/11 of the control group. As noted in chapter 7.3, the excess of females in the CBS group was not unexpected, with some studies reporting this previously (Holroyd et al. 1994, Scott et al. 2001). However, the reasons for the reversal of the gender balance in the control group are unclear. This mis-match in gender between the CBS group and the controls opens up the possibility that the findings could be an artefact due to underlying differences in the brains between the two groups. However, gross differences in brain volume, including in the cerebellum, are controlled for by the VBM analysis at the modulation step, so this is unlikely to be an explanation for the finding.

Some authors have investigated potential gender differences in grey matter volume in the cerebellum, and so their findings are of great relevance to this matter. Raz et al. (2001) demonstrated in an MRI study, using regions of interest defined by the investigators, that there was sexual dimorphism in grey matter volumes in the human cerebellum. However, they found that males had larger grey matter volumes; this would not explain the findings of this study, where the CBS group, with clusters indicating greater grey matter volume, were largely female. Fan et al. (2010) used VBM of MRI scans to investigate sexual dimorphism in the cerebellum, and also found evidence of this. They reported that cerebellar grey matter volume was significantly larger among males in the anterior and middle posterior lobes. Again, the CBS group had more females, and so would have been expected, if anything, to show diminished grey matter volume. This was a large study, with 112 participants, and provides the best evidence that the differences between the groups cannot be explained by known gender differences in cerebellar grey matter volumes.
Finally, the ANCOVA analysis included gender as a covariate in the model, further increasing the confidence that the gender differences are unlikely to explain the presence of the clusters of increased cerebellar grey matter seen.

The other area where there were differences between the groups was in visual functioning, with the control group having better visual acuity. While all participants, both those with CBS and controls, had abnormalities in visual functioning, this better acuity is a concern and could potentially act as a confounder. There is limited evidence in the literature relating to the effects on the cerebellum of deteriorating visual functioning, but Modi et al. (2012) did carry out a VBM study in partially and totally blind patients, and controls with normal vision, which commented on this matter. They found that there was a reduction in cerebellar grey matter volume in those with complete blindness, and no change in this parameter in those who were partially blind. The authors noted the role of the cerebellum in maintaining visual attention and spatial processing (Stoodley and Schmahmann 2009), and concluded that the reduction in grey matter reflected structural reorganisation in the face of a lack of visual input.

So, based on this evidence, the increase in grey matter seen in the Charles Bonnet syndrome group is unlikely to be due to worse visual acuity; if anything, this may have been expected to produce the opposite finding, of atrophy. Nevertheless, the differences in visual functioning were included in the model of the ANCOVA which analysed differences between the groups, in order to further reduce the possibility that this could influence the results obtained. While this should offer reassurance that the difference detected reflects a real difference between the groups, the additional
analysis reduces the power of the study to detect any real differences between the two groups, and increases the risk of a type II error.

Another potential weakness is the Voxel-based morphometry technique itself. While this is a widely used and accepted methodology, it does have critics. Bookstein (2001) claims that there is an interaction between the algorithm that underpins the normalisation step and the subsequent voxel-wise statistical comparison, and that this is especially notable in regions where there is a strong image gradient, such as edges where one tissue type transitions to another. He claims that these gradients can extend a substantial distance from any edge, and questions whether any part of the image would be free enough to be confidently free of resultant confounding. He asserts that VBM results may, instead of detecting true difference between groups, be simply mis-registration errors from the spatial normalisation step.

Asburner and Friston (2001) responded to this criticism of their methodology. They argued that Bookstein fundamentally misunderstood the nature of VBM, as a central component of his critique related to the position of cortical structures, something that Asburner and Friston say VBM cannot precisely comment upon, due to its less precise image registration. They agree that registration errors can potentially be an issue, but contend that this is less of a problem than in manual analysis using operator-identified landmarks, where no entirely precise algorithms for landmark identification exist. They go on to say that non-stationary correction, of the type applied in this analysis (Worsley et al. 1999) further addresses some of the concerns over validity of the statistical analysis the method entails.
A further limitation of VBM is set out by Whitwell (2009). Whitwell argues that interpreting results across VBM studies is difficult due to differences in the processing steps and statistical methods used to conduct the analysis. There is the potential for different registration and segmentation methods, and differences in the smoothing step, and also variations in whether the FWE or FDR correction is applied. There are also potentially confounding factors if studies were carried out in different populations, with different ages or disease severity. Whitwell asserts that comparing the output of statistical tests is therefore of limited meaning, and that the results of VBM studies should be thought of as ‘anecdotal’ evidence of differences from normal in the conditions studied. Standardisation of methodologies is argued to be an important step for the future to deal with this limitation; though this is not a problem for this work, where there is no existing research to compare with.

Finally, this study attempted to make use of T1 weighted images to carry out a VBM analysis of the white matter in the participants. There are limitations inherent in this, as this is not the optimal imaging technique to study white matter. Diffusion tensor imaging techniques would be more powerful, with an ability to investigate the integrity of white matter tracts (Le Behan et al. 2001, Whitwell 2009). However, VBM has been used to investigate between-group differences in white matter (Mueller et al. 2006, Dole et al. 2013), so this is a recognised use to which the technique can be applied.
12.4 Findings of the VBM analysis

The finding of an increase in the grey matter volume bilaterally in the posterior lobe of the cerebellum was unexpected. Previous report in patients with Charles Bonnet syndrome, described in chapters 9.2 and 10.4, led to an expectation that any differences between the groups were more likely to be in the visual or visual accessory cortex, and that occipital lobe atrophy was the most likely finding overall. However, no changes were found in the primary visual cortex, with only a small cluster which failed to reach statistical significance present in the occipital lobe where it borders on the posterior parietal lobe. The fusiform gyrus, found to have increased activity by ffychte et al. (1998), showed no abnormality. It may be relevant that all the reports indicating abnormalities in the visual, or visual accessory cortex, used functional imaging modalities, most commonly SPECT; so it may be that these functional abnormalities have no structural correlate, and so fail to show any differences on MRI scanning. This also applies to the absence of any findings in the thalamus and basal ganglia, which had been identified as often showing abnormalities in the existing literature; again, these findings were made using functional imaging techniques. Finally, the cohort study described in Part II of this work reported findings consistent with deficits in frontal lobe functioning. Atrophy of the frontal lobe has been described in some studies of visual hallucinations (Sanchez-Castaneda et al. 2010, Shin et al. 2012), and abnormalities of the frontal lobe are implicated as the source of the attentional deficits in the perception/attention deficit model of visual hallucinations advanced by Collerton et al. (2005). It is therefore worth noting that no abnormalities were found in this part of the brain to account for the cognitive deficits described in chapter 6.15.
The cerebellar findings in this study were of two large clusters, one of which survived non-stationary correction and ANCOVA analysis to control for potential confounders, and the other which did not. The findings relating to the first cluster appear to be robust, and remain significant even if the more stringent FWE correction, often used only in larger studies (Whitwell, 2009), was applied. The findings relating to the second cluster are more equivocal, given its failure to retain significance when the effects of gender and visual functioning were included in the model. However, the correlation analysis showing a very strong correlation with the magnitude of the first cluster, especially in the CBS group, offer some support to the theory that this is a genuine effect. Given this, the failure to reach significance may be a type II error, resulting from a lack of power in the study design due to the small sample size and sub-optimal controlling.

The finding that there was an increase in grey matter volume was again surprising, as a finding of atrophy was more expected. There are studies which have shown an increase in grey matter in participants, most notably in the hippocampi of taxi drivers (Maguire et al., 2000), and where the increased volume is theorised to arise from increased activity over a long period in the structure concerned. In Maguire et al., the participants were healthy volunteers, and did not suffer from a medical condition which was relevant to the structure being studied, unlike this work. However, the increased grey matter volume found may be of relevance in relation to a study in Lewy body dementia, Miyazawa et al. (2010), discussed in 12.5 below.
12.5 The Role of the Cerebellum in Visual Functioning

Long thought of as being primarily concerned with motor functions, it has become clear over the last 20 years that the cerebellum has a much broader role. Schmahmann and Pandya (1992) found connections between the cerebellum and sensory association areas, including visual association areas, in higher primates. This work was further developed by Glickstein et al. (1994). Following this, neuroimaging studies in humans confirmed the presence of pathways connecting the cerebellum and visual association cortex, and led to the development of a model of the functional topography of the cerebellum. Stoodley and Schmahmann (2009) reviewed the literature on this in and found that good evidence exists for the existence of two separate zones with different connectivities. Lobules V, VI and VIII have connections to the sensorimotor cortex, including the visual cortex, while lobules VI, VII and crus 1 are involved with higher level tasks including emotional, spatial and language processing and executive functioning and are connected to the prefrontal and parietal cortex. Further work by Stoodley et al. (2012) supported this sensorimotor/cognitive and higher functioning topographic separation. The connections between the cerebellum and cerebral cortex travel via nuclei in the pons or thalamus.

These reports are supported by a number of other studies in the literature demonstrating links between visual functioning and the cerebellum. As described in section 12.3 above, Modi et al. (2012) showed that cerebellar grey matter volume decreases in participants with severe visual loss. Two other studies are of particular interest, as they show an increase in grey matter in the cerebellum. Huffner et al. (2011) carried out VBM-MRI analysis of patients with congenital nystagmus, and
found that they had an increase of grey matter in cerebellar lobules VI, crus 1 and 2, and lobules VII, VIII and IX bilaterally. They found a positive correlation between nystagmus severity and the magnitude of the grey matter volume increase, and hypothesise that this could be due to increased activity in an attempt to suppress the oscillopsia. Rosengarth et al. (2013) carried out ocular training in participants with age related macular degeneration, who then underwent MRI scanning. VBM analysis was conducted which showed increases in grey and white matter volume in the left semi-lunar lobule of the inferior cerebellum, and area which has been linked to reading.

Another important role that the cerebellum plays in relation to vision is in the control of saccadic eye movements. A number of authors have set out evidence relating to the cerebellum’s role in the regard, including Noda (1991), Quaia et al. (1999), Desmurget et al. (2000) and Xu-Wilson et al. (2009). In saccadic movements, the eye rapidly switches the point of visual focus to another locus in the visual fields; the movements are brief (20-100ms), rapid (over 300 degrees of arc per second), and ballistic (their destination is predetermined at the outset) (Findlay and Walker, 2012). Saccades are generated by the pedunculopontine nucleus (Smythies 2005), which has projections to the cerebellum, thalamus and sensorimotor cortex (Aravamuthan et al. 2007). Work by Noda (1991) in monkeys, and Desmurget et al. (2000) using PET has identified the vermal parts of cerebellar lobules VI and VII as being active in saccadic processes. As previously discussed, there are limitations in how precisely VBM is able to locate clusters of voxels identified as indicating significant differences, but these structures are relatively close to cerebellar cluster 1 identified in this study—though this did appear to be more in the lateral part of these lobules than the vermal.
Of interest in relation to this, there is some theoretical evidence that relates saccades to visual hallucinations. Smythies (2005), in commentary on Collerton et al. (2005), noted that visual information from the retina is almost entirely suppressed for the duration of the saccade. In the perception/attention deficit model developed by Collerton et al., there is always a process taking place within the brain of matching afferent information from the retina about the outside world, with a range of stored proto-objects in the visual association cortex. Where states of arousal are impaired, or the quality of afferent data from the retina is reduced, it is more likely that an inappropriate proto-object will be selected and experienced as a percept; the less good the match between the proto-object and the surrounding scene, the more likely the object will be experienced as a hallucination. The suppression of afferent data from the eye during the saccade, in states where there may be a deficit of attention, could potentially make selection of an inappropriate proto-object more likely and so increase the chance of experiencing a visual hallucination. Evidence for this hypothesis in practice is lacking though, with Mosimann et al. (2005) failing to find any relationship between saccades and visual hallucinations in Lewy body dementia.

The cerebellum has also been identified as region which has been abnormal in some previous imaging studies of patients with visual hallucinations, including one in Charles Bonnet syndrome. Ball (1991) found significant cerebellar cerebrovascular disease in two patients with CBS on CT scanning. The other two studies were in Lewy body diseases, one in Parkinson’s disease without dementia (Shin et al. 2012) and the other in Lewy body dementia (Miyazawa et al. 2010). Shin et al. (2012) used the techniques of voxel-based morphometry and found atrophy in the cerebellum of patients with Parkinson’s disease, which was more prominent in those with the condition who experienced visual hallucinations. This suggests the opposite of the findings of this work- that visual hallucinations may be related to cerebellar atrophy,
but it does at least suggest a role for the cerebellum in the development of visual hallucinations.

Miyazawa et al. (2010) used PET rather than MRI-VBM, but made an interesting finding that has some potential relevance to this study. As set out in chapter 9.4, they found hypermetabolism in the cerebellum of 18/22 of a cohort with Lewy body dementia, and that there was a strong correlation between this hypermetabolism and the experience of visual hallucinations. This further establishes a possible link between abnormalities in the cerebellum and the development of visual hallucinations, and opens the possibility that the relationship may include cerebellar over-activity, as well as atrophy.

However, this finding is in Lewy body dementia, and not Charles Bonnet syndrome. The relevance to CBS is therefore uncertain. There may however be some relationship between the conditions, with the literature review in Part I of this thesis setting out a number of cases where Lewy body dementia developed in a patient who had been given a diagnosis of Charles Bonnet syndrome, and the study in part II of the thesis, which set out to investigate this further, finding evidence of a another case of CBS where Lewy body dementia emerged during follow-up.

Furthermore, ffytche et al. (1998) set out evidence that similar brain responses could be generated by different conditions, in that the brain activation in Charles Bonnet syndrome-related hallucinations appears to be in the same underlying brain structures as activation generated by a veridical percept. So it is possible that different conditions may produce similar symptoms by causing abnormalities in the
same underlying systems that mediate visual experiences. Clearly, this is a speculative hypothesis at present, but one that may warrant further investigation.

If hypermetabolism was to exist in the cerebellum of patients with Charles Bonnet syndrome, and this was to be related to the development of visual hallucinations, then this may be a sign of chronic increased activity as the hallucinations of CBS can be chronic, with over 50% being present for over a year in this study cohort. Chronic overactivity in the cerebellum is a possible mechanism by which increased grey matter volume could be generated.

The evidence set out in this chapter falls well short of explaining how cerebellar changes may be related to visual hallucinations, but clearly establishes a role for the cerebellum in vision. Localisation of functioning within the cerebellum, including in relation to saccadic eye movements, is described, as is evidence of grey matter changes in other conditions where visual functioning is disturbed. Possible relative proximity between cerebellar regions known to be involved in saccades and the region of increased grey matter volume found in this study is noted, along with a possible role for saccades in the development of visual hallucinations. Furthermore, the relationship between saccades and nystagmus, where increased cerebellar grey matter has been found, is noted. Much of this is necessarily speculative, given the limited evidence relating to the topic, and offers potential avenues for further investigation rather than firm conclusions. Most importantly, it does go some way to establishing that the finding of increased grey matter volume, although unexpected, is at least biologically plausible.
12.6 Implications of Cerebellar Findings

In the light of the evidence set out above, the findings in the cerebellum must represent one of four possible situations:

1. The difference is an artefact, either due to limitations of the VBM analysis, or the differences between the CBS participants and controls. While this cannot be ruled out, the discussion in chapter 12.3 sets out evidence that suggests this is unlikely.

2. The increase in cerebellar grey matter volume in the posterior lobe is a real finding, but the findings do not reflect changes associated with Charles Bonnet syndrome itself, being instead the result of members of the Charles Bonnet group having an underlying Lewy body dementia. The work of Miyazawa et al. (2010), showing cerebellar hypermetabolism, associated with the presence of visual hallucinations, in patients with Lewy body dementia, suggests a possible mechanism by which this could occur. Of note, one case of Lewy body dementia did develop in the Charles Bonnet syndrome group in the longitudinal study set out in Part II above; and the cohort in part II were only followed up for one year, so it is possible that further cases of Lewy body dementia could develop among the CBS group. However, it seems unlikely that Lewy body dementia is so commonly the outcome of Charles Bonnet syndrome that it could produce the results this study reports.

3. The increase in cerebellar grey matter is a real finding, but represents a manifestation of underlying cerebellar disease, rather than being linked to a primary
dementia, or loss of visual functioning. The clinical cohort study described in part II of this thesis noted abnormalities in cognitive functioning in the CBS group, which were significantly more severe than in the control group, in the frontal/executive and language subscales. This is of interest in relation to the cerebellar cognitive affective syndrome (CCAS), described by Schmahmann and Sherman (1998). This syndrome consists of a combination of cognitive deficits alongside personality changes including irritability, distractibility, impulsive behaviour, apathy, dysphoria and obsessive behaviours (Schmahmann 2010). It has been described as a ‘dysmetria of thought’.

The cognitive deficits identified in the syndrome include frontal/executive dysfunction-including verbal fluency deficits, the measure of frontal lobe functioning used in the ACE-R- and language deficits. There are the cognitive domains identified as abnormal in the CBS cohort. Moreover, there is also an association between CCAS and impaired visuospatial organisation and memory (Schmahmann and Sherman 1998), and even a case report of visual hallucinations occurring in the context of CCAS (Yap et al. 2012), albeit in a patient of a very different background to the participants of this study. Finally, the abnormalities responsible for CCAS are reported to be located in the posterior lobe of the cerebellum (Stoodley and Schmahmann 2009), in the same area as the abnormalities found in this study.

Could the cerebellar findings in the CBS participants, and possibly even the presence of visual hallucinations, therefore be due to the presence of CCAS, rather than Charles Bonnet syndrome? While the cognitive profiles of the CBS participants are superficially similar to those seen in CCAS, the specifics are not necessarily the same- for example, the language deficits in CCAS are reported by Schmahman and
Sherman (1998) to be agrammatism and dysprosodia, while the deficits in the CBS patients were more heterogeneous. The CBS patients did not demonstrate the affective abnormalities associated with CCAS, as evidenced by their low scores on the BPRS. And finally, the structural abnormality identified in the CBS cohort by the VBM analysis was an increase in grey matter volume. This does not fit with the existing evidence in CCAS; while there are no VBM-MRI studies of the condition, the imaging studies that have been conducted point to focal deficits or loss of grey matter volume. For example, in the case series reported by Schmahmann and Sherman (1998) which first identified the condition, the commonest findings were of infarct or posterior cortical atrophy. This contrasts with the clinical reports of the MRI scans obtained in this study, and reported in chapter 6.9; in none of the participants was a specific abnormality of the cerebellum commented on.

This is therefore unlikely to be a satisfactory explanation for the VBM findings in the study. The contribution of the cerebellum to the regulation of cognitive and affective functioning, like its contribution to the regulation of visual functioning, is an area that is increasingly recognised as important; however, CCAS appears unlikely to account for the abnormalities reported in this study.

4. The increase in cerebellar grey matter volume in the posterior lobe is a real finding, and reflects a common underlying pathology or process in patients with Charles Bonnet syndrome. Given that CBS is likely to be a heterogeneous condition, with a wide range of underlying causes, the finding of a common brain abnormality shared by many people that is the cause of the hallucinations observed in the condition would be a little surprising. It is more likely that the cerebellar changes are caused by the condition, and a possible explanation could be that the increased
volume reflects chronic overactivity of vision-related areas due to the presence of the hallucinations. Another possible interpretation could be that the ‘increase’ in grey matter actually reflects a relatively smaller loss of grey matter compared to controls. There was no control group with normal vision, and so it is possible, given the findings of Modi et al. (2012), that the controls actually had cerebellar atrophy, which the CBS group were relatively spared from. It could be that the increased input into the visual systems from the hallucinatory experiences preserved functioning in, and so prevented reorganisation of, structures involved in vision; though why this would particularly apply to the cerebellar aspects of the visual system, and not to other areas, is unclear. In this model, it is the presence of the hallucinations themselves which generate the increase, or reduced decrease, in grey matter. As a result, this would predict that a similar increase should be seen in any conditions which lead to visual hallucinations, though the evidence for this, as set out in chapter 10.4, is limited.

With regard to the location of the clusters within the cerebellum, the implications of this is less certain. In 12.5 the role of the cerebellum in visual functioning was discussed, and the functional subdivisions of the organ outlined. Cluster one, being in the region of lobule VI and crus 1, sits on the border between the sensorimotor cerebellum and the cognitive cerebellum. VBM as a technique has an inherent limitation in the precision with which it can site a cluster within the brain, and the anatomical atlases used to define structures such as the cerebellar lobules are limited in their generalisability, often being derived from small samples. As a result, it is not possible to be certain whether this cluster sits in the sensorimotor or cognitive part of the cerebellum, or indeed whether it does lie within both. While Stoodley and
Schmahmann (2009) in their meta-analysis report a role for the cerebellum in visual attention and spatial processing, the data they present suggest that lobule VI is more involved in language functioning; though this study describes only the findings of imaging studies which reported on the findings of specific cognitive testing, and so does not rule out other roles for lobule VI.

Cluster 2 is found in lobule VIII, which is in the sensorimotor part of the cerebellum. Stoodley and Schmahmann (2010) report that this lobule has an association with motor tasks; but as with lobule VI there is little evidence in the literature to draw upon, in relation to the role of the cerebellum in vision, to further interpret these findings. The evidence in the literature which directly relates to visual hallucinations, in the form of the two neuroimaging studies Miyazawa et al. (2010), and Shin et al. (2012), merely noted the presence of increased metabolic activity, or atrophy, in the cerebellum as a whole, and did not further localise this.

12.7 White Matter Findings

As noted in chapter 11.9, none of the white matter clusters reached statistical significance, though one in the right temporal lobe was close to this even after FWE correction. The location of the cluster in the posterior inferior temporal lobe is in the correct area for the ventral white matter visual accessory tracts connecting the visual cortex to the visual accessory areas. This cluster, which suggested decreased white matter volume, is therefore in a biologically plausible location. Visual inspection of the MRI scans did suggest that there were very high levels of white matter ischaemic change present in the CBS participants, and one of the few neuroimaging studies in
this population, Shedlack et al. (1994) also reported increased white matter ischaemic change posteriorly. Disruption in the connectivity between the primary visual cortex and the ventral visual accessory cortex by cerebrovascular disease is an interesting and potentially plausible factor that could lead to the development of Charles Bonnet syndrome for some patients; it could even act as the underlying brain disorder that de Morsier insisted needed to be present.

The failure of the temporal cluster to reach statistical significance may be due to underpowering of the study. It could also be that the technique used, VBM on T1-weighted images, was a less than optimal as way of investigating the issue. Diffusion tensor imaging, or operator scoring of the extent of the white matter changes using a semi-quantitative scale such as that developed by Scheltens et al. (1993) would have probably been more sensitive to any genuine differences between the groups. Of course, it is also possible that the cluster was an artefact or either the VBM process or the statistical analysis, and that there was no true difference between the groups. The theory relating Charles Bonnet syndrome to cerebrovascular disease in the posterior white matter must therefore remain speculative at this time.

12.8 Relationship of Charles Bonnet syndrome to other visual hallucinatory disorders

The literature review in Part I of this thesis, and the longitudinal study described in Part II both raise the issue of the relationship of Charles Bonnet syndrome to dementia, particularly Lewy body dementia. Collerton et al. (2005) report that the prevalence of complex visual hallucinations in Alzheimer’s disease is around 20%,
around 30% in vascular dementia, and over 50% in Lewy body dementia. While clear evidence of a diagnosable dementia would negate the diagnosis of Charles Bonnet syndrome, it seems likely that for some people the visual hallucinations may precede the development of significant memory loss or daily living skills loss. This group are at risk of attracting a diagnosis of Charles Bonnet syndrome in the first instance, before the cognitive deficits become more severe. The finding of high levels of cerebrovascular disease in the CBS group is therefore of note, and longer term follow up of this cohort to see if any develop vascular dementia would be interesting; although, of the two participants that did develop dementia in the longitudinal study, in neither case was this felt to be vascular in aetiology.

This VBM-MRI study also raises the question of the relationship of Charles Bonnet syndrome to peduncular hallucinosis. This condition was described by L'hermitte (1922), and included as the L'hermitte syndrome in de Morsier’s classification of visual hallucinatory syndromes of 1936. de Morsier defined this as visual hallucinations arising from lesions, usually vascular in origin, of the diencephalon and cerebral peduncles; and held that it was a nosologically separate entity from Charles Bonnet syndrome. The concept of peduncular hallucinosis has persisted in the literature ever since, though the condition has seen less research activity than Charles Bonnet syndrome. Manford and Andermann (1998) revisited it in their review of complex visual hallucinations, confirming the vascular aetiology, with lesions in the medial thalamus, pulvinar and rostral brainstem structures described. They noted the absence of a direct involvement of the retinogeniculocortical system, which they note is generally considered necessary in the experience of complex formed shapes and of colour. They held this up as an example of a condition where abnormalities in the ascending cholinergic system could be the cause of complex visual phenomena, a
concept further developed by ffytche (2005), who included Lewy body diseases and Alzheimer’s disease in this category.

However, although Charles Bonnet syndrome and peduncular hallucinosis have been viewed as separate entities, the freeing of CBS from aetiological underpinnings, and its definition in purely phenomenological terms by Gold and Rabins (1987) means that these conditions are not mutually exclusive as they are currently understood. They may overlap phenomenologically too, as described by Manford and Andermann (1998). The Charles Bonnet syndrome group in this study included a number of participants who has significant white matter ischaemic changes and even frank infarcts in the structures of the diencephalon and midbrain, and who would therefore potentially also attract a diagnosis of peduncular hallucinosis.

In many ways, the intentions of de Morsier in 1936, when he set out to classify and bring order and understanding to the field of visual hallucinatory syndromes, have not been realised in the nearly 80 years that have followed. Some of the eponymous syndromes he introduced have persisted, though their definitions have evolved over time, but their relationship to neurodegenerative disorders, their underlying causes, and their independence from each other remain in doubt. Overarching theories to explain the development of visual hallucinations have been developed; notably these include the unitary perception and attention deficit model of Collerton et al. (2005) and the tripartite deafferentation/ascending cholinergic-serotoninergic hypothesis of ffytche (2007). Each of these has considerable explanatory power, but neither provides a complete account of all visual hallucinatory syndromes, with each author making valid criticisms of the other model in published commentary appended to Collerton et al. (2005).
The distinction between the models is of considerable relevance to Charles Bonnet syndrome, as the status of this condition is different in each. In ffytche’s model, CBS is the prototype of the deafferentation syndrome, and so separate aetiologically from peduncular hallucinosis. In the Collerton model, it describes a group of patients where the ‘perception’ aspect of the perception/attention deficit balance is likely to be of greater importance, but where the distinction from other disorders in generating visual hallucinations is less clear cut, and is more likely to be on a continuum. The phenomenological differences claimed by ffytche (2007) offer support for the tripartite model and greater separation of the conditions, but as noted in Manford and Andermann (1998), this theoretical difference is not always apparent in practice.

If anything, this study offers support to the Collerton unitary model. The distinction between Charles Bonnet syndrome and visual hallucinations in dementia was not clear cut either phenomenologically or on testing of cognitive functioning. Also, as noted, some of the Charles Bonnet syndrome group may also have attracted diagnosis of peduncular hallucinosis, had the diagnostic focus been on this condition. The VBM results further support this contention, with the only significant differences in grey matter volume being found not in the retinogeniculocortical system or visual accessory areas as expected, but in the metencephalon.

It is now nearly 20 years since Gold and Rabins’ (1987) definition of Charles Bonnet syndrome in purely phenomenological terms, in order to rescue the condition from the diagnostic confusion described in chapter 1.3. However, Gold and Rabins’ rejection of aetiology was only provisional, pending a better understanding of the processes which generate the symptoms that characterise the disorder. Given the
central place Charles Bonnet syndrome has in developing a better understanding of
the nature of visual hallucinations as a whole, the case for further research into its
origins is clear.
This study makes an important contribution to the existing knowledge in this area. Charles Bonnet syndrome is a common condition, but little research has been done into the underlying brain changes that lead to its development. Existing studies have methodological limitations and are over 15 years old; since their publication, development in the field has been limited to a handful of case reports which mainly describe the clinical findings of functional imaging investigations. As set out in chapter 12.2, this study is rigorously designed, and makes use of a recognised and powerful technique, to try to discover if there are differences in the structure of brains of people with Charles Bonnet syndrome and a visually impaired control group.

The main finding of the study, of increased grey matter in the right postero-lateral cerebellar hemisphere is unexpected; but cerebellar abnormalities are not unprecedented when the visual hallucination literature as a whole is examined. A further area of increased grey matter volume in the left postero-medial cerebellar hemisphere failed to retain statistical significance after controlling for potentially relevant factors, but given its strong correlation in magnitude with the right sided cluster, it is worth noting. The significance of these clusters is uncertain. Possible explanations include the indicating the presence of participants with pre-symptomatic Lewy body dementia in the Charles Bonnet group; or that chronic visual hallucinations, possibly irrespective of their cause, produce remodelling of the cerebellum via a process which at this point is unclear. Given the role of the cerebellum in controlling eye movements and in spatial processing, potential mechanisms could exist for this.
The lack of significant findings in the grey matter analysis of the posterior cortex was also surprising, given the existing evidence; but most of this evidence relates to functional scanning (SPECT and fMRI), so it may be that clinically relevant dysfunction in the visual and visual accessory cortex does not produce structural correlates.

The white matter analysis also failed to find any significant differences between the groups. This could be due to the lack of sensitivity of the technique used, and further analysis of the study data making use of semi-quantitative rating scales to examine the extent of deep white matter ischaemic change is planned.

In summary, this study provides further evidence of linkages between the cerebellum and visual functioning; and provides new evidence as to the neuroanatomical substrates of Charles Bonnet syndrome. If also offers some circumstantial evidence to support the perception and attention deficit model of recurrent visual hallucinations put forward by Collerton et al. (2005). Finally, it also demonstrates that this population, of advanced age and significant disability, can be encouraged to participate in imaging studies. It will hopefully stimulate further research into a field that has suffered relative lack of progress in recent years.

Further VBM-MRI studies could look to replicate the results of this one, to see if the increased cerebellar grey matter volume emerges as a robust and repeatable finding. As noted, further analysis of this data is planned to look again at the white matter, as this is an area that previous work has suggested may be important. Diffusion tensor
imaging would be a powerful way of investigating the integrity of the posterior cerebral white matter tracts, to test the hypothesis that damage to these can lead to the development of Charles Bonnet syndrome.

Further functional imaging studies could look in more detail at the cerebellum to see if the increase in activity seen in Lewy body dementia, and hypothesised as a potential cause of the increased cerebellar grey matter volume seen in this study, is present in a cohort with Charles Bonnet syndrome.

Finally, a study with longitudinal follow up of a cohort of patients with Charles Bonnet syndrome, with repeated volumetric analysis over time, and relating this to the course of the visual hallucinations, and to the emergence of any cognitive impairment, would be of great interest. Such a study would offer the potential of insights into the relationship of CBS to dementia, and into the significance of any structural brain changes seen.

Visual hallucinatory disorders are thought to affect more than one million adults in the United Kingdom (Collerton et al. 2005). Charles Bonnet syndrome is an important condition in this regard, offering a model to develop our understanding of this common presentation. It may also, for some people, signify the presence of serious underlying neurodegenerative disorders such as Lewy body dementia or Alzheimer’s disease (Parts I and II of this thesis). Explanatory frameworks, such as those set out by Collerton et al. (2005) and ffytche (2007), and neuroimaging techniques, now exist that can help guide research in the directions most likely to be productive.
Charles Bonnet syndrome as a diagnosis is now nearly 80 years old. Over that time, its usage has changed, broadened to the point of losing any real meaning, and then cut loose from aetiological roots in order to try to impose some form of diagnostic reliability and rigour. As explanatory models of visual hallucinations become more sophisticated, and understanding of the networks of connections that underpin visual functioning develop, there is a chance to significantly advance our understanding of Charles Bonnet syndrome, and so reconnect it with a theoretical underpinning. It may now be possible to identify the abnormalities in brain structure and function that lead to its development. Were this to happen, it would be a vindication for Georges de Morsier, who maintained that such abnormalities must exist. The case for further imaging studies into this condition is strong and should now be a priority.
Part IV

References and Appendices
14. References


Flournoy T (1902) Le case de Charles Bonnet. Hallucinations visuelles chez un vieillards opera de la cataracte. *Arch de Psychol (Geneva), 1*, 1-23.


Gray M and Jones IR (1997) Type II diabetes presenting as the Charles Bonnet syndrome. *Journal of the Royal Society of Medicine, 90*, 503.


Naville E (1908) Hallucinations visuelles a l’etat normal. *Arch de Psychol (Geneve)*, **8**, 1-8.


15. Appendices

Appendix 1: Diagnostic criteria for Charles Bonnet syndrome

A. de Morsier (1936, 1967)

‘Visual hallucinations in elderly patients, accompanied by insight, and occurring in the apparent absence of confusion, neurological disease, sensory deprivation, or ophthalmological disorder’

B. Hecaen and Garcia Badaracco (1956)

Visual hallucinations in eye disease

C. Damas-Mora et al. (1982)

1. Sudden and unexpected onset of visions
2. Rapid insight into unreality
3. Absence of other sensory disorders
4. Vivid and elaborate character of the visions
5. No delusional ideation coexisting with, or developing secondarily to the visions

D. Gold and Rabins (1989)

1. Visual hallucinations which are
   a. formed
   b. complex
   c. persistent or repetitive
   d. stereotyped
2. Insight is fully or partially retained
3. Absence of primary or secondary delusions
4. Absence of hallucinations in other modalities
E. Podoll et al. (1990)

1. Visual hallucinations with normal consciousness level in an aged person are the dominant clinical symptom
2. No delirium, dementia, organic affective disorder, delusions, psychosis, intoxication or neurological disease affecting the central visual projections or visual cortex
3. Visual impairment due to ophthalmic disease is present in most cases, but not required

F. Teunisse et al. (1996)

1. At least one complex visual hallucination within the past four weeks
2. A period between the first and last hallucination exceeding four weeks
3. Full or partial insight into the unreal nature of the hallucinations
4. Absence of hallucinations in other sensory modalities
5. Absence of delusions
6. Hallucinations cannot be explained by the presence of a psychiatric disorder
## Appendix 2: Summary of Papers Published on Charles Bonnet syndrome

<table>
<thead>
<tr>
<th>Type</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Review articles</td>
<td>321</td>
</tr>
<tr>
<td>2.2 Observational studies</td>
<td>322</td>
</tr>
<tr>
<td>2.3 Case Reports</td>
<td>328</td>
</tr>
</tbody>
</table>
## Appendix 2.1: Review articles identified by systematic review

<table>
<thead>
<tr>
<th>Authors &amp; Date</th>
<th>Speciality</th>
<th>Nationality</th>
<th>Comment on relationship with cognitive impairment and dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al. (1997)</td>
<td>Psychiatry</td>
<td>USA</td>
<td>“CBS may appear with early Alzheimer's disease”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“Peripheral sensory impairment causality differentiates CBS hallucinations from the cortex derived hallucinations of psychosis, dementia and delirium”</td>
</tr>
<tr>
<td>Springer (1999)</td>
<td>Psychology</td>
<td>Canada</td>
<td>No specific comment</td>
</tr>
<tr>
<td>Terao (2001)</td>
<td>Psychiatry</td>
<td>Japan</td>
<td>“There is the possibility that we diagnose the early symptoms of dementia as CBS...”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“Taking the features of DLB and CBS together, we should be aware that particularly in the early stages, some patients with DLB may be diagnosed with CBS”</td>
</tr>
<tr>
<td>Menon et al. (2003)</td>
<td>Ophthalmology</td>
<td>UK</td>
<td>“It has been suggested that patients with CBS manifest neuropsychological changes characteristic of early dementia, which are... overlooked due the lack of sensitivity of screening test measures such as the MMSE...”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“It is therefore proposed that visual hallucinations may represent an early marker for dementia in the elderly”</td>
</tr>
<tr>
<td>Gurwood &amp; Abdal (2003)</td>
<td>Optometry</td>
<td>USA</td>
<td>“By far the most important aspect of managing a CBS patient is reassurance and counselling that their condition is not sure to a psychiatric disorder”</td>
</tr>
<tr>
<td>Jacob et al. (2004)</td>
<td>Neurology</td>
<td>UK</td>
<td>“Firm reassurance that the syndrome is not related to mental illness is in itself a major relief”</td>
</tr>
<tr>
<td>ffytche (2005)</td>
<td>Psychiatry</td>
<td>UK</td>
<td>Proposed that the phenomenology of visual hallucinations due to dementia may be different and clinically distinguishable from those due to eye disease</td>
</tr>
<tr>
<td>Cortes &amp; Rueda (2007)</td>
<td>Psychiatry</td>
<td>Mexico</td>
<td>Dementia mentioned only as a differential diagnosis</td>
</tr>
<tr>
<td>Hedges (2007)</td>
<td>Neuro-ophthalmology</td>
<td>USA</td>
<td>“Its (i.e. CBS) occurrence is not an indication of cerebral problems such as Alzheimer’s disease”</td>
</tr>
<tr>
<td>Cammaroto et al. (2008)</td>
<td>Neurology</td>
<td>Italy</td>
<td>No specific comment</td>
</tr>
<tr>
<td>Walsh &amp; Hilas (2009)</td>
<td>Pharmacy</td>
<td>USA</td>
<td>“patients are commonly misdiagnosed with dementia”</td>
</tr>
<tr>
<td>Schadlu et al. (2009)</td>
<td>Ophthalmology</td>
<td>USA</td>
<td>“It is essential to be aware of the possible dual diagnosis of CBS and early dementia, particularly in elderly patients who are susceptible to both disorders”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“The clinician should be aware that CBS may be an early marker for dementia”</td>
</tr>
</tbody>
</table>
## Appendix 2.2: Observational studies of Charles Bonnet syndrome

<table>
<thead>
<tr>
<th>Authors &amp; Date</th>
<th>Number and source of participants</th>
<th>Number/% patients with CBS</th>
<th>Insight present?</th>
<th>Cognition assessed, and if so, was a specific assessment tool used?</th>
<th>Dementia developed at follow up?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berrios &amp; Brook (1984)</td>
<td>150 consecutive referrals to old age psychiatry service</td>
<td>2 (1.3%)</td>
<td>Yes, in 2/2 cases</td>
<td>Yes- using the “Information-Memory-Concentration Test”- scores for CBS cases not given</td>
<td>No FU</td>
</tr>
<tr>
<td>Kolmel (1985)</td>
<td>120 patients with homonymous hemianopia from ophthalmology clinic</td>
<td>16 cases of VH (13.3%)- CBS diagnosis not used</td>
<td>No comment</td>
<td>No</td>
<td>No FU</td>
</tr>
<tr>
<td>Olbrich et al. (1987)</td>
<td>43 ophthalmic inpatients, over 65 with bilateral eye disease, best eye acuity &lt;0.3 logMAR</td>
<td>5 (11.6%)</td>
<td>No comment</td>
<td>Not specifically- “psychiatric examination” carried out, findings not explicitly documented</td>
<td>No FU</td>
</tr>
<tr>
<td>Norton-Willson &amp; Munir (1987)</td>
<td>434 consecutive referrals to old age psychiatry service</td>
<td>8 (1.8%)</td>
<td>Yes, in 8/8 cases</td>
<td>Yes- “a 16 point-modification of the Tooting Bec-Camden questionnaire” as a test for dementia, no scores given</td>
<td>No FU</td>
</tr>
<tr>
<td>Lepore (1990)</td>
<td>104 patients consulting a neuro-ophthalmology service</td>
<td>complex VH found in 21%</td>
<td>No comment</td>
<td>No</td>
<td>No FU</td>
</tr>
<tr>
<td>Brown &amp; Murphy (1992)</td>
<td>100 consecutive referrals with choroidal neovascularisation to ophthalmology</td>
<td>12 (12%)</td>
<td>No comment</td>
<td>No</td>
<td>No FU</td>
</tr>
<tr>
<td>Cole (1992)</td>
<td>2000 referrals to old age psychiatry</td>
<td>13 (0.7%)</td>
<td>Yes in 3; partial in 1; no in 9</td>
<td>Not specifically- a “careful clinical assessment of their cognition” carried out. 5 had mild dementia, 4 MCI, 4 normal cognition</td>
<td>Yes- 4/13 at one year</td>
</tr>
<tr>
<td>Schultz &amp; Melzack (1993)</td>
<td>14 participants from database of low vision charity</td>
<td>14 (Not available)</td>
<td>No comment</td>
<td>Yes- BDI, MMPI, State-Trait Anxiety Inventory, MMSE (mean score 28.56). See text for discussion</td>
<td>No- 0/14 at 9 months</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Characteristics</td>
<td>Findings</td>
<td>Follow-Up</td>
<td></td>
<td></td>
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<td>------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
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<tr>
<td>Crane et al. (1994)</td>
<td>284 low vision clinic attenders</td>
<td>photopsias in 150, formed VH in 109 (38.3%). No difference in characteristics of those with photopsias compared to formed VH</td>
<td>No FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holroyd et al. (1994)</td>
<td>127 attenders at low vision clinic</td>
<td>8 (6.3%) Yes in 5; partial in 3 Yes- telephone interview for cognitive status (TICS) lower score significantly associated with VH</td>
<td>No FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shedlack et al. (1994)</td>
<td>5 patients with CBS and 8 controls underwent MRI scanning</td>
<td>5 No comment</td>
<td>No FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teunisse et al. (1994)</td>
<td>Patients attending departments of geriatric medicine and psychiatry</td>
<td>14 Yes in 12 (though after delay in 3); variable in 2 Yes- the MMSE. 4 patients had low scores (10-22), 2 due to dementia/ organic amnestic syndrome</td>
<td>No FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teunisse et al. (1995)</td>
<td>300 attendees at low vision clinic, 200 elderly general ophthalmic patients with relatively preserved acuity</td>
<td>33 in low vision group (11%); 2 in preserved acuity group (1%) No comment Yes- the MMSE. Scores ranged from 22 to 30, mean 26.5. No specific comment on this in the discussion section</td>
<td>No FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaphiaides et al. (1996)</td>
<td>41 patients with occipital infarcts</td>
<td>6 had complex VH No comment</td>
<td>No FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adachi (1996)</td>
<td>703 patients with leprosy assessed for presence of CBS</td>
<td>3 (0.4%) found to have CBS No comment No- though those with history of psychiatric illness were reviewed by a psychiatrist</td>
<td>No FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teunisse et al. (1996)</td>
<td>505 patients attending low vision clinic aged 18 +</td>
<td>60 (11.9%) Yes in 49; partial or fluctuating in 11 Not specifically- the Geriatric Mental State Schedule was administered</td>
<td>No FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pliskin et al. (1996)</td>
<td>22 referrals from neurology, psychiatry, ophthalmology; 11 controls</td>
<td>15 of 22 met CBS criteria Yes in 7; no in 8 Yes- WAIS-R, DRS, WMS, RAVLT, CVLT. Abnormalities consistent with MCI in 14/15- see text for discussion</td>
<td>Yes- 1/15 at 16 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Patients/Demographics</td>
<td>Follow-up</td>
<td>Cognitive Functioning</td>
<td>Comments</td>
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<td>----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Holroyd and Rabins (1996)</td>
<td>13 patients from original study followed up after 39 months</td>
<td>13</td>
<td>No comment</td>
<td>Yes- TICS scores repeated, no change found</td>
<td></td>
</tr>
<tr>
<td>Schultz. et al. (1996)</td>
<td>60 patients with CBS had their VH characterised in detail</td>
<td>60</td>
<td>No comment</td>
<td>No</td>
<td></td>
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<tr>
<td>Teunisse et al. (1998)</td>
<td>373 consecutive referrals to low vision clinic aged &gt;65; sub-group of those in Teunisse et al. (1996)</td>
<td>52</td>
<td>No comment</td>
<td>Yes- MMSE administered in addition to GMSS</td>
<td></td>
</tr>
<tr>
<td>Teunisse et al. (1999)</td>
<td>Same group as above</td>
<td>50</td>
<td>No comment</td>
<td>No</td>
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<tr>
<td>Cohen et al. (2000)</td>
<td>60 patients undergoing photocoagulation in AMD</td>
<td>10</td>
<td>No comment</td>
<td>No</td>
<td></td>
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<tr>
<td>Eagan &amp; Williams (2000)</td>
<td>88 attenders at an eye hospital assessed for presence of VH, and those found to have VH followed up over 2 years</td>
<td>9/88 (10%) had VH. At FU hallucinations persisted in 6/9.</td>
<td>No comment</td>
<td>No- though excluded if found to have disorientation</td>
<td></td>
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<tr>
<td>Scott et al. (2001)</td>
<td>86 consecutive patients at a retinal vascular centre</td>
<td>13 (15.1%)</td>
<td>Present in 8, absent in 5</td>
<td>Yes- telephone interview for cognitive status. No significant difference in scores between those with and without VH</td>
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<tr>
<td>Nesher et al. (2001)</td>
<td>89 attendees at glaucoma clinic with visual acuity &lt;20/80</td>
<td>11 (12.3%)</td>
<td>Present in all 11</td>
<td>Yes- a short form of the MMSE. No patients reported to have &quot;impaired cognition&quot;, but actual scores not given, nor a definition of this term</td>
<td></td>
</tr>
<tr>
<td>Tatlipinar et al. (2001)</td>
<td>80 patients referred to low vision clinic aged 18 and over</td>
<td>25 (31.3%)</td>
<td>No comment</td>
<td>No</td>
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<tr>
<td>Study</td>
<td>Sample Description</td>
<td>Vomiting (VH) (%)</td>
<td>Recommendation</td>
<td>Follow-up</td>
<td>Notes</td>
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<tr>
<td>Cohen et al. (2003)</td>
<td>100 patients undergoing photodynamic therapy for AMD</td>
<td>5 (5%)</td>
<td>No comment</td>
<td>No FU</td>
<td>No comment</td>
</tr>
<tr>
<td>Freiman et al. (2004)</td>
<td>41 consecutive patients with visual field deficit after neurosurgery</td>
<td>4 (9.8%)</td>
<td>No comment</td>
<td>No FU</td>
<td>No comment</td>
</tr>
<tr>
<td>Tan et al. (2004)</td>
<td>1077 consecutive patients aged 50+ attending an ophthalmic tertiary referral centre</td>
<td>4 (0.4%)</td>
<td>No comment</td>
<td>Yes</td>
<td>Not specifically- the Mini International Neuropsychiatric Interview was administered, but no comment made beyond “none of the 5 patients had evidence of psychiatric disorder”</td>
</tr>
<tr>
<td>Shiraishi et al. (2004)</td>
<td>1000 consecutive out patients at an ophthalmology department</td>
<td>5 (0.5%)</td>
<td>Present in all 5</td>
<td>Yes</td>
<td>Not specifically- the Mini International Neuropsychiatric Interview was administered, but no comment made beyond “none of the 5 patients had evidence of psychiatric disorder”</td>
</tr>
<tr>
<td>Jackson et al. (2005)</td>
<td>224 patients referred for vision rehabilitation</td>
<td>74 (33%)</td>
<td>No comment</td>
<td>No FU</td>
<td>Follow up- but no assessment of cognitive status</td>
</tr>
<tr>
<td>Menon (2005)</td>
<td>48 consecutive patients attending ophthalmology, in- and out-patients</td>
<td>30 (63%)</td>
<td>Yes in all 30, following initial deception in 18</td>
<td>Yes</td>
<td>Yes- MMSE “with two vision dependent items omitted”. No difference in mean scores between those with and without VH</td>
</tr>
<tr>
<td>Abbott et al. (2007)</td>
<td>53 patients attending ophthalmology department with visual acuity &lt;0.6, and AMD with central scotoma</td>
<td>21 (40%)</td>
<td>No comment</td>
<td>Yes FU</td>
<td>Yes- MMSE (blind) and telephone interview for cognitive status. No differences found between those with and without VH</td>
</tr>
<tr>
<td>Jackson et al. (2007)</td>
<td>225 consecutive low vision referrals assessed for presence of VH, acuity and contrast sensitivity assessed</td>
<td>78 (35%)</td>
<td>No comment</td>
<td>No FU</td>
<td>No comment</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Baseline</td>
<td>Specific</td>
<td>Vascular</td>
<td>Follow-up</td>
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<tr>
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</tr>
<tr>
<td>Poggel et al. (2007)</td>
<td>121</td>
<td>Visual loss</td>
<td>Specific vision restoration therapy</td>
<td>53% in therapy group and 35% in the cohort as a whole had formed VH</td>
<td>No comment</td>
</tr>
<tr>
<td>Vukicevic et al. (2008)</td>
<td>200</td>
<td>Ophthalmology clinics aged over 60 with best acuity 6/12 or less</td>
<td>No comment</td>
<td>35 (17.5%); 30 age-matched controls were selected from the non-VH patients</td>
<td>No comment</td>
</tr>
<tr>
<td>Khan et al. (2008)</td>
<td>360</td>
<td>AMD</td>
<td>No comment</td>
<td>97 (27%)</td>
<td>No comment</td>
</tr>
<tr>
<td>Crumbliss et al. (2008)</td>
<td>50</td>
<td>Vision rehab</td>
<td>No comment</td>
<td>12 (24%)</td>
<td>Used Damas-Mora (1982) criteria which require insight</td>
</tr>
<tr>
<td>Gilmour et al. (2009)</td>
<td>258</td>
<td>Low vision clinic aged 40 or over, 251 controls with little/no vision loss</td>
<td>Insight in 80% from first episode; &gt;10 episodes required in 6%</td>
<td>87 (34%) of low vision patients, 4 (1.6%) of those with normal vision</td>
<td>Yes - the MMSE. Mean scores given in graph, difficult to read, appear to be around 25. No significant differences between cases/controls</td>
</tr>
<tr>
<td>Madill et al. (2009)</td>
<td>10</td>
<td>CBS</td>
<td>No comment</td>
<td>10</td>
<td>No comment</td>
</tr>
<tr>
<td>Jackson &amp; Bassett (2010)</td>
<td>152</td>
<td>Previous study reviewed after one year</td>
<td>No comment</td>
<td>72% of those with VH still experienced these; 24% of those with no VH originally had developed them</td>
<td>No comment</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Population</td>
<td>Key Findings</td>
<td>Follow-Up Notes</td>
<td>FU</td>
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<td>-----------------</td>
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<td></td>
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<tr>
<td>Vojnikovic et al. (2010)</td>
<td>350 patients with macular degeneration</td>
<td>13% diagnosed with CBS. Strong correlation with extent of vision loss.</td>
<td>No comment</td>
<td>No FU</td>
<td></td>
</tr>
<tr>
<td>Miyaoka et al. (2011)</td>
<td>20 patients with CBS were treated in open-label study with Yi-Gan San</td>
<td>Significant decrease in VH as assessed by NPI, CGI, hallucination subscale of PANSS</td>
<td>No comment</td>
<td>No FU</td>
<td></td>
</tr>
<tr>
<td>Singh &amp; Sorenson (2011)</td>
<td>220 patients with AMD being treated with ranibizumab studied to see if improving acuity improves CBS</td>
<td>22 (10%) had CBS. After treatment, 23% of these reported VH better; these were the participants where acuity improved</td>
<td>No comment</td>
<td>No FU</td>
<td></td>
</tr>
<tr>
<td>Jackson et al. (2011)</td>
<td>698 patients attending vision rehabilitation clinic</td>
<td>161 (23%) had recurrent VH. Proportion of those with glaucoma having VH no different from in other diagnoses</td>
<td>No comment</td>
<td>No FU</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 2.3: Case reports identified by systematic review

<table>
<thead>
<tr>
<th>Authors &amp; Date</th>
<th>Speciality</th>
<th>Nationality</th>
<th>Age/Sex of Case</th>
<th>Insight status?</th>
<th>Cognition Assessed?</th>
<th>Dementia developed at follow-up?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abell (1845)</td>
<td>USA</td>
<td>unclear</td>
<td>no comment</td>
<td>no</td>
<td>clinical assessment</td>
<td>No</td>
</tr>
<tr>
<td>Bartlett (1951)</td>
<td>ophthalmology</td>
<td>UK</td>
<td>84 m</td>
<td>full</td>
<td>clinical</td>
<td>No</td>
</tr>
<tr>
<td>Hart (1967)</td>
<td>ophthalmology</td>
<td>UK</td>
<td>79 f</td>
<td>no comment</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73 f</td>
<td>no comment</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Levine (1980)</td>
<td>ophthalmology</td>
<td>USA</td>
<td>77 f</td>
<td>full</td>
<td>“psychiatrist noted she did not have the common deficits noted in an organic mental syndrome”</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70 m</td>
<td>full</td>
<td>“orientated in time, place and person, answers pertinent and reasonable”</td>
<td></td>
</tr>
<tr>
<td>White (1980)</td>
<td>psychiatry</td>
<td>UK</td>
<td>64 m</td>
<td>no comment</td>
<td>clinical assessment- “mental function was good”</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75 m</td>
<td>no comment</td>
<td>clinical assessment- “mental function was good”</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>72 f</td>
<td>full</td>
<td>clinical assessment- “mental function was good”</td>
<td></td>
</tr>
<tr>
<td>Berrios &amp; Brook (1982)</td>
<td>psychiatry</td>
<td>UK</td>
<td>75 m</td>
<td>absent</td>
<td>clinical assessment- Alzheimer’s disease present at diagnosis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>77 m</td>
<td>absent</td>
<td>clinical assessment- “memory failure” present at diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>85 f</td>
<td>absent</td>
<td>clinical assessment- multi-infarct dementia present at diagnosis</td>
<td></td>
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<tr>
<td>Damas-Mora <strong>et al.</strong> (1982)</td>
<td>psychiatry</td>
<td>UK</td>
<td>86 m</td>
<td>full</td>
<td>clinical assessment- “no signs of marked memory impairment”</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>full</td>
<td>clinical assessment- “no signs of intellectual deterioration”</td>
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<tr>
<td>Gittinger <strong>et al.</strong> (1982)</td>
<td>ophthalmology</td>
<td>USA</td>
<td>35 f</td>
<td>no comment</td>
<td>No</td>
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<tr>
<td>McNamara <strong>et al.</strong> (1982)</td>
<td>psychiatry/neurology</td>
<td>USA</td>
<td>64 f</td>
<td>partial</td>
<td>clinical assessment- “memory, abstract reasoning, intelligence intact”</td>
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<tr>
<td>Ram <strong>et al.</strong> (1987)</td>
<td>neurosurgery</td>
<td>Israel</td>
<td>58 f</td>
<td>full</td>
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<tr>
<td></td>
<td></td>
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<td>58 m</td>
<td>no comment</td>
<td>No</td>
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<tr>
<td>Study</td>
<td>Field</td>
<td>Country</td>
<td>Age</td>
<td>Gender</td>
<td>Assessment Type</td>
<td>Results</td>
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<tr>
<td>Rosenbaum et al. (1987)</td>
<td>Neurology</td>
<td>USA</td>
<td>82</td>
<td>f</td>
<td>Partial</td>
<td>Clinical assessment - “no evidence of cognitive dysfunction”</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>66</td>
<td>m</td>
<td>Partial</td>
<td>Clinical assessment - “neuropsychological testing within normal limits”</td>
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<tr>
<td>Crystal et al. (1988)</td>
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<td>70</td>
<td>f</td>
<td>Partial</td>
<td>Yes - “borderline normal score on the Blessed test of orientation, memory and concentration”</td>
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<tr>
<td>Gold &amp; Rabins (1989)</td>
<td>Psychiatry</td>
<td>USA</td>
<td>84</td>
<td>f</td>
<td>Partial</td>
<td>Yes - MMSE 27</td>
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<td></td>
<td></td>
<td></td>
<td>72</td>
<td>m</td>
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<td>Yes - MMSE 25</td>
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<td>69</td>
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<td>82</td>
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</tr>
<tr>
<td></td>
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<td>85</td>
<td>f</td>
<td>Partial</td>
<td>Yes - MMSE 19</td>
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<td></td>
<td></td>
<td></td>
<td>80</td>
<td>f</td>
<td>Full</td>
<td>Yes - MMSE 22</td>
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<tr>
<td>Beats (1989)</td>
<td>Psychiatry</td>
<td>UK</td>
<td>74</td>
<td>m</td>
<td>Partial</td>
<td>Clinical assessment - “normal”</td>
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<td>Hosty (1989)</td>
<td>Psychiatry</td>
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<td>m</td>
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<td>88</td>
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<td>Siatkowski et al. (1990)</td>
<td>Ophthalmology</td>
<td>USA</td>
<td>87</td>
<td>f</td>
<td>Full</td>
<td>Clinical assessment - “normal”</td>
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<td></td>
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<td>84</td>
<td>f</td>
<td>Full</td>
<td>Clinical assessment - “normal”</td>
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<tr>
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<td>78</td>
<td>m</td>
<td>Full</td>
<td>Clinical assessment - “normal”</td>
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<td>Clinical assessment - “normal”</td>
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<tr>
<td>Ball (1991)</td>
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<td>Partial</td>
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<td>m</td>
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<td>Yes - MMSE 27</td>
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<td>84</td>
<td>m</td>
<td>Full</td>
<td>Yes - MMSE 27</td>
</tr>
<tr>
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<td>86</td>
<td>f</td>
<td>Full</td>
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<td>Ballard et al. (1991)</td>
<td>Psychiatry</td>
<td>UK</td>
<td>73</td>
<td>f</td>
<td>Partial</td>
<td>Yes - “35/37 on the 37 item test”</td>
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<td>Sharma (1991)</td>
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<td>Canada</td>
<td>89</td>
<td>m</td>
<td>Partial</td>
<td>Yes - MMSE 22/30</td>
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<td>Brabbins (1992)</td>
<td>Psychiatry</td>
<td>UK</td>
<td>79</td>
<td>f</td>
<td>Partial</td>
<td>Clinical assessment - “memory testing revealed minor deficits”</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>78</td>
<td>f</td>
<td>Partial</td>
<td>Clinical assessment - “disorientation to time and place, patchy long term memory deficits and poor short term memory”</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>f</td>
<td>Partial</td>
<td>Yes - resembling Lewy body dementia</td>
</tr>
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<td>Study</td>
<td>Field</td>
<td>Country</td>
<td>Age</td>
<td>Sex</td>
<td>Test/Assessment</td>
<td>Findings</td>
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<td>Haddad &amp; Benbow (1992)</td>
<td>psychiatry</td>
<td>UK</td>
<td>84 f</td>
<td>partial</td>
<td>yes- Wechsler Adult Intelligence Scale, Benton visual retention task, cognitive scale of Clifton Assessment procedure for the Elderly. Isolated problem with visuospatial skills noted.</td>
<td>yes- within 4 months, general cognitive decline, patient died 16 months later</td>
</tr>
<tr>
<td>Bhatia et al. (1992)</td>
<td>psychiatry</td>
<td>India</td>
<td>38 m</td>
<td>full</td>
<td>yes- Wechsler Adult Intelligence Scale-reported to be normal</td>
<td></td>
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<tr>
<td>Tueth et al. (1993)</td>
<td>psychiatry</td>
<td>USA</td>
<td>83 f</td>
<td>full</td>
<td>clinical assessment- “normal”</td>
<td></td>
</tr>
<tr>
<td>Garcia &amp; Roder (1993)</td>
<td>psychiatry</td>
<td>Chile</td>
<td>90 f</td>
<td>full</td>
<td>“lucid”</td>
<td></td>
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<tr>
<td>Lalla &amp; Primeau</td>
<td>psychiatry</td>
<td>Canada</td>
<td>79 f</td>
<td>full</td>
<td>“normal psychiatric exam”</td>
<td></td>
</tr>
<tr>
<td>Tueth et al. (1993)</td>
<td>psychiatry</td>
<td>USA</td>
<td>78 m</td>
<td>partial</td>
<td>clinical assessment- “normal”</td>
<td></td>
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<tr>
<td>Howard et al. (1994)</td>
<td>psychiatry</td>
<td>UK</td>
<td>83 m</td>
<td>absent</td>
<td>yes- MMSE 24/29- &quot;MCI most probably due to early Alzheimer's disease&quot;</td>
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</tr>
<tr>
<td>Sadanandan Unni (1994)</td>
<td>psychiatry</td>
<td>India</td>
<td>53 m</td>
<td>full</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Arya (1995)</td>
<td></td>
<td>New Zealand</td>
<td>83 f</td>
<td>no comment</td>
<td>No</td>
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<td>Hartmann et al. (1995)</td>
<td>psychiatry</td>
<td>USA</td>
<td>31 m</td>
<td>full</td>
<td>yes- “neuro-cognitive testing showed decreased attention and impaired higher cortical functioning”</td>
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<td>Maricle et al. (1995)</td>
<td>psychiatry</td>
<td>USA</td>
<td>33 f</td>
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<td>clinical assessment- no impairment in cognition found</td>
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<td>Sonnenblick et al. (1995)</td>
<td>ophthalmology/rheumatology</td>
<td>USA/ Israel</td>
<td>87 f</td>
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<td>Adachi &amp; Watanabe (1996)</td>
<td>psychiatry</td>
<td>Japan</td>
<td>76 f</td>
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<td>“fully orientated, normal memory and language”</td>
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<td>69 f</td>
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<td>psychiatry</td>
<td>Spain</td>
<td>68 f</td>
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<td>yes- MMSE 23/? (“vision dependent items excluded”)</td>
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<td>75 f</td>
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<td>73 m</td>
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<td>Nevins (1996)</td>
<td>geriatrics</td>
<td>USA</td>
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<td>no comment</td>
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<td>103 f</td>
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<td>83 m</td>
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<td>psychiatry</td>
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<td>72 f</td>
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<td>100 m</td>
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<td>Spain</td>
<td>80 m</td>
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<td>Ophthalmology</td>
<td>USA</td>
<td>84 f</td>
<td>no comment</td>
<td>No</td>
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<td>Kishi et al. (2000)</td>
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<td>Japan</td>
<td>73 f</td>
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<td>Psychiatry</td>
<td>Belgium</td>
<td>84 m</td>
<td>no comment</td>
<td>Clinical assessment - “no evidence of cognitive decline”</td>
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<td>Psychiatry</td>
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<td>USA</td>
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<td>no comment</td>
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<td>Needham &amp; Taylor (2000)</td>
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<td>USA</td>
<td>71 m</td>
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<td>70 m</td>
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<td>no comment</td>
<td>Clinical assessment - “absence of significant organic brain impairment”</td>
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<td>72 m</td>
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<td>Clinical assessment - “no indication of any cognitive pathology”</td>
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<td>72 m</td>
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<td>Neurology</td>
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<td>24 f</td>
<td>no comment</td>
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<td>Llamas et al. (2001)</td>
<td>Psychiatry</td>
<td>Argentina</td>
<td>83 m</td>
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<td>Yes</td>
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<td>Paulig &amp; Mentrup (2001)</td>
<td>Unclear</td>
<td>Germany</td>
<td>86 f</td>
<td>no comment</td>
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<td>Field</td>
<td>Country</td>
<td>Age/Gender</td>
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<td>clinical assessment- “no short or long term memory problems”</td>
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<td>89 m</td>
<td>partial</td>
<td>clinical assessment- “fully orientated and able to discuss recent events”</td>
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<td>72 m</td>
<td>partial</td>
<td>clinical assessment- “performed well on cognitive testing”</td>
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<td>Chen et al. (2001)</td>
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<td>Taiwan</td>
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<td>yes- MMSE 25/25</td>
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<td>Asensio Sanchez (2002)</td>
<td>ophthalmology</td>
<td>Spain</td>
<td>59 f</td>
<td>full</td>
<td>Yes- “MMSE normal”</td>
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<td>Mewasingh et al. (2002)</td>
<td>paediatrics</td>
<td>Belgium</td>
<td>9 m</td>
<td>full</td>
<td>clinical assessment- “otherwise unremarkable psychobehavioural state”</td>
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<td>Ledesma Perez et al. (2002)</td>
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<td>Spain</td>
<td>82 f</td>
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<td>clinical assessment- “normal”</td>
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<td>Rovner (2002)</td>
<td>psychiatry</td>
<td>USA</td>
<td>75 m</td>
<td>partial</td>
<td>clinical assessment- “no cognitive deficits”</td>
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<td>Maeda et al. (2002)</td>
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<td>Rovner (2002)</td>
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<td>USA</td>
<td>75 m</td>
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<td>clinical assessment- “did not meet DSM dementia criteria”</td>
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<td>89 f</td>
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<td>UK</td>
<td>87 m</td>
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<td>clinical assessment- “cognitive examination normal for age”</td>
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<td>yes- MMSE 26, digit span, &quot;no evidence of executive dysfunction&quot;</td>
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<td>Spain</td>
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<td>clinical assessment- &quot;retained full insight and cognition&quot;</td>
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<td>61 m</td>
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<td>59 m</td>
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<td>79 f</td>
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<td>Italy</td>
<td>62 m</td>
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<td>Spain</td>
<td>71 f</td>
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</tr>
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<td>Japan</td>
<td>66 f</td>
<td>full</td>
<td>clinical assessment- “no cognitive symptoms”</td>
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<tr>
<td>Grau &amp; Paloma (2006)</td>
<td>psychiatry</td>
<td>Spain</td>
<td>80 m</td>
<td>full</td>
<td>yes- “35/35 on the minimental test of Lobo”</td>
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<td>USA</td>
<td>81 f</td>
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<td>Nixon &amp; Mason (2006)</td>
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<td>USA</td>
<td>83 f</td>
<td>no comment</td>
<td>“psychiatric evaluation unremarkable”</td>
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<tr>
<td>Siros (2006)</td>
<td>psychiatry</td>
<td>Canada</td>
<td>82 m</td>
<td>full</td>
<td>yes- MMSE 28/30</td>
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<tr>
<td>Tan et al. (2006)</td>
<td>ophthalmology</td>
<td>Singapore</td>
<td>77 m</td>
<td>full</td>
<td>No</td>
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<td>63 f</td>
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<tr>
<td>Toosy et al. (2006)</td>
<td>ophthalmology</td>
<td>UK</td>
<td>68 m</td>
<td>no comment</td>
<td>No</td>
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<tr>
<td>Rojas-Rojas et al. (2007)</td>
<td>psychiatry</td>
<td>Chile</td>
<td>40 f</td>
<td>partial</td>
<td>clinical assessment- “conserved global memory”</td>
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<td></td>
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<td></td>
<td>50 f</td>
<td>no comment</td>
<td>“dementia/delirium ruled out”</td>
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<tr>
<td>Koh et al. (2007)</td>
<td>ophthalmology</td>
<td>Japan</td>
<td>79 m</td>
<td>no comment</td>
<td>No</td>
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<td></td>
<td></td>
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<td>63 m</td>
<td>no comment</td>
<td>No</td>
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<td></td>
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<td>No</td>
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<td></td>
<td></td>
<td>55 m</td>
<td>no comment</td>
<td>No</td>
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<td>52 m</td>
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<td></td>
<td></td>
<td></td>
<td>74 f</td>
<td>no comment</td>
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<tr>
<td>Nagaratnam (2007)</td>
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<td>Australia</td>
<td>73 f</td>
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<td>yes- MMSE “in the normal range (making allowance for poor vision)”</td>
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<tr>
<td>Mahgoub &amp; Serby (2007)</td>
<td>psychiatry</td>
<td>USA</td>
<td>78 f</td>
<td>partial</td>
<td>yes- MMSE 28/30 yes- mild dementia after several months</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>72 f</td>
<td>full</td>
<td>yes- MMSE 27/30</td>
<td></td>
</tr>
<tr>
<td>Archibaldo Donoso et al. (2007)</td>
<td>psychiatry</td>
<td>Chile</td>
<td>73 f</td>
<td>full</td>
<td>clinical assessment- “no memory deficit”</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>84 f</td>
<td>partial</td>
<td>clinical assessment- normal yes- Alzheimer’s disease after 4 years</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>80 m</td>
<td>partial</td>
<td>yes- MMSE 22/27, diagnosed with MCI yes- Alzheimer’s disease after 1 year</td>
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<td>Ashwin &amp; Tsaloumas (2007)</td>
<td>ophthalmology</td>
<td>UK</td>
<td>74 m</td>
<td>full</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Field</td>
<td>Country</td>
<td>Gender</td>
<td>Type</td>
<td>Assessment Details</td>
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<tr>
<td>Contardi et al. (2007)</td>
<td>neurology</td>
<td>Italy</td>
<td>49 f</td>
<td>full</td>
<td>clinical assessment- “no impairment in consciousness”</td>
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<tr>
<td>Garcia Fraga et al. (2007)</td>
<td>psychiatry</td>
<td>Spain</td>
<td>86 f</td>
<td>full</td>
<td>clinical assessment- “no cognitive impairment”</td>
<td></td>
</tr>
<tr>
<td>Koethe et al. (2007)</td>
<td>psychiatry</td>
<td>Germany</td>
<td>78 f</td>
<td>no comment</td>
<td>No</td>
<td></td>
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<tr>
<td>Lang et al. (2007)</td>
<td>psychiatry</td>
<td>Germany</td>
<td>78 f</td>
<td>full</td>
<td>yes- MMSE 28/30</td>
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<td>Plummer et al. (2007)</td>
<td>neurology</td>
<td>Australia</td>
<td>73 f</td>
<td>partial</td>
<td>No</td>
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<tr>
<td>Plummer et al. (2007)</td>
<td>neurology</td>
<td>Australia</td>
<td>90 m</td>
<td>partial</td>
<td>No</td>
<td></td>
</tr>
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<td>Billings &amp; Pitt (2008)</td>
<td></td>
<td>USA</td>
<td>95 m</td>
<td>full</td>
<td>No</td>
<td></td>
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<tr>
<td>Eng et al. (2008)</td>
<td>ophthalmology</td>
<td>USA</td>
<td>77 m</td>
<td>no comment</td>
<td>“good cognitive functioning”</td>
<td></td>
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<td>Holroyd &amp; Sabeen (2008)</td>
<td>psychiatry</td>
<td>USA</td>
<td>42 f</td>
<td>full</td>
<td>yes- MMSE 28/30</td>
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<tr>
<td>Ugas Ballester et al. (2008)</td>
<td>psychiatry</td>
<td>Spain</td>
<td>27 f</td>
<td>partial</td>
<td>No</td>
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<td>Gupta et al. (2008)</td>
<td>psychiatry</td>
<td>India</td>
<td>60 m</td>
<td>absent</td>
<td>clinical assessment- “unremarkable”</td>
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<tr>
<td>Valencia &amp; Gabriel Franco (2008)</td>
<td>psychiatry</td>
<td>Chile</td>
<td>94 f</td>
<td>full</td>
<td>yes- MMSE 22 on Colombian version, “normal for age and education level”</td>
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<td>Hanyu et al. (2008)</td>
<td>geriatric medicine</td>
<td>Japan</td>
<td>81 f</td>
<td>full</td>
<td>yes- MMSE 27/30                                                                     yes- Lewy body dementia after several years</td>
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<td>Tan et al. (2008)</td>
<td>psychiatry/ ophthalmology</td>
<td>Malaysia</td>
<td>92 m</td>
<td>full</td>
<td>“normal for age, no memory impairment noted”</td>
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<tr>
<td>Walker &amp; Keys (2008)</td>
<td>geriatrics</td>
<td>USA</td>
<td>72 m</td>
<td>full</td>
<td>“no overt signs of dementia”                                                        yes- Lewy body dementia after 3 years</td>
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<td>Dozzi Brucki et al. (2009)</td>
<td>psychiatry</td>
<td>Brazil</td>
<td>90 m</td>
<td>no comment</td>
<td>yes- MMSE 26</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>83 f</td>
<td>no comment</td>
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<td></td>
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<td></td>
<td>68 f</td>
<td>no comment</td>
<td>yes- MMSE 22</td>
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<td></td>
<td></td>
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<td>50 f</td>
<td>no comment</td>
<td>yes- MMSE 23</td>
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<td></td>
<td></td>
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<td>63 m</td>
<td>no comment</td>
<td>yes- MMSE 23</td>
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<td>93 f</td>
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<td>yes- MMSE 27</td>
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<td>Gender</td>
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<td>Maranhao-Filho (2009)</td>
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<td>Brazil</td>
<td>82 f</td>
<td>no comment</td>
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<td>MMSE 29/30</td>
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<td>Ricard (2009)</td>
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<td>UK</td>
<td>82 f</td>
<td>no comment</td>
<td>No</td>
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<tr>
<td>Jackson &amp; Ferencz (2009)</td>
<td>ophthalmology</td>
<td>Canada</td>
<td>69 f</td>
<td>partial</td>
<td>clinical assessment- “clear cognition”</td>
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<tr>
<td>Sabri &amp; Yasin (2009)</td>
<td>psychiatry</td>
<td>Singapore</td>
<td>90 m</td>
<td>partial</td>
<td>“no significant cognitive impairment”</td>
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<tr>
<td>Miyaoka et al. (2009)</td>
<td>psychiatry</td>
<td>Japan</td>
<td>73 f</td>
<td>full</td>
<td>yes</td>
<td>MMSE 25, “32 marks on verbal fluency test”</td>
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<td>Segers (2009)</td>
<td>neurology</td>
<td>Belgium</td>
<td>85 f</td>
<td>full</td>
<td>yes</td>
<td>MMSE 30/30</td>
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<td>psychiatry</td>
<td>Japan</td>
<td>76 f</td>
<td>partial</td>
<td>yes</td>
<td>MMSE 26/30, 7/70 ADAS</td>
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<td>ophthalmology</td>
<td>USA</td>
<td>79 m</td>
<td>full</td>
<td>yes</td>
<td>MMSE 29/30, 3/70 ADAS</td>
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<td></td>
<td></td>
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<td>86 m</td>
<td>full</td>
<td>yes</td>
<td>MMSE 25/27, “intact cognition” reported as unchanged after 1 year</td>
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<td>Khadavi et al. (2010)</td>
<td>ophthalmology</td>
<td>USA</td>
<td>70 m</td>
<td>full</td>
<td>“fully orientated, no cognitive impairment noted”</td>
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<td>Vukicevic (2010)</td>
<td>ophthalmology</td>
<td>Australia</td>
<td>80 f</td>
<td>partial</td>
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<td>psychiatry</td>
<td>USA</td>
<td>79 m</td>
<td>full</td>
<td>yes</td>
<td>MMSE 24/30                   Followed up after 18 months- no change in MMSE or cognition</td>
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<td>Chen &amp; Liu (2011)</td>
<td>psychiatry</td>
<td>Taipei</td>
<td>70 f</td>
<td>full</td>
<td>yes</td>
<td>MMSE 30/30</td>
</tr>
<tr>
<td>Jang et al. (2011)</td>
<td>neurology</td>
<td>South Korea</td>
<td>69 m</td>
<td>full</td>
<td>No</td>
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<td>Cinar et al. (2011)</td>
<td>neurology</td>
<td>Turkey</td>
<td>80 m</td>
<td>full</td>
<td>yes</td>
<td>MMSE 26, excluding vision dependent items</td>
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<td>Gil Navarro et al. (2011)</td>
<td>neurology</td>
<td>Spain</td>
<td>78 m</td>
<td>full</td>
<td>No</td>
<td>yes- Lewy body dementia after 2 years</td>
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<td>Ghaffarinejad &amp; Estilaee (2011)</td>
<td>ophthalmology</td>
<td>Iran</td>
<td>72 f</td>
<td>full</td>
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<td></td>
<td>UK</td>
<td>66 m</td>
<td>no comment</td>
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<td>Yacoub &amp; Ferrucci (2011)</td>
<td>ophthalmology</td>
<td>USA</td>
<td>85 m</td>
<td>no comment</td>
<td>psychiatric evaluation concluded “patient did not have dementia”</td>
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<td></td>
<td></td>
<td></td>
<td>77 m</td>
<td>no comment</td>
<td>No</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>91 m</td>
<td>full</td>
<td>No</td>
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</table>
Appendix 3: Manuscript of Systematic Review Submitted to International Psychogeriatrics

Charles Bonnet syndrome and cognitive impairment: a systematic review

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Abstract

Background

Charles Bonnet syndrome (CBS) is defined as complex persistent visual hallucinations in the absence of mental disorder. It is common in conditions causing significant visual impairment. Many authors advise reassurance, considering the condition benign. However others have suggested that CBS may represent the early stages of dementia in some patients. This review seeks to systematically examine the evidence for any link between CBS and cognitive impairment.

Methods

Literature search using OVID Medline, PsychINFO and Embase.

Results

Three studies where cognitive functioning was the primary focus of the research were found. All were small, did not properly apply diagnostic criteria, and reported conflicting results. Eight other studies commented on cognitive functioning, but none used tests sufficiently sensitive to detect changes seen in early dementia. One hundred and thirty four case reports were scrutinised, and reports found of 16 patients with CBS where dementia emerged. High rates of partial insight at diagnosis of CBS were seen in these cases.
Conclusions

There have been no adequately powered studies, using accepted diagnostic criteria, where changes in cognitive functioning were the primary outcome. Existing studies are of limited methodological quality and allow no conclusion regarding a relationship between cognitive impairment and CBS to be reached. Numerous case reports of dementia developing in patients with CBS and partial insight raise the possibility of a link between these conditions. There is a clear need for properly constructed studies to investigate this.

Key Words

Charles Bonnet syndrome; dementia; visual hallucinations; cognitive impairment

Running Title

Charles Bonnet syndrome and cognitive impairment
Introduction

Background

The eponym “Charles Bonnet syndrome” (CBS) was introduced by a Genevan neurologist, Georges de Morsier, in a paper discussing the nature of visual hallucinations (de Morsier 1936). It was initially held to describe the occurrence of visual hallucinations in older adults with intact cognition and no demonstrable mental disorder. The name chosen was a reference to his fellow Genevan, the natural philosopher Charles Bonnet, who in 1760 published an account of the hallucinations experienced by his grandfather, Thomas Lullin. Following procedures to remove cataracts from both eyes, Lullin experienced visual hallucinations of people, carriages, birds and entire landscapes. The hallucinations persisted for around six months, but ceased when his vision deteriorated further. Despite the presence of a condition causing visual impairment in the case described by Bonnet, de Morsier did not consider loss of vision to be integral to the syndrome, stressing the role of an undetermined abnormality of the brain in generating the symptoms.

Around twenty years later, Hecaen and Garcia Badaracco (1956) reviewed the condition, and proposed a change in its definition. They promoted a relationship to eye disease as being fundamental to the development of the syndrome. In response, de Morsier returned to the subject of CBS, presenting a review of 18 cases (de Morsier, 1967). He noted that in five of the cases vision was recorded as being normal, or nearly normal. In his conclusion he
stated that “there exists no correlation between visual hallucinations and lesions of the ocular globe”. He denied that impairment in visual afferents could lead to hallucinations, claiming that they are always caused by pathology of the brain, and suggesting the pulvino-cortical pathways may be the site of the lesion. This observation, that CBS can occur in the presence of normal visual functioning, remains the key evidence against it occurring purely as the consequence of reduced visual functioning.

The relationship between CBS and cognitive impairment has also been a matter of debate through most of the history of the condition. de Morsier was clear that significant cognitive impairment excluded the diagnosis, stating that the diagnosis called for ‘complete integrity of other cerebral functions’. When Burgermeister et al. (1965) presented a series of 11 patients suffering from visual hallucinations in an influential paper, de Morsier noted that all their patients suffered from dementia, and stated “by definition, none of these cases had Charles Bonnet syndrome, contrary to what the authors think” (de Morsier, 1967).

In the English language literature, while there are reports of people experiencing visual hallucinations in the absence of psychiatric morbidity dating back as far as the 19th century (Abell, 1845; Ormond, 1925; Bartlett, 1951; White, 1980), the term “Charles Bonnet syndrome” was not used until 1982. In that year Damas-Mora et al. reviewed the existing literature and suggested a number of criteria they regarded as central characteristics of the syndrome. These criteria were modified by Gold and Rabins (1989) and again
by Teunisse et al. (1996), to arrive at an operationalized set of diagnostic criteria for the condition. The Teunisse criteria are set out in table 1 below.

\textit{(insert table 1 here)}

From the point of its introduction to the English language literature, diagnostic criteria have explicitly set out to avoid the issue of aetiology, due to the controversies outlined above, and the lack of empirical evidence to allow their resolution. As a result, CBS is a diagnosis still made at a syndromal level, with the pathological processes that lead to its occurrence, and its relationship with other conditions which feature visual hallucinations, remaining uncertain.

**Insight and Cognition**

This requirement for there to be insight into the nature of the experiences has been incorporated into diagnostic criteria ever since those of Damas-Mora et al. (1982). The Gold and Rabins (1989) criteria softened the stance a little, allowing for insight to be “fully or partially retained”, and this acceptance of “partial” insight was retained by Teunisse et al. (1995). Related to insight is cognitive impairment. As the use of the term “Charles Bonnet syndrome” broadened, some authors departed from the criteria set out by de Morsier, and included patients with a diagnosis of dementia (Burgermeister et al., 1965; Berrios and Brook, 1982; Cole, 1992). However, most authors agree that a diagnosis of Charles Bonnet syndrome should not be made in the
presence of dementia, or other conditions known to cause visual
hallucinations (Podoll, 1990; Teunisse et al., 1996; Hedges, 2007).

So, while dementia would preclude a diagnosis of CBS, the prevalence and
significance of milder degrees of cognitive impairment is less certain. Much of
the research on CBS has been carried out by ophthalmologists, who are less
familiar with the clinical presentation of mild cognitive impairment, or the tools
to detect it. Moreover, the mini-mental state examination (Folstein et al., 1975)
is the most frequent instrument used to quantify cognitive impairment in CBS
research, and this is known to be poor at detecting both mild cognitive
impairment, and the patterns of impairment seen in Lewy body dementia
(Bak, 2006).

This uncertainty should be a source of concern. Many authors recommend
that reassurance be given to patients with Charles Bonnet syndrome that their
symptoms are benign and not an indication of developing mental health
problems (Norton-Willson and Munir, 1987; Teunisse et al., 1996; Menon et
al., 2003; Hedges, 2007; Crumbliss et al., 2008). However, concerns have
been raised that, for some patients, Charles Bonnet syndrome may actually
be the first indication of the development of dementia (Holroyd et al., 1994;
Pliskin et al., 1996; Terao, 2001; Menon et al., 2003; Schadlu et al., 2009).
This is a particular concern with Lewy body dementia, where visual
hallucinations may often appear early and dominate the clinical picture (Terao
and Collinson, 2000). This raises the possibility that some people presenting
with visual hallucinations may be given a diagnosis of Charles Bonnet
syndrome and reassured, when in fact they are developing a serious neurodegenerative condition for which there is treatment potentially available.

To date, no review has specifically set out to systematically examine the relationship between Charles Bonnet syndrome and cognitive impairment. Given the potential significance of such a relationship, this is a significant gap in the literature. It is the intention of this review to systematically assess the existing literature on Charles Bonnet syndrome to determine if there is evidence for such a relationship.

Methods

We conducted a systematic review using the search engine Ovid, and searched the databases Medline, PsychINFO and Embase. The multi-field option was selected, and searches using the following terms were executed: Charles Bonnet$ AND dementia; Charles Bonnet$ AND cognitive impairment; Charles Bonnet$ AND Alzheimer$; Charles Bonnet$ AND Lewy body.

The abstracts were reviewed, and papers satisfying the following criteria were obtained for further review:

1. The paper described the results of an observational study of good methodological quality.
2. Charles Bonnet syndrome was confirmed using recognised diagnostic criteria.
3. Examination of the relationship between Charles Bonnet syndrome and cognitive impairment was a significant part of the study design.

Despite the large numbers of papers identified by the search strategy, none met all the criteria for inclusion. However, most of the papers published on Charles Bonnet syndrome were in the form of case reports and therefore not eligible for inclusion in this review. These reports sometimes made mention of the results of a cognitive examination, and some described changes in cognitive functioning over time. There were also descriptive studies where some of the inclusion criteria were met.

We were also aware from the reference lists of the papers identified that there were articles that our search strategy had failed to identify, but which seemed no less relevant than those that were found. We therefore revised the search strategy and sought to review all studies and case reports relating to people with Charles Bonnet syndrome. We used the same databases and search engine, but used the search term ‘Charles Bonnet$’, initially using the multi-field function. The search dates included were from the start of the period covered by the database to January 2012. A brief review of the results indicated that a high proportion of them were of no relevance. The search was repeated with ‘Charles Bonnet$’ in the title field. The results seemed to be much more relevant to the purpose of the review. The abstract for each was reviewed and the paper obtained if it was either a case report, or an observational study, on a patient or patients reported as having Charles Bonnet syndrome. Rigorous application of diagnostic criteria was not possible
as there was often insufficient information. However, where the information provided was in direct conflict with the Teunisse criteria the paper was excluded. Papers in languages other than English or Spanish were also excluded.

Results

After duplicates were removed our search identified 316 papers. One hundred and ninety papers were excluded, and table 2 summarises the reasons for exclusion.

<insert table 2 here>

One hundred and twenty six papers were included in the review consisting of 26 observational studies and 100 case reports or case series. The references of the papers obtained were scrutinised and the abstract of any other paper which looked like it might be relevant was obtained; the paper was included if it met the above criteria. The search also identified review papers. The reference lists of these were searched for any relevant papers not found by the other methods. A further 55 relevant papers were identified by this method (19 observational studies and 36 case reports), making 45 studies and 136 case reports/series, in total. These are discussed in the results section below.
Observational Studies

Schultz and Melzack (1993) carried out psychometric testing on 14 patients with Charles Bonnet syndrome over a period of up to 12 months. The tests used included the Minnesota multiphasic personality inventory, The Beck depression inventory, the trait form of the state-trait anxiety inventory, and the MMSE. They found no evidence of abnormalities in cognitive function in this group, and concluded that they had “ruled out the hypothesis that the hallucinations were caused by dementia”. The study was important, as it was the first to administer a range of psychometric instruments to people with Charles Bonnet syndrome. It did have a number of weaknesses however. The criteria by which Charles Bonnet syndrome was diagnosed were not made clear; and, although there was contact with participants at two points, testing was only carried out at one of these, so change in cognition with time could not be assessed. The instrument used to assess cognition was the MMSE, which is known to be poor at detecting early dementia; and the sample size was small. Given these limitations, the evidence does not seem to support the robust conclusion the authors reach.

These findings contrast with Pliskin et al. (1996), who described cognitive abnormalities in 14 of 15 cases with Charles Bonnet syndrome. They used measures including the Wechsler Adult Intelligence Scale-Revised, the Dementia Rating Scale, the MMSE and the Wechsler Memory Scale. They proposed that Charles Bonnet syndrome can be an indication of the early stages of dementia. They used the Gold and Rabins criteria for making the
diagnosis of Charles Bonnet syndrome. However, their study was criticised by Teunisse (1997) for including a substantial number of cases (8/15) who did not have insight, contrary to these criteria. The authors responded by noting that even among those who did have insight, 6/7 had cognitive abnormalities, and that the one patient with normal cognition was found to have developed dementia 16 months later.

The instruments used in this study did seem more appropriate for detecting potential cognitive impairment than those in Schultz and Melzack (1993). However, the inclusion of people lacking insight, and even suffering from delusions, is a weakness, as most clinicians would not consider these people had Charles Bonnet syndrome. There was no longitudinal component to the study to determine if the abnormalities found were progressive, and the sample size (in effect only seven) was too small.

Holroyd and Rabins (1996) described findings in 13 patients reporting symptoms consistent with CBS who were contacted by telephone 39 months after their participation in a cross sectional study (Holroyd et al., 1994). Only 10 of the 13 could be contacted. The Telephone interview for Cognitive Status was administered, and scores compared to TICS scores at baseline. There was no significant change in the scores on the TICS over the study period. The authors conclude that this should be reassuring information for patients with macular degeneration who experience visual hallucinations. However, there were a number of limitations of the study; it was again very small, and the loss of 3/13 to follow up could be significant. There are also limitations in
the breadth of a cognitive assessment delivered by telephone. While the authors cite data suggesting good correlation with the MMSE, a telephone test must be limited in its coverage of visuo-spatial items.

In addition to the paper described above, there were eight studies where cognitive functioning was described as one of the study parameters, though it was not the main focus of the study. These are described in Table 3. A number of these are large studies. Four included 30 or more people experiencing complex visual hallucinations. All of them assessed cognitive functioning using a validated instrument, the MMSE in seven and the TICS in the other. All but one of these studies reported no significant between cognitive impairment and CBS. Only Holroyd et al. (1994) found an association with a lower score on the TICS; but the participants they reported on were the same cohort who were described in the later study discussed above (Holroyd and Rabins 1996), and where no deterioration in cognitive performance was reported over time.

However, there are some concerns over these findings. The studies were generally samples of convenience, mostly being consecutive attenders at outpatient clinics. Only Teunisse et al. (1995) and Gilmour et al. (2009) provided data on the number of potential participants who declined to participate, and no study gave information on whether those that did agree to participate were different from those who declined. This limits confidence in how applicable these results are to other populations.
Moreover, only the three studies authored by Teunisse and colleagues confirmed diagnosis of CBS with reference to broadly accepted criteria. In three there was no psychiatric history and mental state examination undertaken by a psychiatrist (Menon, 2005; Crumbliss et al., 2008; Gilmour et al., 2009). This is of particular importance given the cognitive test used was the MMSE in all but one study. The lack of a significant difference in the scores found cannot therefore be taken as having excluded significant impairments in cognitive functioning. The milder abnormalities reported in MMSE scores in some studies (Shedlack et al., 1994; Teunisse et al., 2005) could be consistent with clinically relevant deficits in functioning.

Indeed, Gilmour et al., (2009) explicitly mention that people taking medication for Alzheimer’s disease were included in the study, but do not provide further details of how many people this applied to or what group they were in. It is likely that some of the participants labelled as having CBS in Gilmour et al. (2009) had mental disorders accounting for their visual hallucinations, invalidating the CBS diagnosis.

Of the studies described, Teunisse et al. (1995) and Teunisse et al. (1998) appear the most robust. Large numbers of participants were recruited, accepted CBS criteria applied, an examination by a psychiatrist was part of the protocol and the control group was relevant. The finding of no impairment in cognitive functioning is therefore of interest. However, even these studies relied on the MMSE, and so were unable to rule out the presence of mild but important deficits in cognitive functioning.
Case Reports

The 136 papers where cases consistent with CBS were described were reviewed to determine whether a comment was made on the patients’ cognitive functioning, and whether any follow up observations were made in regard to this. These papers reported details of 225 cases where the information provided was not explicitly in conflict with the Teunisse criteria, though it should be noted that in many cases the information provided was very limited. Information regarding these articles is available from the authors, on request.

A total of 16 papers describe 22 cases where cognitive functioning was described at baseline and follow up. Of these, 11 papers detail 15 cases where dementia was reported as developing after a period of follow up. These were published between 1988 and 2011, and are summarised in Table 4. Six of the cases were in males, and nine in females. Ages ranged from 70 to 87 at time of diagnosis of CBS, with a mean age of 79.2 years. A range of ophthalmic diagnoses were involved, though this information was frequently not given in the case report.

In 11/14 cases insight was reported as being partial or fluctuating; this was a much higher rate of partial insight than in reported cases of CBS as a whole. The period of time that visual hallucinations were present before diagnosis of dementia was made varied. It was less than one year in 3/15 cases, one to
three years in 7/15 cases, and over three years in 5/15 cases. The type of dementia was recorded as Lewy body dementia in 5/15 cases and Alzheimer’s disease in 4/15 cases. In the remaining six cases, a specific dementia type was not reported.

Among the cases where dementia did not develop (Levine, 1980; Sadananda Unni, 1994; Ukai et al., 2004; Bourgeois et al., 2010; Hartney et al., 2011), there were 4 males and 3 females. The periods of follow up ranged from one to six years. The mean age of this group was younger, at 67.3 years, and more of the group had full insight at the time of diagnosis (5/6 where insight status was reported).

Discussion

Review Findings

This review establishes a number of points. The recording of insight and cognitive ability in the literature relating to CBS has generally been limited in completeness and quality. There are no well-constructed, adequately powered studies which describe the rates or patterns of cognitive impairment in this condition, or which establish the rates of emergence of dementia. The three studies that directly address this question are too small, have methodological weaknesses, and come to contradictory conclusions. All are now over 17 years old.
The other cross sectional study data adds little to this. Few studies have assessed cognitive functioning at all, and none have done so with instruments of sufficient sensitivity to reliably detect mild but clinically relevant deficits. While in general the studies do not provide evidence of cognitive impairment being present in CBS, the larger studies all had limitations which prevent this being taken as a robust finding. This is not unexpected, as these studies were not designed primarily to investigate the relationship between CBS and cognition.

The case report literature does contain a number of cases where CBS appears to have been a pre-dementia state. The commonest dementia type diagnosed in this group was Lewy body dementia. However, although this confirms that dementia does develop in CBS, this finding does little to clarify what the relationship between the conditions it, as these cases reported may not be representative of CBS cases as a whole. Information in the case reports was often patchy, and recognised diagnostic criteria were commonly not referred to.

The finding that dementia did develop in 15 cases (16 including the case described in Pliskin et al., 1996) is therefore hard to interpret. The mean age of this group was nearly 80, and the baseline incidence of dementia in this age group would be expected to be around 2% per annum (Riedel-Heller et al., 2001). It would therefore be expected that some of the patients described in the case reports would develop dementia anyway, and that the presence of CBS would be coincidental. Nonetheless, this finding lends some weight to
the clinical impression that dementia developing in patients who have been diagnosed with CBS is an outcome which occurs frequently enough to be of clinical relevance.

**Implications for Aetiology of CBS**

CBS has been defined in terms that avoid reference to aetiology throughout its existence in English-language literature. However, advances in cognitive science and neuroimaging have allowed some progress to be made in relating the syndrome to underlying disturbances in brain structure and functioning. Three studies have used a range of neuroimaging modalities to investigate CBS, and found abnormalities were present in those with the condition. Shedlack et al. (1994) found excess posterior white matter ischaemic changes; ffytche et al. (1998) found increased activation in the fusiform gyrus; and Adachi et al. (2000) used a combination of MR and SPECT, reporting occipital atrophy, and hyperperfusion in the temporal lobe, striatum and thalamus. In addition to these studies, there have been numerous case reports, mostly using SPECT, but a consistent picture of where abnormalities are located has failed to emerge.

Another approach has been to try to develop an overarching theory of how visual hallucinations are generated, and to locate CBS within this framework. Significant contributions in this area have been made by Collerton et al. (2005) and ffytche (2007). Collerton et al. (2005) introduced a 'perception/attention deficit' model of visual hallucinations, in which afferent
stimuli are 'compared' to proto-objects present in the visual accessory cortex, with the 'best fit' being experienced as the conscious percept. In states of reduced afferent information, or impaired attention, errors in selecting the proto-object are more likely to occur, which may be experienced as a hallucination. In the Collerton model, the content of the hallucinations is held to be similar whatever the underlying cause. The association with impaired visual acuity in CBS fits with the 'perception' part of the Collerton model; but as discussed above, this is not sufficient to explain why most people with poor vision do not experience hallucinations, suggesting that a co-existing abnormality leading to reduced attention may also be present in the condition.

ffytche (2007) made an attempt to distinguish the aetiology of different visual hallucinatory syndromes on phenomenological grounds. He described three separate syndromes, related to deafferentation, acetylcholine deficits in the midbrain, and excess serotonin, which he suggested differed in the content of hallucinations experienced. In this framework CBS is the prototypical deafferentation syndrome, and the symptoms emerge as a result of abnormalities in the retinogeniculocalcarine syndrome.

Neither of these models has yet been supported by conclusive empirical evidence in relation to CBS, but they offer frameworks which are testable and which should help shape future research in the area; and they offer the prospect of both moving CBS onto a clear aetiological footing, and defining its relationship to other visual hallucinatory disorders.
The findings of this review are unable to offer much new evidence to support either of the models described. The cases that developed dementia would be classified in a different category in the ffytche (2007) framework, and would potentially have differences in the content of the hallucinations experienced. However, the descriptions of the hallucinations provided in the reports lacked sufficient detail to allow this theory to be tested.

The findings of the review in relation to insight are of interest in relation to the perception/attention deficit model of Collerton et al. (2005). In cases where a period of follow-up was described, partially impaired insight was more likely to be associated with the development of dementia than full insight. It is possible that the subgroup of CBS cases who show partial insight may be different from those where insight is preserved, and that this group may be at a higher risk of going on to develop dementia. In the Collerton model, the cases where dementia develops would be likely to form a group where the ‘attention deficit’ component of the model is of greater importance than the ‘perception’ component. They would potentially be indistinguishable on the content of the hallucinations, but the presence of impaired or fluctuating insight early in the course of the syndrome could alert clinicians to the possibility of a different aetiology.

**Implications for Clinicians**

This review establishes that the relationship between CBS and cognitive impairment is at present unclear, but that there appear to be a sub-group of
people who meet diagnostic criteria for the syndrome who are at risk of subsequently developing dementia. The evidence does not allow any estimate of the frequency of this outcome to be made, which makes it hard to provide guidance to clinicians who see patients with the condition. Conditions causing visual impairment are common in the population at risk of dementia, and CBS is common in visual impairment; so a recommendation that all patients presenting with CBS should have neuroimaging and referral to specialist memory services would have major resource implications. Referral to a memory clinic also has the potential to cause significant levels of anxiety in large numbers of people who have no underlying cognitive disorder.

A pragmatic solution would be to recommend that everyone diagnosed with CBS, and an informant who knows them well, should be asked some basic questions about whether their memory has worsened over the previous 12 months. Where there are concerns identified in this area obtaining neuroimaging and referral to a memory service would be appropriate. Partial or fluctuating impairment at diagnosis of CBS would also warrant further investigations for underlying cognitive disorders. Where no problems with memory or insight are noted, the patient’s primary care physician could be alerted about the diagnosis of CBS, and the potential for dementia to develop. This would allow ongoing monitoring for the possible emergence of cognitive impairment to be undertaken.
Conclusion

Many authors still advise that CBS is a benign, self-limiting condition, with no relationship to serious mental disorder. However, reports of severe and progressive cognitive impairment occurring in patients with CBS have occurred with sufficient frequency to suggest that CBS may on some occasions represent the first signs of an emerging dementia. This offers the possibility of a new pathway to early diagnosis and treatment.

Conditions causing visual impairment are common in the elderly population at risk of dementia. For example, Owen et al. (2012) report prevalence rates of Age related macular degeneration among those aged over 80 to be around 12%. Epidemiological studies indicate that the prevalence of CBS in the elderly population with significant visual impairment may be as high as 63% (Menon, 2005); so there are potentially large numbers of people who could be identified as being higher risk of dementia. If this relationship was confirmed it could lead to closer working between ophthalmology departments and memory assessment services, and could offer another way to help meet the Prime Minister's challenge of increasing rates of timely diagnosis of dementia (DoH, 2013).

Moreover, progress in the understanding of the neurological basis of CBS is likely to lead to a better understanding of visual hallucinations as a whole. Explanatory frameworks have been developed that offer the prospect of more clearly defining the relationship between CBS and other disorders which
cause visual hallucinations. The case for carrying out well designed, adequately powered studies to investigate the rates of dementia in CBS, the factors which predict development of dementia, and the neurological abnormalities which underlay the condition, is now compelling.

Conflict of Interest

None.

Description of Authors’ Roles

G. Russell identified the topic for the research, designed the search strategies, collected the data and wrote the paper. A. Burns advised on the research design and assisted in writing the article.

Acknowledgements

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References

**Abell, T.** (1845) Remarkable case of illusive vision. *Boston Medical and Surgical Journal*, 33, 409-413.


*Psychogeriatrics*, 2, 6-14.


Table 1: The Teunisse diagnostic criteria for Charles Bonnet syndrome

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>At least one complex visual hallucination within the past four weeks</td>
</tr>
<tr>
<td>2.</td>
<td>A period between the first and last hallucination exceeding four weeks</td>
</tr>
<tr>
<td>3.</td>
<td>Full or partial insight into the unreal nature of the hallucinations</td>
</tr>
<tr>
<td>4.</td>
<td>Absence of hallucinations in other sensory modalities</td>
</tr>
<tr>
<td>5.</td>
<td>Absence of delusions</td>
</tr>
<tr>
<td>6.</td>
<td>Hallucinations cannot be explained by the presence of a psychiatric disorder</td>
</tr>
</tbody>
</table>

Table 2: Reasons for excluding papers identified by second search

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language other than English or Spanish</td>
<td>50</td>
</tr>
<tr>
<td>Not a case report or study (mostly letters, poster presentations)</td>
<td>49</td>
</tr>
<tr>
<td>Other relevant medical, psychiatric or medication related problem present</td>
<td>19</td>
</tr>
<tr>
<td>Review article</td>
<td>18</td>
</tr>
<tr>
<td>Not a clinical article</td>
<td>18</td>
</tr>
<tr>
<td>Duplicate report, not removed by search engine</td>
<td>17</td>
</tr>
<tr>
<td>Explicitly in conflict with Teunisse criteria</td>
<td>16</td>
</tr>
<tr>
<td>Paper not obtainable</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 3: Observational Studies

<table>
<thead>
<tr>
<th>Study design and focus</th>
<th>Population</th>
<th>Cognitive Assessment</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holroyd et al. (1994)</td>
<td>127 visual disorder patients, 100 general medical patients. 8 in total had VH. Other medical or psychiatric causes of VH excluded</td>
<td>Telephone interview of Cognitive status (TICS).</td>
<td>Lower cognitive score on TICS significantly associated with VH, p&lt;0.001 on ANOVA</td>
<td>Follow up in Holroyd and Rabins (1996) did not show progression of cognitive impairment</td>
</tr>
<tr>
<td>Shedlack et al. (1994)</td>
<td>5 patients with VH, no primary psychiatric disorder; 12 normal controls, health volunteers</td>
<td>MMSE</td>
<td>Scores among VH patients 21-27/30; and among controls 28-30/30. No mean/median score given, no comment on differences</td>
<td>Significantly more white matter changes posteriorly in the VH group. Controls younger than patients (74.6 vs 81.4), no comment on significance of this</td>
</tr>
<tr>
<td>Teunisse et al. (1994)</td>
<td>14 patients with CBS from psychiatry/geriatric medicine. Gold and Rabins criteria applied. Mean age 81.8 years, gender ratio 13:1 F:M</td>
<td>MMSE</td>
<td>Mean score on MMSE 26.2/29.4. Four patients excluded, two with severe cognitive impairment present, one who was very uncooperative with testing and one who was hard of hearing</td>
<td>Source of patients different from many other studies, so may represent a different population. No follow up of cohort to monitor changes in cognition over time</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Sample Description</td>
<td>MMSE</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
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<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Teunisse et al. (1995).</td>
<td>Cross sectional, comparing prevalence of</td>
<td>500 patients attending ophthalmology services (300 low vision patients, 200 general</td>
<td>Mean score 26.5 in CBS patients (22-30); scores for those</td>
<td>Large study, using accepted criteria, applied robustly, so findings of interest. Scores on cognitive testing were difficult to interpret, as mean age of CBS group not given and no comparison data for those with no VH</td>
</tr>
<tr>
<td></td>
<td>CBS in low vision vs. general ophthalmic</td>
<td>elderly ophthalmic patients). 11% of low vision patients vs 1% general patients had</td>
<td>without CBS in each group not given</td>
<td></td>
</tr>
<tr>
<td></td>
<td>patients</td>
<td>CBS, as diagnosed by Teunisse criteria</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teunisse et al. (1998).</td>
<td>Cross sectional. Examed risk factors for</td>
<td>Low vision clinic; 52 patients with CBS and 80 clinic attenders with no VH.</td>
<td>No connection of CBS with cognitive impairment was found</td>
<td>Large study, relevant and similar control group. Widely accepted criteria for diagnosis of CBS used</td>
</tr>
<tr>
<td></td>
<td>CBS</td>
<td></td>
<td></td>
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<tr>
<td>Menon (2005)</td>
<td>Case/control cross sectional study.</td>
<td>48 participants with visual acuity of 20/200 or worse in better eye compared with 48 controls with VA of 20/40 in better eye. 30/48 of low vision group had VH, compared to only 2/48 controls</td>
<td>MMSE (excluding 2 items designated as visually dependent)</td>
<td>Insight also commented on - all attained this, but in 18/30 there was an initial period of deception. Reasonably sized study, but limited by use of MMSE</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Study Design</td>
<td>Study Population</td>
<td>MMSE</td>
<td>Findings</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Crumbliss et al. (2008)</td>
<td>Longitudinal study evaluating low vision rehabilitation intervention reduces CBS hallucinations, follow up period 2-8 weeks</td>
<td>50 consecutive patients presenting at visual rehabilitation centre, 12 found to have CBS.</td>
<td>MMSE</td>
<td>Mean score in CBS group 25.4, in non-CBS group 25.5. No significant correlation found between improved visual acuity and reduction in VH. MMSE not repeated at follow up, which was of too short duration to be of value in tracking changes in cognition.</td>
</tr>
<tr>
<td>Gilmour et al. (2009)</td>
<td>Cross sectional case/control study</td>
<td>258 low vision clinic attenders and 251 controls; CBS in 34% LVC patients, &lt;2% of controls</td>
<td>MMSE. Those scoring &lt;22 excluded; this included 12 LVC patients and 1 control</td>
<td>No significant differences in MMSE scores between any groups. Precise scores not given, graph appears to show scores around 25 in all groups. Large study. Exclusion for low MMSE presumably to exclude dementia, but some participants were taking medication for Alzheimer’s disease. Calls into question validity of findings, as Alzheimer’s diagnosis would rule out CBS</td>
</tr>
</tbody>
</table>
Table 4: Details of case reports of patients with CBS who went on to develop dementia

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Age/gender</th>
<th>Ophthalmic diagnosis</th>
<th>Visual acuity in best eye</th>
<th>Insight status</th>
<th>Cognition assessed at baseline?</th>
<th>Neuroimaging or other investigations</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal et al. (1988)</td>
<td>70, female</td>
<td>Not given</td>
<td>20/50</td>
<td>Present initially</td>
<td>‘borderline normal score on the Blessed test of orientation, memory and concentration’</td>
<td>CT and EEG were normal</td>
<td>Alzheimer’s disease emerged 1 year after onset of visual hallucinations</td>
</tr>
<tr>
<td>Gold and Rabins (1989)</td>
<td>84, female</td>
<td>Not given</td>
<td>No comment</td>
<td>Partial, fluctuating</td>
<td>MMSE 27</td>
<td>Normal</td>
<td>Alzheimer’s disease after two years, MMSE then 14</td>
</tr>
<tr>
<td></td>
<td>72, male</td>
<td>Not given</td>
<td>No comment</td>
<td>Partial, fluctuating</td>
<td>MMSE 25</td>
<td>Normal</td>
<td>‘Dementia’ after 18 months, MMSE then 15</td>
</tr>
<tr>
<td>Brabbins (1992)</td>
<td>79, female</td>
<td>Bilateral cataracts</td>
<td>No comment</td>
<td>Partial, present at times but fluctuating</td>
<td>Clinical assessment- ‘memory testing revealed minor deficits’</td>
<td>No comment</td>
<td>Probable Lewy body dementia developed 2-3 years after onset of VH</td>
</tr>
<tr>
<td></td>
<td>80, female</td>
<td>No comment</td>
<td>No comment</td>
<td>Partial, present at times but fluctuating</td>
<td>No comment</td>
<td>No comment</td>
<td>Over one year period, fluctuating and increasing impairment in cognitive functioning; probable Lewy body dementia</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Age, Gender</td>
<td>Visual Acuity</td>
<td>Initial Cognitive Function</td>
<td>Imaging Findings</td>
<td>EEG Findings</td>
<td>Diagnosis</td>
<td></td>
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<tr>
<td>Haddad and Benbow (1992)</td>
<td>84, female</td>
<td>Not given</td>
<td>'corrected visual acuity satisfactory'</td>
<td>partial</td>
<td>Blessed Roth Cognitive function scale 25/26; Wechsler adult intelligence scale, Benton visual retention task, cognitive scale of Clifton assessment procedure for elderly. Isolated problems with visuospatial skills noted</td>
<td>EEG normal; CT carried out after emergence of cognitive symptoms showed involutional change, most pronounced parietally</td>
<td>General cognitive decline evident 9 months after emergence of VH; patient died 21 months after VH started. Authors felt diagnosis was either Alzheimer’s disease or Lewy body dementia</td>
</tr>
<tr>
<td>Lefroy (1999)</td>
<td>87, female</td>
<td>'retinal degeneration' and cataracts</td>
<td>'unable to count fingers'</td>
<td>full</td>
<td>Clinical assessment 'normal', MMSE 30/30</td>
<td>CT- moderate atrophy; EEG-“abnormal, did not support epilepsy”</td>
<td>Unspecified dementia after three years</td>
</tr>
<tr>
<td>Johnson and Barnes (2001)</td>
<td>87, male</td>
<td>Age related macular degeneration</td>
<td>Finger counting at 1 metre</td>
<td>No comment made</td>
<td>Clinical assessment, 'no short or long term memory problems'</td>
<td>No comment</td>
<td>Unspecified dementia</td>
</tr>
<tr>
<td></td>
<td>72, male</td>
<td>Not given</td>
<td>6/60</td>
<td>partial</td>
<td>'performed well on cognitive testing'</td>
<td>CT- moderate vascular changes and frontal atrophy</td>
<td>Unspecified dementia</td>
</tr>
<tr>
<td>Magoub and Serby (2007)</td>
<td>78, female</td>
<td>Venous occlusion, cataracts</td>
<td>Not stated</td>
<td>Present initially, then lost</td>
<td>MMSE 28/30</td>
<td>CT ‘normal’</td>
<td>Unspecified dementia, treated with donepezil, after around 18 months of VH</td>
</tr>
<tr>
<td>Name</td>
<td>Age</td>
<td>Gender</td>
<td>Diagnosis</td>
<td>Visual Acuity</td>
<td>Visual Field</td>
<td>Cognitive Assessment</td>
<td>Imaging Findings</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>--------</td>
<td>------------------------------------</td>
<td>--------------------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Archibaldo Donoso et al. (2007)</td>
<td>84</td>
<td>Female</td>
<td>Cataracts bilaterally, traumatic injury left eye</td>
<td>Right eye- complete loss of vision</td>
<td>Partial- not present initially</td>
<td>Clinical assessment 'normal'</td>
<td>CT showed mild generalised atrophy</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>Male</td>
<td>Glaucoma</td>
<td>Finger counting</td>
<td>Partial- fluctuates</td>
<td>MMSE 22/27, ‘mild cognitive impairment’</td>
<td>EEG- diffuse slowing; CT- age related involutional change, white matter changes</td>
</tr>
<tr>
<td>Hanyu et al. (2008)</td>
<td>81</td>
<td>Female</td>
<td>Cataracts</td>
<td>No comment</td>
<td>Full</td>
<td>MMSE 27/30</td>
<td>MR showed mild generalised atrophy, SPECT showed mild hypoperfusion in medial occipital lobe</td>
</tr>
<tr>
<td>Walker and Keys (2008)</td>
<td>72</td>
<td>Male</td>
<td>Progressive diabetic macular oedema</td>
<td>20/100, worsening to finger counting over years</td>
<td>Partial (present initially then lost)</td>
<td>No comment</td>
<td>No comment</td>
</tr>
<tr>
<td>Gil Navarro et al. (2011)</td>
<td>78</td>
<td>Male</td>
<td>Optic nerve ischaemia</td>
<td>No comment</td>
<td>Full insight</td>
<td>No comment</td>
<td>Two years later: SPECT- severe perfusion impairment bilaterally, posterior structures more affected</td>
</tr>
</tbody>
</table>
Appendix 4: Protocol

Is Charles Bonnet Syndrome associated with the development of Lewy Body dementia?

A prospective cohort study

Study reference number 09/H1003/118

A proposal and protocol for a research project

Dr Gregor Russell

Speciality Registrar (ST6) in Old Age Psychiatry

Version 9  1st December 2009
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1. Background

Charles Bonnet Syndrome (CBS) was described by Georges de Morsier in 1936. Its name pays tribute to the work of Charles Bonnet, a brilliant naturalist and philosopher who resided in Geneva in the 18th century. Bonnet’s achievements were many, including becoming the youngest member of the French Academy of Sciences (Hedges 2007). However the work for which he is best remembered for was an essay written in 1760 on his grandfather, who at the age of 87 experienced a wide array of complex visual hallucinations, in the context of advanced cataract disease to both eyes. Bonnet’s description of his grandfather’s condition was unprecedented in its precision and detail, and he even proposed a biological mechanism through which it could occur. It has even been described as ‘the beginnings of a modern approach to psychiatric phenomenology’ (ffytche 2005).

However, from the outset, there has been debate about what components should make up CBS. Over the years, various authors have argued for or against the necessity of eye pathology, advanced age and insight into the unreal nature of the experiences (ffytche 2005). Even de Morsier himself seems to have changed his position, initially referring to CBS as “senile syndromes with lesions of the eye” (ffytche 2005), but later clarifying his position with this statement: “there is no correlation between visual hallucinations and lesions of the ocular globe” (Hedges 2007). This lack of clarity over what exactly constitutes CBS has led to wide variations in estimates of its prevalence. These have ranged from 0.5% (Shiraishi et al 2003) to 40% (Abbott et al 2007). This nearly hundred-fold range is partly accounted for by differences in the population studied, and partly by variations in the criteria used to identify cases. In studies that have looked at elderly populations with significant visual impairment, prevalence figures of 10-15% are found fairly consistently (Teunisse et al 1996, Menon et al 2003). Interestingly, this is similar to the rate of visual hallucinations found in a study of patients attending an old age psychiatry out patient department (Soeda et al 2004).
2. Charles Bonnet Syndrome and Cognitive Impairment

The relationship between CBS and other conditions known to be associated with visual hallucinations is also unclear. Insight into the unreal nature of the experiences is held by many authors as a core feature of the syndrome (Jacob et al. 2004, Damas-Mora et al. 1982, Teunisse et al. 1996, Shiraishi et al. 2004), allowing it to be distinguished from psychiatric conditions such as schizophrenia and mood disorders. Most authors would also hold that the presence of dementia would preclude CBS, as intact cognition is a prerequisite for the diagnosis (de Morsier 1967, Hedges 2007, Jacob et al. 2004, Abbott et al. 2007). However, much of the work in this area has either assessed for cognitive impairment using the Mini Mental State Examination (Menon 2005, Abbott et al. 2007, Brucki et al. 2009)), or not quantified cognitive impairment at all (Teunisse et al. 1996, Teunisse et al. 1999, Shiraishi et al. 2004). This is a concern, as it is well recognised that the MMSE is poor at picking up mild levels of cognitive impairment (Plummer et al. 2007, Pliskin et al. 1996), and is poor at detecting the pattern of cognitive impairment seen in Lewy body dementia (Bak 2006).

Moreover, there is a certain amount of evidence that some patients given a diagnosis of CBS go on to develop a frank dementia (Menon et al. 2003). This is mostly in the form of case reports: for example, Archibaldo et al. (2007) detail three patients with CBS, two of whom were later given a diagnosis of Alzheimer’s disease. Terao (2007) notes that, given the widely used criteria for diagnosing CBS, patients with visual hallucinations in early Lewy Body dementia are likely to be given this diagnosis if they present prior to the onset of more definitive cognitive deficits. Evidence suggesting successful treatment of CBS with the cholinesterase inhibitor donepezil (Ukai et al. 2004) adds to the suspicion that some cases of CBS may actually be early DLB.
Little work has examined this matter with more rigorous methodologies; Schultz and Melzack (1993) did examine patients with CBS using more detailed psychological tools, and followed the study group for up to a year. They concluded that the hallucinations they described were not due to psychopathology or cognitive impairment. However, the cognitive assessment used was again the MMSE, the time of follow up was too short to confidently rule out DLB, and their sample size was small, with only 14 subjects included.

Only one study has attempted to characterise putative cognitive deficits in CBS using more sensitive tools. Pliskin et al (1996) administered a range of instruments, including the Wechsler Memory Scale and Mattis Dementia rating scale. They did find significant differences in cognitive function between patients with CBS and ‘community dwelling controls’, and concluded that isolated visual hallucinations may be an early indicator of dementia. However, the number of subjects in the study was again small; and its conclusions do not seem to have shaped wider thinking in the area.

So, while there is an active debate ongoing about what the true nature of CBS is (ffytche 2005), there still seems to be more of a consensus about what it is not, with a recent review article concluding that it ‘is not an indication of cerebral problems such as Alzheimer’s disease’ (Hedges 2007). This position seems questionable, given the concerns a number of authors have expressed over the possibility that a sub-group of those diagnosed as having CBS may in fact be in the early stages of dementia. This is more likely to be an issue with DLB, where visual hallucinations may present early in the course of the illness, than with Alzheimer’s disease, where complaints of forgetfulness usually pre-date other symptoms.
3. Potential Approaches for New Research

More research is needed to accurately describe the nature of any more subtle cognitive deficits that may exist in patients with CBS, so as to better recognise those at risk of developing a dementia. This needs to particularly address the issue of the diagnostic criteria having inadequate resolution to distinguish between CBS and early DLB. It would ideally identify available diagnostic tools that have promise in distinguishing between these two conditions.

A number of procedures and investigations may offer promise in this matter. Firstly, the availability of psychometric tools to describe cognitive impairment has markedly changed in the 34 years since the publication of the MMSE. A recent addition to this area is the Addenbrooke’s Cognitive Examination- Revised (Mioshi et al 2006). This is a battery of cognitive tests which has been shown to have a comparable sensitivity to the Dementia Rating Scale (Bak & Mioshi 2007). It includes domains such as frontal-executive function and visuo-spatial skills that are poorly covered by the MMSE (Bak & Mioshi 2007), but that are reported as being abnormal in early DLB. It is relatively quick to administer in a clinical environment, and does not require extensive training to use. As such, it is a potentially useful instrument to elicit milder degrees of cognitive impairment that may be present early in the course of DLB, and which may be able to distinguish this from CBS. Additionally, there are instruments that can be used to systematically gather information from someone who knows a person who may be suffering from cognitive impairment. One such instrument is the Short IQCODE (Jorm 1994). This 16-item instrument has been shown to have comparable validity to the long (26 item) version, and has been established to have high reliability (Jorm 2004). It validly reflects past cognitive decline, and predicts incident dementia. It may therefore be another tool that offers some promise in detecting which patients with CBS may go on to develop DLB.
Secondly, the content of the hallucinations may offer the potential to distinguish between CBS and DLB. There has been work carried out which describes categories of visual hallucinations and relates them to specific locations within the visual association cortex as visualised by fMRI scanning (ffytche et al. 1998, ffytche & Howard 1999). In a subsequent review, ffytche (2005) postulated that there may be two phenomenologically distinct syndromes of visual hallucinations in elderly people. The first is characterised by lines, colours, lattices, distorted faces, unfamiliar figures in bizarre costumes and landscape scenes; ffytche held that this may be related to ophthalmic, visual pathway and visual cortex pathology. The second, characterised by isolated, often familiar, figures and animals, extracampine hallucinations, sometimes with delusional elaboration, is held to be associated with DLB, Parkinson’s disease and other psychiatric disorders. This suggestion is supported by Burke (2002), who describes his own hallucinations, geometric and grid-like in nature, following the development of macular pathology. This offers the possibility that carefully eliciting the nature of the hallucinations being experienced may help guide the diagnosis.

Thirdly, progress in neuroimaging offers the potential for improved diagnostic capability. Many patients presenting with symptoms of visual hallucinations in older age would be referred for a structural imaging procedure, such as a computed tomography scan or a magnetic resonance imaging scan. This would primarily be to exclude gross structural pathology such as cerebrovascular disease or neoplastic processes. However a recent paper (Burton et al. 2002) described characteristic patterns of cerebral atrophy in patients with DLB, with bilateral grey matter volume loss in the frontal and temporal lobes, and insular cortex, compared to control. While voxel-based morphometry (VBM) is still a research technique, there is nonetheless the possibility of looking to see whether this technique offers promise in differentiating DLB from CBS.
Arriving at the correct diagnosis for these patients is of considerable clinical relevance; the conditions have markedly different prognoses, and there is a recognised treatment (cholinesterase inhibitors) which can be of considerable benefit in DLB, while the recommended management for CBS remains reassurance and remediation of the visual deficit. Moreover, such research could potentially help towards achieving objective two of the recent National Dementia Strategy, good quality early diagnosis and intervention (Department of Health, 2009)
4. Proposal

I propose to undertake a prospective cohort study to begin to address these issues. Abbott et al (2007) reported a prevalence of CBS in patients attending the Royal Manchester Eye Hospital of 40%. This suggests there are a large number of patients attending NHS services locally who could potentially be participants in a project examining this matter. I have spoken to Professor Abadi, the corresponding author of the above paper, who introduced me to Dr Robert Harper, Consultant Optometrist at the Low Vision Clinic in Royal Manchester Eye Hospital. He informed me that the Low Vision Clinic has around 1500 referrals each year, of people with a wide variety of eye pathology; and that it would in principle be possible to recruit participants from this group of patients. I propose to collaborate with Dr Harper and other optometrists to recruit a cohort of patients with Charles Bonnet syndrome. We will characterise in detail their visual abnormalities and cognitive functioning, and carry out neuro-imaging to look for the presence of specific abnormalities. We will then follow them up for the period of one year to determine whether there is a sub-group that go on to develop progressive cognitive impairment. We will also recruit a control group at the initial assessment.
5. Hypothesis

Within a group of patients who meet the criteria for the diagnosis of Charles Bonnet syndrome, there will be a sub-group who are in fact presenting with the early symptoms of Lewy body dementia. While this group would not present as sufficiently impaired to attract a diagnosis of dementia at the outset of the study, there will be a measurable decline of their cognitive functioning over the course of a year. Moreover, this group will be identifiable at entry to the study by abnormalities on measures of cognitive functioning, the content of their visual hallucinations, and abnormalities on MRI.
6. Aims

The aims of the project are to provide evidence to help answer the following questions, derived from the hypothesis stated above:

1. What proportion of people who receive a diagnosis of Charles Bonnet Syndrome who go on to develop Lewy Body dementia in the following year?

2. What proportion of participants demonstrate abnormalities in cognitive functioning at diagnosis of Charles Bonnet syndrome that are not severe enough to warrant a diagnosis of dementia?

3. Is there a correlation between those who show abnormalities in cognitive functioning at diagnosis of Charles Bonnet syndrome, and those who later develop Lewy Body dementia, or progressive cognitive impairment falling short of dementia?

4. Are there differences in the content of the hallucinations between those that develop Lewy body dementia, or progressive cognitive impairment falling short of Lewy body dementia, and those that do not?

5. Are there abnormalities detectable on MRI scanning at diagnosis of Charles Bonnet syndrome that predict the subsequent development of Lewy body dementia, or progressive cognitive impairment falling short of dementia?
7. Protocol

With the agreement of the senior optometrists at the low vision clinic, I would plan to include the 4 item screening test from the North-East Visual Hallucination Interview (Mosimann et al 2007) as part of the standard new patient assessment for patients over the age of 65. Those that screen positive, and meet the other inclusion criteria:

- having a friend or relative able to act as an informant
- having a visual acuity of between log MAR 1.6 and log MAR 0.6
- being able to speak English

will be invited to participate in the study, and provided with an information leaflet regarding it. Should they express an interest in participating, they will be invited to an interview with the main investigator, GR.

This interview will either be at the participant’s home, or at a clinic on a Manchester Mental Health and Social Care NHS Trust site, at the participant’s preference. At this interview, the nature of the study will be explained in more detail, and information leaflets provided for them to consider. They will be given 48 hours to weigh up whether they wish to participate. Should they give consent to participate, permission will be sought to access both the details of their assessment at the low vision clinic and their general practice records. This information will be used to determine if they meet the exclusion criteria:

- a pre-existing diagnosis of dementia, Parkinson’s disease or psychosis
- contra-indication to MRI scanning.

Those not excluded will be invited to a further interview with an optometrist at the low vision clinic. At this they will have a more detailed examination of their visual functioning, including contrast sensitivity (Pelli-Robson) testing and Amsler testing. They will also be asked to complete the remainder of the NEVHI to characterise their visual hallucinations.
Following this, they will be invited to a second interview with GR, at which a medical and psychiatric history will be elicited and a *neurological examination* will be carried out. Then the following instruments will be administered:

1. The Addenbrooke’s Cognitive Examination- Revised. Some of the materials used have been adapted to allow participants with poor vision to complete the items that require reading or copying/recognising shapes.

2. The Short IQCODE will be administered to an *informant* to gather relevant information about functional capabilities.

3. The Brief Psychiatric Rating Scale will be administered to assess in a structured way for the presence of a range of psychiatric symptomatology.

The information gathered in these initial assessments will be used to carry out a number of tasks. These will include confirming the diagnosis of Charles Bonnet syndrome, according to the criteria used by Teunisse *et al* (1996). These are modified from the criteria proposed by Gold & Rabins (1989), which were devised in order to set aside debate over aetiology and focus on a consistent clinical presentation. The Teunisse criteria have since been used by other authors (Shiraishi *et al* 2004) and consist of five components:

- at least one complex visual hallucination within the past four weeks
- a period between the first and last hallucinations exceeding four weeks
- full or partial retention of insight into the unreal nature of the hallucinations
- absence of hallucinations in other sensory modalities
- absence of delusions

Any participant found not to have Charles Bonnet syndrome according to these criteria will be excluded. Likewise, any participant found to have a medical or psychiatric condition which could account for their presentation, other than Charles Bonnet syndrome, will be excluded from the study. The numbers of people falling into these categories will be recorded. For those excluded, with their permission, a letter would be sent to the Low Vision Clinic and
their GP noting any active concerns, for example, a previously unrecognised psychiatric illness. Their demographic details and reason for exclusion would be retained.

Following this, participants will be invited to undergo a *neuro-imaging procedure*, an MRI scan, at the University of Manchester MRIF.

*One year* following the initial interview, participants will be invited to further interviews with GR and an optometrist. At these interviews, the procedures and instruments administered will be repeated, including history taking and examination, visual acuity, the NEVHI, the IQCODE, the BPRS and the ACE-R.

In total, we would look to recruit 24 participants with CBS over the course of around one year to take part in the study. In addition to the group identified as suffering from CBS, we will look to recruit a control group of around 12 participants. This group will be recruited from the Manchester Eye Hospital low vision clinic, and will consist of people matched for age, sex and visual impairment, but who are not suffering from visual hallucinations. They will undergo the same procedures as the CBS group at the initial assessments. They will not be followed up at one year. Their data will be used to assist in the voxel based morphometry analysis of MRI scans, to derive a ‘normal’ brain against which to compare those of people suffering from CBS. Given that the Addenbrooke’s Cognitive Examination has not been specifically validated in this population, the controls will also provide useful data to help interpret result obtained by using this instrument.
8. Data Collection and Analysis

The data would be collected onto specially designed forms, and would be anonymised, with each participant being given a unique reference number. A key, linking participants to data collection sheets, would be maintained only as long as was necessary, and would be kept in a locked facility on NHS trust property in a separate location from the data collection sheets. Any data held on computer would be anonymous. Ethical approval will be sought from the appropriate REC, and R&D approval will be sought from the trusts involved.

Statistical analysis will be carried out on the results. Given the small numbers involved, this is likely to consist mainly of descriptive statistics. These will include the proportion of the CBS population that go on to develop DLB, and the means and distributions of scores on the ACE-R and IQCODE in the CBS and control groups at the study outset. We also hope to look at correlations between abnormalities on MRI scanning and the subsequent diagnosis of DLB; between initial scores on the ACE-R and IQCODE and the subsequent development of DLB; and between the nature of the content of visual hallucination and the subsequent development of DLB. Finally, in the event of very small numbers developing DLB, the above analyses may be of little value. As a result, we plan to look at correlations between the above variables and the magnitude of changes in the ACE-R and IQCODE over the course of the year.

Analyses will be carried out on SPSS on computers in the offices of the University of Manchester Psychiatry Research Group.
9. Dissemination of Findings

This is intended to form the basis of a submission for the degree of MD at the University of Manchester. In addition to this, as the study has the potential to offer new insights into the aetiology and management of these common medical conditions, I would intend to write this work up with the intention of disseminating any worthwhile findings by various means, including presentations to learned societies, and submission as a paper to a peer reviewed journal.
10. References


Department of Health (2009) Living well with dementia: a national dementia strategy


Appendix 5: Sample of Study Documents

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5.3 Participant Consent Form  426
INFORMATION SHEET FOR PARTICIPANTS

1. Introduction
You have been invited to take part in a research project. The title of this is “Charles Bonnet syndrome and memory loss: a cohort study”. The project is designed to investigate the relationship between Charles Bonnet syndrome and memory loss, or other forms of cognitive impairment. You have been invited because you have been identified by an Optometrist at Manchester Royal Eye hospital as possibly suffering from Charles Bonnet syndrome. The purpose of this leaflet is to provide you with information to help you decide if you would like to take part in this project.

2. What is Charles Bonnet syndrome?
Charles Bonnet syndrome (CBS) is a condition affecting people with poor vision. They can experience visual hallucinations. This is the name given to the experience of seeing shapes or objects which do not actually exist. A lot of the time people
know these experiences are not real, but sometimes people can be tricked by their eyes and think that the things they see actually exist. The images seen may be enjoyable, but can be frightening or upsetting. The cause of CBS is unknown, but it may be that when the brain gets less information from the eyes, it starts to ‘fill in the gaps’ by generating signals of its own. There is currently no known cure for this condition; some medications for other conditions do sometimes help, but these are used with caution as they all have their own side effects. Frequently the hallucinations stop on their own, although in some cases they can last many months.

3. What is cognition?
Cognition, or cognitive functioning, includes things like memory, using and understanding language, concentration, judgement and planning, and finding places or objects from memory. Problems in this can lead to forgetfulness, having problems with everyday tasks like making meals or using household appliances, and getting lost or wandering. In certain conditions an impairment, or worsening, of cognitive functioning occurs. An example of such a condition would be dementia, but there are many others.
4. **What is the link between Charles Bonnet syndrome and cognitive impairment?**

There is no link known at present, and there may be none, but there has been little research in this area so far. However, people with a condition called Lewy body dementia sometimes develop visual hallucinations before they notice much in the way of memory problems. It is possible that some people diagnosed with Charles Bonnet syndrome may actually be developing Lewy body dementia. This would be important to know, as there are treatments which may help in Lewy body dementia that would otherwise not be given. Also, early recognition of the diagnosis being dementia would allow the person to get help, and to plan for the future. This study aims to find out how often people with Charles Bonnet syndrome suffer from cognitive impairment, and whether this ever develops into Lewy body dementia.

5. **What will happen to me if I take part?**

You will be invited to attend a further assessment at the optometry department of the Royal Manchester Eye hospital. This interview should be with the same person that saw you when you first came to the Low Vision clinic. At this appointment, the optometrist will carry out a more detailed
examination of your vision. After this, you will be invited to attend an interview with the Chief Investigator, Dr Gregor Russell. This can either be at Wythenshawe hospital or your own house. You will be invited to bring a family member or a friend along; this is important, and is necessary to take part in the study. At this interview, you will be asked a number of questions; these will aim to see if you suffer from Charles Bonnet syndrome, or whether there is another medical or psychiatric cause for your experiences. You will be asked to undergo a brief physical examination. You will then be asked to complete a test of “cognitive functioning”, which involves a number of questions related to your memory, to drawing shapes and to using words. Your family member or friend will also be asked to complete a questionnaire asking how you manage with day-to-day tasks.

After this, you will be invited to attend for a Magnetic Resonance Imaging (MRI) scan of your brain. This is a special scan which can examine parts of the brain which can be abnormal in Lewy body dementia. More information is given about this scan later in this leaflet. This part of the study is optional, and can be omitted should you prefer to.
Around one year after your first interview, a researcher will arrange to visit you again. At this second interview, you will be asked to repeat a number of the parts of the first interview, to see if you still suffer from visual hallucinations, and to see if your “cognitive functioning” has changed.

6. Will you want to access any other information about me?
As part of the project, we would like to be able to look at your general practice and eye hospital notes, to see if you have experienced any other conditions that may be of relevance to your current problems. We will need your consent to do this, and will ask you to sign a form to allow this.

7. Are there any risks to me from taking part in this study?
As described in paragraph 5, the study consists of a number of interviews, and an optional brain scan. As such, the risks in the study are very small. It is possible you may find the interviews tiring, or even upsetting. We have explained in paragraphs 9 and 10 what would happen in such circumstances. If you choose to take part in the part of the study that includes a brain scan, this is a Magnetic Resonance Imaging scan, and as such
does not use X-rays. There are rarely harmful effects of this investigation; more information on this is given in paragraphs 11 and 12. Very rarely, these scans discover previously unrecognised medical conditions. Paragraph 13 outlines what we would plan to do in the unlikely event of this. Finally, it is possible that we may discover your symptoms are due to a condition other than Charles Bonnet syndrome. We do not anticipate this will often be the case, but it could be distressing should it happen. However, if this does happen, then we will be able to organise for you to be referred for appropriate medical treatment and support, and you may benefit from having this recognised earlier than would have been the case had you not taken part in the study.

8. Are there any benefits to me in taking part in this study? As mentioned above, it may be that in some cases, the symptoms of visual hallucinations have a cause other than Charles Bonnet syndrome. If this is the case, you may receive a diagnosis and treatment faster than would otherwise have been the case. If the study confirms that you have no other cause for your symptoms, then this may come as an additional reassurance to you. Moreover, you will be contributing to our knowledge of this area, and this may in the future lead to better diagnosis and treatments for these conditions.
9. What if I find the interview too tiring?
There are a lot of questions; if it is too tiring, just say, and we can arrange to complete them over two days.

10. What if I become anxious, upset or distressed during the interviews?
As described above, as part of the study you would be asked to complete a questionnaire which is designed to measure cognitive functioning. Occasionally, people can find this tiring, anxiety-provoking or even upsetting. The Chief Investigator, Dr Gregor Russell, is an experienced doctor working in the field of psychiatry. As such, he has considerable skill in helping people complete such questionnaires without causing distress, and in recognising at an early point if people are becoming tired, anxious or upset. If at any point you found it was causing upset or distress, we would stop the interview. In such a circumstance, we could try again at a later date; or, if you decided you did not want to continue with the study, you would be free to do so, without having to give any reason for this.

11. What is the MRI scan like?
You will be invited to the Magnetic Resonance Imaging Facility at the University of Manchester. This part of the study is optional, and can be omitted should you prefer. However, this form of scan would provide useful data. If you do feel able to
take part in this part of the study, the team will arrange for the scan to take place at a mutually convenient time.

If you do agree to this procedure, when you arrive, you will be asked if you still want to have the scan; if you agree, you will be asked to lie down in the scanner. The scan will take approximately 20 minutes, and for that time you would need to lie still on your back. The scanner is quite enclosed, and people who do not like enclosed spaces may find it upsetting; it is also rather noisy. If either of these things upset you, you may wish to decline to take part in this part of the study. However, it is very safe, and unlike an X-ray, there is no exposure to radiation.

**12. Does the scan have any other side effects?**
Waves used in the scan can heat tissues and metals; it is possible to get burnt if you come into contact with metal objects, such as metal in clothes. The staff will check this to make sure you are safe.

**13. What will you do if you find any unexpected problems on the scan?**
This is a rare event, and is unlikely to happen. If we did find an abnormality, the Chief Investigator, Dr Gregor Russell, would arrange to meet you to discuss the finding. We would then
recommend that we inform your General Practitioner, who would be able to organise further tests or treatment, if this was appropriate.

14. Will you tell anyone I am taking part in this?
We will, with your permission, send a letter to your general practitioner (GP) informing them that you are taking part in this study. We would also inform the Consultant Ophthalmologist responsible for your care at the Royal Manchester Eye Hospital.

15. Who are the researchers?
The research is being carried out by Dr Gregor Russell, a Consultant in Older Peoples’ Mental Health based in Bradford. Dr Russell is carrying out this project as part of the research degree of Doctor of Medicine at the University of Manchester. He is being supervised by Professor Alistair Burns, Honorary Consultant in old age psychiatry at Wythenshawe hospital, and Deputy Dean of the school of medicine at the University of Manchester. Other people involved are Dr Roland Zahn, a researcher in the Neuroscience and Aphasia research unit at the University of Manchester; Dr Robert Harper, the Chief Optometrist at the Manchester Royal Eye Hospital; Claire Parkes and Julie Lennon, Optometrists at the Manchester
Royal Eye hospital; and Miss Fiona Spencer, Consultant Ophthalmic Surgeon at Manchester Royal Eye hospital.

16. Will the researchers be paid for carrying this out?
The researchers will not receive any money over and above their existing salaries for carrying out this research.

17. Will I be paid for taking part in this?
There is no fee for participating in this research. We will arrange to refund any expenses incurred in attending for appointments or investigations. Please obtain receipts and speak to Dr Gregor Russell should you wish to have travelling expenses reimbursed.

18. Has this project been reviewed by any external agencies?
Yes. It has been considered by the Greater Manchester South Research Ethics Committee. This panel looks at all aspects of the study, from its scientific worth to the potential discomforts and harms that participants may experience, and only projects that satisfy their requirements are allowed to take place. The committee includes experts in a range of areas of medical research, and lay members.
19. What will you do with my information?
We will follow legal and ethical practice, and all information about you will be handled in confidence. Any information you give the researchers will be held in secure offices in the University of Manchester. It will be made anonymous on collection, with a code allowing the identification of individual’s data held separately and securely. It is the intention of the researchers to publish a report drawn from this project in a scientific journal; any such report will have no information in it that could identify you.

20. What do I do now?
Hopefully this leaflet has been able to answer many of the questions you might have about this project. You will be contacted by Dr Russell, who will arrange to meet you to go through this leaflet with you and answer any questions you may have. At that point, if you wish to participate in the project, you will be asked to sign a consent form to state your wish to be included.

21. What if I don’t want to take part?
That’s fine, you are under no obligation to do so. If you do not wish to participate, let us know. You don’t even need to give a reason. The care you receive will not be affected in any way by this.
22. What if I agree to take part now, and change my mind later?
If, during the course of the study, you decide you do not wish to take part, please let Dr Russell know and you will be withdrawn from the study. Some demographic details will be retained to allow us to keep a record of whether the people that withdraw are different in some way from those that continue.

23. What if there is a problem and I wish to complain?
If you have a concern about any aspects of this study, you should ask to speak to the researchers, who will do their best to answer your questions. The Chief Investigator, Dr Gregor Russell, can be contacted on 0161 291 6956. If you remain unhappy and wish to complain formally, you can do this via the Manchester Mental Health and Social Care NHS Trust complaints procedures. The Patient Advice and Liaison Service (PALS) can assist in this process, and can be contacted on 0161 918 4047.

This study is covered by indemnity provided by its sponsor, Manchester Mental Health and Social Care NHS Trust. In the event that something goes wrong and you are harmed during this research, and this is due to someone’s negligence, then
you may have grounds for a legal action for compensation against Manchester Mental Health and Social Care NHS Trust. You may still have to pay your legal costs.

24. What happens after the study ends?
We will, if you wish, send you a copy of the findings of the research. This will make no reference of you in person, but will contain the combined data of all the people who have taken part in the study. If the study identifies any new medical problems that your general practitioner is unaware of, with your permission we will contact them to allow you to receive the proper investigations and treatment.

25. What are the contact details of the researchers?
The Chief Investigator is:
Dr Gregor Russell
Consultant in Older Peoples’ Mental Health
Room 3.304, Jean McFarlane Building
University of Manchester
M13 9PL
0161 306 7944
The associate investigator is:
Dr Varinder Singh
Speciality Registrar in Old Age Psychiatry
Daisyfield Mill, Appleby street
Blackburn
BB1 3BL
01254 226 975

The research is being supervised by:
Professor Alistair Burns
Professor of Old Age Psychiatry
Laureate House
Wythenshawe Hospital
Manchester M23 9LT
0161 291 6956

Professor Robert Baldwin
Edale House
Consultant in Old Age Psychiatry
Manchester Royal Infirmary
M13 9WL
0161 276 5317
The research is being carried out in collaboration with colleagues from the Manchester Royal Eye hospital, under the supervision of:

Dr Robert Harper
Consultant Optometrist
Manchester Royal Eye Hospital

Miss Fiona Spencer
Consultant Ophthalmic Surgeon
Manchester Royal Eye Hospital
Appendix 5.2

Charles Bonnet syndrome and memory loss : a cohort study
Study reference number 09/H1003/118
Version 2  8th June 2010

INFORMATION SHEET
FOR CONSULTEE OF PARTICIPANT WHO HAS LOST CAPACITY

1. Introduction

One year ago, your relative/friend was invited to take part in a research project. The title of this is “Charles Bonnet syndrome and memory loss: a cohort study”. This is because they were identified by an Optometrist at Manchester Royal Eye hospital as possibly suffering from Charles Bonnet syndrome. This condition is explained in paragraph 12 below. It would now be time for them to receive a follow-up assessment. However, when speaking to them, I believe that they no longer have the capacity to consent to take part in this study.

In such circumstances, the law requires that we to talk to a person that the participant knows well, and take their advice about whether the participant would wish to continue to be included in the study. This person is known as a “consultee”. You have been identified as a person who could possibly act as a consultee for your relative/friend. The purpose of this leaflet is to provide you with information to help you decide if you wish to take on this role, and if so, you help you offer your opinion about what your relative/friend would have wished to happen in the current circumstances.
2. What is capacity?
Capacity is the ability, having heard all the advantages or costs of a course of action, to make a decision to take it or not. It applies to all areas of a person’s life, but is specific to the decision needing to be made. So, a person could have capacity to decide on some things, like what they wish to wear or eat, but not for other, more complicated things, like buying or selling a house. There is a law, the “Mental Capacity Act”, that tells us how to decide if someone has capacity, and how to help make decisions for them if they don’t.

3. What does the Mental Capacity Act say about research?
It has helped make it clear to us how to decide if a person who lacks capacity should continue to be involved in research. The Act says we can continue to include such a person, provided the research is about the condition they suffer from, and provided they may stand to benefit from taking part, and provided this would not be unduly restrictive or invasive to them. We do however have to be as clear as we can that the person would have wanted to take part, were they still able to take that decision.

4. What would I have to do?
In order to try to work out if the person would have wanted to take part, the Mental Capacity Act requires that we consult with someone that knows the person well, and is happy to help make this decision. The friend or relative will need to say two things: whether they would be happy for the person to undergo the interviews described in the information provided below; and whether they think the person would still wish to participate.
5. How would I go about this?
Your friend/relative gave fully informed consent to take part when they entered a year ago. This included taking part in the follow-up part of the study, which is what we are proposing to do. You might think back to what your friend/relative has said about being in the study. Have they said anything that indicated they changed their mind about wanting to be included? You may also wish to think about, given what you know of your friend/relative, is this the sort of thing they would have wished to contribute to? And, given what we propose to do (two interviews and examinations), and what you know of their wishes and feelings, would you be happy for them to take part?

6. What if I think they should take part?
Dr Russell will contact you to find out what you think. If you think they should take part, then the interviews will go ahead as normal. We would be grateful if you were able to be present at them, to help make sure your friend/relative is comfortable with what is asked of them.

7. What if I think they shouldn’t take part?
That is fine. They are under no obligation to, and when they had capacity, they had an absolute right to leave the study at any point, without having to give a reason. If they do leave the study, their treatment will not be affected in any way.

8. What if I don’t feel happy with taking part in this decision?
That is fine too. There is no requirement for you to do this. All we would ask is whether you know of anyone else that the person would be happy for us to consult with over this matter, and how we might get in touch with them.
9. If I do decide to act as a consultee, what do I do now?
We would ask that you read the rest of this leaflet, as it will tell you about the study, and the contribution your relative/friend would be asked to make to it. Hopefully this leaflet will be able to answer many of the questions you might have about this project. You will be contacted by Dr Russell, who can arrange to meet you to go through this leaflet with you and answer any questions you may have. At that point, if you think that your relative/friend would still wish to participate in the project, and you are happy for them to do so, you will be asked to sign a form to record your decisions. This form is called a “consultee declaration form”. We will give you a copy of this to keep.

10. What if I change my mind later about my relative/friend taking part?
If, during the course of the study, you decide your friend/relative would not wish to take part, please let Dr Russell know and they will be withdrawn from the study. The information we had collected relating to them up to this point would be retained and included in the analysis.

11. What is the research project about?
This project is being carried out by researchers from the University of Manchester and Manchester Royal Infirmary. It is investigating whether there is a link between a condition called Charles Bonnet syndrome and memory loss, or other forms of cognitive impairment.
12. What is Charles Bonnet syndrome?
Charles Bonnet syndrome (CBS) is a condition affecting people with poor vision. They can experience visual hallucinations. This is the name given to the experience of seeing shapes or objects which do not actually exist. A lot of the time people know these experiences are not real, but sometimes people can be tricked by their eyes and think that the things they see actually exist. The images seen may be enjoyable, but can be frightening or upsetting. The cause of CBS is unknown, but it may be that when the brain gets less information from the eyes, it starts to ‘fill in the gaps’ by generating signals of its own. There is currently no known cure for this condition; some medications for other conditions do sometimes help, but these are used with caution as they all have their own side effects. Frequently the hallucinations stop on their own, although in some cases they can last many months.

13. What is cognition?
Cognition, or cognitive functioning, includes things like memory, using and understanding language, concentration, judgement and planning, and finding places or objects from memory. Problems in this can lead to forgetfulness, having problems with everyday tasks like making meals or using household appliances, and getting lost or wandering. In certain conditions an impairment, or worsening, of cognitive functioning occurs. An example of such a condition would be dementia, but there are many others.

14. What is the link between Charles Bonnet syndrome and cognitive impairment?
There is no link known at present, and there may be none, but there has been little research in this area so far. However, people with a condition
called Lewy body dementia sometimes develop visual hallucinations before they notice much in the way of memory problems. It is possible that some people diagnosed with Charles Bonnet syndrome may actually be developing Lewy body dementia. This would be important to know, as there are treatments which may help in Lewy body dementia that would otherwise not be given. Also, early recognition of the diagnosis being dementia would allow the person to get help, and to plan for the future. This study aims to find out how often people with Charles Bonnet syndrome suffer from cognitive impairment, and whether this ever develops into Lewy body dementia.

15. What will happen to my relative/friend if they take part?
Your relative/friend has already been participating in this study for around a year. They have attended appointments at the Royal Manchester Eye hospital, and been visited by the Chief Researcher, who examined them and got them to answer a series of questionnaires. They have also undergone a scan of their brain. At this stage, they would only have to undertake two more visits. One of these would be to return to the eye hospital and meet the optometrists again. They would undergo a detailed examination of their vision and answer a questionnaire. They would also be visited by Dr Russell, the chief researcher, who would interview and examine them, and complete some more questionnaires. There would also be a questionnaire for their relative/friend to complete. You could be the person to complete this if you wish. This would complete their involvement in the study.

16. Will you want to access any other information about me?
As part of the project, we obtained your relative’s/friend’s consent to be able to look at their general practice and eye hospital notes. This was to
see if they had experienced any other conditions that may be of relevance to the study. We would like to review these notes, and would need your agreement that you believe your relative/friend would be happy to continue to allow this access. There will be a paragraph related to this on the consultee form we will ask you to sign.

17. Is there any risk to my relative/friend in taking part?
As described in paragraph 15, the study consists of a number of interviews, and a brain scan. At this point, all that remains for them to do is to take part in two interviews. As such, the risks in the study are very small. It is possible they may find the interviews tiring, or even upsetting. We have explained in paragraphs 19 and 20 what would happen in such circumstances. Finally, it is possible that we may discover their symptoms are due to a condition other than Charles Bonnet syndrome. Given that they have developed a condition which has caused them to lose capacity to make decisions for themselves, the chances that this has occurred are increased. However, if this does happen, then we will be able to organise for them to be referred for appropriate medical treatment and support, and they may benefit from having this recognised earlier than would have been the case had they not taken part in the study.

18. Are there any benefits to him/her in taking part in this study?
As mentioned above, it may be that in some cases, the symptoms of visual hallucinations have a cause other than Charles Bonnet syndrome. If this is the case, they may receive a diagnosis and treatment faster than would otherwise have been the case. If the study confirms that they have no other cause for their symptoms, then this may come as an
additional reassurance to them. Moreover, they will be contributing to our knowledge of this area, and this may in the future lead to better diagnosis and treatments for these conditions.

19. What if they find the interviews too tiring?
There are a lot of questions; if these prove too tiring, we can arrange for them to be completed over two days.

20. What if the person takes part, but is upset by the interviews or examinations?
In such circumstances, we would stop the procedure. The law is clear on this, we can only include the person as long as they show no signs they are objecting to it. The Chief Investigator, Dr Gregor Russell, is an experienced doctor working in the field of psychiatry. As such, he has considerable skill in helping people complete such questionnaires without causing distress, and in recognising at an early point if people are becoming tired, anxious or upset.

21. Who are the researchers?
The research is being carried out by Dr Gregor Russell, a Speciality Registrar in old age psychiatry at Wythenshawe hospital. Dr Russell is carrying out this project as part of the research degree of Doctor of Medicine at the University of Manchester. He is being supervised by Professor Alistair Burns, Honorary Consultant in old age psychiatry at Wythenshawe hospital, and Deputy Dean of the school of medicine at the University of Manchester. Other people involved are Dr Roland Zahn, a researcher in the Neuroscience and Aphasia research unit at the University of Manchester; Dr Robert Harper, the Chief Optometrist at
the Royal Manchester Eye Hospital; Claire Parkes and Julie Lennon, Optometrists at the Royal Manchester Eye hospital.

22. Will the researchers be paid for carrying this out?
The researchers will not receive any money over and above their existing salaries for carrying out this research.

23. Will my relative/friend be paid for taking part in this?
There is no fee for participating in this research. We will arrange to refund any expenses incurred by you and you relative/friend in attending for appointments. Please obtain receipts and speak to Dr Gregor Russell should you wish to have travelling expenses reimbursed.

24. Has this project been reviewed by any external agencies?
Yes. It has been considered by the Greater Manchester South Research Ethics Committee. This panel looks at all aspects of the study, from its scientific worth to the potential discomforts and harms that participants may experience, and only projects that satisfy their requirements are allowed to take place. The committee includes experts in a range of areas of medical research, and lay members.

25. What will you do with my relative’s/friend’s information?
We will follow legal and ethical practice, and all information will be handled in confidence. Any information given to the researchers will be held in secure offices in the University of Manchester. It will made anonymous on collection, with a code allowing the identification of individual’s data held separately and securely. It is the intention of the researchers to publish a report drawn from this project in a scientific...
journal; any such report will have no information in it that could identify your relative/friend.

26. What if there is a problem and I wish to complain?
If you have a concern about any aspects of this study, you should ask to speak to the researchers, who will do their best to answer your questions. The Chief Investigator, Dr Gregor Russell, can be contacted on 0161 291 6956. If you remain unhappy and wish to complain formally, you can do this via the Manchester Mental Health and Social Care NHS Trust complaints procedures. The Patient Advice and Liaison Service (PALS) can assist in this process, and can be contacted on 0161 918 4047.

This study is covered by indemnity provided by its sponsor, Manchester Mental Health and Social Care NHS Trust. In the event that something goes wrong and your relative/friend is harmed during this research, and this is due to someone’s negligence, then they may have grounds for a legal action for compensation against Manchester Mental Health and Social Care NHS Trust. They may still have to pay their legal costs.

27. What happens after the study ends?
We will, if you wish, send you and your relative/friend a copy of the findings of the research. This will make no reference to your relative/friend in person, but will contain the combined data of all the people who have taken part in the study. If the study identifies any new medical problems that your relative’s/friend’s general practitioner is unaware of, with your permission we will contact them to allow your friend/relative to receive the proper investigations and treatment.
28. What are the contact details of the researchers?

The Chief Investigator is:
Dr Gregor Russell
Laureate House
Wythenshawe Hospital
Manchester M23 9LT
0161 291 6956

The research is being supervised by:
Professor Alistair Burns
Laureate House
Wythenshawe Hospital
Manchester M23 9LT
0161 291 6956

Professor Robert Baldwin
Edale House
Manchester Royal Infirmary
M13 9WL
0161 276 5317
Appendix 5.3

Charles Bonnet syndrome and memory loss: a cohort study
Study reference number 09/H1003/118
Version 4  4th march 2011

PARTICIPANT INFORMED CONSENT FORM

Please initial each statement if you agree with it, to confirm you have read and accept it

1. I confirm that I have read and understood the information sheet relating to this study, have had the opportunity to ask questions, and have had these answered to my satisfaction.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without my care or legal rights being affected.

3. I understand that a family member or friend will be asked questions about me and I agree to this.

4. I understand that sections of my medical notes held in the ophthalmology department of Manchester Royal Infirmary, and by my General Practitioner, may be looked at by the
investigators in order to access and make a note of information that is of relevance to this study. I give permission for these individuals to have access to my records.

5. I agree to my General Practitioner, and the consultant responsible for my care at Royal Manchester Eye hospital, being informed of my participation in this research.

6. I understand that I will receive a signed copy of this form.

7. I agree to take part in this study.

Name of Participant

Signature

Date

Name of Investigator

Signature

Date
8. MRI Scan Component

I understand that as part of this research, I be offered the opportunity to have a magnetic resonance imaging procedure (MRI scan). I have read the paragraphs relating to this in the information sheet provided. Should I agree to this procedure, I am aware that staff members at the magnetic resonance imaging department will need to have access to a minimum amount of personal information about me in order to carry out this procedure safely.

*Please indicate your preference regarding the MRI scan part of the study by deleting the statement that does not apply:* 

- I agree to have a MRI scan
- I do NOT agree to have a MRI scan

Name of Participant

Signature

Date

Name of Investigator

Signature

Date
Appendix 6: Study Instruments

6.1 Screening Tool 430
6.2 North-East Visual Hallucination Inventory (NEVHI) 432
6.3 Informant Questionnaire for Cognitive Decline in the Elderly (short form) 439
6.4 Brief Psychiatric Rating Scale (18 item) 441
### 6.1 Screening Tool

**Charles Bonnet syndrome and memory loss:**

**A cohort study**

**Screening Tool for use in Low Vision Clinic**

**When seeing patients, please check if any meet the inclusion criteria-**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 65 years or over</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having a relative or friend able to act as an informant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If patients screen positive, then progress to the questions below. If not, then only note age and sex.

**Some people see things that other people can not see. Please reply to the following questions with ‘yes’ or ‘no’.”**

1. **Do you feel that your eyes ever play tricks on you?**

   If answered yes, note details:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this a simple visual hallucination?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this a complex visual hallucination?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Have you ever seen things that other people could not see?**

   If answered yes, note details:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this a simple visual hallucination?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this a complex visual hallucination?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Have you ever had visual hallucinations?  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If answered yes, note details:

<table>
<thead>
<tr>
<th>Is this a simple visual hallucination?</th>
<th>Yes / No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this a complex visual hallucination?</td>
<td>Yes / No</td>
</tr>
</tbody>
</table>

4. Have you ever had other visual experiences?  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If answered yes, note details:

<table>
<thead>
<tr>
<th>Is this a simple visual hallucination?</th>
<th>Yes / No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this a complex visual hallucination?</td>
<td>Yes / No</td>
</tr>
</tbody>
</table>

Contact Details and Demographic Information:

Note: only age and gender to be completed unless person wishes to participate in study

| Patient's name: | ______________________________ |
| Age (DOB for participants): | ______________________________ |
| Gender: | ______________________________ |
| Address: |
|Telephone Number: | ______________________________ |
|Informant Name: | ______________________________ |
|Informant Contact Information: | ______________________________ |

For use by Chief Investigator:

| Contacted on this date: | ______________________________ |
| Agreed to initial interview: | Yes | No |
| Date arranged for initial interview: | ______________________________ |
| Location for initial interview: | ______________________________ |
6.2 North-East Visual Hallucination Inventory

Charles Bonnet syndrome and cognition: a cohort study

6. Workbook for NEVHI at initial visit

Participant’s URN: ____________________
Completed by: ____________________
Signed: ____________________
Date: ____________________

The purpose of this assessment is to record in detail the nature of the visual hallucinations the person is experiencing, their duration and frequency, and the person’s reaction to them. The assessment consists of three parts. Part one consists of the same items used in the screening questionnaire. Please repeat this, and record any new or changed experiences. If there are no new or changed experiences please enter “refer to screening”. Parts two and three are new, and should be completed in full. There are sections in italics which should be read aloud to the participant; and sections in bold which form instructions to the interviewer. The same definitions of simple and complex hallucinations are used as in the screening, these are repeated again below:

**Simple visual hallucinations** are taken to mean: photopsias, lines or patterns, including zigzags or circles

**Complex visual hallucinations** are taken to mean a broad range of more complex percepts, including: people or faces, including smaller and larger than life, and distorted in shape; animals; complex geometrical or branching structures; landscapes; objects or decorations in a room; or the subject themselves, including at earlier stages of their life.
Part One: Nature of Visual Experiences

Please read the following statement to the participant:

Some people see things that other people can not see. Please reply to the following questions with ‘yes’ or ‘no’.

1. Do you feel that your eyes ever play tricks on you?  
<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

   If answered yes, note details:

   Type of hallucination: Simple / Complex

2. Have you ever seen things that other people could not see?  
<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

   If answered yes, note details:

   Type of hallucination: Simple / Complex
3. Have you ever had visual hallucinations?  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If answered yes, note details:

Type of hallucination: Simple / Complex

4. Have you ever had other visual experiences?  

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If answered yes, note details:

Type of hallucination: Simple / Complex

Explain that you will refer to the experiences as hallucinations in the subsequent sections. If this term is rejected, use another term, e.g. visions, visual experiences. Then proceed to part two.
Part Two: Frequency and Duration of Hallucinations

Please read the follow statement to the participant, and mark their reply in the relevant box:

The following questions are about the visual hallucinations you have just described.

When did your hallucinations first start?

<table>
<thead>
<tr>
<th>Within the last week</th>
<th>Within the last month</th>
<th>Within the last six months</th>
<th>Within the last year</th>
<th>Greater than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How long do your hallucinations usually last?

<table>
<thead>
<tr>
<th>Up to one minute</th>
<th>One minute to one hour</th>
<th>One to two hours</th>
<th>Over two hours, but less than all the time</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When was your last hallucination?

<table>
<thead>
<tr>
<th>Within the last 24 hours</th>
<th>Within the last week</th>
<th>Within the last month</th>
<th>Within the last year</th>
<th>Over one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How often have you had hallucinations during the last month?

<table>
<thead>
<tr>
<th>Daily</th>
<th>Weekly</th>
<th>Every fortnight</th>
<th>Only once in the last month</th>
<th>Not in the last month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The interview ends here for those with no, or only one, episode of hallucinations during the last month. For all others please complete part three.
Part 3: Response to Hallucinations

Please read out the following statements, and record the participant’s score below the statement where prompted. Score as follows:

Never = 0 ; Seldom = 1 ; Quite Often = 2 ; Very Often = 3 ; Always = 4

I will now ask you a number of questions related to your hallucinations. Please answer with ‘never’, ‘seldom’, ‘quite often’, ‘very often’ or ‘always’.

1. How often were your hallucinations nice?
   Score:

2. How often were your hallucinations pleasant?
   Score:

3. How often were your hallucinations irritating?
   Score:

4. How often were your hallucinations frightening?
   Score:

5. How often could you control the start of your hallucinations?
   Score:

6. How often could you control the end of your hallucinations?
   Score:

7. How often could you control the content of your hallucinations?
   Score:

8. Whilst you were experiencing hallucinations, how often have you been aware than you were experiencing a hallucination?
   Score:
   (for this item, apply following transformation: 0=4, 1=3, 2=2, 3=1, 4=0)

9. Whilst you were experiencing hallucinations, how often did you do something in response to them?
   Score:
Part 4: Factor scores for perception of hallucinations

a) Perceived control (items 5 + 6 + 7) = _____
b) Perceived pleasantness (items 1 + 2) = ______
c) Perceived distress (items 3 + 4) = ______
d) Perceived awareness (items 8 + 9) = ______
Part 5: Classification of Experiences

This section is to be completed after the interview, and involves allocating the described experiences to one or more categories. Please mark as present as many of the types of hallucination as are felt to be present, given the participant’s descriptions. For definitions of types of hallucinations, refer to explanatory notes.

Category A Experiences

<table>
<thead>
<tr>
<th>Type of hallucination</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Perseveration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illusory Visual Spread</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micropsia/macropsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperchromatopsia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Category B Experiences

<table>
<thead>
<tr>
<th>Type of hallucination</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosopometamorphopsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyopia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tessellopsia</td>
<td></td>
<td></td>
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<tr>
<td>Dendropsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfamiliar figures in bizarre costumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landscape scenes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confinement to part of visual field</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Category C Experiences

<table>
<thead>
<tr>
<th>Type of hallucination</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familiar figures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracampine hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of simple hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer duration (hours to days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multimodal hallucinations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scoring

For every category B experience scored as present, add one point
For every category C experience scored as present, subtract one point
For every category A experience scored as present, neither add nor subtract anything

This will give a score between +7 and -6. Record that here: ____________
6.3 Informant Questionnaire for Cognitive Decline in the Elderly (short form)

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 19__. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

**Compared with 10 years ago how is this person at:**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Remembering things about family</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>and friends e.g. occupations,</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>birthdays, addresses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Remembering things that</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>have happened recently</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Recalling conversations a few</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>days later</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4. Remembering his/her address and</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>telephone number</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Remembering what day and month</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>it is</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Remembering where things are</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>usually kept</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Remembering where to find things</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>which have been put in a different</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>place from usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Knowing how to work familiar</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>machines around the house</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td>---</td>
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<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>9. Learning to use a new gadget or machine around the house</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>10. Learning new things in general</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>11. Following a story in a book or on TV</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>12. Making decisions on everyday matters</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>13. Handling money for shopping</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>14. Handling financial matters e.g. the pension, dealing with the bank</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
<tr>
<td>16. Using his/her intelligence to understand what's going on and to reason things through</td>
<td>Much improved</td>
<td>A bit improved</td>
<td>Not much change</td>
<td>A bit worse</td>
<td>Much worse</td>
</tr>
</tbody>
</table>
6.4 Brief Psychiatric Rating Scale (18 item)

Charles Bonnet syndrome and memory loss: a cohort study

4. BPRS Initial Workbook

Participant’s URN: ______________________
Completed by: ______________________
Signed: ______________________
Date: ______________________

*Items rated on following scale, circle the one that best fits:*
1 = not present 2 = very mild 3 = mild 4 = moderate 5 = moderately severe 6 = severe 7 = extremely severe

*There are prompt questions given for each of the items which are rated on the content of the participant’s answer. Use the scoring guidance to help derive score. The numbers of the items relate to the numbers they are given on the scoring guidance sheet.*
1. Somatic Concern

1 2 3 4 5 6 7

“have you been concerned about your physical health”
“have you had any physical illness, or seen a medical doctor lately”
“has anything interfered with your ability to perform your usual activities”
“how often are you concerned about…”
“have you expressed any of these concerns to others”

2. Anxiety

1 2 3 4 5 6 7

“have you been worried a lot during the last month”
“have you been nervous or apprehensive”
“when you are feeling nervous, do your palms sweat/heart beat fast/tremble/feel you are choking”
“how much of the time have you been”
“has it interfered with your ability to perform your usual activities”
3. Depressive Mood

```
1 2 3 4 5 6 7
```

“How has your mood been recently”
“Have you felt depressed, sad, unhappy”
“Are you able to switch your attention to more pleasant topics when you want to”
“Have you lost interest in or get less pleasure from things you used to enjoy”
“How long do these feelings last”
“Has it interfered with your ability to perform your usual activities”

5. Guilt Feelings

```
1 2 3 4 5 6 7
```

“Do you tend to blame yourself for things that have happened”
“Is there anything you feel guilt about”
“How often have you been thinking about…”
“Have you told anyone else about these feelings”
6. Hostility

1  2  3  4  5  6  7

“Have you been getting along with people”
“Have you been irritable or grumpy lately”
“How do you show it”
“Were you ever so irritable that you would shout at people or start arguments”

8. Grandiosity

1  2  3  4  5  6  7

“Do you have any special abilities or powers”
“Have you thought that you may in fact be rich, or famous”
“How often have you been thinking about this”
“Have you told anyone else about what you have been thinking”
“Have you acted on any of these ideas”
9. Suspiciousness

1  2  3  4  5  6  7

“Does it ever seem as though others are watching you”
“Are you concerned about anyone’s intentions towards you”
“Is anyone going out of their way to give you a hard time, or trying to hurt you”
“Do you feel in any danger”
“how often have you been concerned that….?”
“Have you told anyone about these experiences”

10. Hallucinatory Behaviour

1  2  3  4  5  6  7

“Do you ever hear your name being called”
“have you ever heard people talking about you when there has been nobody around”
“what did the voice/voices say”
“do you ever have visions or see things that others do not see”
“or smell odours that others cannot smell”
“have any of these experiences interfered with your ability to perform your usual activities”
“how often do they occur”
11. Unusual Thought Content

1  2  3  4  5  6  7

“have you been receiving any special messages from people, or from the way things are arranged around you”
“have you seen any references to yourself on the TV, radio or newspapers”
“is anything like electricity, radio waves or X-rays affecting you”
“can anyone read your mind”
“are thoughts put into your head which are not your own”
“have you felt that you are under the control of another person or force”
“how often do you think about…..”
“have you told anyone about your experiences”
“how do you explain these things”

14. Disorientation

1  2  3  4  5  6  7

Impression and results of cognitive testing
15. Conceptual Disorganisation

1  2  3  4  5  6  7

RATER ASSESSED

16. Blunted Affect

1  2  3  4  5  6  7

RATER ASSESSED

17. Emotional Withdrawal

1  2  3  4  5  6  7

RATER ASSESSED
18. Motor Retardation
1  2  3  4  5  6  7
RATER ASSESSED

19. Tension
1  2  3  4  5  6  7
RATER ASSESSED

20. Uncooperativeness
1  2  3  4  5  6  7
RATER ASSESSED
21. Excitement
1 2 3 4 5 6 7
RATER ASSESSED

24. Mannerisms and Posturing
1 2 3 4 5 6 7
RATER ASSESSED

TOTAL SCORE:
Appendix 7: Definitions of terminology for describing categories of visual hallucinations

Visual perseveration: this is the continuing experience of a visual sensation after the stimulus is gone.

Illusory visual spread: objects in the visual field may take on the textures or colours of neighbouring objects.

Micropsia/macropsia: objects are experienced as being larger or smaller than in reality.

Hyperchromatopsia: colours of objects are experienced as being exceptionally vivid.

Prosopometamorphosia: faces are experienced as being misshapen or distorted.

Polyopia: multiple copies of objects are experienced in the visual field.

Tesselopsia: this is a hallucination consisting of repeated geometric patterns featuring tiles, brickwork, triangles, hexagonal figures, and grid-like patterns.

Dendropsia: this is a hallucination consisting of irregular branching forms which may look like trees, branches, or roadmaps.

Extracampine hallucinations: in relation to visual hallucinations, these are percepts experienced outside the normal visual field, for example seeing objects behind the person's head, or the inside of a room in a distant familiar building.
Appendix 8: Figures generated as part of assumption testing for ANCOVA

8.1 Q-Q plots
8.2 Scatter plots
8.3 Scatter plot testing for homoscedasticity

8.1a Q-Q plot for CBS participants
8.1b Q-Q plot for controls

Normal Q-Q Plot of ACE-R at F/U

participant type: CTL
8.2a Scatterplot for dependent variable = ACE-R

participant type

CBS, CTL

CBS: \( R^2 \) Linear = 0.558
CTL: \( R^2 \) Linear = 0.393
8.2a Scatterplot for covariate = visual acuity best eye
8.3 Scatterplot testing homoscedasticity

![Scatterplot image]

Dependent Variable: ACE-R at F/U

Regression Standardized Residual

Regression Standardized Predicted Value

$R^2$ Linear = 2.220E-16