Neuropsychological, eye tracking and neuroimaging perspectives on Posterior Cortical Atrophy.

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SIGNED DECLARATION

I, Timothy James Shakespeare, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, or conducted in collaboration with other researchers, I confirm that this has been indicated in the thesis (Appendix section 1).

Timothy James Shakespeare

Abstract

This thesis describes investigations of the clinico-radiological syndrome Posterior Cortical Atrophy, addressing two broad themes: the consequences of PCA for everyday activities (particularly scene perception) and the heterogeneity of symptoms in PCA.

Despite improvements in the recognition and characterisation of PCA, we have little understanding of what the world looks like to someone with PCA. This thesis investigates patients' perception of real-world stimuli (scenes) using a number of methodologies; characterising their response times when categorising scenes and giving a novel qualitative report of patients' verbal descriptions (Chapter 2). It is possible that oculomotor behaviour is a contributory factor in these tasks, therefore a study of fixation, saccades and smooth pursuit was carried out. This characterised in detail for the first time the oculomotor abnormalities present in PCA (Chapter 3), facilitating further investigation of patients' eye movements when viewing scenes (Chapters 4 and 5), revealing a striking impairment in the ability to change fixation patterns in response to task demands.

The consequences of PCA for everyday activities are also investigated through a questionnaire given to carers allowing a wide range of symptoms and behaviours to be investigated over different stages of disease severity (Chapter 6). The range of symptoms and severity that this questionnaire measures will eventually allow better characterisation of the heterogeneity within PCA, and the early onset Alzheimer's Disease spectrum more broadly. One specific manifestation of this heterogeneity is investigated in Chapter 7, demonstrating that a proportion of PCA patients show asymmetric motor symptoms (myoclonus and limb rigidity on the left side) associated with atrophy of motor cortex in the right hemisphere.

Together, these studies improve our knowledge of the consequences of PCA for scene perception and more general everyday activities, and address aspects of heterogeneity in the syndrome; with implications for interventions to improve diagnosis and clinical management.

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1 General introduction

1.1 Overview

Posterior Cortical Atrophy (PCA) is an early onset degenerative syndrome characterised by insidious onset of impairments in vision, calculation and spelling due to progressive atrophy of the parietal, occipital and occipito-temporal regions of the brain. As a relatively recently recognized syndrome (the term was coined by Benson in 1988), there are many aspects yet to be investigated. Whilst there are published criteria for the diagnosis of PCA (Mendez et al., 2002; Tang-Wai et al., 2004), development of an internationally agreed framework to allow easier communication between centres is ongoing (Crutch, Schott, et al., 2013). There have been studies of heterogeneity within the PCA syndrome, particularly with regards to the types of visual symptoms experienced (Galton et al., 2000; Lehmann, Barnes, et al., 2011; Tsai et al., 2011) and the histopathological processes that underlie the disease (Renner et al., 2004; Tang-Wai, Josephs, Boeve, Petersen, et al., 2003). However there have been very few studies that investigate the consequences of PCA in terms of the patient's experience; although progressive visual dysfunction is the primary diagnostic feature, perceptual deficits have largely been explored using abstract experimental stimuli that do not inform us about how the real world is perceived by individuals with PCA. Oculomotor abnormalities are likely to contribute significantly to real world perception in this patient group but have not previously been studied in detail. The following sections describe what is known about PCA and provide the background for the research carried out in this thesis.

1.2 Posterior cortical atrophy

1.2.1 Clinical phenotype

PCA is a clinico-radiological syndrome, in which cognitive visual deficits and atrophy on neuroimaging (of parietal and occipital lobes) form the central features. Patients with PCA typically present to the clinician with initial deficits in complex visual tasks, demonstrating impairment in visuo-spatial (seeing where things are) and visuo-perceptual (seeing what things are) function, for example difficulties in reading, locating objects, or judging distance, depth or volume (Crutch et al., 2012). These

deficits can manifest with problems such as veering out of lane when driving, or walking into low objects. Elements of Balint's syndrome (simultanagnosia, oculomotor apraxia, optic ataxia) and Gerstmann's syndrome (dysgraphia, dyscalculia, finger agnosia, left-right disorientation) are commonly reported (Mendez et al., 2002; Tang-Wai et al., 2004).

A small proportion of patients experience visual hallucinations and/or motor deficits similar to those seen in Parkinson's disease (McMonagle et al., 2006; Tang-Wai et al., 2004). A minority of patients also develop early aphasic symptoms – particularly slow or reduced speech and impaired naming (Crutch, Lehmann, et al., 2013). In contrast to these deficits, episodic memory and insight into the condition remain relatively spared until late into the disease process, as does general cognitive reasoning (Crutch et al., 2012; Mendez et al., 2002; Tang-Wai et al., 2004).

The most widely used clinical criteria for PCA are shown in Table 1-1. Criteria include presence of visual complaints in the absence of primary visual dysfunction, insidious onset, and relatively preserved insight and memory (Mendez et al., 2002). Non-visual symptoms have also been described in people with PCA, for example motor symptoms (e.g. myoclonus; Snowden et al., 2007), oculomotor apraxia (McMonagle et al., 2006; Mendez et al., 2002; Tang-Wai et al., 2004) and aspects of Gerstmann's syndrome (dysgraphia, dyscalculia, finger agnosia and left-right disorientation; Mendez et al., 2002; Tang-Wai et al., 2004) . A number of histopathological causes of PCA have been identified (discussed in detail in the 'Pathology' section), but Alzheimer's disease is by far the most common underlying pathology (Renner et al., 2004). Whilst these different pathologies lead to a similar syndrome, some differences have been described. For example clinically, PCA due to Dementia with Lewy Bodies (DLB) is discriminated from PCA due to Alzheimer's Disease (AD) by a higher prevalence of visual hallucinations, delusions, Parkinsonian motor features and fluctuations. However, due to the rarity of these more unusual causes of PCA, a detailed comparison of clinical features between groups of patients with different underlying pathologies has not been conducted.

Table 1-1 Diagnostic criteria for PCA (from Mendez et al., 2002).

1.	**Core diagnostic features (all must be present)** • Insidious onset and gradual progression • Presentation with visual complaints with intact primary visual functions • Evidence of predominant complex visual disorder on examination • Elements of Balint's syndrome • Visual agnosia • Dressing apraxia • Environmental disorientation • Proportionally less impaired deficits in memory and verbal fluency • Relatively preserved insight with or without depression
2.	**Supportive diagnostic features** • Presenile onset • Alexia • Elements of Gerstmann's syndrome • Ideomotor apraxia • Physical examination within normal limits • Investigations • Neuropsychology: predominantly impaired perceptual deficits • Brain imaging: predominantly occipitoparietal abnormality (especially on functional neuroimaging) with relative sparing of frontal and mesiotemporal regions

1.2.2 Epidemiology

The prevalence and incidence of PCA are not well established. Most studies of PCA involve small numbers of patients who have been referred to a specialist clinic, the results of which cannot easily be extrapolated to a wider population. A study of 523 consecutive referrals with Alzheimer's disease to a specialist dementia clinic in the UK found 5% to have a visual presentation (Snowden et al., 2007). Whilst a specialist centre is likely to have a bias towards a greater proportion of 'unusual' cases such as those with an early onset or visual presentation, PCA is not widely known to general

practitioners, general neurologists, or optometrists (to whom patients are likely to report first). This leads to the tentative suggestion that it may be under-diagnosed.

The age at onset (AAO) in PCA tends to be earlier than that of typical Alzheimer's disease (tAD). A number of studies report disease onset in patients' late 50s and early 60s (McMonagle et al., 2006; Mendez et al., 2002) whilst a wider range of 40-86 years has also been reported (Tang-Wai et al., 2004). Most cases of PCA are therefore classed as early onset – an arbitrary label given to patients with AAO of less than 65. It is thought that life expectancy in PCA-AD is similar to that in tAD.

The evidence on gender distribution is inconclusive; some studies show no difference between numbers of males and females (McMonagle et al., 2006), whilst others have shown more females with the condition (Snowden et al., 2007). It is possible that referral bias influences the gender balance of patients in specialist centres (Kokmen et al., 1996). Unfortunately, no studies have been carried out that investigate age of onset, prevalence and gender bias of PCA in a prospective population-based cohort study.

1.2.3 Neuropsychological characteristics

The neuropsychological hallmarks of PCA are visuoperceptual and visuospatial deficits. Benson coined the term posterior cortical atrophy, reporting progressive dementia resulting in disorder of higher visual function including alexia, agraphia and visual agnosia (Benson et al., 1988). Subsequent studies have improved the characterisation of this syndrome with larger numbers of patients, and whilst there are striking similarities between the cognitive deficits in patients with PCA, significant heterogeneity has been reported. For example, there is disagreement as to whether a patient with spelling and calculation impairment, but without gross visual impairment should be given the label of PCA. In order to address all of the neuropsychological aspects of PCA, I shall outline cognitive deficits under headings of vision, memory and insight, language, and other findings. The majority of neuropsychological studies do not involve pathologically confirmed cases, and either no assumption is made, or AD is presumed to be the underlying pathology.

1.2.3.1 Visual perception

Some of the most frequently reported cognitive deficits in PCA are visual agnosia, visual disorientation and optic ataxia. These deficits (at the apperceptive level of visual processing) are common to most patients with PCA (Charles & Hillis, 2005; Lehmann, Barnes, et al., 2011; McMonagle et al., 2006; Mendez et al., 2002; Tang-Wai et al., 2004; Tsai et al., 2011). Studies comparing PCA with tAD show greater impairments in visual perception (for example on the Cortical Vision Screening Test - Charles and Hillis, 2005) and visually-mediated performance IQ subtests (McMonagle et al., 2006) in PCA than tAD.

Visual processing at this level can broadly be described following two relatively separate but highly interactive and parallel streams. The ventral stream originates in V1 and V2, following on to V4 and then to the inferior temporal cortex (IT), including areas TEO and TE. The dorsal stream follows from V2 to area MT/V5 and on to posterior parietal cortex (PPC – see Figure 1-1). Single unit recording in macaque monkeys, fMRI and double dissociations in neuropsychology have been used to define their function as vision for perception, or what things are (ventral) and vision for action, or where things are and how they are used (dorsal) (Milner & Goodale, 2008). However, whether these broad distinctions capture the parallel and interactive nature of visual processing is disputed (de Haan & Cowey, 2011). Some researchers have argued that there are ventral and dorsal subtypes in PCA (Galton et al., 2000; Ross et al., 1996) and a number of studies of PCA have directly addressed this issue.

Figure 1-1 Dorsal and ventral pathways in visual processing.

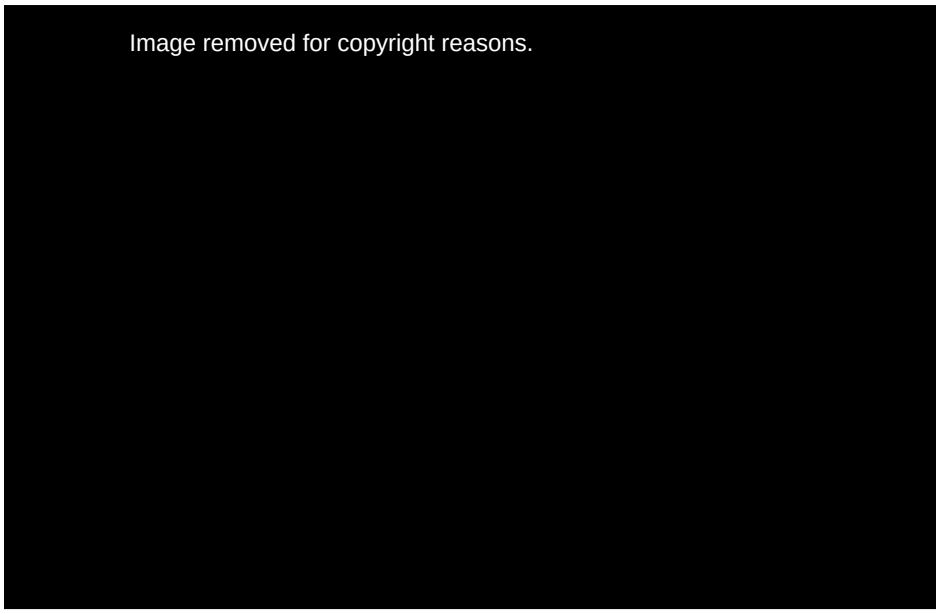
McMonagle et al. (2006) designed a test battery to assess ventral visual function (Object, Face & Color Agnosia Screen [OFCAS]), and contrasted performance on this battery with tasks aimed at dorsal stream function (complex pictures and compound stimuli). They found that dorsal stream deficits were most prevalent. No pure ventral stream syndromes were found. Similarly, Tsai et al. (2011) found 26 of 30 patients showed a dorsal presentation and 4 showed a ventral presentation (based on cluster analysis on a number of ventral and dorsal visual tests). In contrast, Galton et al. (2000) claimed to demonstrate three subtypes of PCA, in which 'biparietal' patients have dorsal pathology along with visuospatial deficits, agraphia and dyspraxia, whilst 'occipitotemporal' ventral patients suffer from apperceptive agnosia, visual distortion and alexia, and a third 'primary visual' variant affects more basic visual processing. It should be noted that this distinction is based on three patients.

Another study of dorsal and ventral subgroups in PCA divided a number of tests into those that have greater dorsal visual demands and those with greater ventral demands. Patients were split into a dorsal and ventral group based on a composite score of ventral and dorsal tests (Lehmann, Barnes, et al., 2011). In this study, the participants did not fall into discrete ventral and dorsal groups, rather individual performance revealed a continuum of variation in PCA, with some patients showing a more dorsal set of deficits, some showing a more ventral presentation, and many falling in between these extremes (see Figure 1-2).

The distinction between impairments at basic and higher visual processes has been investigated in detail. Whilst some studies only consider visual performance at the whole single object level (e.g. McMonagle et al., 2006), tests of basic visual function (such as form, motion and colour processing) in PCA patients reveal that impairment in aspects of visual processing at the basic sensory level (Lehmann, Barnes, et al., 2011) are present (in this study, every patient was impaired on at least one test of basic visual function). This suggests that these aspects contribute to apperception of higher order percepts, an aspect often not accounted for in studies of PCA. In the present thesis we consider even more complex multi-object stimuli (scenes from the real world). For these more complex stimuli it is very important to not only consider basic components of perception but also basic aspects of oculomotor control, as participants

need to move their eyes around in order to appreciate them and extract global and task-relevant information.

Figure 1-2 Separation of PCA patients into object and space subgroups. From Lehmann, Barnes, et al., 2011.



1.2.3.2 Visual attention

The posterior parietal lobes (part of the dorsal stream) are also known to have an important role in visual attention, therefore one would expect some reduction in the efficacy of visual attention, or signs of neglect in PCA. Given the visual disorientation and loss of form discrimination in some patients, assessing this effectively is a challenge. Commonly used tests to investigate neglect are line bisection and cancellation tests, such as the bells test. These were carried out with 24 patients with PCA, along with a clinical visual field test by a neurologist (Andrade et al., 2010). Patients showed a range of performance in the visual fields test. Some patients performed normally, whilst others missed all the left-sided stimuli. In four patients, the extinction on visual field testing and deviations on line bisection were in opposite directions, suggesting that the tests were either unreliable or invalid in these cases. 13/24 patients were reported to show neglect on line bisection whilst 7/24 patients showed an impairment in the bells test. Whilst there are likely to be signs of neglect in some PCA patients, finding a reliable and valid method to identify them is problematic.

Some studies report visual field deficits in PCA, but it is likely that attentional or more basic form and location processing deficits (Hickman et al., 2005) rather than (or at least in addition to) a complete lack of sensitivity to stimuli in that part of the field contribute to such findings, especially given the variation in results between eyes and over time (evident in the supplementary material of Pelak et al., 2012). One study has compared cognitive visual performance in PCA due to probable DLB and PCA due to probable AD, showing spared early visual processing in PCA-DLB whilst patients with PCA-AD were impaired in all visual tasks (Metzler-Baddeley et al., 2010).

1.2.3.3 Language

Reading is often impaired in PCA (Mendez et al., 2002). Some patients have been demonstrated to have attentional dyslexia (Saffran & Coslett, 1996), with intact reading of single words, but errors when reading displays of two-words (errors were particularly due to migration of letters from one word to another, leading to the suggestion that loss of location information underlies performance). Letter-by-letter reading, a condition in which there is a linear relationship between reading latencies and word length, has also been reported in patients with PCA (Catricalà et al., 2011). In other patients, reading of single words is not possible (Crutch & Warrington, 2007). An abnormal crowding effect in letter identification tasks (in which letters or digits presented to either side of a target stimulus interfere with identification of the central target stimulus) has been demonstrated in PCA, and is likely to contribute to impaired reading of words and sentences. Some patients demonstrate an inverse size effect for reading, with better performance for small than large letters and words perhaps due to a restricted 'spotlight' of visuospatial attention (Crutch et al., 2011).

Whilst writing and reading are often impaired, verbal language production is relatively preserved in PCA at presentation (McMonagle et al., 2006) but as the disease progresses, anomia and phonological processing deficits may develop (Crutch, Lehmann, et al., 2013).

1.2.3.4 Memory and insight

Clinically, patients with PCA have relatively preserved episodic memory compared to their visual cognition deficits (by definition) and insight often remains intact until late into the disease process. This is reflected in relatively better recognition and recall

memory performance compared to tAD patients in tests such as CERAD word list recall (Mendez et al., 2002) and the Rey Auditory Verbal Learning Test (combining recognition and recall memory - Charles & Hillis, 2005). However, the trend for better memory in PCA than tAD failed to reach significance in the Dementia Rating Scale (McMonagle et al., 2006) and short story recall (Aresi & Giovagnoli, 2009). Unfortunately, many tests of memory are designed with visual presentation of stimuli and this can confound results in patients with visual deficits. Tests that can be administered verbally are therefore preferable.

1.2.3.5 Other cognitive functions

Impairment in calculation is often present on neuropsychological testing (Lehmann, Barnes, et al., 2011), however a direct comparison of calculation deficits in PCA and tAD revealed no significant difference (Mendez et al., 2002). This could be due to limited sensitivity of the easy items used (simple calculations from the Neurobehavioral Cognitive Status Examination), the severity of patients tested (if both patient groups have progressed from initial focal deficits towards a wider set of cognitive impairments). Spelling deficits have also been described but are rarely quantified (O'Dowd & de Zubicaray, 2003).

Executive function is thought to be relatively spared in PCA, this assertion is based mainly on clinical symptoms, as most executive function tests are confounded by visual presentation.

1.2.3.6 Unusual symptoms

A number of case studies have described unusual symptoms in patients with PCA, for example prolonged colour after-images (Chan et al., 2001), better reading of small than large letters, and perceived motion of static stimuli (Crutch et al., 2011). These unusual findings may provide clues to the way in which the pathology affects specific aspects of processing, for example the existence of prolonged colour after-images led to the suggestion that there may be a relative sparing of inhibitory inter-neurons in V1 (Chan et al., 2001).

1.2.3.7 Neuropsychology conclusions

In conclusion, the neuropsychological deficits described in PCA are primarily of higher order 'apperceptive' visuospatial and visuoperceptual dysfunction. Although rarely

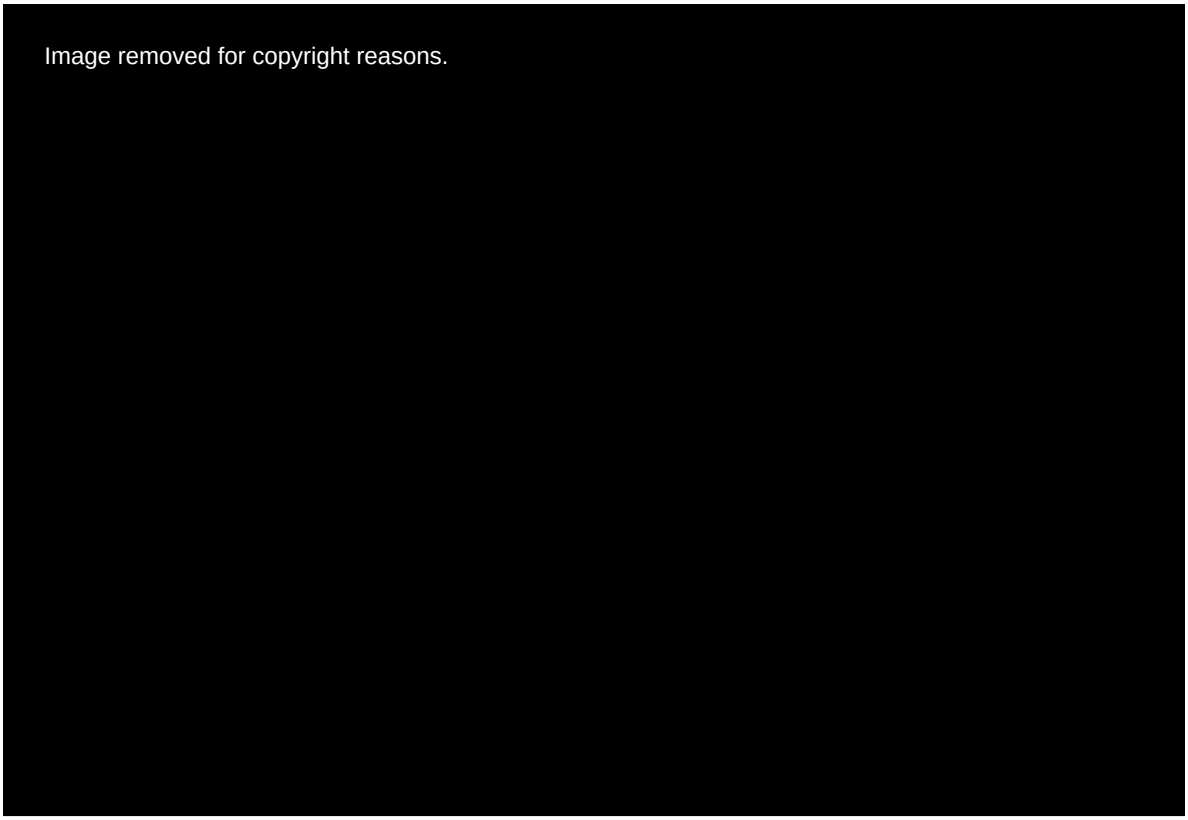
tested, basic sensory functions such as visual localisation and form detection underlie these deficits to some extent. There is variation in the extent to which patients experience deficits in visual processing, language and memory, it seems that this is likely to take the form of a spectrum of impairment rather than distinct subtypes. A number of unusual symptoms have been reported in PCA, providing insight into possible mechanisms of visual dysfunction. The visual deficits in PCA provide a challenge for neuropsychological assessment of other domains as many existing tests require visual presentation of stimuli. Memory performance in PCA is relatively spared by definition, however if we consider the atypical forms of AD together, we may see a more varied picture with continuous variation in the extent of memory, language and visual cognitive deficits.

1.2.4 Pathology

1.2.4.1 Post mortem

Post mortem (PM) confirmation is currently the only way of definitively ascertaining the location and type of pathology underlying a patient's symptoms. As expected, PCA patients show cortical atrophy on post mortem, and at this stage atrophy may be generalised although this may still be particularly pronounced at the back of the brain (Hof et al., 1993; see Figure 1-3). One of the first PM studies of PCA compared the distribution of pathology in a subset of AD patients who presented with a major impairment of visuospatial skills (then referred to as Balint's syndrome, but could be considered Posterior Cortical Atrophy), with those with a typical amnestic presentation (Hof et al., 1990). This study found a higher incidence of neurofibrillary tangles (NFT) and neuritic plaques (NP) in occipital cortex (Brodmann's areas (BA) 17, 18, 19), increased NFT density in the superior colliculus, increased NP density in the parietal (BA 7) and posterior cingulate cortex (PCC), and reduced NFT density in prefrontal areas (BA 9, 46, 45), compared to tAD. The authors concluded that these PCA patients differed in the striate-parietal (dorsal) visual stream compared to tAD, but did not appear significantly different in the striate-inferior temporal (ventral) pathway. There are a number of further single cases with similar findings of visuospatial cognitive decline due to underlying AD primarily affecting the occipital and parietal cortex (Hof et al., 1993; Levine et al., 1993; Ross et al., 1996).

Figure 1-3 Pronounced occipital atrophy in a post mortem case of PCA. Lateral view of the right hemisphere reproduced from Hof et al., 1993. There is generalized cortical atrophy with particularly severe involvement of the occipital lobe (arrows). Scale bar = 2 cm.



A detailed review the cortical visual pathways affected by PCA has also been carried out (Hof et al., 1997). In PCA-AD, prefrontal cortex (PFC) was relatively spared whilst there was a gradient of NFT density from low density in V1 to high density in visual association areas of parietal cortex and PCC. NFT densities in areas TE and TEO (inferior temporal areas, part of the dorsal stream) were lower than those in the PCC and inferior parietal cortex (part of the ventral stream). Compared to tAD, the largest differences in NFT and NP density were in V2, V3/V4 and MT, whilst smaller significant differences were found in BA 7 (parietal cortex) and BA 23 (PCC). Whilst PCA-AD patients had fewer NPs in area 9 (part of dorsolateral prefrontal cortex), NP density was comparable between PCA-AD and tAD in frontal areas 45 (Broca's area) and 46 (also part of dorsolateral prefrontal cortex). Investigation of the input and output layers most affected in different cortical areas revealed that PCA involves a more specific corticocortical disconnection syndrome than tAD, particularly of the projections between V1 and V2 and feed forward projections to V2/V3, V4, MT and 7b. The authors reported notably high densities of NFTs and NPs in the PCC suggesting

that this area could be pivotal in PCA-AD. In this study, all cases showed greater pathology density in posterior parietal cortex than inferior temporal cortex, although another case is noted in which a preferential distribution of NFTs in IT cortex at PM was associated with prosopagnosia and apperceptive visual agnosia as the first manifestation of the disease (Hof & Bouras, 1991).

There is some inconsistency in the neuropathological findings, as some studies show no significant differences in parietal burden of senile plaques and neurofibrillary tangles between progressive posterior cortical dysfunction (equivalent to PCA) and tAD patients (Renner et al., 2004). Another study showed higher NFT density in PCA-AD than tAD in primary and association visual cortices, and fewer NPs in the hippocampus and subiculum in PCA, but they did not find NP differences in other cortical areas (Tang-Wai et al., 2004). It is likely that different inclusion criteria and methodologies are responsible for the discrepant findings.

Although the majority of PCA cases that have gone to PM show AD as the underlying pathology, there are a number of cases that have shown a different pathology. In a neuropsychological study of six cases of Creutzfeldt-Jakob disease (CJD), one is described as having disturbed vision with an age at onset of 51 (Snowden et al., 2002). The symptoms described are quite unusual compared to the deficits usually seen in PCA due to AD. This patient showed no fixation on objects and reported only seeing light, which would suddenly become dimmed. At PM, there was mild atrophy in posterior parietal and occipital lobes, enlargement of the posterior lateral ventricle, with spongiosis and astrocytosis in pyramidal and sub-pial layers of primary visual and visual association cortex. Another striking difference between this case and those of PCA-AD is the very short duration of illness (4 months).

A number of other non-AD pathological findings have been reported. One case report of PCA shows a similar pattern of AD pathology as Hof et al., 1990, but also concurrent synuclein positive Lewy bodies in the substantia nigra, amygdala, entorhinal cortex and cingulate gyrus (Tang-Wai, Josephs, Boeve, Petersen, et al., 2003). The first symptoms in this case were of visuospatial dysfunction, but at 62, he was noted to move in a stiff manner, not swinging his left arm, and at 67 vivid hallucinations and paranoid delusions were reported. Another report of two cases of PCA due to corticobasal degeneration describes development of motor difficulties in their non-dominant hand

soon after initial visuospatial deficits (Tang-Wai, Josephs, Boeve, Dickson, et al., 2003). Victoroff et al., 1994 describe three PCA patients with three separate neuropathologic entities: subcortical gliosis, Alzheimer's disease, and Creutzfeldt-Jakob disease.

These studies suggest that a number of different pathologies can lead to similar (although not identical) cognitive deficits that fit into the syndrome of posterior cortical atrophy. The rarity of the disease and PM confirmation makes it difficult to compare the prevalence of different underlying pathologies in PCA. However, a study of 27 individuals with 'Progressive posterior cortical dysfunction' (this seems synonymous with PCA although atrophy was not consistently seen in the patients – perhaps because scans were early in the disease or not acquired in a high quality systematic fashion) found at post-mortem that most had AD (n=13), 2 had AD with coexistent Lewy Bodies, 2 had corticobasal degeneration, 1 had CJD (the history in this case was similar to that of other PCA patients, c.f. Snowden et al. 2002), 1 had fatal familial insomnia and one had AD plus Parkinson disease (Renner et al., 2004). This provides convincing evidence that a number of different pathologies lead to similar symptoms, but numbers are not large enough to satisfactorily identify subtle differences in symptoms between patients with different pathologies.

In conclusion, post mortem data suggests that a similar syndrome - of relatively selective deficits in occipital and parietal functions such as visual space and object perception, calculation and spelling, accompanied by atrophy of posterior cortices – can be caused by different underlying pathologies. Alzheimer's disease is the most common cause, but DLB can also underlie PCA (in which case hallucinations are common), as can corticobasal degeneration (in which case asymmetric disorders of hand movement are common) and CJD (showing very fast disease progression). In the PCA-AD cases, the majority have greater parietal than inferior temporal involvement, although one case has been described with the opposite clinical and pathological features, a high density of NFTs and NPs in the PCC is notable. Unfortunately there are not enough detailed studies or large enough participant numbers to investigate whether there are differences in the parietal and occipital cognitive functions affected between different pathologies causing PCA.

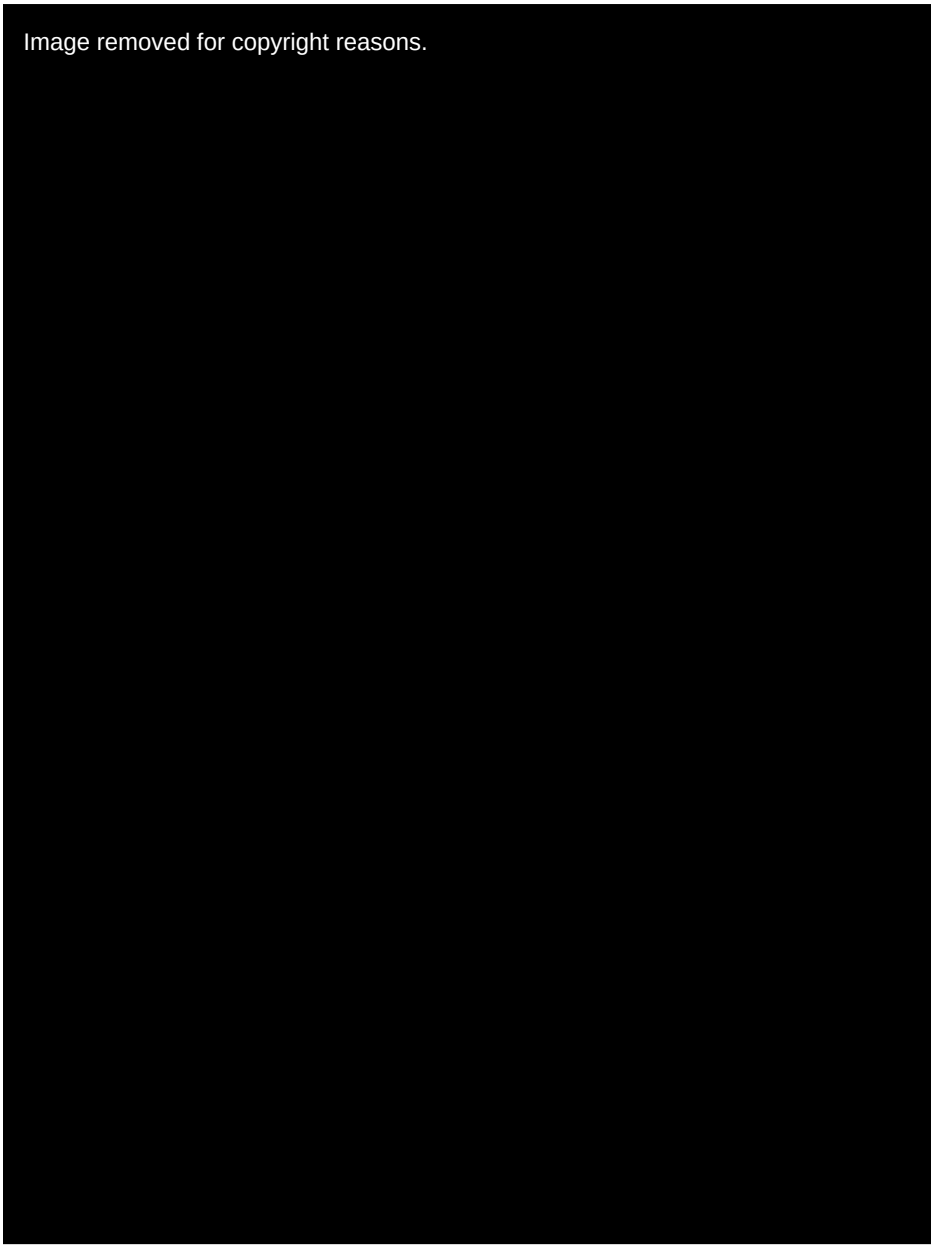
1.2.4.2 CSF and amyloid imaging

One weakness of post mortem data is that one can only observe pathology at the end stage of the disease. It is not possible to track change over time or associate cognitive performance at an earlier stage with pathological processes at that stage. A number of methods give an indication of the underlying pathological process *in vivo*. Analysis of amyloid beta 1-42, total tau and phosphorylated tau protein in cerebrospinal fluid (CSF) can indicate an underlying diagnosis of Alzheimer's disease (a ratio of low amyloid beta to high tau is indicative of AD). In a recent study of 9 cases of PCA, all were shown to have a similar CSF profile to typical AD (Baumann et al., 2010). This finding has been replicated in two further studies, in which CSF profile did not differentiate tAD from PCA (de Souza et al., 2011; Formaglio et al., 2011). This gives further weight to the assertion that the majority of PCA cases are due to AD.

A number of Positron Emission Tomography (PET) ligands have been developed which bind specifically to fibrillar Abeta, allowing imaging of amyloid in the brain. One such ligand known as PiB-PET ([11C]-labelled Pittsburgh compound B) has been used in studies investigating amyloid burden in PCA, allowing comparison of the amyloid burden between tAD and PCA-AD in vivo. PiB binding was shown to be similar in PCA-AD and tAD, with increased binding in posterior cortices in three case studies (Kambe et al., 2010; Ng et al., 2007; Tenovuo et al., 2008). However, studies of PCA-AD patients and matched tAD controls suggest that amyloid deposition measured by PET does not explain the difference in clinical presentation between groups (de Souza et al., 2011; Lehmann et al., 2013; Rosenbloom et al., 2011; see Figure 1-4). It is possible that neurofibrillary tangles may contribute to the different clinical features observed in PCA, thus explaining the lack of in PiB-PET signal despite phenotypic differences. Alternatively, there may be a ceiling effect, as PiB-PET signal is known to increase long before symptom onset (Morris et al., 2009), so by the time of scanning (mean disease duration = 5 years in Rosenbloom et al., 2011), this very sensitive measure can no longer detect any differences. It is possible that the post mortem data and PiB-PET data would be concordant if these methodological issues were resolved by scanning earlier in the disease, matching for age and disease duration, and using strict neuropsychological entry criteria to ensure the patient groups are well defined.

The findings in CSF and amyloid imaging are broadly concordant with post mortem data – often showing the same pathology in PCA and tAD. These in vivo methods provide valuable markers of pathology, allowing more accurate differential diagnosis.

Figure 1-4 Amyloid deposition measured using PiB-PET PCA and typical AD patients show amyloid deposition compared to healthy controls, but the direct comparison between patient groups shows very little difference. Reproduced from Rosenbloom et al., 2011. T-score maps presented at a threshold of $p<0.001$, uncorrected for multiple comparisons.



1.2.5 Genetics

With the exception of a single case of PCA with a novel mutation in the Presenilin 1 gene, which was not demonstrated to be causal (Sitek et al., 2013), there have been no reported dominantly inherited cases. A number of studies have investigated the role of Apolipoprotein E (ApoE), in PCA-AD. ApoE is a protein involved in regulating Abeta levels in the brain, has been shown to be important in determining genetic risk of developing tAD. It has three major isoforms that translate into three alleles of the gene, e2, e3 and e4. In tAD, carriers of two e4 alleles are at increased risk, as are those with one e4 and one e3 allele, albeit to a lesser extent. The e3/e3 genotype is at normal risk, as is the e4/e2 genotype. The genotype e3/e2 is at lower risk, thus the e2 allele is thought to be protective against AD (Corder et al., 1994).

Studies investigating the role of ApoE in PCA are inconsistent; some show similar ApoE prevalence between tAD and PCA-AD (Baumann et al., 2010; Mendez et al., 2002; Pendleton et al., 2002; Tang-Wai et al., 2004), but others do not find an association between PCA-AD and ApoE genotype (Davidson et al., 2007; Schott et al., 2006; van der Flier et al., 2006). This is the subject of an ongoing collaborative multi-centre study (to which recruitment as part of my PhD project has contributed).

More generally, early onset Alzheimer's disease (EOAD) cases have a lower e4 frequency (Davidson et al., 2007), despite e4 being strongly related to a younger age at onset in late onset Alzheimer's disease (LOAD). Some researchers suggest that ApoE is related to vulnerability of specific networks in AD – as ApoE e4 genotype seems to related to susceptibility of medial temporal areas and episodic memory, whilst EOAD ApoE e4 negative patients are likely to have networks other than the memory mediating medial temporal areas affected (van der Flier et al., 2011) resulting in different syndromes, e.g. PCA-AD and Logopenic Aphasia (LPA). They suggest that other unknown environmental and genetic factors, and their interactions, are likely to determine the networks affected in these cases. How environmental and genetic factors differ between different EOAD clinical profiles is also not yet known – large collaborative studies of EOAD patients with differing phenotypes are required to address this question.

1.3 Neuroimaging in posterior cortical atrophy

Structural MRI scans are used in many studies of PCA, the characteristic focal loss of volume (gyral thinning and loss of grey and white matter) in the occipital and parietal lobes is often apparent from visual inspection of T1 weighted MRI. Relatively few studies have used automated quantitative methods over the whole brain to assess the differences in atrophy between PCA, healthy controls and typical Alzheimer's disease. One such method is voxel based morphometry (VBM), which uses grey matter and white matter intensity on T1 scans as an indicator of atrophy. This method revealed atrophy of occipital, parietal and posterior temporal regions in 38 PCA patients (diagnosed clinically) compared to healthy controls (Whitwell et al., 2007). A direct comparison of patient groups showed greater atrophy of right visual association cortex and less atrophy of the left hippocampus in PCA than tAD. This finding has been replicated by Lehmann, Crutch, et al., 2011 using cortical thickness measurements (automatically generated by the Freesurfer software package) in similar regions, to reveal greater atrophy of right superior parietal lobe and less atrophy of entorhinal cortex in PCA versus tAD (see Figure 1-5). A VBM analysis carried out in the same study found wider areas of significant atrophy in PCA compared to tAD extending to bilateral posterior parietal regions and the occipital lobe. These extended findings could be accounted for by the stricter entry criteria of preserved recognition memory and impaired visual or non-visual parietal function on neuropsychological testing in the Lehmann, Crutch, et al., 2011 study.

The existence of ventral and dorsal subgroups with PCA has been investigated using cortical thickness measurements. A group of PCA participants was subdivided into 'object' and 'space' subgroups based on neuropsychological performance (see Figure 1-2). After correcting for average cortical thickness, the space subgroup showed reduced cortical thickness compared to the object subgroup in the occipital inferior parietal and medial temporal lobe, whilst the object subgroup showed reduced cortical thickness in the right fusiform gyrus, lateral inferior temporal lobe and frontal lobe (Lehmann, Barnes, et al., 2011). Substantial anatomical overlap made clear separation difficult and supported the notion of a continuous variation of deficits rather than distinct subtypes.

A similar notion of continuous variation rather than distinct subtypes is suggested by studies investigating differences between people with different cognitive phenotypes of sporadic early onset Alzheimer's disease. In addition to participants with typical memory-led Alzheimer's disease and PCA, a number of people with early onset Alzheimer's disease present with progressive impairments in language – particularly naming and sentence repetition. This is a syndrome called logopenic progressive aphasia (Gorno-Tempini et al., 2008). Comparing atrophy between the subtypes using VBM reveals large overlapping regions of atrophy in bilateral parietal, occipital, precuneus, PCC, posterior temporal and hippocampal regions, but small symptom-specific regions in each group, right ventral-occipital and superior parietal cortex in PCA, left middle and superior temporal gyri in LPA and prefrontal cortex and left hippocampus in tAD with early onset (albeit these direct group differences were not significant when corrected for multiple comparisons). An alternative approach, using multivariate machine learning algorithms to visualise the spectrum of participants, demonstrated moderate separation between patients with PCA and LPA, while patients diagnosed with tAD were distributed along a continuum between these extremes (Ridgway et al., 2012).

Figure 1-5 Regional variation in cortical thickness in PCA compared to typical AD reproduced with permission from (Lehmann, Crutch, et al., 2011). The colour scale for statistical difference represents FDR-corrected p values at a 0.05 significance level, whereas the colour bar for percent difference represents magnitude of cortical thickness difference. Red and yellow (positive values) represent lower cortical thickness in PCA than tAD whereas dark and light blue (negative values) represent greater cortical thickness in PCA than tAD. L: left hemisphere, R: right hemisphere, A: anterior, P: posterior.

Recently, longitudinal changes in grey matter have been investigated in two studies. The first, a single case study of a PCA patient over 4 years with 6 time points demonstrated initial inferior temporal and posterior parietal atrophy, which spread over the course of the investigations to occipital cortices and to more anterior regions (Kennedy et al., 2012). The second demonstrated a similar initial pattern of relatively selective posterior atrophy, with widespread changes over time, primarily in temporal and parietal regions, but also changes in the frontal lobes (Lehmann et al., 2012).

When carrying out statistical analysis of imaging data, a mass univariate approach is often used, meaning a statistical test is carried out at each voxel. The large number of tests means that multiple comparison correction needs to be carried out, so that the threshold of statistical significance controls the level of false positives not just for a single test, but for the whole family of tests. One simple correction for multiple comparisons is the Bonferroni correction, however imaging data have a degree of spatial correlation (due to factors such as physiological properties and spatial preprocessing) which violates the assumption of independence of probability values, which is required for Bonferroni correction. This means that the Bonferroni correction is overly conservative. As a result, alternative techniques have been developed to correct for multiple comparisons. For the Family-Wise Error (FWE) correction technique (Worsley et al., 1996; implemented in SPM) the data is smoothed by applying a Gaussian kernel thus reducing the number of independent observations, but as this number is no longer quantifiable, random field theory is used to calculate the threshold for statistical significance. The number of resels in the image (resolution elements) is calculated (this represents the smoothness of the image). The number of resels is used to find the expected Euler characteristic of the image at different thresholds. The Euler characteristic is effectively the number of regions (not the number of voxels) that remain after the image has been thresholded. If we choose a threshold that gives an expected Euler characteristic of 0.05, we can then apply this threshold and any scores above this threshold can be given a p value of <0.05.

An alternative approach is to control the false discovery rate (FDR). This means controlling the expected proportion of false positives amongst those voxels declared positives (the discoveries) rather than controlling the probability of ever reporting a

false positive. This approach results in a less conservative threshold than FWE and was implemented for neuroimaging by Genovese et al., 2002. However, this implementation has been criticised as it controls the FDR at the voxel level, whilst inferences are generally made at the cluster/feature level (Chumbley & Friston 2009).

In conclusion, structural MRI findings in PCA are consistent with the neuropsychological deficits observed. There is considerable variation within the PCA group, and this can be considered within the framework of different relative involvement of the ventral and dorsal visual processing streams. There is also variation in comparison to other early onset forms of AD. Both of these forms of variation appear to be in the form of relative impairment along a spectrum, rather than distinct subgroups. As the disease progresses, atrophy becomes more widespread, and can be detected in all cortical lobes of the brain.

1.4 Eye tracking in Alzheimer's disease

Despite the reports of oculomotor apraxia in PCA (e.g. Mendez et al., 2002, McMonagle et al., 2006, Tang-Wai et al., 2004), when this PhD project started, there had been only one study involving eyetracking of a PCA patient (Mannan et al., 2009; a study of scene perception). Other than the work presented here, there remains only one recent study of scene perception involving a single patient with PCA (Foulsham et al., 2011), a study examining face perception in PCA (Meek et al., 2013) and a single case study examining the unusual symptom of perceived motion among static objects (Crutch et al., 2011). The effects of PCA on basic aspects of oculomotor function have not previously been investigated.

However, there is previous work assessing eye movements in patients with typical Alzheimer's disease. This research has tended to focus on establishing the utility of such measurements as a tool for diagnosis. In addition, a number of studies have used eye tracking in order to measure cognitive performance in novel paradigms. In PCA, due to the involvement of the parietal lobe in the eye movement system, one would expect a greater deficit in eye movements than typical Alzheimer's disease, and it may be possible to use this method to investigate novel aspects of cognitive performance.

1.4.1 Fixation stability

Although few studies investigate fixation instability, high frequency of saccadic intrusions have been reported during fixation in a study including patients with probable Alzheimer's disease (n=9) and vascular dementia (n=6; Schewe et al., 1999). The increased frequency of saccadic intrusions in the combined patient group was correlated with MMSE, and replicated findings in a previous study of four Alzheimer-type patients (Jones et al., 1983). In contrast to these studies, a comparison of 31 patients with mild to moderate probable AD (mean MMSE = 20) and 31 age matched controls revealed no difference in the number of intrusive saccades and the duration of the longest period of fixation between groups (Bylsma et al., 1995). The eye tracking technique differed between the studies – Bylsma used vertical and horizontal electro-oculography (EOG), whilst the other studies used infrared methods. Bylsma had a separate fixation experiment (participants were instructed to fixate a dot for 30 seconds) whilst Schewe took fixation data from fixation parts of a saccade experiment. This latter difference provides a possible explanation for the differing findings; when fixating in between trials of a saccade task, AD patients make more saccades in anticipation of the next saccade, or searching for the next target, whereas when it is a straightforward fixation task they may not do this.

1.4.2 Visually guided saccades

Visually guided saccades, also known as pro-saccades or reflexive saccades, are made from a fixation point to a visually presented target. A number of studies investigating saccades in Alzheimer's disease and controls showed increased latency for visually guided saccades (longer time between when the target was presented and the eyes started moving towards the target; Bylsma et al., 1995; Fletcher & Sharpe, 1986; Yang et al., 2011, 2013). When looking at the velocity and the amplitude (or distance) of saccades, studies differ in their outcomes. Fletcher and Sharpe (1986) report lower peak velocity for saccades, and reduced amplitude of saccades in Alzheimer's disease (n=13; mean MMSE=18) whereas Bylsma et al. (1995) do not report such differences in their study (n=31; mean MMSE=20). Normal saccade amplitude and velocity are also reported in Yang et al., 2011 and Yang et al., 2013.

Two studies address the issue of using saccade measures to differentiate corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), Alzheimer's disease and

frontotemporal lobar degeneration (FTLD) variants, and include ROC analyses of sensitivity and specificity with comparison to other techniques, allowing a good assessment of the diagnostic utility of the measures. The earlier paper (Garbutt et al., 2008) identified some oculomotor abnormalities in all the clinical syndromes tested except for semantic dementia. The most dramatic oculomotor impairments were in PSP, and vertical saccade gain and velocity were superior to neuropsychological tests for differentiating these patients from CBS, FTLD and AD. In this paper, downward saccade velocities were able to differentiate CBS from AD participants, but it is important to note that cases in the study were not autopsy-confirmed.

In the follow up paper (Boxer et al., 2012) in which participants were autopsy-confirmed, patients with AD were compared to patients with FTLD-TDP43 and FTLD-tau. With the benefit of autopsy confirmation, the authors found that 3 out of 4 patients with CBD did not show abnormalities in visually-guided saccades, and suggested that previous descriptions of increased latency in CBS may reflect cases with underlying AD pathology.

1.4.3 Anti-saccade performance

Anti-saccade tasks test the ability of participants to suppress the natural reaction to look towards a visually presented stimulus, as participants are instead instructed to look in the opposite direction (for a review on antisaccades in AD, see Kaufman et al., 2010). This review concludes that antisaccades do not differentiate AD from healthy ageing better than measures of episodic memory, but may have potential to give a functional index of dorsolateral prefrontal cortex damage, and as a tool for monitoring disease progression.

A number of studies show poor performance in the antisaccade task in people with Alzheimer's disease compared to healthy controls. The number of uncorrected errors on this task is negatively correlated with MMSE (Crawford et al., 2005). Comparing performance on the antisaccade task between patient groups, PSP, CBS, FTLD and AD patients all show a greater error rate compared to controls, and whilst FTLD patients are able to spontaneously self-correct anti-saccade errors as well as controls, people with AD, CBS and PSP were not (Garbutt et al., 2008). The finding of a greater error rate in PSP, CBS, FTLD and AD compared to healthy controls was replicated in an autopsy-confirmed cohort (Boxer et al., 2012).

1.5 Taking the carer's perspective

As reviewed above, PCA has a wide ranging and devastating impact upon the vision and other cognitive functions of individuals affected by the syndrome. The nature and extent of the visual deficits mean that the condition is particularly disabling, with many individuals requiring assistance with basic activities of daily living from an early stage in the disease process. Nonetheless, formal description and quantification of the impact of PCA upon daily life has been lacking to date. For typical AD and other degenerative diseases, questionnaires given to a carer or friend of a patient with dementia have been developed. Initially these questionnaires were developed to assess neuropsychiatric symptoms (e.g. the Neuropsychiatric Inventory; Cummings et al., 1994) such as delusions, hallucinations, anxiety, and disinhibition. A caregiver perspective on these issues is particularly useful in patients who may lack insight into their symptoms. Following this, assessment of patients' ability to carry out activities of daily living has been formalised in questionnaires to allow assessment of the impact of dementia on daily-living abilities such as eating, dressing and using a telephone (e.g. Bristol Activities of Daily Living Scale; Bucks et al., 1996). Influenced by these developments, the Cambridge Behavioural Inventory combines aspects of neuropsychiatric symptoms, activities of daily living and cognitive impairments such as memory and orientation, with the aim of discriminating between patients with frontotemporal lobar degeneration and Alzheimer's disease (Wedderburn et al., 2008). No such investigation has previously been carried out in patients with PCA, and whilst clinical reports demonstrate that neuropsychiatric symptoms are not a primary feature (Tang-Wai et al., 2004), it would be of interest to measure and report the impact of PCA on activities of daily living. The carer's perspective on how PCA has affected a patient's ability to carry out their everyday activities and interact in real-world situations would complement attempts to improve understanding of how patients perceive the world through testing perception of more naturalistic stimuli.

Furthermore, neuropsychological tests undertaken in a research centre rely on a high degree of attention and the ability to visit a research centre, so it is unusual for more than three longitudinal visits to be possible, limiting the range of disease stages that may be characterised. A questionnaire given to a carer provides the opportunity to collect data at later stages of the disease. This is of great interest in PCA, and may help

to answer questions of the time scale over which the relatively focal PCA syndrome gives way to more global cognitive impairment.

1.6 Thesis outline

This thesis describes five experimental projects that were carried out to investigate how patients with PCA perceive the world, how their deficits affect aspects of every-day life, and heterogeneity within the PCA syndrome, particularly with regards to the motor symptoms that patients experience.

In Chapter 2, I investigate how perception of single and multi-object stimuli are affected by PCA, in an attempt to better understand the effect of patients' visual deficits on everyday perceptual tasks, and how this relates to lower-level deficits in visual processing.

Chapter 3 describes work carried out to investigate how PCA affects the oculomotor system, examining abnormalities in fixation, saccades and smooth pursuit in this patient group – characteristics that have not been studied in detail previously, but may be informative when considering how PCA affects patients' perceptual abilities.

Chapter 4 describes a pilot study using eye tracking to investigate scene perception in more detail, establishing that this technique can be effective in identifying differences between PCA patients and healthy controls. This is extended in chapter 5, in which scenes were presented under different task conditions, allowing investigation of the extent to which image salience, top-down goals and oculomotor deficits (identified in chapter 3) influence performance in a relatively natural task.

The work in Chapter 6 is strongly motivated by the requests that members of the support group make. They are less interested in specific cognitive impairments, but more interested in having access to a broad staging, wanting to know what stage of the disease they are at, and how the disease is likely to progress over time. Whilst answering these questions is currently difficult, this investigation takes a first step in that direction by giving a questionnaire to carers and investigating differences in everyday skills, and cognitive abilities across patients with PCA and tAD at different stages.

Finally, in Chapter 7 I describe an experiment carried out in order to improve understanding of the overlap of PCA with clinical features of motor dysfunction.

Myoclonic jerks and limb rigidity are often associated with cortico-basal syndrome or cortico-basal degeneration but are also relatively common in PCA. This experiment investigates differences in brain atrophy between groups of PCA patients with and without these symptoms in order to expand understanding of the heterogeneity of PCA and the relationship between the PCA syndrome and bordering syndromes involving degeneration of posterior cortices (e.g. corticobasal syndrome).

2 Scene perception in Posterior Cortical Atrophy: a study of categorisation and description

2.1 Chapter introduction

Balint's syndrome (simultanagnosia, optic ataxia, and ocular apraxia) is a central feature of the clinico-radiological syndrome of posterior cortical atrophy (PCA; Benson et al., 1988). In addition to partial or complete Balint's syndrome, prominent cognitive impairments include visuoperceptual and other visuospatial impairments, alexia, Gerstmann's syndrome (acalculia, agraphia, finger agnosia, left–right disorientation), and limb apraxia (Lehmann, Barnes, et al., 2011; McMonagle et al., 2006; O'Dowd & de Zubicaray, 2003; Tang-Wai et al., 2004). Many of the visual deficits commonly reported in PCA are underpinned by basic visual deficits of elementary form and motion processing (Lehmann, Barnes, et al., 2011).

Partial or complete Balint's syndrome is a core element of both current sets of diagnostic criteria for PCA (Mendez et al., 2002; Tang-Wai et al., 2004), and constitutes one of the most frequently observed clinical features. A review of 84 reported PCA patients (Mendez et al., 2002) indicated the presence of partial or complete Balint's syndrome in 68% of patients (compared with prominent peripheral alexia in 80%). A subsequent case series of 40 patients found partial or complete Balint syndrome in 88%, with simultanagnosia the most commonly observed component (82%) but only 3 patients (8%) demonstrating a complete Balint syndrome at presentation (Tang-Wai et al., 2004). In keeping with these figures, one recent group study of PCA (N=39; mean disease duration 3.8±2.1years) found that 92% of patients exhibited simultanagnosia, 49% optic ataxia, 38% ocular apraxia, and 31% demonstrated a complete Balint's syndrome (Kas et al., 2011). These symptoms were found to be associated with hypo-perfusion of the bilateral dorsal occipito-parietal regions.

Individuals with PCA exhibit a multiplicity of cognitive deficits including a combination of basic and higher order visual deficits. Accordingly, their perception is more in keeping with definitions of simultanagnosia that stress a relative impairment in identifying multiple stimuli and interpreting complex scenes (Riddoch & Humphreys, 2004) than descriptions which specify normal recognition of individual objects (Huberle & Karnath, 2010). The influence of stimulus size upon PCA perceptual

performance (Coslett et al., 1995; Crutch et al., 2011; Stark et al., 1997) also permits closer comparison with some accounts of simultanagnosia which suggest a restricted spatial window of visual attention (Dalrymple et al., 2010, 2011) than others in which size effects are not reported (Huberle & Karnath, 2010; Kinsbourne & Warrington, 1962; Montoro et al., 2011). It should be noted however that with their diffuse bilateral parieto-occipito-temporal cortical atrophy, individuals with PCA may not provide an ideal opportunity for distinguishing the contribution of rapid form perception, spatial attention, and efficient eye movement control to simultanagnosia.

Heterogeneity within the PCA syndrome (Galton et al., 2000; Lehmann, Barnes, et al., 2011; Tsai et al., 2011) and discrepancies in visual abilities in different real world contexts mean that, despite our improving characterisation of the syndrome, we have little understanding of what the world looks like to someone with PCA. This understanding is further limited by the fact that in order to constrain variables and simplify tasks, most neuropsychological tests of perception involve either isolated objects or simple visual arrays, deprived of contextual information which would normally be available in real world perception. As a result, the consequences of their impairments (measured by specific neuropsychological tests) for everyday visual abilities are not always clear. In the current study we examine the ability of individuals with PCA to categorise scenes relative to single items such as objects and faces (Experiment 1) and to describe what they perceive when viewing a photograph of a real world scene (Experiment 2).

A number of previous investigations have examined the stimulus attributes and cognitive processes required for scene perception. In patients with visual agnosia, spared aspects of basic visual processing (for example colour and texture) can contribute to scene perception, even when object recognition is impaired (Steeves et al., 2004). In healthy controls, the ability to quickly recognise a scene ('scene gist') is mediated in part by colour information when this information is predictive of a scene category, and this can be supported by a coarse organisation of colour (Oliva & Schyns, 2000). This is consistent with the findings of Steeves et al., 2004 who found the greatest effect of colour on control participants' response latencies in a scene categorisation task was for natural scenes (a category in which colour is diagnostic) rather than man-made ('non-natural') scenes. Furthermore, whilst unlocalised

information such as spatial frequency and orientation distribution may contribute to scene categorisation, the ability to process localised information is necessary for successful scene categorisation (Loschky & Larson, 2008). In this context, it is of note that an analysis of basic visual function in PCA revealed colour processing to be relatively spared compared with aspects of basic form and motion processing (Lehmann, Barnes, et al., 2011).

Evidence from neuropsychology and functional magnetic resonance imaging (fMRI) demonstrates that visual processing of faces, scenes and objects are represented in different areas of the brain. For example, single object perception is dependent upon the lateral occipital complex (LOC; e.g., Grill-Spector et al., 2001; Malach et al., 1995), whilst scene perception in general involves the parahippocampal place area (PPA; e.g. (Epstein & Higgins, 2007; Epstein & Kanwisher, 1998), and natural scenes in particular the PPA, LOC and retrosplenial cortex (RSC; Walther et al., 2009). However, PCA patients exhibit a diffuse pattern of parieto-occipito-temporal atrophy undermining the perception of both single and multiple object arrays.

As stated above, the aim of the current study was to describe and characterise everyday scene perception in PCA. This was addressed by a simple categorisation task involving subcategory judgments about scenes, faces and objects (Experiment 1). Our hypothesis is that multi object scenes will be more difficult for patients to perceive than single items. Building on previous work suggesting a particular role for colour processing in the perception of natural scenes and evidence suggesting relatively preserved colour perception in PCA, it was also predicted that PCA patients would show superior perception of natural scenes under colour as compared to black and white presentation. The aim of describing PCA scene perception is also addressed by a qualitative analysis of spontaneous descriptions during scene perception (Experiment 2). In this experiment we hypothesise that PCA patients will describe fewer elements of the scene than controls.

2.2 Experimental Investigations

2.2.1 Experiment 1 - Picture categorisation

The first experiment used a three alternative forced choice categorisation paradigm to test the ability of PCA patients to perceive scenes relative to individual objects and faces.

2.2.1.1 Methods

2.2.1.1.1 Participants

Data were collected from 13 patients (5 male; Mean [SD] age = 65.1 [7.6] years) fulfilling standard clinical criteria for PCA (Mendez et al., 2002; Tang-Wai et al., 2004). Ten healthy control participants were also recruited (5 male; Mean [SD] age = 63.3 [4.1] years). This project was approved by the NRES Committee London - Queen Square.

Each patient completed a background neuropsychological assessment including MMSE, recognition memory tests, synonym comprehension, naming, calculation, spelling, visual acuity, basic visual processing, and object and space perception. Patients also completed a colour discrimination task. The stimuli (N = 48) were pairs of matte colour chips presented adjacently. The colours were selected from the Munsell colour system and had fixed value and chroma (6/6). The task was to determine whether the hues in each pair were the same or different. Test scores are shown in Table 2-1.

2.2.1.1.2 Characterisation of patient atrophy

9 controls and 7 patients had a T1 MRI scan within 1 year of psychology testing. Scans were not available for the remaining participants (1 control had a pacemaker, 6 patients were unable to attend the Dementia Research Centre for assessment at the time this experiment was carried out, and were instead tested at home). T1-weighted volumetric MR brain scans were acquired on a 3.0T Siemens TIM Trio scanner (Siemens, Erlangen) using a magnetisation prepared rapid gradient echo (MPRAGE) sequence.

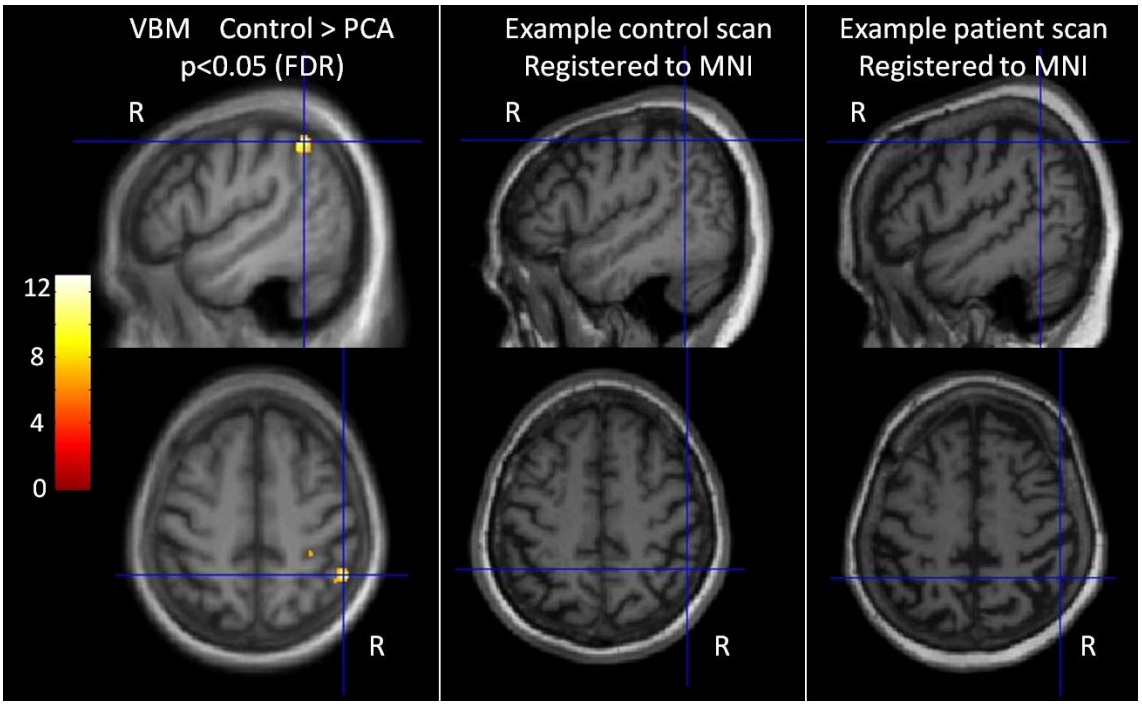
Voxel-based morphometry (VBM) was carried out using SPM8. Scans were segmented into grey and white matter using SPM8's segment toolbox with default settings

(Ashburner & Friston, 2005; Weiskopf et al., 2011). Segmentations were produced with rigid alignment to MNI space and resampled to 1.5mm isotropic voxels for use with DARTEL (Ashburner, 2007). DARTEL then iteratively registered the grey and white matter segments to an evolving estimate of their group-wise average (Ashburner & Friston, 2009). The native space tissue segments were then normalized to MNI space using the DARTEL transformations, modulated to account for local volume changes. A 6mm full width at half maximum (FWHM) Gaussian smoothing kernel was applied. Total intracranial volume (TIV) for each participant was estimated using Jacobian integration of deformation fields (Ridgway et al., 2011). An explicit mask was applied to include only voxels for which the intensity was at least 0.1 in at least 80% of the images (Ridgway et al., 2009).

A general linear model (GLM) was used to assess group differences in grey matter volume controlling for age, gender and TIV. Statistical significance of between-group differences was tested using false discovery rate (FDR) correction at $p<0.05$. Maps showing statistically significant differences between the control and patient groups were generated. Results are shown in Figure 2-1 (left hand panel).

The VBM analysis revealed a small area of significantly greater atrophy in the PCA patient group than the control group in the right parietal lobe (MNI co-ordinates of location of maximum t value [51, -49.5, 51]. This is consistent with the locus of maximal difference within a much larger area of parietal, occipital and occipitotemporal volume change and reduction in cortical thickness observed in larger group comparisons of PCA with healthy controls and typical Alzheimer's disease patients (Lehmann, Crutch, et al., 2011). There were no areas with significantly greater atrophy in the control group compared to PCA. Visual inspection of patient's brain scans showed atrophy and sulcal widening, greater in posterior areas (see Figure 2-1, right hand panels).

Figure 2-1 Imaging features of participants in the categorisation task. The left-most panel shows difference in grey matter volume between controls and PCA patients. T scores are shown for areas with statistically significant lower grey matter in the patient group compared with controls (FDR corrected at p<0.05), overlaid on the average T1 image. Images are shown in neurological convention (right on right). Cross hairs indicate t score global maxima. The middle and right panel show individual participants' brain scans registered to MNI space. The PCA patient scan shows reduced grey matter volume (and sulcal widening), particularly in the parietal lobe.



2.2.1.1.3 Stimuli

The stimuli were 180 photographic images drawn equally (n=60) from the categories of scenes, objects and faces (see Figure 2-2 for examples). Each of these categories was formed of two subcategories containing 30 images.

Scenes: Natural (with choices of forest, desert or beach) and man-made (city, market or room) scenes were chosen. These were a selection of items from Google images (http://www.google.co.uk).

Objects: The two subcategories of objects were natural and man made objects. The natural objects were animals (bird, land or sea) and the man made objects were tools, clothes and furniture. All object stimuli were shown from a canonical view.

Faces: The two subcategories of face stimuli were age and emotion. Age faces were taken from the Centre for Vital Longevity face database (http://agingmind.utdallas.edu/facedb; Minear & Park, 2004). The three choices were from three distinct age groups; young (18-22), middle aged (35-55), and old (75-85) in

order to avoid subjectivity in age categorisation. All age faces had a neutral facial expression. Emotion faces (happy, sad and angry) were taken from the NimStim database (http://www.macbrain.org/resources.htm; Tottenham et al., 2009). All images were faces with direction of head and gaze straight ahead, showing the entire face and upper shoulders only.

All photographs were presented in both colour and greyscale giving a total of 360 stimuli. The faces had a resolution of 623x800 pixels whilst the scenes and object photographs had a resolution of 800x800 pixels.

Figure 2-2 Example stimuli from the categorisation task in the emotion and age face, and natural and man-made scene and object categories, in colour and in grayscale.

Table 2-1 Background neuropsychology for scenes, faces and objects, assessments conducted at the time of the experimental investigations.

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	PCA Mean (SD)	*N* below 5th %ile	Normative Mean (SD)
Age (years)	66.6	58.1	68.6	61.9	62.5	54.5	60.8	72.7	85.3	63.2	65.7	62.0	64.0	65.1 (7.6)	-	-
Gender	M	F	M	M	F	F	F	F	F	M	F	M	F	8f, 5m	-	-
Disease duration (years)	4.7	0.3	4.5	3.8	10.5	2.4	5.6	4.0	3.1	6.5	5.5	1.8	8.9	4.7 (2.8)	-	-
General Function																
MMSE (/30)[a]	16	24	24	25	20	NT	17	NT	27	18	17	22	15	20.5 (4.1)	-	-
sRMT words (/25)[b]	15	21	25	23	23	14	18	20	24	19	24	20	20	20.5 (3.4)	7	23.7 (1.8)
sRMT faces (/25)[b]	13	21	23	24	18	20	18	19	16	14	17	24	10	18.3 (4.5)	8	22.8 (1.9)
Concrete synonyms (/25)[c]	19	24	18	21	22	14	20	24	24	21	NT	24	11	20.2 (4.2)	2	20.8 (3.0)
Naming from description (/20)[d]	17	19	16	18	5	3	17	16	11	6	4	20	4	12.0 (6.6)	8	18.9 (1.5)
Non-visual parietal																
Calculation (/26)[e]	20	11	17	16	10	1	12	14	19	8	10	17	7	12.8 (5.5)	7	20.7 (3.1)
Spelling (/20)[f]	12	18	16	11	0	0	7	18	19	6	7	17	3	10.3 (7.0)	6	19.49 (6.49)
Perceptual																
Acuity (Snellen equivalent)[g]	6/9	6/9	6/18	6/12	6/18	UT	6/9	6/12	6/18	6/9	6/18	6/9	6/12	-	-	-
Figure ground (/20)[h]	20	17	20	20	10	10	17	18	11	16	15	18	11	15.6 (3.9)	10	19.9 (0.3)
Fragmented letters (/10)[h]	4	8	11	19	0	0	13	11	0	0	4	17	1	6.8 (6.8)	11	18.8 (1.4)
Object decision (/20)[h]	11	15	14	18	5	11	8	15	7	8	6	16	7	10.8 (4.3)	9	17.7 (1.9)
Number location (/10)[h]	5	5	7	10	0	0	4	6	5	3	2	8	0	4.2 (3.2)	11	9.4 (1.1)
Colour discrimination (/48)[i]	47	48	46	48	28	39	47	43	41	44	44	46	38	43.0 (5.6)	11	47.9 (0.2)

Note: Raw scores for each patient are presented, with mean and standard deviation scores for the PCA patient group and relevant normative data. UT = untestable, NT = not tested. Normative data samples: a mini-mental state examination; Folstein et al., 1975; b Warrington, 1996; c Warrington et al., 1998; d Randlesome (unpublished data N = 100); e Crutch (unpublished data); f Baxter & Warrington, 1994; g cortical visual screening test (CORVIST) James-Galton et al., 2001; h Warrington & James-Galton, 1991; i Connell (unpublished data; N=54).

2.2.1.1.4 Procedure

Stimuli were presented in subcategory blocks (order: age-faces, emotion-faces, natural scenes, manmade scenes, natural objects, manmade objects) in an ABCDEF FEDCBA design. Each block consisted of 15 colour and 15 greyscale stimuli, and within these blocks there were 5 of each of the three choices for that subcategory. The experiment was split into two halves with colour condition (colour/black & white) varied in an ABBA design: in the first half, 15 colour photos were shown before 15 greyscale photos in each block, in the second half this order was reversed.

Stimuli were presented on a Dell laptop using Superlab 4.0 software (Cedrus Corporation, 2006) and subtended a visual angle of 23^{o} from an approximate viewing distance of 50cm. Patients responded verbally. Accuracy was recorded and voice response time was measured manually for each trial. The onset of each stimulus was accompanied by an auditory tone, and response times were defined as the temporal distance between the onset of sound waves corresponding to the stimulus onset and the point at which the utterance (with the correct answer) could be detected, using visually presented waveforms in the digital audio software Audacity (v2.0.2 http://audacity.sourceforge.net/).

Participants were asked to complete a three alternative forced verbal categorisation task in which the question participants were asked reflected the stimuli in that subcategory. For natural scenes participants were asked 'Is this a forest, a desert or a beach?', for man made scenes participants were asked 'is the a city, a market or a room?'. In the object category, participants were asked 'is this a bird, an animal that would usually live on land, or an animal that would usually live in the sea?' in the natural subcategory, and in the man made subcategory, participants were asked ' is this a tool, an item of clothing, or furniture?'. Finally in the age-face category participants were asked 'does this person look young, middle-aged or old?', and in the emotion-face category participants were asked 'is this person happy angry or sad?'.

Where necessary, participants were reminded of the choices before trials. Each block of a novel category was preceded by a practice trial to orient the participant to the stimuli. In addition, participants received a definition of the response options in the face condition (young is 18-22 years old, middle aged is 35-55 and old is 75-85), with accompanying example stimuli. Each trial consisted of a blank screen (710ms),

followed by a central fixation cross (180ms), followed by a photograph stimulus which remained on the screen until the participant responded.

2.2.1.1.5 Statistical analyses

Bootstrap confidence intervals (Efron & Tibshirani, 1993) were calculated for the mean error rate by group, stimulus category (and subcategory) and stimulus colour. Bootstrapping was used to accommodate both potential non-normality in the distribution of error rates across subjects and heterogeneity of variances by group and category. Bias corrected and accelerated 95% confidence intervals were constructed from 100,000 bootstrap samples. Bootstrap samples were stratified by group and clustered by subject so as to match the design of the study.

Error rate by stimulus category and group was compared using an extension of repeated measures analysis of variance (ANOVA). The extension involved the use of robust Huber-White (Huber, 1967; White, 1980) standard errors. Such an approach assumes normality of residuals but relaxes the assumption of constant residual variance made when using standard repeated measures ANOVA. Additionally, as a check on the robustness of results, an analysis using bootstrap confidence intervals was carried out (thereby also relaxing the normality assumption). Since results were similar using the two techniques, and because joint statistical tests cannot easily be carried out when utilising the bootstrap, the results with robust standard errors are reported here. For each participant the error rate (percentage error) was computed for each of the combinations of stimulus category and colour. Separately for the PCA patients and controls a repeated measures analysis of variance model (with robust standard errors) with colour and stimulus category and their interaction as predictor variables was fitted to these counts. To assess the interaction between group and category an additive model was assumed. Robust Huber-White; (Huber, 1967; White, 1980) standard errors were computed to allow for potential non-constant residual variance. A three-way model (incorporating all two and three way interactions between group, colour and stimulus category) was also fitted to the data from both groups. The analysis was performed using the xtset and xtgee commands with the robust option in STATA (version 12.1).

The distribution of response times was very skew, so analysis was carried out on the reciprocal of response times, with harmonic means (the reciprocal of the mean of

reciprocals) accordingly presented. The mean of the reciprocals of response times, ignoring response times where the response was incorrect, was computed for each of the six stimulus category and colour combinations and the same modelling strategy as described above for the error counts implemented.

Discarding response times from trials where the response was incorrect can result in bias. As a check on the robustness of the above results, linear mixed models with crossed random subject and item effects were fitted to the individual (reciprocals of) response times. Although such models can allow for the bias that will occur if some items are simultaneously subject to higher errors and to longer responses, they do make the additional assumptions that item effects are normally distributed and independent of subject effects, and so are not necessarily to be preferred to the simpler models described above.

In the PCA group, pairwise Spearman's correlation coefficients were calculated to assess the association between accuracy in the scene, object and face conditions, MMSE, disease duration, spelling, calculation, and visual tests from the background neuropsychology assessment.

2.2.1.2 Categorisation results

Results are reported here for overall accuracy and comparison of the main stimulus categories (scenes, faces and objects). Mean error rate and harmonic mean response times for these categories are reported in Table 2-2, Figure 2-3 and Figure 2-4.

2.2.1.2.1 Stimulus category and colour results: error rate

Patients with PCA showed a greater error rate than healthy controls in each of three categories (scenes (β = 8.97, $\chi^2(1, N=23) = 16.96$, $p<0.001$), objects (β = 5.59, $\chi^2(1, N=23) = 10.41$, $p<0.001$) and faces (β = 12.67, $\chi^2(1, N=23) = 25.04$, $p<0.001$). Means and confidence intervals are presented in Figure 2-3.

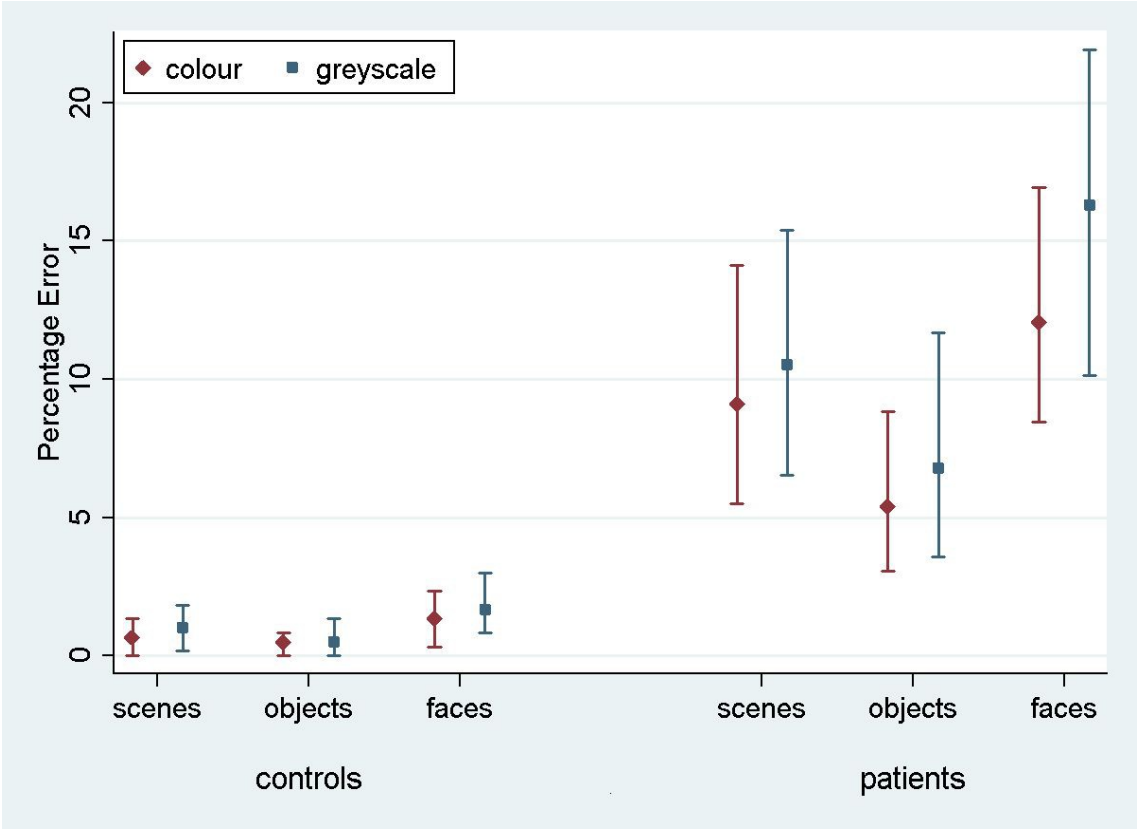
In PCA patients, response accuracy differed significantly between stimulus categories ($\chi^2(2, N=13) = 21.27$, $p<0.001$, joint test; see Figure 2-3). The error rate was greatest for faces (β = 4.36, $\chi^2(1, N=13) = 7.13$, $p=0.008$ for comparison with scenes and β = 8.08, $\chi^2(1, N=13) = 18.77$, $p<0.001$ for comparison with objects) and next greatest for scenes (β = 3.72, $\chi^2(1, N=13) = 12.26$, $p<0.001$ for comparison with objects). There was also evidence among the patients that the error rate was greater for greyscale than colour

stimuli (β = 4.23, χ^2(1, *N*=13) = 5.77, p=0.02). There was no evidence of an interaction in the effects of stimulus category and colour (p=0.17, joint test).

In controls, the error rate was low and there was no statistically significant effect of colour (p=0.42) or stimulus category (p=0.08, joint test). Controls made fewer errors for objects than faces (p=0.03; see Figure 2-3) but differences between faces and scenes (p=0.31), and scenes and objects (p=0.49) were not statistically significant.

In a joint model comparing PCA cases with controls, the differing effects of colour (p=0.03) and stimulus category (p<0.001, joint test) between the groups were both statistically significant.

Figure 2-3 Mean error rate (percentage error) for controls and PCA patients by stimulus category. Error bars show 95% bias corrected and accelerated bootstrap confidence intervals (100,000 replications). See Table 2-2 for a table of means.



2.2.1.2.2 Stimulus category and colour results: response time

Patients with PCA had longer response times than healthy controls in each stimulus category (scenes (β = 0.47, χ^2(1, *N*=23) = 50.18, p<0.001), objects (β = 0.46, χ^2(1, *N*=23) = 45.06, p<0.001) and faces (β = 0.37, χ^2(1, *N*=23) = 34.37, p<0.001).; see Figure 2-4).

Analysis of PCA patients' response times revealed further evidence of differences between stimulus categories ($\chi^2(2, N=13) = 64.33$, $p<0.001$, joint test; see Figure 2-4). Response times were longest for scenes ($\beta = 0.07$, $\chi^2(1, N=13) = 20.96$, $p<0.001$ for comparison with objects and $\beta = 0.11$, $\chi^2(1, N=13) = 62.26$, $p<0.001$ for comparison with faces), and next greatest for objects ($\beta = 0.04$, $\chi^2(1, N=13) = 6.99$, $p<0.008$ for comparison with faces). Directionally there was a suggestion of shorter response times for greyscale faces and objects compared with colour, but of longer response times for greyscale scenes compared with colour (see Figure 2-4). However there was no statistically significant evidence that response times differed for greyscale and colour stimuli ($p=0.70$) nor of an interaction between colour and stimulus category ($p=0.23$, joint test).

Figure 2-4 Harmonic mean response times (secs) for controls and PCA patients by stimulus category. Error bars show 95% bias corrected and accelerated bootstrap confidence intervals (100,000 replications). See Table 2-2 for a table of harmonic means.

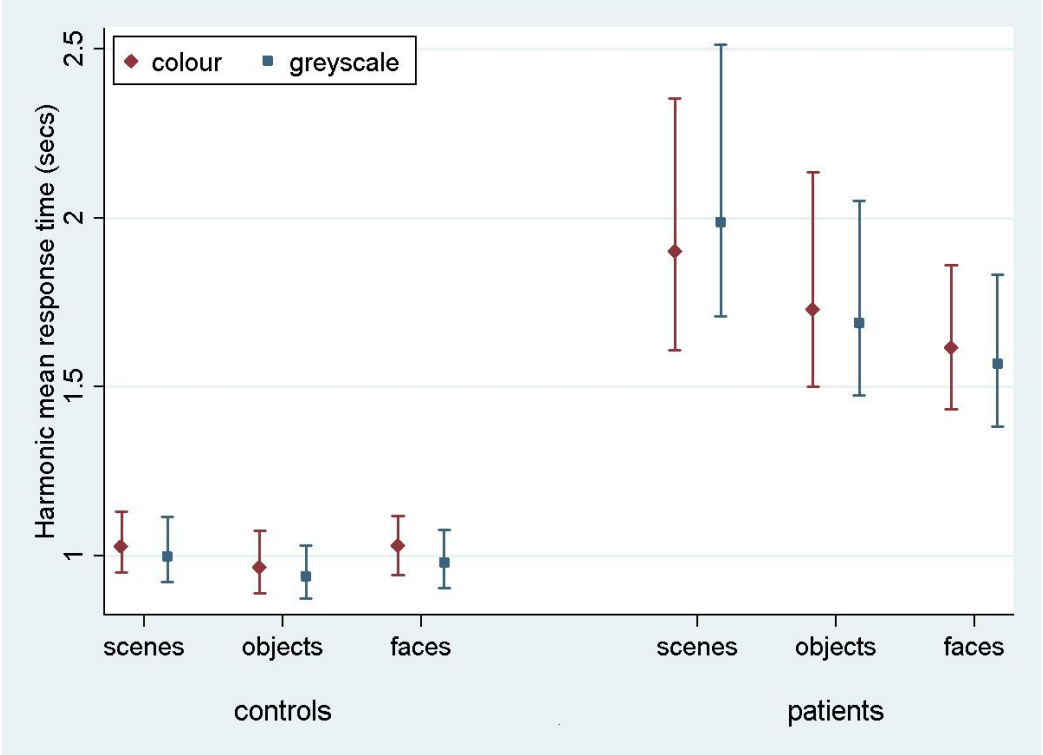


Table 2-2 Mean error rate and harmonic response times for controls and PCA patients by stimulus category.

A. Mean error rate (percentage error)								
	Controls				Patients			
	Scene	Object	Face	Total	Scene	Object	Face	Total
Colour	0.67	0.50	1.33	**0.83**	9.10	5.38	12.05	**8.85**
Greyscale	1.00	0.50	1.67	**1.06**	10.51	6.79	16.28	**11.20**
Total	**0.83**	**0.50**	**1.50**	**0.94**	**9.81**	**6.09**	**14.17**	**10.02**
B. Harmonic mean response times (seconds)								
	Controls				Patients			
	Scene	Object	Face	Total	Scene	Object	Face	Total
Colour	1.03	0.97	1.03	**1.01**	1.90	1.73	1.62	**1.75**
Greyscale	1.00	0.94	0.98	**0.97**	1.99	1.69	1.57	**1.75**
Total	**1.01**	**0.95**	**1.01**	**0.99**	1.94	**1.71**	**1.59**	**1.75**

In controls there was evidence of differences between stimulus categories ($p<0.001$, joint test). Response times were longer for scenes than objects ($p<0.001$) and longer for faces than objects ($p=0.01$), but times for faces and scenes were similar ($p=0.55$). There was again no statistically significant evidence of an interaction between stimulus category and colour ($p=0.18$, joint test), but otherwise the pattern was rather different. Although the magnitude of the effect was small (see Figure 2-4), response times were significantly shorter for greyscale than colour images ($\beta = 0.05$, $\chi^2(1, N=10) = 15.83$, $p<0.001$).

In a joint model comparing PCA cases with controls, the differing effects of stimulus category ($\chi^2(2, N=23) = 29.87$, $p<0.001$, joint test) and of colour ($\chi^2(2, N=23) = 6.95$, $p=0.01$) between the two groups were both statistically significant, showing a greater effect of colour (colour slower than greyscale) in the control than PCA group. In the scenes category, the interaction between colour effects (greyscale vs. colour) and group (patients vs. controls) was statistically significant ($p=0.02$), whereas for objects and faces this comparison was not significant ($p=0.31$ and $p=0.11$ respectively).

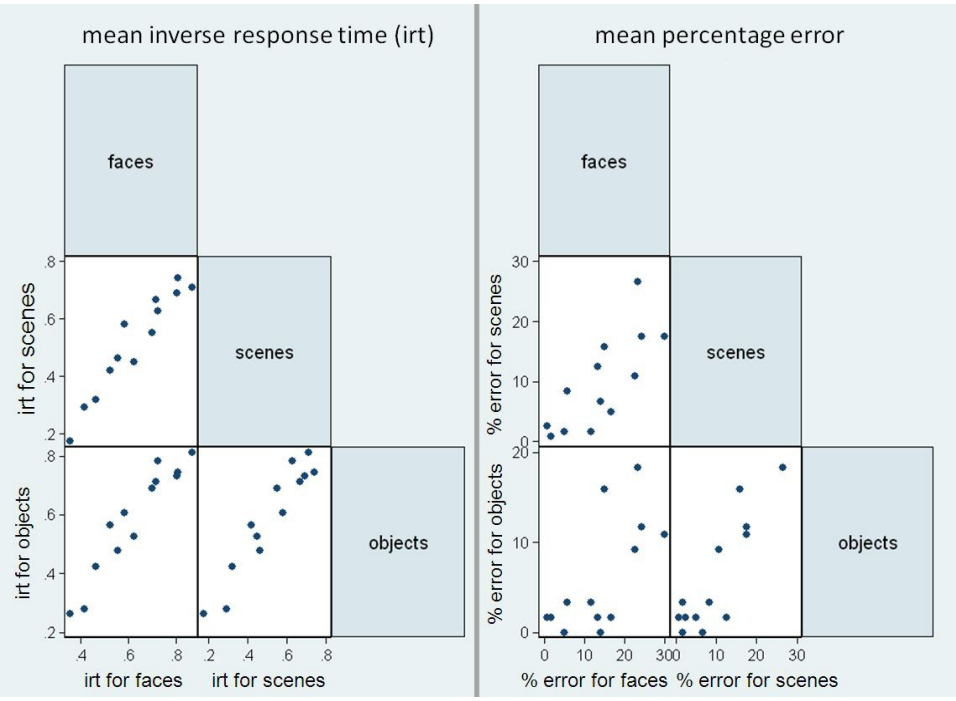
Analysis of the reciprocals of the individual response times, using a linear mixed model with crossed random effects for participant and item, gave similar results to the above.

Figure 2-5 shows scatter matrices of response time and accuracy for patients, suggesting that performance across categories is related.

2.2.1.2.3 Relationship of categorisation performance with background tests of visual function

In an analysis restricted to the patient group, there were statistically significant pairwise associations between accuracies on the scenes, objects and faces components of the categorisation task (see Table 2-4 for Spearman correlation coefficients and p-values). There were also statistically significant Spearman correlations showing greater error rate in categorisation of all three categories was associated with poorer performance on background tests of early visual function (figure-ground discrimination), visuoperceptual processing (fragmented letters, object decision) and visuospatial processing (number location). Greater accuracy for scene and object categorisation was associated with better performance in the colour perception task. There was no evidence for an association between categorisation performance and tests of non-visual parietal function (calculation and spelling), or disease severity (MMSE score and estimated disease duration), with the exception of a weak association between disease duration and object categorisation accuracy ($p=0.049$).

Figure 2-5 Scatter matrices for mean inverse response time (irt) and sum of errors in the patient group, plotting performance in the three stimuli categories against one another.



2.2.1.3 Stimulus subcategory results

Owing to the focus in the current paper on scene processing, the face and object subcategory results are not reported here. Mean error rate and harmonic mean response times for the scene subcategories are presented in Table 2-3.

2.2.1.3.1 Error rate

There was no statistically significant difference in the error rates between natural and manmade scenes (p=0.12) or colour and greyscale stimuli (p=0.29). Mean control error rates were very low (ranging from 0% to 1.67%, resulting in low statistical power. For this reason subcategory error analysis in controls is not presented.

2.2.1.3.2 Response time

PCA patients were slower for natural than manmade scenes (p<0.001), and also slower for greyscale than colour scenes although this difference was not statistically significant (β = 0.02, $\chi^2(1, N=13)$ = 1.2, p=0.27). There was also evidence of an interaction between colour and subcategory (p=0.037). Controls were also significantly slower for natural scenes (p=0.01), but conversely also slower for colour

than greyscale stimuli (p=0.002) (with no evidence for an interaction (p=0.21)). The interaction between stimulus subcategory and group was not statistically significant (p=0.89).

2.2.1.4 Comment

PCA patients' categorisation performance was impaired not just for scenes but for all categories. There were discrepancies between categories in terms of accuracy and response time, with patients being least accurate with faces (faces<scenes<objects) but slowest with scenes (scenes>objects>faces). High correlations both between categories and between categorisation performance and tests of basic visual function are consistent with the widespread visual dysfunction previously reported in PCA. PCA patients showed a relative advantage for colour stimuli in terms of both overall accuracy and response time, but these effects were relatively modest.

Table 2-3 Subcategory error rates and response times for controls and PCA patients.

	Mean error rate (%) Patients		**Harmonic mean of response time** (secs) Patients	
	Scenes-Natural	Scenes-Manmade	Scenes-Natural	Scenes-Manmade
Colour	10.51	7.69	1.99	1.83
Greyscale	13.08	7.95	2.16	1.85
Total	**11.80**	**7.82**	**2.08**	**1.84**
	Mean error rate (%) Controls		**Harmonic mean of response time** (secs) Controls	
	Scenes-Natural	Scenes-Manmade	Scenes-Natural	Scenes-Manmade
Colour	1.33	0.00	1.05	1.01
Greyscale	1.67	0.33	1.04	0.97
Total	**1.50**	**0.17**	**1.05**	**0.99**

Table 2-4 Spearman correlations between error rate (percentage error) on the categorisation tasks and neuropsychology tests.

		Scenes	Objects	Figure Ground	Fragmented Letters	Object Decision	Number Location	Colour Perception	Calculation	Spelling	MMSE	Disease Duration
Scenes	rho	-	-	-0.78	-0.76	-0.78	-0.76	-0.63	-0.36	-0.54	-0.44	0.52
	p	-	-	0.002**	0.003**	0.003**	0.003**	0.02*	0.23	0.055	0.17	0.07
Objects	rho	0.88	-	-0.90	-0.71	-0.72	-0.79	-0.85	-0.48	-0.55	-0.29	0.56
	p	<0.001**	-	<0.001**	0.006**	0.005**	0.001**	<0.001**	0.10	0.051	0.38	0.049*
Faces	rho	0.77	0.68	-0.70	-0.77	-0.76	-0.67	-0.49	-0.36	-0.44	-0.26	0.39
	p	0.002**	0.01**	0.007**	0.002**	0.003**	0.01**	0.09	0.23	0.13	0.45	0.21

* indicates $p<0.05$, ** indicates $p\leq0.01$

2.2.2 Experiment 2 – Scene description

The response times and error rates collected in Experiment 1 provide information about the relative ease or difficulty with which participants perceive different categories of visual stimuli. However, in order to answer the more qualitative question of what the world looks like to individuals with PCA, it is necessary to evaluate their subjective experience of viewing real world scenes. In Experiment 2, the same participants viewed 12 scenes and were simply asked to describe what they saw.

2.2.2.1 Methods

All patients from Experiment 1 and 5 controls completed the scene description task. The stimuli were 12 previously unseen photographs of scenes, comprising both natural and manmade scenes. Stimuli had a resolution of 800x800 pixels and were presented on a Dell laptop using Superlab 4.0 software (Cedrus Corporation, 2006) subtending a visual angle of 23^{o} from an approximate viewing distance of 50cm. The scenes were displayed sequentially under free viewing conditions for an unlimited period. Participants were encouraged to describe each scene for around 30 seconds, or until they had finished describing what they could see. Descriptions were recorded using a digital voice recorder.

Responses were transcribed and content words extracted, allowing a list of the described features to be made for each scene and each participant. A list of control features was defined for each stimulus, with an item being added to the list if described by more than one control. Each participant's description was then quantified by the percentage of these features that were given. The number and type of errors made by each participant – defined as features which were inaccurate or inappropriate to the viewed scene - were extracted.

2.2.2.2 Results

On average, only 40% (SD=16.9%) of items on the control feature list were described by patients (controls described 72.8% [SD=10.3%] of those features). Whilst only one error was made by a control participant (mistaking a microwave for a TV), 6/13 (46%) of PCA patients made errors. Misperceptions of objects or parts of the scene were most frequent, accounting for 15/31 (48%) errors made by patients. These errors were always consistent with the patient's overall impression of the scene. Examples include

mistaking fruit and vegetables for flowers in the context of a market scene, and mistaking a round sign for a satellite dish (whilst perceiving the scene as a town centre). Some global misperceptions were made (n=12), such as saying a desert was a beach (the sky was misperceived as the sea coming in), or mistaking a family kitchen for a cafe.

One patient made errors of familiarity, claiming that 2 of the 12 scenes were in their local town, whilst another made a left-right error, reporting a door was on the left when it was on the right of a room. It is not clear whether the latter error reflects left-right spatial disorientation or incorrect word retrieval. Whilst some errors were quickly retracted "That's more residential. No it isn't, that's shops", others persisted and seemed to influence further description; looking at a mother preparing breakfast for two children in a domestic kitchen, one patient said "they're in a cafe...at the seaside...having a cup of tea...that's the waitress".

2.2.2.3 Comment

The two main findings from this scene description task are that misperceptions were consistent with the perceived theme of a scene and that uncorrected misperceptions seem to influence further apprehension of the scene. Taken together, the observations suggest that scene perception in PCA, at least under unlimited presentation conditions, continues to be influenced by active, top-down strategies.

2.3 Chapter conclusions

This paper presents results from two experimental paradigms investigating scene perception in people with Posterior Cortical Atrophy – categorisation and description. These individuals exhibit a complex visual disorder including partial or complete Balint's syndrome, but to our knowledge, this is the first group study to systematically examine the effect of PCA upon scene perception.

Summarising the results, in Experiment 1 PCA patients made more errors and were slower to categorise all stimuli than age-matched healthy controls. PCA patients and controls were both most accurate for objects (PCA accuracy: faces<scenes<objects; Control accuracy: faces=scenes, objects=scenes, faces<objects). By contrast, response time analyses showed PCA patients were slowest to respond to scenes with controls slower for scenes and faces than objects (PCA response times: scenes>objects>faces;

Control response times: scenes and faces > objects). Comparing performance on colour and greyscale stimuli, PCA patients showed a relative advantage for colour stimuli in terms of both overall accuracy and response time. Examining these interactions separately for the three stimulus categories, the only significant interaction between group and colour was observed in response times to scenes. Consistent with previous evidence that basic visual processing deficits underpin higher order perceptual and spatial deficits in PCA, patients showed strong correlations between tests of basic visual function and categorisation performance. In Experiment 2, scene description revealed a lack of detail in participants' description of scenes with fewer features described and many more misperceptions made by patients than controls. Importantly, perceptual errors were always consistent with patients' overall impression of the scene theme, and in some cases appeared to influence subsequent interpretation of the scene.

Considering first the categorisation task (Experiment 1) which aimed to provide a broad description of scene perception in PCA, the main observation was that scene categorisation was in fact more accurate, although slower, than face perception. The contrast between less accurate face categorisation but slower response times with scenes may reflect a speed accuracy trade-off. Complex scenes take more time to process but contain multiple cues to a common scene theme which constrains errors. By contrast, faces have fewer distinguishing features (at least fewer features relevant to the emotion and age categorisation of unfamiliar faces involved in Experiment 1), so responses may be faster but perceptual errors have a greater effect upon overall response accuracy. The importance of exposure time is recognised in some models of simultanagnosia (Henderson & McClelland, 2011), and may explain some of the variability in PCA real-world perceptual performance; unlike in the current task where stimulus exposure was unlimited, many goal-directed behaviours in everyday life occur at a pace which does not allow for PCA patients' slowed processing of the surrounding visual environment.

A number of observations may shed light on how components of Balint's syndrome influence PCA patients' ability to perceive real-world scenes. Both PCA patients and controls responded more slowly to natural than manmade scenes, likely reflecting the different perceptual demands created by such stimuli (at least in the context of the

current categorisation task). Many natural scenes require integration of a number of spatially separate features. For many man-made scenes however, the global ecological properties of the scene may be more diagnostic (Greene & Oliva, 2009). For example, greater openness, expansion and mean depth suggest a city, whilst low rankings of these properties suggest a room. Furthermore, there was also a lower density of features in the natural scene stimuli, whilst manmade scenes were more likely to contain a number of identifying features (e.g. car – city, desk – room, fruit – market). If natural scenes have more sparse features, this may place greater demands on spatial attention and localisation skills to direct gaze towards the key diagnostic features within a scene. In addition, the interaction between group and colour showing relatively better patient performance with colour than greyscale scenes may reflect the fact that natural scenes have more prototypical and consistent colour, and colour may be more diagnostic for natural than manmade scenes (Oliva & Schyns, 2000).

Strong associations between tests of basic visual function and categorisation, but not MMSE or disease duration, suggest that patients' performance in categorisation of scenes objects and faces is underpinned at least to some extent by impairments in more basic visual processes. This is consistent with a previous study of basic visual processing in people with PCA, which found impairments in at least one out of five tested aspects of basic visual processing (form detection, form discrimination, colour discrimination, motion detection and point localization) in each individual with PCA (Lehmann, Barnes, et al., 2011). The finding from Experiment 1 that overall patients were more accurate when categorising colour compared to greyscale stimuli, is also consistent with evidence from the Lehmann, Barnes, et al., 2011 study that colour processing was marginally less impaired than other aspects of early visual processing in PCA.

Turning to the free scene description task (Experiment 2), PCA patients named fewer features and made more misperceptions than controls. In some cases, scene identification was a slow, cumulative process, with theories regarding the global theme of the scene evolving with (or being driven by) the gradual acquisition of more local information. For example, when viewing a picture of Brighton Pier, one patient said "it looks like a park...or a station...or a building site...looks like the thing they're trying to elect [sic] for the Olympics...or it could be the beach...down here looks a bit

sandy...looks like Brighton or somewhere like that". However, in other cases, the participant would describe the global identity immediately, and then this identity (whether correct or incorrect) would influence the subsequent description of features within the scene based on expectation rather than perception (e.g. "Seaside...pier...people on the beach...there'll be children about somewhere...pier going out...they always have something on the pier don't they – a restaurant or playhouse"). It was notable that misperceptions were consistent with the perceived theme of a scene and that uncorrected misperceptions seemed to influence further apprehension of the scene.

In the present experiment, the objective of the neuroimaging analysis was to give an idea of the pattern of atrophy exhibited by the patients. Unfortunately, the small number of scans available meant there was little power to detect differences. We used FDR correction as it is more lenient and allowed demonstration of at least some difference between groups. However, only a small region was significantly different in comparison to the regions identified in previous studies comparing PCA and healthy controls (Lehmann, Crutch et al., 2011). This likely reflects the small sample size in this analysis and perhaps only reflecting the peak of a more widespread atrophy pattern. In Chapter 7, the neuroimaging results were a key part of the investigation, we used FWE correction as it is more conservative and provides a stronger level of evidence, such that if regions did reach significance at this level we could have more confidence in the interpretation.

Finally, several potential weaknesses of the current study are worthy of consideration. First, differences in the accuracy and speed of response to different stimulus types (scene vs face vs object) could reflect differences in depth of categorisation (and associated semantic and executive demands). For example, the scene categories are broad and simple, whilst the face categories are relatively more fine-grain. Whilst mistaking a middle aged for an old face might be regarded as a minor error, mistaking a desert for a beach might seem a more glaring error, so inducing participants to be slower and more cautious in providing the correct response for scenes. Second, the description of scenes task (Experiment 2) placed a significant linguistic demand upon participants. Given recent evidence of a mild logopenic phonological aphasia with prominent anomia in PCA (Crutch, Lehmann, et al., 2013), the features listed by

patients may be an underestimate of their true perceptual achievements, although the targets of any descriptions which contained phonological errors or were circumlocutory in nature were included in the analysis. It is worth noting that the findings of the present study may not be specific to PCA. Similar deficits could occur in typical AD, other degenerative disorders, or in patients without a degenerative disease, but with isolated lesions of the visual cortices. The patients tested in this study had a wide range of disease severity, notably three patients had particularly low scores on the test of colour discrimination; this may have contributed to the fact that the effects of colour in the categorisation task were very modest. The decision to include participants at various stages of the disease reflects the need to compromise between recruiting a sufficient number of participants with this relatively rare condition, and ensuring that all participants have a similar syndrome. This is discussed further in the general discussion (section 8.2).

Our findings demonstrate that whilst perception of scenes is impaired in PCA (and slower compared to other stimulus categories), patients' perceptual deficits are due to a combination of higher order and more basic visual deficits, and should be considered in the context of diffuse bilateral parieto-occipito-temporal atrophy. The next chapter describes how another more basic aspect – oculomotor function – may be affected by PCA, and the consequences of this form part of the further investigations of scene perception described in Chapter 4.

3 Abnormalities of fixation, saccade and pursuit in Posterior Cortical Atrophy

3.1 Chapter introduction

Whilst the majority of studies of PCA focus on cognitive visual deficits (often at the apperceptive level of visual processing, e.g. (McMonagle et al., 2006; Mendez et al., 2002; Tang-Wai et al., 2004), it is clear that deficits at more basic levels of visual processing contribute to these impairments (Lehmann, Barnes, et al., 2011; Shakespeare et al., 2013), as would be expected from the extensive pattern of atrophy in these patients (Lehmann, Crutch, et al., 2011; Whitwell et al., 2007). Investigation of oculomotor deficits in PCA is important for the same reasons. Previous studies demonstrate that disruption of the parietal lobes - a primary site of atrophy in PCA - results in longer saccadic latencies and accuracy, and deficits in pursuit (Braun et al., 1992; Pierrot-Deseilligny et al., 1991). Disruption of the frontal eye fields - noted to be hypometabolic in PCA (Nestor et al., 2003) – also results in oculomotor deficits such as impaired saccadic latency, hypometric saccades, and impairment of smooth pursuit (Pierrot-Deseilligny et al., 1996). Thus one would expect to find oculomotor abnormalities in PCA patients. Indeed a number of studies note oculomotor abnormalities observed through clinical assessment. These have indicated 'sticky fixation' (a deficit in disengagement from a target, Delamont et al., 1989) and ocular apraxia (difficulty in directing gaze to novel stimuli, McMonagle et al., 2006; Mendez et al., 2002; Nestor et al., 2003; Tang-Wai et al., 2004), but often only in a subset of patients.

Despite the anatomical rationale for investigating eye movements in PCA, and the reports of ocular apraxia in a number of studies, there have been no detailed investigations of oculomotor abnormalities in PCA using sensitive techniques until this point. Furthermore, interpretation of visuo-perceptual impairment in patients with PCA identified using eyetracking devices (e.g. scene and face perception; (Foulsham et al., 2011; Mannan et al., 2009; Meek et al., 2013; Shakespeare et al., 2013) necessitates a prior understanding of lower-order oculomotor function. Oculomotor dysfunction is likely to make a particular contribution to multi-object scene perception, given the requirement to move the eyes to relevant aspects of these more complex

stimuli (this may be different from the oculomotor demands when perceiving a single, simple form such as a briefly presented in a fixed, pre-marked location).

A number of studies have investigated oculomotor deficits in more typical (memory-led) Alzheimer's disease (tAD). Patients with tAD show a high frequency of saccadic intrusions during fixation (Jones et al., 1983; Schewe et al., 1999). The majority of intrusions in these studies are described as square wave jerks (typically saccades of 1-2 degrees horizontally, followed after around 200ms by a saccade bringing the eye back to its previous fixation location (Kennard et al., 1994). However, these findings have not been reliably replicated - Bylsma et al., 1995 reported no difference in the number of intrusive saccades or longest period of fixation between a group of tAD patients and healthy controls. Differences in factors such as task, disease severity or recording equipment could contribute to these differing findings.

Tests of visually guided saccades (rapid eye movements from a fixation point to a visually presented target; also known as pro-saccades or reflexive saccades) also bear some discrepancies. Four studies comparing saccades in Alzheimer's disease and controls showed increased latency in AD (longer time between target presentation and initiation of saccade towards the target; Bylsma et al., 1995; Fletcher & Sharpe, 1986; Yang et al., 2011, 2013), whilst one study showed no such differences (Mosimann et al., 2005). When looking at the velocity and the amplitude (or distance) of saccades, studies differ in their outcomes. Fletcher & Sharpe, 1986 report lower peak velocity for saccades, and reduced amplitude of saccades in Alzheimer's disease whereas more recent larger studies do not show such differences (Bylsma et al., 1995; Mosimann et al., 2005; Yang et al., 2011, 2013).

An alternative saccadic paradigm that has been informative in typical Alzheimer's disease is the antisaccade task (Antoniades et al., 2013; Hallett, 1978). In this task participants are instructed to make a saccadic eye movement in the opposite direction to a visually presented target. The number of uncorrected errors on this task is negatively correlated with MMSE (Abel & Yee, 2002; Crawford et al., 2005). However, rather than representing oculomotor function, this task may be better considered as an impairment of inhibitory control and error-correction (Crawford et al., 2005). In this context, the task has been of great interest as a marker of disease progression in frontotemporal lobar degeneration patients (e.g. Burrell et al., 2012).

The smooth-pursuit mechanism has also been an object of study in people with tAD. Studies note decrease in gain and a high incidence of saccadic intrusions, particularly anticipatory saccades (Fletcher et al., 1998, Zaccara et al., 1992; Garbutt et al., 2008).

Here we administered tests of fixation, saccades (with a gap and overlap condition to investigate disengagement of attention or 'sticky fixation') and smooth pursuit to patients with PCA, tAD, and a group of healthy controls. Our primary interest was to undertake a detailed assessment of oculomotor function in patients with PCA, to explore the extent to which higher-order visual processing deficits relate to lower-order oculomotor impairment. We also sought to identify possible clinical biomarkers that may help differentiate these patients from typical AD.

3.2 Methods

3.2.1 Participants

3.2.1.1 Patient demographics

Data were collected from 20 PCA patients (eight male), 12 patients with tAD (seven male) and 22 healthy controls (five male). All participants completed the fixation task. Four PCA patients did not complete the saccade task, with three of these patients and one other PCA patient not completing the pursuit task due to fatigue.

PCA patients fulfilled standard clinical criteria for PCA (Mendez et al., 2002; Tang-Wai et al., 2004) and had a clinical diagnosis of probable Alzheimer's disease (Dubois et al., 2007, 2010). Typical AD patients fulfilled Dubois criteria for AD.

This project was approved by the NRES Committee London - Queen Square, all participants provided written informed consent.

3.2.1.2 Clinical presentation

In the tAD group, hospital notes were available for all patients. Ten patients had episodic memory as the first noted symptom, one patient had word finding difficulties followed by episodic memory and one patient had difficulties in navigation closely followed by episodic memory.

In the PCA group, hospital notes were available in 14/20 patients, and a detailed history was taken by a neurologist at the first research visit in all patients. With the

exception of one patient in whom the first noted symptom was repeating questions (closely followed by visuospatial symptoms), all PCA patients reported their initial symptoms to be visuospatial, visuoperceptual or calculation difficulties.

3.2.2 Equipment

Stimuli were presented on a Dell 2120 desktop computer from a fixed viewing distance of 60cm. Eye movements were recorded using a head-mounted infrared video-based eye tracker (Eyelink II; SR Research, Canada). Gaze position was recorded at 250Hz and corneal reflection was used when possible (8 PCA, 5 tAD, 13 healthy controls). Participants used a chin rest (wide HeadSpot; University of Houston College of Optometry) to provide stability and maintain viewing distance throughout the experiment. Saccades were parsed by the Eyelink system, using standard velocity and acceleration thresholds (30°/s and 8000°/s^2). Periods during which no saccadic movement occurred were automatically identified as fixation periods. We used built-in programs provided with the eye tracker for calibration and validation purposes (five points presented in a random sequence). All the data analyzed were obtained from recordings with an average Cartesian prediction error of <1° during the validation procedures. Calibration was repeated before the start of a new task if the participant needed a break from the eye tracker between tasks, or if there was slippage of the eye tracker between tasks. Each trial was initiated by a single target presented at the centre of the display (drift correct stimulus; grey inner circle (0.1 degrees) with black outer circle (subtending 0.4 degrees of visual angle). When the participant was fixating the target, the experimenter initiated the trial, and any discrepancy between gaze location and the target location was corrected.

3.2.3 Procedure

Testing took place in a quiet darkened room. All stimuli were presented on the display with a mid-grey background (RGB 128,128,128). The experimenter sat in the same room as the participant to provide verbal encouragement and to administer the tests, but was out of view of the participant in order to avoid distraction.

3.2.3.1 Fixation

Following the centrally presented drift correct stimulus, a red cross (RGB 255,0,0) (+) subtending 0.5 degrees of visual angle was presented for 10 seconds. Participants were

given one practice trial, followed by a further three trials. Participants were instructed to 'look as closely as you can at the red cross without blinking for 10 seconds'.

3.2.3.2 Saccade

In the saccade task the participant initially fixated a centrally presented stimulus, and was instructed to 'look as quickly and accurately as you can to the new dot when it appears'. Two stimuli were used in the saccade task. The central fixation point was a circle the same size as that used for the drift correction, but with a white inner circle. The target was a larger version (inner white circle 0.25 degrees, outer black circle 0.75 degrees).

Stimuli were presented at 5, 10 and 15 degrees horizontally, and 5 and 10 degrees vertically from the centre of the display, giving a total of 10 target locations. There were 4 trials at each target location.

The central fixation point was presented for 500ms. In half the trials target onset occurred 200ms after fixation offset (gap condition), and in half target onset occurred 200ms prior to fixation offset (overlap condition). There were an equal number of targets at each location in the gap and overlap conditions.

Trials were split into four equal blocks, the first block consisted of gap trials, the second of overlap trials, and then this was reversed. The number of trials at each location was balanced between blocks.

Once presented, the target remained on the display until a fixation of minimum 250ms in duration was made within 1.5 degrees of visual angle of the centre of the target, or until 5000ms from target onset.

3.2.3.3 Sinusoidal pursuit

6 trials of sinusoidal pursuit were administered, 3 horizontal and 3 vertical. The pursuit target was a red (RGB 255,0,0) circle 0.5 degrees of visual angle in diameter. The movement had a total amplitude of 20 degrees (10 degrees either side of the centre). The frequency of the sinusoidal target oscillation was set at 0.25Hz. Each trial lasted 10 seconds (2.5 cycles).

3.2.4 Analysis

Analysis was carried out at the group level using linear regressions to test group differences. Due to known heterogeneity within patient groups, we were also interested to investigate the number of patients in each group who showed deficits. For this purpose, we report the number of participants in each group that fell outside normal control performance (more than 2 standard deviations away from the control mean).

3.2.4.1 Fixation

Data from the practice trial were discarded.

3.2.4.1.1 Number of square wave jerks

Square wave jerks were identified using an algorithm and defined as a saccade of <2 degrees in amplitude, taking the gaze away from the target position, followed within 300ms by another saccade with an amplitude similar to the first (difference in amplitude between saccades < 0.75 degrees), which takes gaze back towards the target position (Leigh & Zee, 2006). The number for each participant was counted.

Linear regression was carried out for each of the fixation metrics listed above with group as the independent variable, and age included as a covariate of no interest.

3.2.4.1.2 Number of large intrusive saccades

Saccades containing blinks were removed. The number of saccades greater than two degrees in amplitude was counted for each participant. Linear regression was carried out with these counts as the dependent variable, and group as the independent variable, controlling for age.

3.2.4.1.3 Longest period of fixation

The maximum period of fixation (length of time between saccades) over all three trials was recorded for each participant.

3.2.4.2 Saccade

3.2.4.2.1 Saccade amplitude, latency and velocity

Saccade amplitude, velocity and latency were calculated for the first main saccade towards the target. This saccade was identified using a predetermined algorithm based on pilot work; any saccade that included a blink, started before the target appears, started more than 2.5^{o} from the central fixation point, or was in the wrong direction (error in angle of more than 45^{o}) was removed. The first saccade remaining for each trial was kept. A trial was discarded if the saccade for that trial was the 6^{th} saccade or later.

The error in saccade amplitude was calculated as the difference between the amplitude of the main saccade and the eccentricity of the target. A positive value represents overshoot (hypermetria) whilst a negative value represents undershoot (hypometria).

Saccade latency was calculated as the time between onset of the target and the start of the main saccade (identified automatically using the algorithm described above). The distribution of saccade latency was very skew, so analysis was performed on a square-root transform of latency, with values of saccade latency greater or less than the 2 standard deviations from the mean of each group removed after transformation.

Peak saccadic velocity is very closely related to saccade amplitude (e.g. Boghen et al., 1974), thus if saccadic amplitude was reduced in a patient group, we would expect peak saccadic velocity to also be reduced. Therefore in the comparison of peak saccadic velocity between groups, saccade amplitude was included as a covariate of no interest so that differences in velocity could be analysed independently from differences in saccadic amplitude.

Saccade amplitude and velocity were provided by the Eyelink software. The group and condition differences in these three dependent variables were tested using three separate linear regressions.

3.2.4.2.2 Number of saccades made

The number of saccades that were made after the target appeared, did not include a blink and were greater than 2^{o} were counted. This count was compared between participants using linear regression.

3.2.4.2.3 Time to first fixation upon target

The time between the onset of the target and the first fixation made within 2.5^{o} of the target was compared between groups. The distribution of time to first fixation upon target was not normally distributed, so analysis was performed on a square-root transform, with values greater or less than the 2 standard deviations from the mean of each group removed after transformation. Differences due to group and condition were tested using linear regression.

3.2.4.3 Sinusoidal pursuit

3.2.4.3.1 Pursuit gain

Pursuit gain was calculated for each measurement sample of the eye tracker using instantaneous estimates (provided by the Eyelink system) of stimulus and gaze velocity. Blinks, saccades and periods of pupil occlusion (and samples 50ms either side of any of these) were removed. Gain was calculated for the remaining period, and outliers were removed (due to the differing nature of this measurement, the method used to remove outliers for latencies [removing samples where gain was greater 2 standard deviations from the mean of that participant's group] removed too much of the distribution of gain values, resulting in a biased group comparison; thus outliers were removed by cutting off the tails of the distribution of gain, defined by visual inspection of histograms at -1 and +2). Differences due to group and pursuit direction (horizontal vs vertical) were tested using linear regression.

3.2.4.3.2 Number of saccades

The number of saccades of amplitude greater than 2^{o} was counted (not including blinks). This count was compared between participant groups using linear regression.

3.2.4.4 Association between oculomotor metrics and demographics

In order to assess whether impaired performance on the fixation, saccade and pursuit tasks was related to patients' age, disease duration and MMSE, Pearson's correlations were computed. One metric for each task was selected: the number of large intrusive saccades (fixation), time taken to the first fixation upon the target (saccade) and pursuit gain (smooth pursuit). Correlations were computed separately for the control, tAD and PCA groups.

3.2.5 Neuroimaging

Thirteen of the 20 PCA patients had a contemporary T1-weighted volumetric MR brain scan. Scans were acquired on a 3.0T Siemens TIM Trio scanner using a magnetisation prepared rapid gradient echo (MPRAGE) sequence. Voxel-based morphometry (VBM) was used to investigate the association of 6 metrics of oculomotor function with grey matter atrophy. Metrics were included from the fixation task (maximum fixation duration and number of large intrusive saccades during fixation), saccade task (saccade amplitude error, time to first fixation upon target and overlap-gap effect) and smooth pursuit task (pursuit gain).

VBM was carried out using SPM8 (Statistical Parametric Mapping, version 8; Wellcome Trust Centre for Neuroimaging, London, UK). Scans were segmented into grey and white matter using SPM8's new segment toolbox with default settings (Ashburner & Friston, 2005; Weiskopf et al., 2011). Segmentations were produced with rigid alignment to standard space (Montreal Neurological Institute (MNI) space) and resampled to 1.5mm isotropic voxels for use with DARTEL (Ashburner, 2007). DARTEL then iteratively registered the grey and white matter segments to an evolving estimate of their group-wise average (Ashburner & Friston, 2009). The native space tissue segments were then normalized to MNI space using the DARTEL transformations, modulated to account for local volume changes. A 6mm full width at half maximum (FWHM) Gaussian smoothing kernel was applied. Total intracranial volume (TIV) for each participant was estimated using Jacobian integration of deformation fields (Ridgway et al., 2011). An explicit mask was applied to include only voxels for which the intensity was at least 0.1 in at least 80% of the images (Ridgway et al., 2009).

Six separate general linear models (GLM) were used to assess associations of grey matter volume and each oculomotor metric of interest. Volume was modelled as a function of the oculomotor metric of interest, adjusting for age, gender and TIV (all mean centred). Statistical significance of the associations were tested using false detection rate (FDR) correction at $p<0.05$.

3.3 Results

3.3.1 Patient characteristics

In terms of age at assessment, the healthy control group (mean [sd] age = 63.3 [6.2] years) did not differ significantly from the PCA group (63.2 [8.9] years; two-sample t-test p=0.97). However, the tAD group (69.7 [5.1] years) was significantly older than both the control (p=0.005) and PCA (p=0.03) groups. The difference in age between the PCA and tAD groups reflects the relatively early onset of PCA, and controls were recruited to be matched to the PCA patients. As described in the analysis section, age was controlled for in statistical analyses.

The PCA and tAD groups did not differ in terms of disease duration (PCA: 4.6 [2.0] years; tAD: 4.7 [2.4] years; p=0.9) or Mini Mental State Examination score (PCA: 18.9 [4.5]; tAD: 20.1 [5.9]; p=0.50).

Biomarkers of molecular pathology were available in 7/20 PCA and 7/12 tAD patients (results shown in Table 3-1). These were supportive of underlying Alzheimer's Disease pathology in 5/7 PCA cases and 6/7 tAD cases. One tAD and one PCA patient showed a non-diagnostic profile (CSF tau:abeta ratio close to one), and one PCA patient had a CSF profile not consistent with Alzheimer's Disease (a ratio of 0.64).

Table 3-1 Molecular pathology biomarkers in patients

Diagnosis	PCA	PCA	PCA	PCA	PCA	PCA	PCA
CSF total tau (pg/ml)	412	787	325	898	310	561	841
CSF abeta 1-42 (pg/ml)	402	297	177	702	488	451	264
CSF Tau:Abeta ratio	1.02	2.65	1.84	1.28	0.64	1.24	3.19

Diagnosis	tAD	tAD	tAD	tAD	tAD	tAD	tAD
CSF total tau (pg/ml)	289	600	371	843	1099	828	800
CSF abeta 1-42 (pg/ml)	280	125	245	129	195	125	297
CSF Tau:Abeta ratio	1.03	4.80	1.51	6.53	5.64	6.62	2.69

3.3.2 Fixation

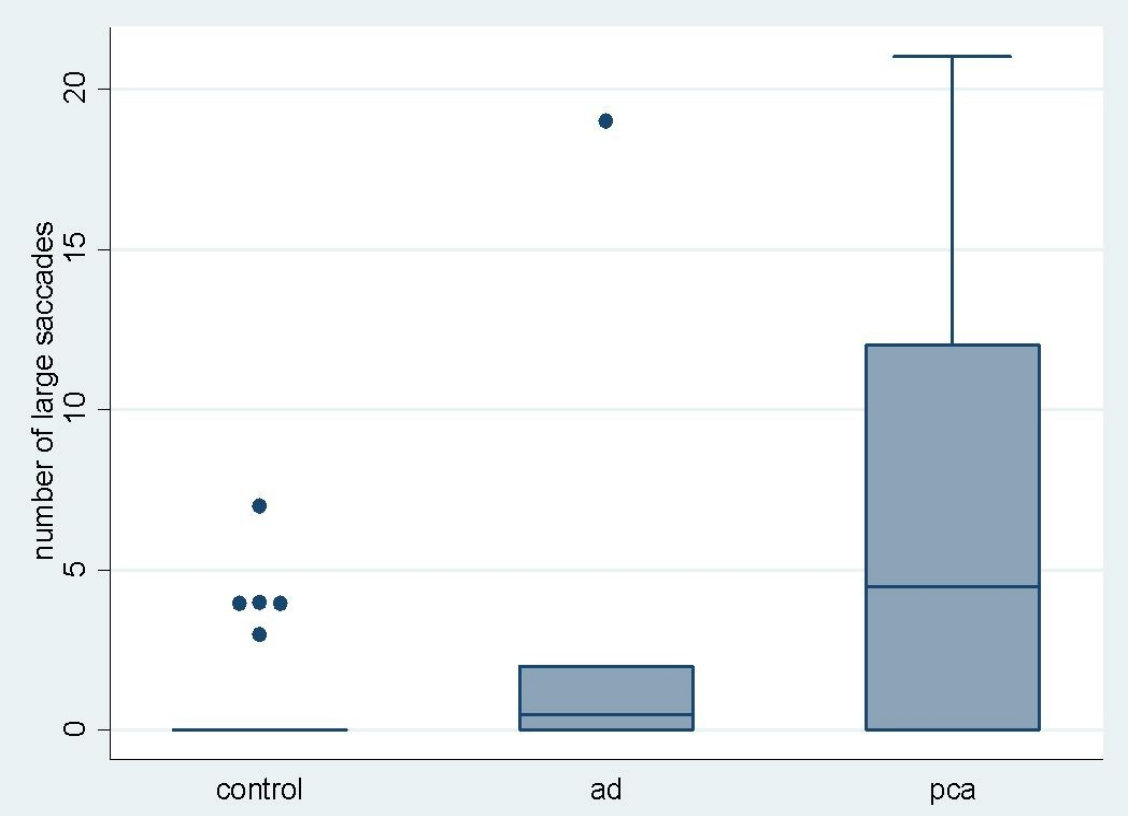
3.3.2.1 Square wave jerks

Position traces of two patients with a high frequency of square wave jerks are presented in Figure 3-2, with comparison to a healthy control participant. There was a trend towards a greater number of square wave jerks (per 30 seconds of fixation, as defined in the analysis section) in the PCA (mean=3.15 sd=3.36) than the healthy control group (mean=1.5, sd=2.2; β = 1.65, $t(40) = 1.75$, p=0.09). Whilst typical AD patients made more square wave jerks (mean=3.83, sd=3.66) than healthy controls (β = 2.37, $t(32) = 2.05$, p=0.046), there was no statistically significant difference in the frequency of square wave jerks between the PCA and typical AD groups (β = 0.72, $t(30) = 0.61$, p=0.54). At the individual level, 2 controls (9.1%), 4 typical AD patients (33.3%) and 2 PCA patients (10%) had a frequency of square wave jerks greater than two standard deviations from mean control performance.

3.3.2.2 Number of large intrusive saccades

Healthy controls made very few intrusive saccades of greater than 2 degrees in amplitude (mean=1, sd=2). As demonstrated in Figure 3-1, only five healthy controls made such saccades. PCA patients had a much greater frequency of large intrusive saccades (mean=6.5, sd=7.1) than controls (β = 5.51, $t(40) = 3.45$, p=0.001) and typical AD patients (mean=2.3, sd=5.3; β = 4.80, $t(30) = 2.4$, p=0.02), but the tAD patients did not differ from controls (β = 0.70, $t(32) = 0.36$, p=0.72). At the individual level, 1 control (4.5%), 1 typical AD patient (8.3%) and 9 PCA patients (45%) had a frequency of large intrusive saccades greater than two standard deviations from the control mean (see Figure 3-2 for a PCA patient trace showing large intrusive saccades during fixation).

Figure 3-1 Box plot showing the number of large intrusive saccades (>2o amplitude) in each participant group. The majority of controls and AD patients make very few large saccades, whilst PCA patients show an increased frequency.

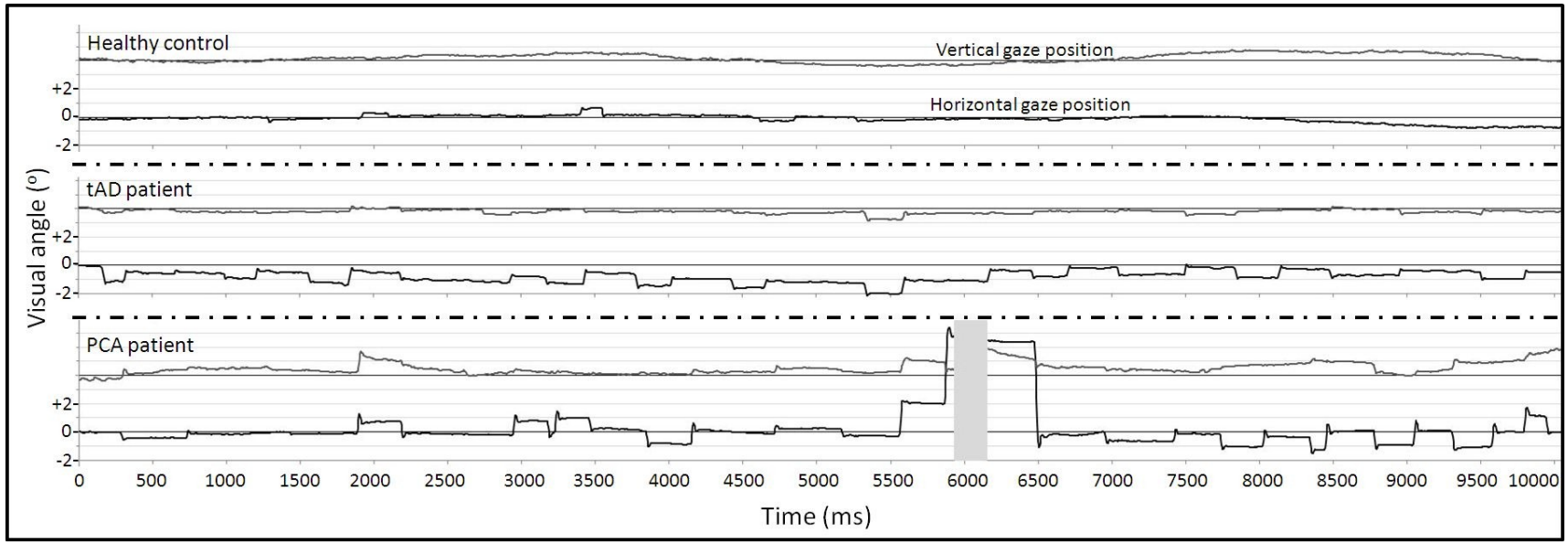


*The line inside the box shows the median, the extent of the box shows the 25th and 75th percentiles. Whiskers extend to the furthest observation within 1.5*inter-quartile range of the 25th/75th percentile.*

3.3.2.3 Longest period of fixation

The longest period of fixation (time without any saccades made) was shorter in the PCA group (mean=4366ms, sd=3038ms) than the control group (mean=7321ms, sd=2709ms; β = 2957, $t(40) = 3.20$, p=0.002) but did not differ from the typical AD group (mean=4927ms, sd=3304ms; β = 731, $t(30) = 0.63$, p=0.53). Typical AD patients showed a trend towards a shorter maximum fixation period than the healthy controls (β = 2225, $t(32) = 1.96$, p=0.056). Individually, no control participants had a longest period of fixation greater than two standard deviations from the control mean, whilst 2 typical AD patients (16.7%) and 6 PCA patients (30%) fell outside this measure of normal control performance.

Figure 3-2 Representative traces from the fixation task in a healthy control, a typical AD patient and a PCA patient.

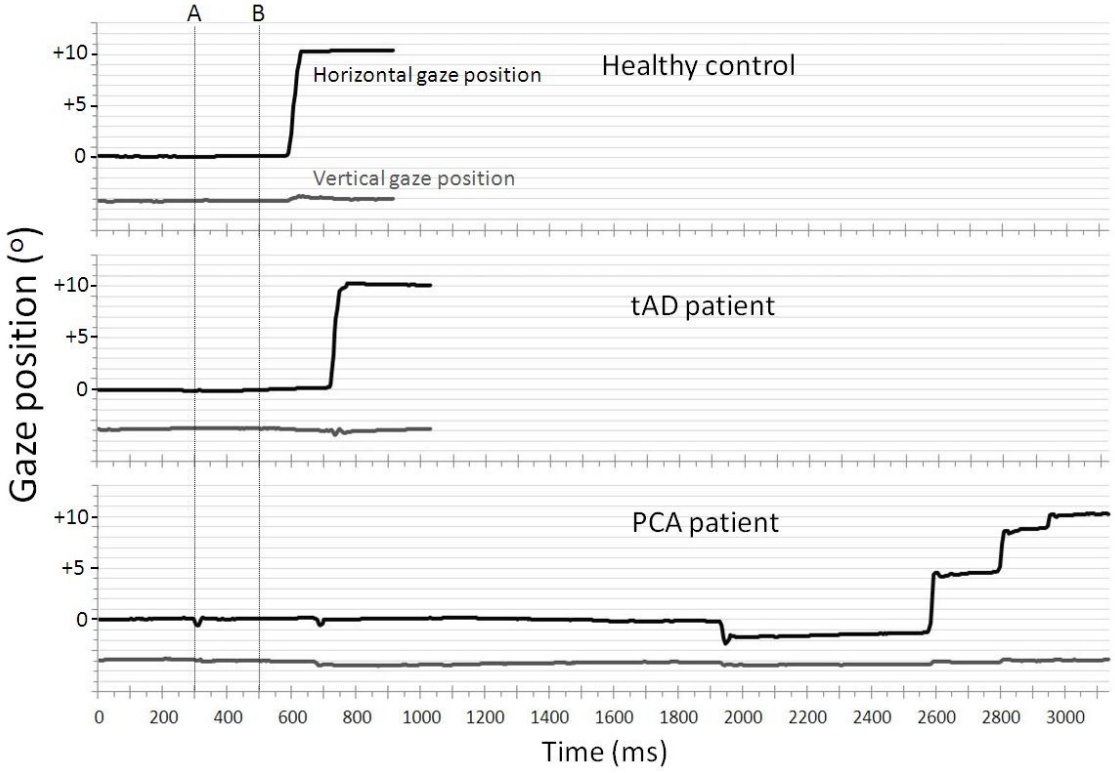


The upper plot (grey line) for each participant shows gaze position in the y (vertical) axis, the lower plot (black line) shows gaze position in the x (horizontal) axis. The location of the target stimulus is represented by thin black lines behind the traces. Gridlines show displacement of 1^{o} of visual angle. The grey area in the plot for the PCA patient represents a blink (therefore x and y gaze coordinates are not available for this period). Positive values of gaze position indicate rightward gaze. The healthy control maintains steady fixation upon the target, whilst both patients show saccadic intrusions in the form of square-wave jerks. Additional large saccadic intrusions are evident in the PCA trace.

3.3.3 Saccade

Example traces from 3 participants illustrating differences in their saccades are presented in Figure 3-3. The results presented in this section combine trials where the target was presented to the left and right, and above and below fixation. Analysis of left-right differences, presented in the Appendix (section A4), did not reveal significant group differences in the discrepancy between saccade amplitude and latency for targets presented on the left compared to the right.

Figure 3-3 Representative traces from the saccade task for a healthy control, a typical AD patient and a PCA patient in an 'overlap' trial.



The upper plot (grey line) for each participant shows gaze position in the y (vertical) axis, the lower plot (black line) shows gaze position in the x (horizontal) axis. Gridlines show displacement of 1^{o} of visual angle. Positive values of gaze position indicate rightward gaze. A central fixation point was present from the start of the trial until timepoint B (500ms). The target appeared at 10^{o} horizontally to the right of the central fixation point at timepoint A (300ms) and remained present until the end of the trial. The healthy control and tAD patients make a single saccade towards the target. The PCA patient takes a long time to initiate their first saccade (in the incorrect direction), followed by a number of small saccades to reach the target location.

3.3.3.1 Saccade amplitude, velocity and latency

3.3.3.1.1 Saccade amplitude error

The main saccade towards the target was hypometric rather than hypermetric on average in each participant group, for each target distance (5, 10 and 15 degrees; means shown in Table 3-2). Pairwise group comparisons at each target distance revealed a smaller amplitude of main saccades in the PCA group than the control and the typical AD group at each target distance (PCA vs controls: 5^o β = 0.79, $F(1,36)$ = 16.41, p<0.001; 10^o β = 1.98, $F(1,36)$ = 23.29, p<0.001; 15^o β = 3.76, $F(1,36)$ = 33.15, p<0.001; PCA vs tAD: 5^o β = 0.92, $F(1,26)$ = 11.66, p=0.001; 10^o β = 1.76, $F(1,26)$ = 10.73, p=0.002; 15^o β = 2.91, $F(1,26)$ = 13.89, p<0.001). The healthy control and tAD groups did not differ significantly in saccade amplitude error at any of the target distances (5^o β = 0.13, $F(1,32)$ = 0.29, p=0.59; 10^o β = 0.22, $F(1,32)$ = 0.26, p=0.61; 15^o β = 0.85, $F(1,32)$ = 1.85, p=0.18). There was an interaction between the effect of group and target distance (p<0.001), with the difference between the PCA group and control/tAD group becoming greater as the target distance increases (see Table 3-2). At the individual level, one tAD patient (8.3%) had severely hypermetric saccades (a mean saccade amplitude greater than 2 standard deviations from the control average). Twelve PCA patients (75%) and one tAD patient (8.3%) had severely hypometric saccades using this definition.

3.3.3.1.2 Saccade latency

As described in the analysis section, linear regression was carried out on the square root transform of latency, with outliers removed. PCA patients had longer latencies for the first main saccade towards the target than the control group at each target distance (means shown in Table 3-2; PCA vs controls: 5^o β = 1.96, $F(1,36)$ = 18.15, p<0.001; 10^o β = 2.54, $F(1,36)$ = 19.12, p<0.001, 15^o β = 2.06, $F(1,36)$ = 4.05, p=0.0497;) and longer latencies than the typical AD group at 5^o (β = 1.49, $F(1,26)$ = 5.87, p=0.02) and 10^o (β = 2.03, $F(1,26)$ = 7.85, p=0.007), but not at 15^o (β = 1.37, $F(1,26)$ = 1.52, p=0.22). Latencies in the typical AD group were not statistically different from those in controls at 5^o (β = 0.47, $F(1,32)$ = 1.24, p=0.27), 10^o (β = 0.50, $F(1,32)$ = 1.15, p=0.29), and 15^o (β = 0.69, $F(1,32)$ = 2.03, p=0.16). There was no statistically significant interaction between group and target distance (i.e. the difference in saccade latencies

between groups was similar for each target distance; p=0.67). At the individual level, one control (4.5%), four tAD patients (33.3%) and ten PCA patients (62.5%) had latency greater than 2 standard deviations slower than the control mean. One healthy control had saccade latencies 2 standard deviations faster than the control mean.

A linear regression investigating whether the effect of the gap/overlap manipulation differed between groups (group*gap/overlap interaction) revealed a non-significant interaction (p=0.22). Three separate regressions showed that there was a trend towards an interaction between group and gap/overlap difference comparing PCA patients and controls (p=0.09) but not comparing tAD patients and controls (p=0.62) or comparing the PCA and tAD groups (p=0.23). This pattern is evident in the gap and overlap condition latencies presented in Table 3-2.

3.3.3.1.3 Saccade velocity

Saccade velocity (once saccade amplitude was accounted for) did not differ significantly between the PCA (mean=264.0^{o}/s, sd=64.0) and control groups (mean=294.9^{o}/s, sd=60.5; β = 16.11, $F(1,36) = 0.95$, p=0.33). However, the typical AD group (mean=334.3^{o}/s, sd=53.7) showed increased peak saccadic velocity compared to the healthy control group (β = 51.67, $F(1,32) = 14.09$, p=0.005), and the PCA group (β = 35.55, $F(1,26) = 5.37$, p=0.02) after controlling for saccade amplitude.

3.3.3.2 Number of saccades made

PCA patients made more saccades per trial (mean=2.08, sd=0.78) than healthy controls (mean=1.21, sd=0.16; β = 0.86, $t(36) = 4.21$, p<0.001) and showed a trend towards more saccades than typical AD patients (mean=1.53, sd=0.61; β = 0.51, $t(26) = 1.88$, p=0.07). Typical AD patients showed a trend towards more saccades than healthy controls (β = 0.35, $t(32) = 1.90$, p=0.06). At the individual level, 1 healthy control (4.5%), 3 typical AD patients (25%) and 13 PCA patients (81.3%) made more saccades than 2 standard deviations from mean control performance.

3.3.3.3 Time to first fixation upon target

As described in the analysis section, linear regression was carried out on the square root transform of time taken, with outliers removed. Box plots of group results are

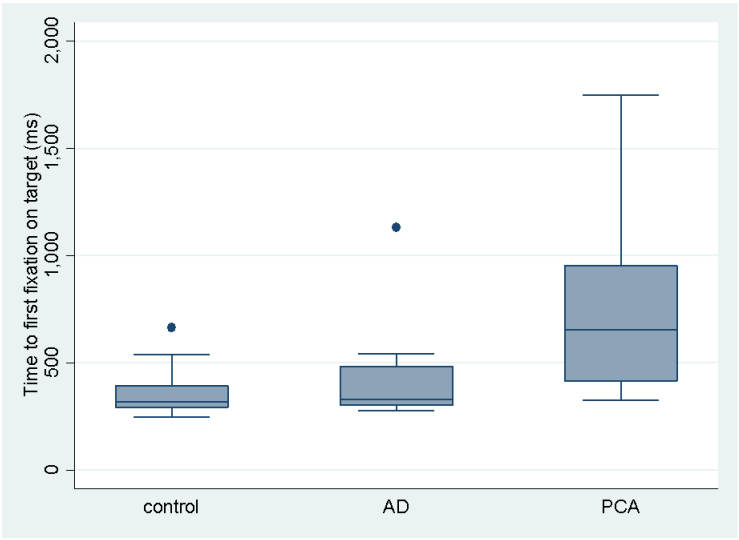
shown in Figure 3-4. The time taken to first fixation upon the target measure revealed very similar results to the latency of the main saccade measure. PCA patients took longer to reach the target than the control group at each target distance (means and standard deviations are shown in Table 3-2; PCA vs controls: 5^o β = 3.91, *F*(1,36) = 17.15, p<0.001; 10^o β = 6.62, *F*(1,36) = 36.16, p<0.001; 15^o β = 5.74, F(1,36) = 22.56, p<0.001;) and similarly took longer than the typical AD group at (5^o β = 4.46, F(1,26) = 13.83, p=0.005; 10^o β = 5.67, F(1,26) = 18.63, p<0.001; 15^o β = 4.45, F(1,26) = 10.40, p=0.002). Latencies in the typical AD group were not statistically different from those in controls at 5 or 10 degrees of eccentricity, whilst there was a trend to significant difference at 15 degrees (5^o β = 0.64, *F*(1,32) = 1.18, p=0.28; 10^o β = 0.96, *F*(1,32) = 1.60, p=0.21; 15^o β = 1.29, *F*(1,32) = 3.39, p=0.07). This difference in time taken to fixate the target between PCA patients and controls/tAD patients was greater at longer stimulus distances (interaction between group and distance p<0.001, see Table 3-2 for table of means). At the individual level, one control (4.5%), one tAD patient (8.3%) and ten PCA patients (62.5%) showed a substantially longer time to fixation upon the target (greater than 2 standard deviations from the control mean).

A separate linear regression investigating whether the effect of the gap/overlap manipulation differed between groups (group*gap/overlap interaction) revealed a significant interaction (p=0.003). Three separate regressions showed that there was an interaction between group and gap/overlap difference comparing PCA patients and controls (p=0.001) and when comparing the PCA and tAD groups (p=0.01) but not comparing tAD patients and controls (p=0.39).

Table 3-2 Performance in the saccade task. Mean and standard deviation of amplitude error and latency of the main saccade, and time to first fixation upon the target at each target distance. Additionally, gap and overlap performance is shown for latency measures (as these are the outcomes of interest for this experimental manipulation).

		Target distance (°)					
amplitude error (°)	mean(sd)	5	10	15			
	Control	-0.49 (0.55)	-1.44 (0.90)	-2.29 (1.26)			
	tAD	-0.26 (0.64)	-1.60 (1.47)	-3.02 (2.22)			
	PCA	-1.34 (0.67)	-3.51 (1.58)	-6.34 (2.52)			
					Gap / Overlap		
Latency (ms)	mean(sd)	5	10	15	Gap	Overlap	Overlap-Gap
	Control	219.2 (46.3)	226.7 (30.4)	237.8 (38.8)	201.8 (41.0)	249.4 (38.1)	47.6
	tAD	232.6 (41.3)	270.2 (86.6)	333.6 (135.3)	226.8 (46.1)	301.8 (92.5)	75.0
	PCA	339.1 (131.1)	398.5 (129.3)	411.8 (201.2)	318.0 (148.7)	432.2 (143.6)	114.2
Time to fixation on target (ms)	mean(sd)	5	10	15	Gap	Overlap	Overlap-Gap
	Control	310.6 (121.3)	359.9 (90.6)	425.7 (153.4)	332.2 (110.2)	371.9 (107.2)	39.6
	tAD	321.1 (126.1)	453.6 (261.7)	614.6 (439.9)	398.1 (225.1)	465.3 (252.3)	67.2
	PCA	567.4 (332.8)	862.9 (433.4)	892.4 (550.8)	644.7 (366.9)	851.1 (428.7)	206.4

Figure 3-4 Box plot showing the time taken to make the first fixation upon the target in the saccade task, for each participant group. The majority of controls and AD patients fixate upon the target within 500ms, whilst PCA patients show much greater latencies.



*The line inside the box is the median, the extent of the box shows the 25th and 75th percentiles. Whiskers extend to the furthest observation within 1.5*inter-quartile range of the upper/lower quartile.*

3.3.4 Sinusoidal pursuit

Example traces from 3 participants illustrating performance in smooth pursuit are shown in Figure 3-6.

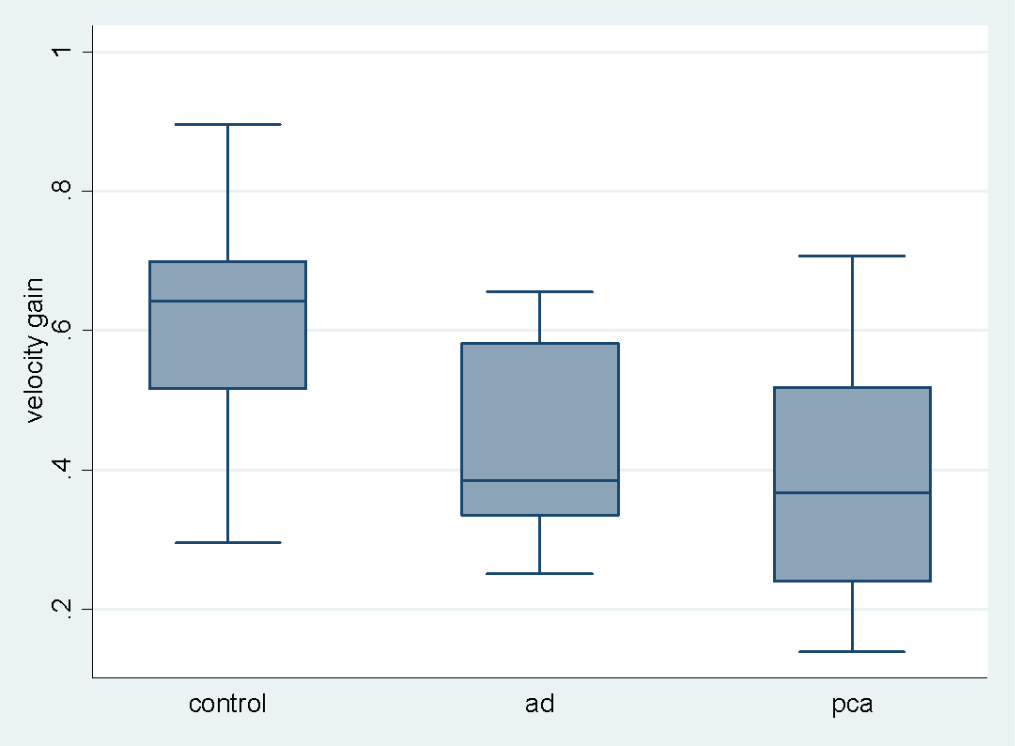
3.3.4.1 Pursuit gain

Mean pursuit gain (velocity calculated for periods that were not in saccade, blink or pupil occlusion) is shown in Figure 3-5. Gain was significantly lower in the PCA group (mean=0.38 sd=0.17) than the healthy control group (mean=0.61, sd=0.16; β = 0.23, $t(36) = 4.27$, $p<0.001$) but did not differ significantly between the PCA group than the typical AD group (mean=0.44, sd=0.14; β = 0.09, $t(26) = 1.55$, $p=0.13$). The typical AD group also showed significantly lower gain than the control group (β = 0.14, $t(32) = 2.50$, $p=0.02$). At the individual level, 1 tAD patient (8.3%) and six PCA patients (35.3%) showed a substantially lower gain than the control group mean (greater than 2 standard deviations from the control mean). Whilst participants showed lower gain for vertical compared to horizontal pursuit (β = 0.23, $t(48) = 6.85$, $p<0.001$), this effect was similar between patient groups (no interaction between group and pursuit direction; $p=0.87$)

3.3.4.2 Number of saccades

PCA patients made more saccades per trial (mean=13.06, sd=4.67) than healthy controls (mean=7.40, sd=4.21; β = 5.68, $t(36) = 3.87$, $p<0.001$), but did not differ from typical AD patients (mean=13.32, sd=4.58; β = 0.18, $t(26) = 0.10$, $p=0.92$). Typical AD patients also made more saccades per trial than controls (β = 5.51, $t(32) = 3.25$, $p=0.002$). At the individual level, 1 healthy control (4.5%), 5 typical AD patients (41.7%) and 4 PCA patients (23.5%) fell outside 2 standard deviations from mean control performance.

Figure 3-5 Box plot of velocity gain in each participant group.



*The line inside the box is the median, the extent of the box shows the 25th and 75th percentiles. Whiskers extend to the furthest observation within 1.5*inter-quartile range of the upper/lower quartile.*

3.3.5 Association between oculomotor metrics and demographics

Correlation coefficients and p values for the Pearson's correlations are presented in Table 3-3.

The association between performance on the fixation task (number of large intrusive saccades), saccade task (time to first fixation upon the target) and smooth pursuit task (pursuit gain) and age was very weak, with the exception of a significant negative correlation (p=0.03) between age and pursuit gain in the typical AD group (older typical AD patients had lower gain).

Associations with disease duration in the PCA group were stronger, with longer disease duration associated with a significantly higher frequency of large intrusive saccades (p=0.005), and a trend towards longer latency to fixate upon the target (p=0.08) and lower pursuit gain (p=0.08).

There were also significant correlations between MMSE and oculomotor metrics. In the PCA group, lower MMSE was associated with a higher frequency of large intrusive

saccades (p=0.03) and there was a trend towards a correlation between lower MMSE and lower pursuit gain in the tAD group (p=0.052).

Table 3-3 Correlation between oculomotor metrics and demographics. Associations of the frequency of large intrusive saccades in the fixation task, time taken to first fixation upon the target in the saccade task, and pursuit gain in the smooth pursuit task with age, disease duration and MMSE are presented. Significant correlations are highlighted in dark red, whilst trends are highlighted in light red.

		Age			Disease duration		MMSE	
		Control	tAD	PCA	tAD	PCA	tAD	PCA
Large intrusive saccades	**rho**	0.13	0.01	0.19	-0.45	0.59	-0.36	-0.49
	p	0.576	0.982	0.408	0.146	0.005	0.223	0.025
Time to fixate target	**rho**	0.04	0.01	-0.01	-0.36	0.43	-0.48	-0.24
	p	0.878	0.965	0.963	0.252	0.083	0.112	0.352
Pursuit gain	**rho**	0.20	-0.62	-0.03	0.49	-0.44	0.57	0.12
	p	0.383	0.030	0.240	0.105	0.079	0.052	0.650

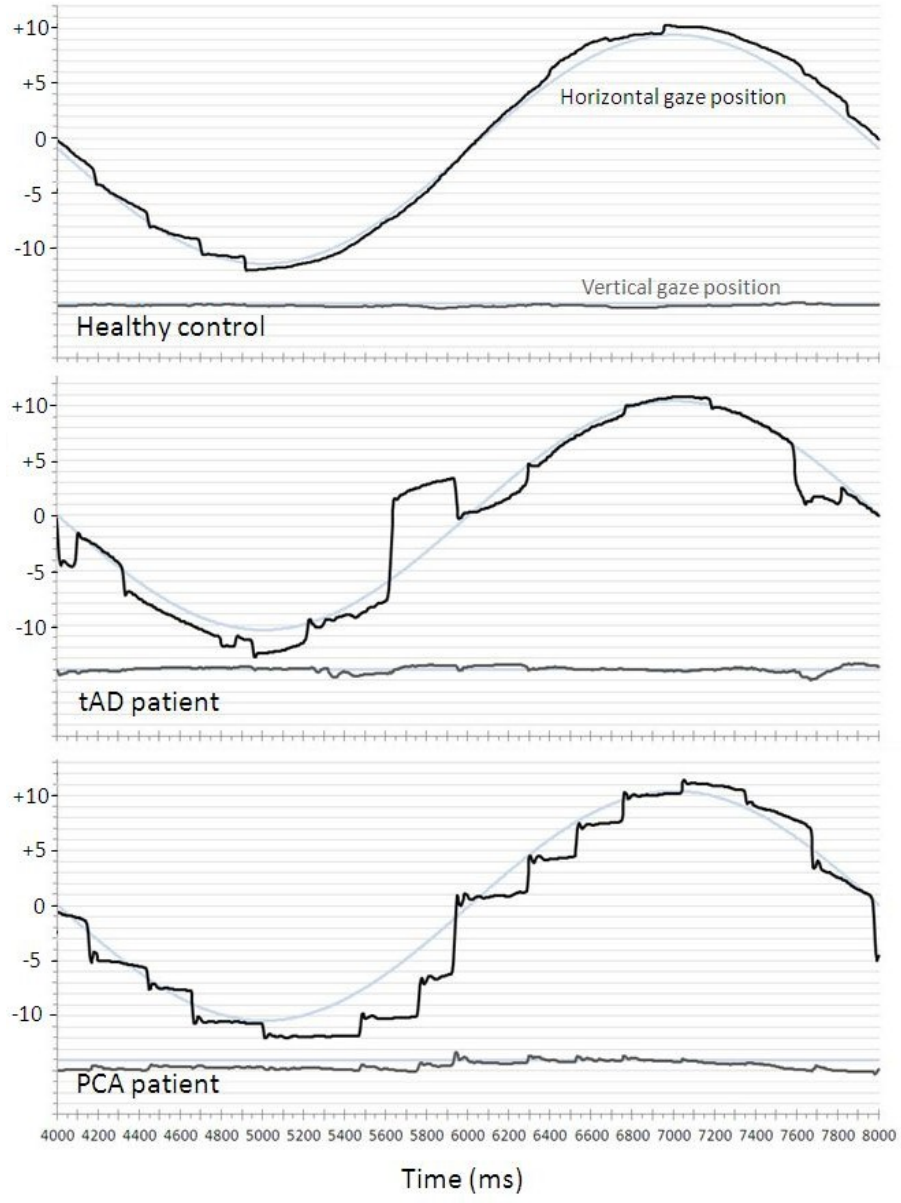
3.3.6 Neuroimaging

There were no significant associations between grey matter atrophy and oculomotor function in the six metrics tested (maximum fixation duration, number of large intrusive saccades during fixation, saccade amplitude error, time to first fixation upon target, overlap-gap effect and pursuit gain) after correcting for multiple comparisons across the whole brain. For completeness, effect size maps are presented in Figure A-2 of the Appendix.

Whilst no results reached significance, there is weak evidence for some trends in the spatial distribution of effects. Most areas in which grey matter atrophy was more strongly associated with poor task performance were in the right hemisphere. In terms of metrics of fixation, areas with a relatively stronger effect size included the orbitofrontal gyrus in the association with maximum fixation duration, and the right post central gyrus in association with the number of saccades made during fixation. For metrics of saccade performance, the right superior parietal lobule showed relatively strong effect sizes in the association with amplitude error and time to

fixation on target. Whilst effect sizes were very small in the model including overlap-gap performance, there were relatively stronger effect sizes in the right occipital fusiform gyrus for the association with pursuit gain. Unexpectedly, there was a relatively strong effect size for the association between less atrophy and greater saccade amplitude error in the cerebellar vermis.

Figure 3-6 Representative traces from the pursuit task for a healthy control, a typical AD patient and a PCA patient.



The figure shows a cycle towards the middle of the trial (seconds 4-8 from a trial of 10 seconds). Positive values of gaze position indicate rightward gaze.

The upper plot (grey line) for each participant shows gaze position in the y (vertical) axis, the lower plot (black line) shows gaze position in the x (horizontal) axis. Target position is represented by a faint blue line. Gridlines show displacement of 1^{o} of visual angle.

3.4 Chapter conclusions

This chapter describes the first detailed assessment of basic eye movement behaviour in a group of patients with Posterior Cortical Atrophy. The results demonstrate abnormalities in maintaining fixation in PCA patients compared to healthy controls. Saccades were hypometric and saccade latencies increased in the PCA group. However, the peak velocity of saccades was normal (after accounting for saccade amplitude) indicating relative preservation of motor aspects of eye movement generation. Finally, a sinusoidal smooth pursuit task demonstrated lower velocity gain and greater frequency of saccades in the PCA group compared to healthy controls.

This pattern of oculomotor dysfunction observed in PCA patients differs from that seen in the tAD group, whilst tAD patients showed some abnormalities in fixation (an increased frequency of square wave jerks), they did not show a greater frequency of intrusive saccades compared to controls. In the saccade task, tAD patients did not differ significantly from controls in terms of their saccade amplitude or latency, although peak saccadic velocity was increased in the tAD groups compared to controls. Like PCA patients, tAD patients showed reduced gain in the smooth pursuit task.

Comparing the two patient groups directly revealed a number of similarities and differences between the groups. In the fixation task, the PCA patients had a similar frequency of square wave jerks and similar maximum duration of fixation, but an increased frequency of large saccadic intrusions (saccades $>2^{o}$) compared to tAD. In the saccade task, PCA patients showed significant impairments in the amplitude and latency of saccades compared to tAD patients, along with longer time taken to first fixation upon the target and a larger number of saccades made and significant impairments in disengagement (overlap-gap difference, when measuring time taken to reach the target). In the sinusoidal smooth pursuit task, pursuit gain and frequency of saccades were similar between the two patient groups, with both groups performing worse than healthy controls. Thus PCA patients were as impaired or more impaired than typical AD patients on all the metrics tested, with particular impairments in the saccade task. This is despite the fact that they were younger than the tAD patients and the patient groups were matched for MMSE and disease duration (note that age was included as a covariate in statistical analyses).

The finding of increased frequency of square wave jerks and reduced period of fixation in PCA and tAD compared to healthy controls is consistent with previous reports of saccadic intrusions during fixation in Alzheimer's disease (Jones et al., 1983; Schewe et al., 1999). Square wave jerks are not specific to Alzheimer's disease. An increased frequency is associated with advancing age (Herishanu & Sharpe, 1981) and other neurological conditions such as Parkinson's disease (Rascol et al., 1991; White et al., 1983). In this study we note a higher frequency of large saccadic intrusions (>2^{o}) in the PCA group. Whilst some of these intrusions likely reflect larger square wave jerks, PCA patients also made saccadic intrusions that were not followed by a corrective saccade after a short interval (see Figure 3-2). The fact that PCA patients show a greater frequency of these intrusions compared to tAD, but not a greater frequency of smaller square wave jerks suggests that these large saccadic intrusions have a different origin, perhaps associated with more severe visual disorientation or visual inattention. Whilst square wave jerks of the kind measured here in tAD and PCA are not generally considered to have strongly adverse affects on visual perception, these larger saccadic intrusions that shift gaze to a new location and do not involve a rapid return to the target mean that the individual may completely lose track of the target they were trying to monitor. Not only is there an initial intrusion, but there is also an impaired re-fixation process (perhaps related to an impairment in visual search due to inadequate perceptual or attentional resources).

In contrast to previous studies of pro-saccades in typical Alzheimer's disease (Bylsma et al., 1995; Fletcher & Sharpe, 1986; Yang et al., 2011, 2013), we did not see any systematic differences between our tAD group and the healthy control group, with the exception of a trend towards greater saccadic latency in the tAD group for targets at 15^{o}, (4/12 [33%] tAD patients had mean latencies more than 2 standard deviations lower than the control mean). This substantial variation between studies in terms of oculomotor abnormalities reported in Alzheimer's disease, reinforces the need for replication of the results in the present study, using a different sample. Previous studies of PCA note the occurrence of oculomotor apraxia (also known as ocular apraxia; a reduced ability to make voluntary saccades) on informal clinical testing in some PCA patients, but the proportion varies considerably between studies (e.g. 9/19 of patients [47%] in McMonagle et al., 2006; 4/15 [27%] in Mendez et al., 2002; 4/40

[10%] in Tang-Wai et al., 2004). The present study provides a more detailed, quantitative examination of eye movements, revealing impairments in saccade amplitude in 11/16 (68.7%) of patients with PCA (defined by performance more than 2 standard deviations from the control mean). This raises the possibility that oculomotor apraxia (when measured formally) may be considerably more common in PCA than previously thought. In addition to taking longer to initiate the main saccade towards the target, PCA patients also took longer to reach the target, and made more saccades in order to do so. This increase in the number of saccades required was present in the majority of PCA patients (13/16 PCA patients [81.3%]).

Furthermore we found a significantly greater effect of the gap/overlap manipulation upon latency in the PCA group compared to the typical AD and healthy control groups when measuring the time taken to reach the target; however this effect was not significant when measuring the latency of the main saccade towards the target. Although there is disagreement on the exact basis of the gap/overlap effect, it is likely that continued engagement of visual attention (Fischer & Weber, 1993) or oculomotor fixation (Klein et al., 1995) to the central fixation point results in longer latencies in the overlap condition. In PCA patients this effect was enhanced suggesting a deficit in disengagement from the fixation point in PCA. In patients with typical AD, two studies have reported that there was not a gap/overlap effect (Abel & Yee, 2002 and Crawford et al., 2013) whilst one study reported that there was such an effect (Yang et al., 2013). The results from the present study add weight to the former findings, as there was no difference in the gap/overlap effect between typical AD patients and controls. However, these results should be interpreted with caution as they were only found in one of the measures of saccade latency (time taken to reach the target), not the latency of the first saccade towards the target. One possibility is that the difference in results between the measures reflects an ongoing difficulty in moving away from the fixation point over the multiple saccades that PCA patients make, that is not picked up in the latency of the main saccade towards the target.

In smooth pursuit, the PCA and typical AD groups did not differ from one another, with both groups showing lower gain than the healthy controls and an increased frequency

of intrusive saccades. This is consistent with previous studies of smooth pursuit in tAD (Fletcher & Sharpe, 1988; Garbutt et al., 2008; Zaccara et al., 1992).

The possible mechanistic and neurological basis of the abnormalities in oculomotor control described in the present paper are worthy of discussion. Two accounts could be given to explain the deficits observed in PCA patients. The first is that the basis for the deficits lies in the oculomotor system; an impairment of the basic automatic mechanisms and reflexes underlying stable fixation, saccade initiation and planning, and smooth pursuit. The second is that more cognitive, higher-order cortical visual processing deficits are responsible for the performance observed here. In this account, deficits in visuo-perceptual, visuo-spatial processing or attention result in a weak or inaccurate representation of the form and spatial location of the target. Whilst these two accounts cannot be completely disentangled, we will consider whether the nature of the abnormalities observed lend themselves to particular interpretations.

Some features of eye movements observed in PCA patients suggest deficits in a basic level of oculomotor function, such as the impaired smooth pursuit shown in Figure 3-6. This PCA patient is clearly tracking the target (suggesting that the representation of target motion and planned gaze location is intact), but does so with many saccades and very little smooth pursuit (suggesting an impairment in the oculomotor mechanism underlying smooth pursuit). Similarly the increased frequency of square wave jerks in patients with tAD and PCA likely reflects changes in basic oculomotor mechanisms rather than cognitive processes, as these eye movements are not under cognitive control.

Other features observed could be considered more consistent with a higher-order cognitive deficit, for example the hypometria of PCA patients' saccades could be accounted for by a poor spatial representation of the target location and a decreased effective field of vision, resulting in saccades being shorter than required and therefore a requirement for multiple saccades and more time to reach the target. It is quite possible that a combination of more basic and higher order deficits underlie performance in these tasks.

In terms of the anatomical basis for the oculomotor abnormalities observed in patients, the prior knowledge that atrophy in PCA is primarily cortical (by definition),

and that areas important for oculomotor function are affected (e.g. atrophy of the parietal lobes, Whitwell et al. 2007, and hypometabolism of the frontal eye fields, Nestor et al. 2003) suggest that these areas are most likely to be responsible for the deficits observed. Consistent with this, neither the PCA or tAD patients showed impairments in saccadic velocity, which suggests cortical rather than brainstem atrophy may be responsible (c.f. progressive supranuclear palsy, Garbutt et al., 2008; Gröschel et al., 2004). Considering the gap/overlap effect in PCA patients, whilst lesions of the superior colliculus have a role in the release of fixation (Dorris & Munoz, 1995; Neggers et al., 2005), the parietal atrophy known to exist in patients with PCA is perhaps a more likely explanation in this patient group.

A voxel-based morphometry analysis attempting to investigate associations between atrophy in PCA patients and task performance did not provide strong evidence to aid the localisation of deficits. Significant associations were not found in any brain region after correcting for multiple comparisons. Effect size maps revealed a trend towards stronger associations in the right hemisphere, with regions in the frontal, parietal and occipital cortex showing relatively stronger effects. These trends should be interpreted with caution due to the fact that they did not reach statistical significance.

It is notable that there were associations of metrics of fixation, saccade and smooth pursuit with disease duration in the PCA group, suggesting that more severely affected patients are likely to perform worse on these measures. However these associations were not very strong (correlation coefficients were small, and only the association between the number of large intrusive saccades and disease duration was significant, the association between latency to target in the saccade task and smooth pursuit gain showed a trend to significance), suggesting that there may also be an element of inter-individual variability not related to disease severity.

Finally, it is worth considering the potential weaknesses of this study. Whilst all the PCA patients met clinical criteria for the syndrome, and did not exhibit symptoms suggestive of pathologies other than Alzheimer's Disease (e.g. hallucinations, delusions and fluctuations suggesting Lewy Body Disease), it remains possible, perhaps likely, that some of the participants do not have Alzheimer's disease, or have coexistent pathologies (Renner et al., 2004). Also, the PCA and tAD groups were not matched for

age, this age difference in our patient populations reflect clinical reality, as patients with atypical presentations tend to have an earlier onset. However, our statistical analyses covaried for age, and given that the PCA patients (who were younger) performed worse than tAD on many of the tasks this suggests that if there is an effect of age, it would result in an underestimate of the differences between the PCA and tAD patients.

To conclude, this is the first systematic quantitative evaluation of oculomotor control in PCA. We found that patients with PCA demonstrate significant abnormalities in their oculomotor behaviour, including fixation instability, delayed initiation and hypometria of saccades (with an increased gap/overlap effect) and impaired smooth pursuit (marked by lower gain and higher frequency of intrusive saccades). Deficits in these tasks were much more common than previous studies involving clinical evaluation have appreciated.

4 Perception of scenes in Posterior Cortical Atrophy: a pilot eyetracking study

4.1 Chapter introduction

In Chapter 2 I described the severe impairments of PCA patients in terms of accuracy and response times when categorizing photographs of scenes, whilst in Chapter 3, the abnormalities in oculomotor function of PCA patients were characterised. This chapter describes a pilot study designed to investigate scene perception in PCA in more detail, using fixation patterns measured using eye tracking.

Scene perception relies on a combination of basic visual, visuomotor and higher order perceptual and executive processes. Comparisons of the eye movements of patients with parietal lesions and healthy controls during scene perception has revealed a common initial fixation pattern which then diverges in later fixations (Mannan et al., 2009). This suggests that in scanning a scene, eye movements are initially driven by low level bottom-up features such as edges and contrast but are also increasingly influenced by the evolving top-down understanding of the scene (Mannan et al., 2009). By contrast, other researchers have argued that top-down processes influence perception throughout the process of scanning a scene (Foulsham et al., 2011). Both these studies included a single patient with PCA; in the current study we compare the two predictions in a group of PCA patients using similar eye tracking measures to evaluate of scene scanning.

The aim of the current study was to describe and characterise everyday scene perception in PCA, with a further intention to discriminate between different accounts of the role of bottom-up and top-down influences upon scanning behaviour when viewing a complex scene. We test the hypothesis that PCA patients show a greater initial reliance than controls upon bottom-up than top-down processing by determining whether the fixation patterns of PCA patients and controls diverge over successive fixations (in line with the hypothesis) rather than proceed in parallel (suggesting the involvement of top-down strategies from the outset when scanning a scene).

4.2 Methods

4.2.1 Participants

Data were collected from 7 PCA patients (5 male; Mean [SD] age = 63.1 [7.2] years; Mean [SD] disease duration = 4.9 [1.5] years), 6 healthy age matched controls (4 male; Mean [SD] age = 62.8 [10.7] years) and a group of 17 young controls (5 male; Mean [SD] age = 33.8 [10.1] years).

4.2.2 Stimuli

The stimuli were 10 colour photographs of scenes, such as a beach, a living room and a forest path. The stimuli had a resolution of 800x600 pixels and were taken from Google images. The first two patients and controls tested viewed only 5 of the scenes.

4.2.3 Procedure

Stimuli were presented on an 17" Acer monitor using SR Research Eyelink Experiment Builder software (SR Research Ltd., Osgoode, ON, Canada) and subtended a visual angle of 23^{o} from an approximate viewing distance of 50cm. A free viewing paradigm was used. Each picture was presented for five seconds, following a drift-correct stimulus. The participant was instructed to view the picture in a natural way, as if looking at a postcard. Participants were not asked to name or describe the scenes.

Eye movements were recorded using the head-mounted Eyelink II system, an infrared video-based eye tracker. The Eyelink II recorded gaze location at 250Hz, and corneal reflection was used where possible in order to improve stability. Fixations and saccades used in the present analysis were parsed by the Eyelink system using standard velocity and acceleration thresholds ($30^{o}/s$ and $8000^{o}/s^{2}$). Five point calibration was carried out at the start of the experiment, and a single point drift-correct was carried out prior to each trial. Blinks were indentified and removed using Eyelink's automated blink detection.

4.2.4 Analysis

The duration of fixations and saccade amplitude were compared between patients and controls using a linear regression model with robust (Huber-White) standard errors that took account of the multiple measurements from each participant. Due to non-

normality of the distribution of fixation duration and saccade amplitude, the linear regression was carried out on a log-transformation of the data.

Fixation duration maps were created for each scene from the fixations of the 17 young controls. These were generated using Eyelink Data Viewer software (version 1.11.1) with default settings. This applies a smoothing kernel of 1.5 degrees of visual angle over all fixations to create a fixation duration heat map. A fixation duration cut off was defined as the value giving the greatest area under the curve in a receiver operator characteristic curve analysis separating the young control from the PCA group. This cut off was used to make a region of interest (ROI) for each scene.

The proportion of fixations within this ROI for each fixation was calculated for each group. The first fixation was omitted from this analysis as it was predetermined by a central drift correction at the start of each trial. The next 6 fixations were used, as this was the maximum number of fixations available over all participants. These fixations were split into three time periods 'early' (fixations 2 and 3) 'middle' (4 and 5) and 'late' (fixations 6 and 7).

A logistic regression model fitted using generalised estimating equations (GEE; Zeger & Liang, 1986) to allow for the multiple measures per subject was used to investigate the effects of group and time period and their interaction upon the binary variable indicating whether the fixation was inside or outside the control-defined ROI. The GEE model used a working assumption of independence and robust standard errors were used for inferences.

4.3 Results

Descriptive statistics of fixation duration and saccade amplitude in each group are presented in Table 4-1.

There was no statistically significant evidence for a difference in saccade amplitude between patients and age-matched controls ($\beta = 0.23$, $t(11) = 1.44$, $p=0.16$) or a difference in fixation duration between patients and age matched controls ($\beta = 0.02$, $t(11) = 0.14$, $p=0.89$).

The proportion of fixations inside the young-control defined ROI for the age-matched control group and PCA group in the three time periods is shown in Figure 4-1, and was

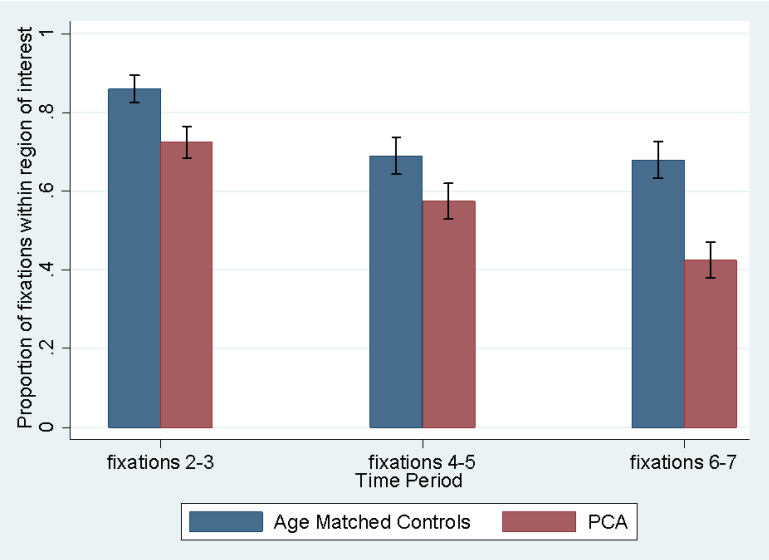
significantly lower in PCA patients than age-matched controls (OR = 0.47, z = 1.98, p=0.047).

Investigating differences over the three time periods between PCA patients and age-matched controls, there was a significant effect of time period, such that later fixations were less likely to be inside the ROI ($\chi^2(2, N=13) = 30.19$, $p<0.001$), but there was no evidence that the magnitude of this effect differed between groups (interaction of time period and group; $\chi^2(2, N=13) = 2.04$, $p=0.36$).

Table 4-1 Mean and standard deviation of fixation duration and saccade amplitude for each participant group.

	Mean	**S.D.**
Fixation Duration (ms)		
Young controls	272.96	50.90
Age-matched controls	268.94	25.82
PCA patients	302.10	85.60
Saccade Amplitude (degrees of visual angle)		
Young controls	5.00	0.93
Age-matched controls	3.68	1.03
PCA patients	3.22	1.38

Figure 4-1 Proportion of fixations inside the young control defined region of interest, by time period. The first fixation is omitted as it is predetermined by a central drift correction at the start of each trial. Error bars show standard error.



4.4 Chapter conclusions

These results confirm previous evidence of significant differences in the fixation patterns of PCA patients and healthy control when viewing scenes. However, the results differ from the previous case studies (Mannan et al., 2009) in that there was no evidence for an increased difference in the location of fixations between patients and controls at later time periods. The comparability of group differences at both initial and subsequent fixations may be consistent with the notion that top-down strategies have an influence upon performance at even the earliest stages of scanning the scene (Foulsham et al., 2011).

The locations of patients' fixations were compared to those of controls using a control-derived region of interest. Using a different metric, (Mannan et al., 2009) have previously reported one PCA patient and one individual with recurrent posterior cortical haemorrhages who showed similar locations of fixation to controls for the first few fixations of each trial, with patients' locations deviating from those that were made by controls at later fixations. They suggested that initial saccades were driven by bottom-up features, and did not differ between patients and saccades, whereas patients' later fixation locations differed from those of controls due to employment of

goal-driven mechanisms. However, an alternative pattern of data in which there was no significant deviation of patient and control fixation patterns between initial and subsequent fixations has also been reported and interpreted as suggesting the involvement of top-down processes from the earliest stages of scene perception (Foulsham et al., 2011). In the present group study, there was no significant interaction between group and time period. These data are more in keeping with those reported by Foulsham et al., and may suggest that PCA patients do engage, or at least attempt to engage top-down strategic control of scanning when presented with an unfamiliar scene. However, it should be noted that a number of patients made fixations to uninformative parts of the scene, without having fixated details that were commonly fixated by controls.

Differences between the task demands in the current task (free viewing) and previous studies (e.g. Mannan et al., 2009, required participants to describe each scene following stimulus presentation) may have contributed to subtle differences between the fixation patterns reported (i.e. the interaction between time period and group found in Mannan et al. but absent in the current study).

Importantly, this investigation demonstrated that systematic differences could be found between PCA patients and healthy controls when viewing scenes. However the extent to which poor eye movement control and/or an inability to follow a successful scanning strategy to elicit the details of the scene contributes to the results remains unclear. A more detailed study of scene perception in PCA patients, taking into account their ability to make saccades follows in the next chapter. Also, whilst one might make inferences about top-down vs bottom-up influences based on the timescale over which differences emerge (as we have done here in emulating Mannan et al., 2009), we have not directly tested these competing influences here. The following chapter builds on these findings, investigating scene perception under different task conditions, and measuring low-level scanpath salience, allowing the effects of top-down goals and bottom up processes to be compared more directly.

5 Reduced modulation of scanpaths in response to task demands in Posterior Cortical Atrophy.

5.1 Chapter introduction

Alfred Yarbus' landmark book *Eye Movements and Vision* brought to wide attention his innovative studies of human eye movement behaviour (Yarbus, 1967; see Tatler et al., 2010). In perhaps the most often-cited experiment, Yarbus presented a participant with Repin's *An Unexpected Visitor* under seven different task conditions (e.g. free examination, remember the clothes worn by the people, estimate the material circumstances of the family in the picture). From this qualitative but nonetheless compelling data, Yarbus concluded '…that the distribution of the points of fixation on an object, the order in which the observer's attention moves from one point of fixation to another, the duration of the fixations, the distinctive cyclic pattern of examination, and so on are determined by the nature of the object and the problem facing the observer at the moment of perception' (Yarbus, 1967, p196). Together with Buswell's (1935) demonstration of the effect of test instructions upon viewing behaviour, Yarbus's work stimulated a continuing controversy over the mechanisms by which low-level image features and higher-level cognitive representations shape the way in which we view and understand the world around us. In the current study, we apply Yarbus' paradigm to individuals with neurodegeneration of the visual cortices (posterior cortical atrophy; PCA) to better understand how these profoundly visually-disabled individuals perceive their environment.

Scene perception involves the acquisition of information from the region surrounding the centre of gaze during brief periods of relative stability (fixation) before gaze is re-oriented to another area of the scene by means of a rapid eye movement (saccade). Two broad classes of explanation have been provided as to how the location of fixations within a scene are determined: low-level image features and high-level knowledge structures. Low-level image features include scene components such as colour, contrast and orientation of edges (Itti & Koch, 2000, 2001; Koch & Ullman, 1985). These low-level features, and more specifically their spatial contrast from the surrounding, can be combined to compute maps that model the low-level salience

across an image (known as saliency maps). High-level knowledge structures (or prior knowledge) can be categorised as short-term episodic scene knowledge (e.g. my cup is currently on my desk), long-term episodic scene knowledge (e.g. my coffeemaker always sits on shelf under the window), scene scheme knowledge (e.g. office computers are typically found on desks) and task knowledge (e.g. changing lanes while driving requires checking the side-view mirror; examples from Henderson, 2011).

Another factor known to affect the location of fixations when viewing pictures is the central fixation bias (Parkhurst et al., 2002; Tatler et al., 2005), by which observers have a tendency to fixate regions of the picture towards the centre of the screen. This has been demonstrated to occur irrespective of task or of the distribution of image features within a scene (Tatler, 2007).

Whilst there is debate about the timing and relative contribution of low- and high-level influences on gaze direction especially during the first few fixations following scene presentation (Foulsham et al., 2011; Mannan et al., 2009), most authors acknowledge that image features and knowledge structures have to be combined. Nonetheless very few studies have addressed the interaction of these factors (see Henderson et al., 2009; Rao et al., 2002; Torralba et al., 2006). In the current experiment we attempted to examine the interaction between high- and low-level influences in two ways. First, by administering a Yarbus-style paradigm (varying task whilst holding image features [scene] constant) to individuals with and without basic perceptual impairment and testing whether the effect of the task given differs between the participant groups. Second, more directly, by examining how participants' scanpaths during different tasks corresponded to saliency maps of the scenes being viewed and testing for differences in the saliency effect across both task and group. Following Yarbus, the same scenes were presented under four conditions: encoding, recognition, search and description. Task selection was guided not only by a need to use simple, easily comprehensible task instructions for the patients, but also because fixation has been tied tightly to memory encoding (Ballard et al., 1995; Nelson & Loftus, 1980) and language production (e.g. Griffin, 2004) as well as visual search as illustrated in the original Yarbus and Buswell experiments. The primary comparison of interest was between search and non-search tasks.

A limited number of studies have examined high-level influences upon scene perception using the Yarbus paradigm. This work has either been concerned with replicating the original single-case observations in a quantitative group study (DeAngelus & Pelz, 2009) or identifying which eye movement parameters are affected by task (in normal participants, task has been found to influence selection of scene regions but not duration of individual fixations; Castelhano et al., 2009). However, comparable studies of task influence upon scene perception in neurological populations are very limited (free viewing versus search in hemispatial neglect patients; Machner et al., 2012). Furthermore, we are unaware of any previous studies which have explored the interaction between high- and low-level influences upon eye movement behaviour during scene perception in neurologically-impaired individuals.

Here we examine influences upon the gaze behaviour of a group of patients with posterior cortical atrophy PCA. The goals of the study were to shed light on the mechanisms by which high level cognitive schemes interact with low level perception, and in doing so to characterise scene perception deficits in PCA. A critical distinction between this study and previous studies employing the Yarbus paradigm was our aim not only to demonstrate task effects upon eye movement behaviour but to examine how the extent and nature of those task effects differed between healthy individuals and two neurodegenerative disease populations (PCA and typical AD). The null hypothesis was that the visual dysfunction observed in PCA would have a uniform effect upon scene perception across search and non-search tasks. The alternative hypothesis was that despite holding perceptual demands constant (same scenes), individuals with varying levels of basic visual dysfunction (grave – PCA; mild – tAD; no deficits - controls) would respond differently to search and non-search tasks.

The interaction between image feature and knowledge-driven control of scene perception was tested directly by comparing the low-level salience of fixated regions between different task conditions.

5.2 Methods

5.2.1 Participants

Data were collected from seven PCA patients, eight patients with typical AD (tAD) and 19 healthy controls, recruited from research cohorts at the Dementia Research Centre, UCL. PCA patients fulfilled standard clinical criteria for PCA (Mendez et al., 2002; Tang-Wai et al., 2004), had a clinical diagnosis of Alzheimer's disease (Dubois et al., 2007, 2010) and scored in the normal range (>5th %ile) on the short Recognition Memory Test for words (sRMT; Warrington, 1996) at the time of assessment. tAD patients (4 male) fulfilled Dubois criteria for AD and scored in the impaired range (<5th %ile) on the RMT for words. An additional eligibility criterion of mild-moderate disease severity (MMSE score greater than 15/30) was applied to both patient groups. This project was approved by the NRES Committee London - Queen Square, according to guidelines established by the Declaration of Helsinki.

5.2.2 Stimuli and procedure

5.2.2.1 Background saccade-gain task

Participants completed a background pro-saccade (visually guided saccade) task to identify basic differences in oculomotor function and provide a saccade-gain covariate for the main scene perception task. A fixation dot subtending 0.4° was presented at the centre of the screen for 500ms, followed by a target stimulus subtending 0.8° for 5000ms or until the target had been fixated for 250ms. Targets were presented at 5° of eccentricity, left, right, up, or down from the fixation dot (8 trials in each direction). In half the trials target onset occurred 200ms after fixation offset (gap condition), and in half target onset occurred 200ms prior to fixation offset (overlap condition). These trials were collected as part of a wider experiment that consisted of a total of 80 trials split over 4 blocks. Each trial was preceded by a centrally-presented fixation point used as a drift correct stimulus, with the trial initiated by the experimenter.

5.2.2.2 Scene stimuli

The stimuli were 30 photographic images of street scenes selected from a readily available dataset (Ehinger et al., 2009; see Figure A-3 in the Appendix). Stimulus

resolution was 800x600 pixels and images subtended a visual angle of 19.5°x14.9° from a fixed viewing distance of 60cm. All photographs were taken from a conventional human perspective with all elements conforming to standard physical (e.g. gravity, space) and semantic (e.g. cars located on roads not on buildings or trees) constraints. Vegetation was selected as the search target (see below) in order to employ perceptually variable targets which could appear in multiple locations anywhere in a scene rather than a homogenous stimulus category whose potential locations were more circumscribed (e.g. faces).

5.2.2.3 Scene Procedure

Scene stimuli were presented under four different task conditions:

1. Encoding: 10 images (scenes 1-10) were presented sequentially. The participant was instructed to remember the photographs.

2. Recognition: The 10 images presented in the encoding task (scenes 1-10) were re-presented, interleaved with 10 novel images which acted as distractors (scenes 11-20). Participants were asked "Did I show you this picture before?' and their responses were recorded. Thus the task comprised 'familiar' (N=10) and 'novel' (N=10) subconditions.

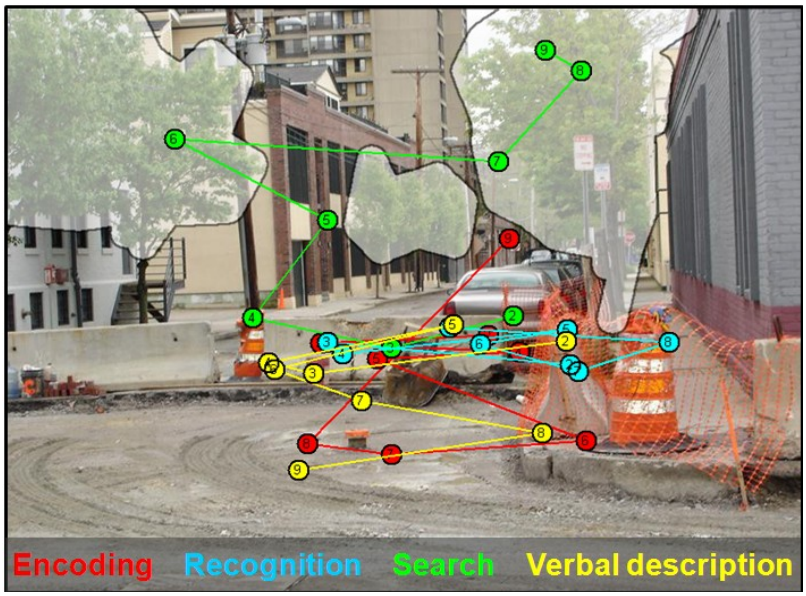
3. Search: Images presented at encoding were presented again together with 10 further novel images (scenes 21-30). The participant was instructed to "look at all the trees, grass and plants; all the vegetation in the scene". As with the recognition task, the task comprised 'familiar' (N=10) and 'novel' (N=10) subconditions.

4. Verbal description. Scenes 1-10 were presented and participants were asked to describe the scene. Owing to the homogeneity of the scenes (all street scenes) most participants offered a description of some or all of the features. Word finding difficulties were evident in most of the patient sample (see background psychology results Appendix Table A-1). For these reasons the content of verbal descriptions was not analysed.

All photographs were presented for 5 seconds each except in the description condition where photographs were presented for 20 seconds. As with the saccade task, each trial was preceded by a centrally-presented fixation point used as a drift correct stimulus, with the trial initiated by the experimenter. Images were presented in a fixed

random order within each task, and tasks were administered to all participants in the same order. Example scanpaths under each of the four different tasks are shown in Figure 5-1.

Figure 5-1 Example scan paths of one healthy participant viewing scenes under different task conditions: encoding (remember the scene), recognition (novel/familiar judgment), search (look at the vegetation), and verbal description (describe the scene). Circles show the location of fixations, and numbers in circles show the serial order of the fixations over time. The highlighted area shows the target-area for the search task.



5.2.3 Apparatus

The saccade-gain and scene tasks were presented on a Dell 2120 desktop computer from a fixed viewing distance of 60cm. Eye movements were recorded using a head-mounted infrared video-based eye tracker (Eyelink II; SR Research, Canada). Gaze position was recorded at 250Hz and corneal reflection was used when possible (17 participants). Fixations and saccades were parsed by the Eyelink system, using standard velocity and acceleration thresholds (30°/s and 8000°/s^2). We used built-in programs provided with the eye tracker for calibration and validation purposes (five points presented in a random sequence). All the data analyzed were obtained from recordings with an average Cartesian prediction error of <1° during the validation procedures. Participants used a chin rest (wide HeadSpot; University of Houston

College of Optometry) to provide stability and maintain viewing distance throughout the experiment.

5.2.4 Pre-processing and analysis

5.2.4.1 Background saccade-gain task

Analysis was carried out on the dominant saccade made towards the target. Data were cleaned to identify this saccade by removing: (i) blinks (using Eyelink's automated blink detection); (ii) saccades made before the target appeared; (iii) saccades in the wrong direction (saccade-target angle discrepancy >45^{o}); (iv) saccades starting >5° from the fixation point. Following this, only the first remaining saccade of each trial was kept. If this saccade was later than the 5th saccade, the trial was removed. As a result, 6.9% of trials were removed in healthy control participants, compared to 6.3% of trials in tAD patients and 9.8% of trials in PCA patients. Linear regression was carried out in STATA to compare amplitude of the dominant saccade between groups, controlling for age. The mean gain of the dominant saccade (saccade amplitude / target amplitude) for each participant was saved for use as a covariate in later analyses.

We also investigated whether the relationship between peak saccade velocity and saccade amplitude (the main sequence) differed between patient groups, by comparing peak saccadic velocity between groups, after controlling for saccade amplitude (amplitude was included a covariate in the linear regression; as in chapter 3).

5.2.4.2 Scene task pre-processing

Before data from the scene task were analysed, saccades identified by the Eyelink system as containing blinks were removed. All analyses excluded the first fixation of each trial (location determined by the pre-trial fixation point). Analyses also excluded the 10th fixation onwards (as per Mannan et al., 2009) leaving fixations 2-9; with the exception of basic saccade amplitude, fixation duration and the measure of proportion of fixations within the target-area, where the data from the first five seconds of each trial were included.

5.2.4.3 Scene task analysis

Linear and logistic regression models (using repeated measures) were employed, with age and saccade-gain from the background saccade-gain task included as covariates of no interest in order to control for their potential influences (except for the analysis of fixation duration and recognition performance which were not corrected for saccade-gain). In the analysis of fixation duration and saccade amplitude, analysis was carried out on the log transformation of the data, and atypical observations for each participant were discarded by excluding observations outside of two standard deviations of each participant group's mean.

The dependent variable in the analysis of performance on the recognition task was the number of items correct (/20). Dependent variables in the analysis of performance on the search task were proportion of fixations in target area and time to first fixation within the target-area. The target-area was manually drawn around the vegetation in each photograph to generate an in/out binary variable (see Figure 5-1). Central fixation bias was examined by comparing the distance of fixations from the centre of the stimulus between groups and conditions. Two further analyses (index of similarity and scanpath saliency) merit more detailed consideration:

5.2.4.3.1 Index of similarity

This analysis used the revised index of similarity metric described by Mannan et al., (2009). This compares the spatial locations of fixations in any two scanpaths, but does not consider the order of fixations. Briefly, for each pair of scanpaths, the combination of unique pairs of fixations that minimizes the average squared distance between fixation pairs is identified, and this is considered in a ratio with the average squared difference between scanpaths of the same observer to two different images. Thus an index of similarity of 0% represents two scanpaths that are only as similar as eye movements made to two different images, whilst an index of similarity of 100% indicates that the two scanpaths had identical fixation locations. A detailed description of the method can be found in the supplementary material of Mannan et al., 2009. The index of similarity metric was used to measure the similarity of each participant's scanpath between repeated presentations of identical photographs under the four tasks (between-task similarity), and the similarity of each participant's scanpaths to

those of every other participant for the same task and picture (between-observer similarity). The between-task similarity metric was calculated for each possible task-pairing of scenes 1-10 (i.e. encoding-recognition, encoding-feature search, recognition-feature search, recognition-description, and feature search-description). Between-observer similarity was calculated both within group (each participant to each other participant in the same group; i.e. PCA vs PCA, tAD vs tAD and control vs control) and between group (each participant from one group to each participant in another group; i.e. PCA vs control, tAD vs control, PCA vs tAD).

5.2.4.3.2 Normalised scanpath saliency

Each photograph was analysed using the graph-based visual salience (GBVS) toolbox (Harel et al., 2007) to generate a low-level salience map (see Figure 5-4). This toolbox was chosen due to its improved prediction over classical algorithms (e.g. Itti et al., 1998). The tool creates three feature maps for each image (representing variation in colour, intensity and orientation), and then combines these feature maps into a master map representing the computed salience at each pixel. These maps were then normalized to have a mean value of 0 and standard deviation of 1 across pixels. The salience of each fixation was extracted and compared between groups and conditions.

5.3 Results

5.3.1 Patient characteristics

PCA patients (two male; Mean [SD] age = 58.9 [6.3] years) were significantly younger than tAD patients (four male; Mean [SD] age = 69.7 [4.7] years; two sample t-test p=0.002), reflecting the fact that PCA is typically an early-onset condition. Healthy control participants (5 male; Mean [SD] age = 63.1 [5.2] years) did not differ significantly in age from the PCA patients (two sample t-test p=0.097) but were younger than the tAD group (p=0.005).

Patient groups were matched for disease duration (mean [SD] PCA = 3.31 [2.0] years; tAD = 4.34 [2.2] years, p=0.34) and MMSE (mean [SD] PCA = 22.6 [2.57]; tAD = 22.6 [4.50], p=0.98). Performance of PCA patients on further neuropsychological tests is presented in the Appendix (Table A-1).

Biomarkers of molecular pathology (amyloid PET scan or CSF sample) were available in 3/7 PCA patients. These were supportive of underlying AD in two cases (see Table 5-1). The remaining case had a CSF profile that was not supportive of AD. CSF was available in 4/8 tAD patients, with a profile supportive of AD in three cases and borderline compatible with AD in the remaining case.

Table 5-1 Molecular pathology biomarkers in scene perception

Diagnosis	PCA	PCA	PCA	tAD	tAD	tAD	tAD
CSF total tau (pg/ml)	787	310	841	289	843	828	800
CSF Aβ 1-42 (pg/ml)	297	488	264	280	129	125	297
CSF Tau:Aβ ratio	2.65	0.64	3.19	1.03	6.53	6.62	2.69

5.3.2 Background saccade-gain task

Mean saccade gain (amplitude of dominant saccade divided by distance of target from central fixation point) was lower in PCA patients (mean [SD] gain=0.75 [0.26]) than controls (0.90 [0.26]; β = 0.16, $t(24) = 2.89$, p=0.007) or tAD patients (0.97 [0.24]; β = 0.25, $t(13) = 3.72$, p=0.002). tAD patients showed a trend towards greater gain than controls (β = 0.09, $t(25) = 1.89$, p=0.07). The abnormalities in saccade gain (reduced in PCA, moderately increased in tAD) justify the inclusion of saccade gain as a covariate in the subsequent analyses.

There was no difference saccade peak velocity (having accounted for saccade amplitude) between the healthy controls and PCA patients (β = 8.97, $t(24) = 0.53$, p=0.60), or between the PCA and tAD patients (β = 23.95, $t(13) = 1.22$, p=0.23), although the typical AD patients showed increased peak velocity compared to the healthy controls (β = 32.92, $t(25) = 2.70$, p=0.01).

5.3.3 Scene task - global eye movement measures

5.3.3.1 Fixation duration

PCA patients (mean=272.0ms, SD=35.9ms) did not differ from controls (mean=261.6ms, SD=24.1ms) β = 0.02, *t*(24) = 0.35, p=0.73) or tAD patients (mean =287.6ms, SD=31.9ms; β = 0.09, *t*(13) = 1.25, p=0.22) in terms of fixation duration. However there was a trend towards longer fixations in the tAD group than control group (β = 0.11, *t*(25) = 2.00, p=0.054). Further analysis showed that tAD patients had significantly longer fixations than controls for the non-search tasks (encoding, recognition, description; p=0.03) but not for the search task (p=0.16).

5.3.3.2 Saccade amplitude

Controlling only for age, the amplitude of saccades made by PCA patients when viewing scenes (mean = 2.73^{o}, SD = 1.83^{o}) was less than controls (mean = 3.48^{o}, SD=2.44^{o}; β = 0.21, *t*(24) = 4.16, p<0.001) and tAD patients (mean = 3.60^{o}, SD=2.32^{o}; β = 0.28, *t*(13) = 4.37, p<0.001). tAD patients did not differ significantly from controls (β = 0.07, *t*(45) = 1.25, p=0.22). When controlling for age and saccade gain, PCA patients' saccades remained significantly shorter than those of controls (β = 0.10, *t*(24) = 2.15, p=0.04), but did not differ significantly from tAD (β = 0.11, *t*(13) = 1.52, p=0.14); tAD patients and controls remain not significantly different (β = 0.003, *t*(25) = 0.05, p=0.96).

5.3.3.3 Central fixation bias

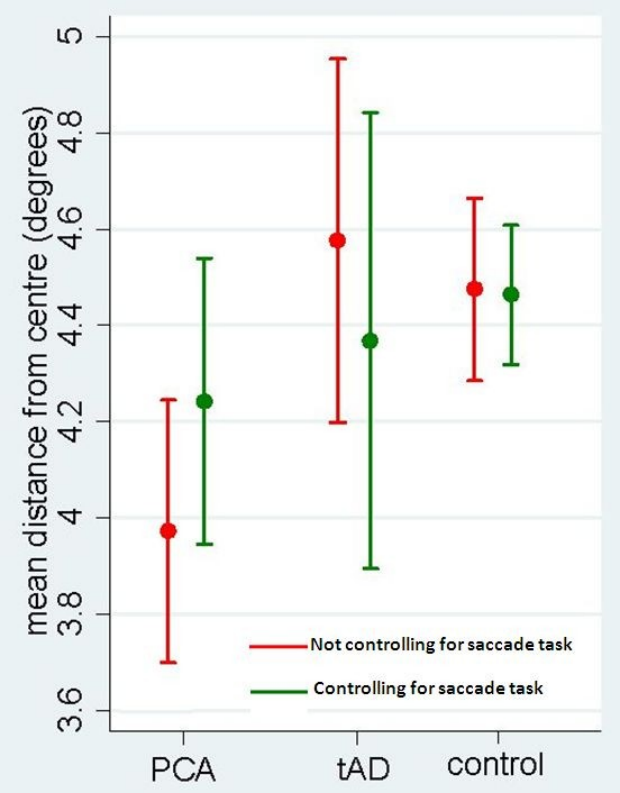
Controlling only for age, PCA patients' fixations remained significantly closer to the centre of the scene images compared to tAD patients (β = 0.64, *t*(13) = 2.53, p=0.02) and there was a a similar effect relative to controls (β = 0.527, *t*(24) = 3.03, p=0.005). There was no difference in central fixation bias between tAD patients and controls (β = 0.11, *t*(25) = 0.52, p=0.61).

However, when controlling for saccade gain in the background task, these group differences between PCA and tAD (β = .17, *t*(13) = 0.48, p=0.63) and PCA and controls (β = 0.25, *t*(24) = 1.34, p=0.19) were no longer significant (see Figure 5-2). This indicates that it may be important to obtain an independent measure of saccade gain as a covariate that can be controlled for in future tests.

5.3.3.4 Recognition task

PCA (mean proportion correct=0.81, SD=0.12) and tAD patients (mean=0.81, SD=0.14) showed poorer performance than controls (mean=0.98, SD=0.04) in the familiar/novel discrimination of the recognition task (PCA vs control OR = 0.11, z = 4.43, p<0.001; tAD vs control OR = 0.11, z = 4.34, p<0.001). The performance of PCA patients and tAD patients did not differ significantly (OR = 0.99, z = 0.03, p=0.98; see Discussion for different explanations of scene recognition in these two groups).

Figure 5-2 Central fixation bias measured as the mean distance of fixations from the centre of the screen, both controlling (green) and not controlling (red) for saccade-gain. Bars show 95% confidence intervals.

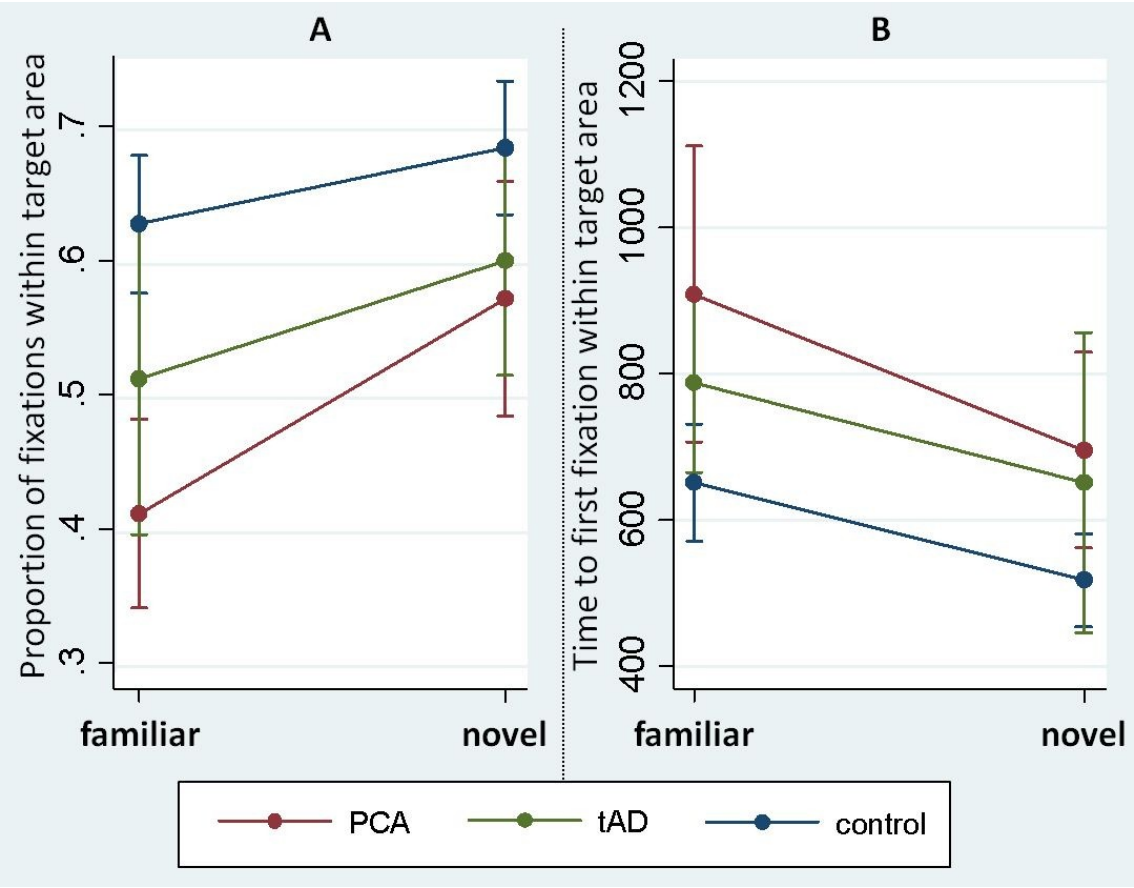


5.3.3.5 Search task

PCA patients performed poorly in the search task, with a lower proportion of fixations in the target area (mean=0.50, SD=0.08) than the control group (mean=0.66, SD=0.11; OR = 2.42, *z* = 4.08, p<0.001). tAD patients (mean=0.55, SD=0.10) also showed a non-significant trend towards a lower proportion of fixations within the target area than controls (OR = 0.62, *z* = 1.87, p=0.07). The PCA and tAD groups did not differ from one another significantly (OR = 1.51, *z* = 1.21, p=0.22). However, there was a significant interaction between the effects of group and novelty (p=0.004; see Figure 5-3); PCA patients showed a greater relative impairment when searching familiar as compared with novel scenes for the target 'vegetation', suggesting reduced benefit from previous exposure to and memory for the (familiar) scenes. There were also significant differences between groups in the time taken to make the first fixation in the target-area, with PCA patients much slower (mean=845ms, SD=182ms) than controls (mean=586ms, SD=144ms; β = 257.21, *t*(24) = 2.30, p=0.03), and tAD patients

(mean=680ms, SD=154ms) showing a trend towards slower performance than controls (β = 135.96, *t*(25) = 1.81, p=0.08). PCA and tAD groups were not significantly different (β = 121.25, *t*(13) = 0.98, p=0.34). Unlike the search accuracy data, there was no evidence for an interaction between group and novelty in the search timing data (p=0.75).

Figure 5-3 Performance in the search task in terms of proportion of fixations within the target-area (A) and time taken to make the first fixation within the target-area (B). Bars show 95% confidence intervals.



5.3.3.6 Between-task similarity

Between-task similarity measures the similarity of two scanpaths made by the same participant to identical scenes presented under different tasks (see Figure 5-1 and Figure 5-4 for example scanpaths, and Figure 5-5A for means and CIs). In the comparisons of *non-search tasks* (e.g. recognition vs description), PCA patients showed significantly lower scanpath consistency than controls (β = 15.85, *t*(24) = 2.79, p=0.009) or tAD patients (β = 18.87, *t*(13) = 2.23, p=0.03). Control participants and tAD patients

did not differ in scanpath -consistency between non-search tasks (β = 3.02, *t*(25) = 0.49, p=0.63). However, when comparing *search and non-search tasks* (e.g. search vs recognition); controls demonstrated a task-appropriate difference in scanpaths (reflected in zero consistency – similar to consistency between different scenes) that was not observed in either of the patient groups; PCA patients showed a trend towards *higher* scanpath consistency than controls (β = 28.56, *t*(24) = 1.76, p=0.09) and tAD patients showed significantly *higher* consistency than controls (β = 32.42, *t*(25) = 2.34, p=0.03;) (see Figure 5-5 illustrating between-task similarity for these comparisons). There was no significant difference between PCA and tAD patients (β = 3.87, *t*(13) = 0.17, p=0.87). These results demonstrate that controls completely modulate their scanpaths in a search task – but PCA and tAD patients do not. Overall, there was a significant interaction (p=0.006) between group and comparison type (non-search/non-search vs search/non-search), reflecting the greater, task-appropriate modulation of controls' scanpaths when viewing scenes under different task demands.

5.3.3.7 Between-observer similarity

Between-observer similarity measures the similarity of scanpaths made by all the participants of each group when confronted with the same scenes under the same task conditions. Across both the non-search tasks and search tasks (see Figure 5-5B for means and CIs), there was significantly lower scanpath similarity among PCA patients than among either controls (β = 20.82, *t*(24) = 3.45, p<0.001 for search, β = 23.53, *t*(24) = 7.88, p<0.001 for non-search) or tAD patients (β = 42.90, *t*(13) = 5.66, p<0.001 for search and β = 18.56, *t*(13) = 4.95, p<0.001 for non-search). Typical AD patients showed a much smaller but still significant difference in scanpath similarity to controls on non-search tasks (β = 4.97, *t*(25) = 2.61, p=0.01) but showed significantly greater scanpath similarity on the search task (β = 22.08, *t*(25) = 5.43, p<0.001). There were also significant overall (all three groups) and pairwise group by condition (search vs nonsearch) interactions (overall p<0.001, PCA vs tAD p=0.004, tAD vs healthy controls p<0.001), and a trend towards a significant interaction in the PCA vs healthy control comparison (p=0.054). These results suggest (i) much greater variability in gaze behaviour among PCA patients, (ii) a further discrepancy between PCA and tAD performance with tAD scanpath similarity rates differing by a lesser extent on the non-

search tasks, and (iii) controls' task-appropriate response to the search task leading to idiosyncratic scanpaths as participants fixate multiple target areas in different regions from one another – consistent with the between-task similarity findings.

5.3.3.8 Low-level salience (normalized scanpath saliency)

Normalised scanpath saliency was calculated using the low-level salience maps generated for each scene (see Figure 5-4). PCA patients fixated on more salient regions (mean salience=1.02, SD=0.09) than controls (mean=0.92, SD=0.08; β = 0.09, $t(24) = 2.29$, p=0.03); tAD patients (mean=0.97, SD=0.12) showed an intermediate tendency to fixate high salience regions, not significantly different from that of PCA patients (β = 0.03, $t(13) = 0.43$, p=0.67) or controls (β = 0.06, $t(25) = 0.93$, p=0.36; see Figure 5-5). There was no group by task (search vs non-search) interaction, suggesting the salience effect did not depend on the task condition under which the scene was viewed (see Figure 5-5).

Figure 5-4 Scanpaths and salience maps. Example scanpaths from two healthy controls (A and B) and two PCA patients (C and D) demonstrating greater modulation of the scanpath for the search task (green) compared with a non-search task (encode; red) in controls than patients. The between-task similarity is abnormally high for patients (C=83%; D=84%) relative to controls who view different parts of the scene in a more task-appropriate manner (A=-17.7%; B=-60.5%). The highlighted area shows the search target area (all vegetation). Panels E and F show example computer generated low-level salience maps. Low-level salience maps were created using the GBVS toolbox (Harel et al., 2007) with default settings. The tool creates three feature maps for each image (representing variation in colour, intensity and orientation), and then combines these feature maps into a master map representing the computed salience at each pixel. These maps were then normalized to have a mean value of 0 and standard deviation of 1 across pixels. The salience of each fixation was extracted and compared between groups and conditions.

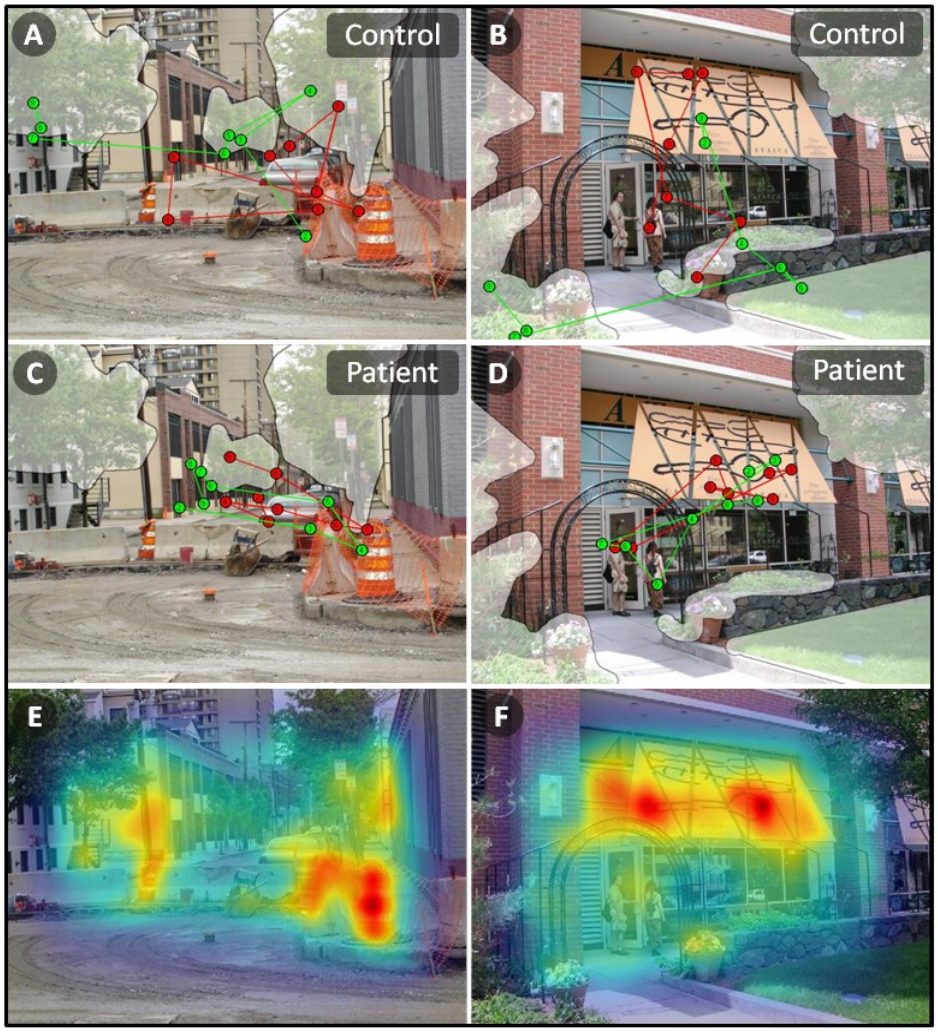
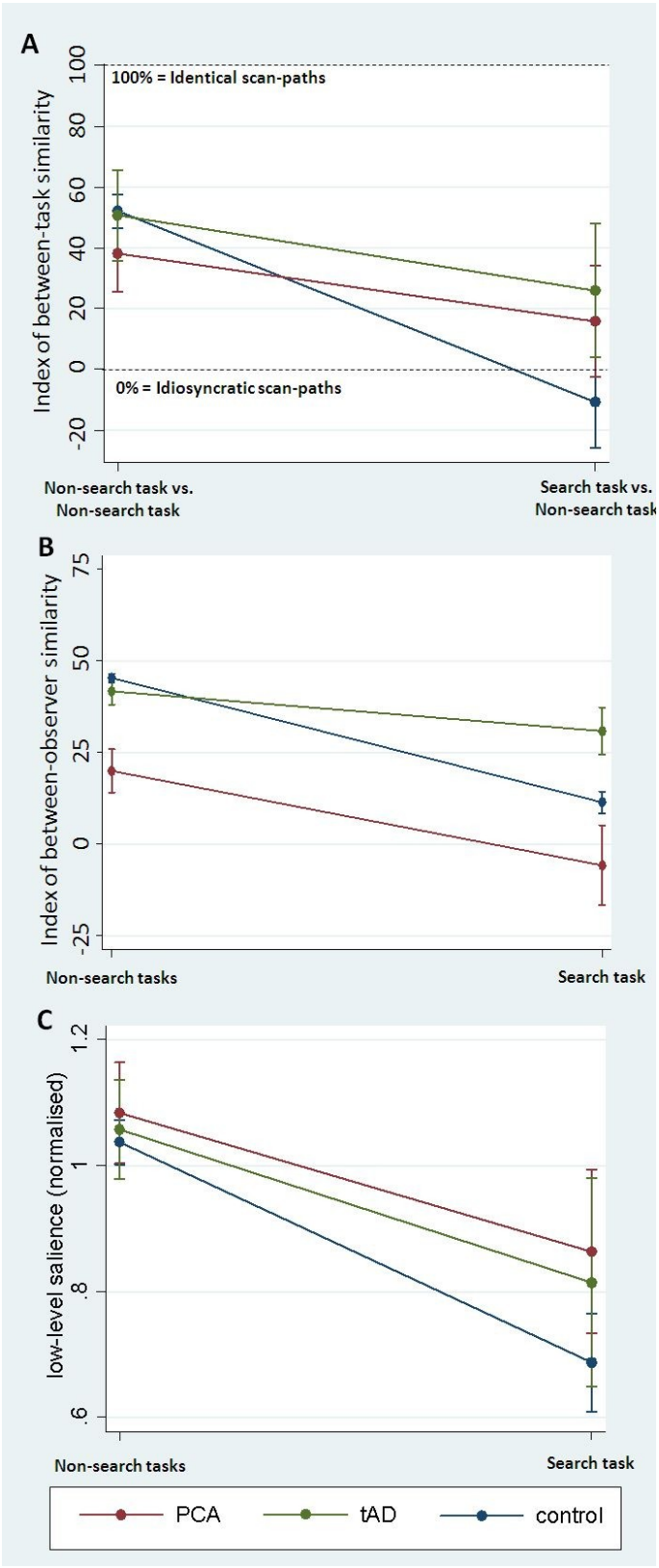


Figure 5-5 Search task vs non-search task performance in terms of (A) the between task similarity (B) the similarity of scanpaths between participants in the same participant group (between-observer similarity) and (C) scanpath salience. Bars show 95% confidence intervals.



5.4 Chapter conclusions

The current study examined cognitive influences upon scene perception by adapting Yarbus' classic paradigm for use with individuals with progressive visual impairment associated with posterior cortical atrophy. Patients' capacity to adapt their eye movement behaviour was tested by viewing scenes under four types of task instruction: encoding, recognition, search and description. Overall PCA patients showed reduced saccade amplitude and gain relative to tAD patients and controls, hence all subsequent analyses were corrected for saccade gain to permit us to explore cognitive influences upon scene perception distinct from discrepancies in basic oculomotor function. Notably tAD patients showed significantly longer fixation durations than controls, but PCA patients showed no such increase. On the search task PCA patients' fixations fell less frequently and more slowly upon targets and there was evidence of an enhanced central fixation bias related to their reduced saccade gain (disappeared when saccadic gain was controlled). PCA patients also exhibited greater difficulty searching for the target 'vegetation' in familiar compared with novel scenes. The other three non-search tasks (encoding, recognition and description) contributed primarily to the between-tasks analysis; however it was noted that both PCA and tAD patients showed significantly impaired scene recognition relative to controls which we attribute primarily to poor perception in the PCA group and poor memory in the tAD group given that absence/presence of memory dysfunction formed part of the participant selection criteria.

On the main examination of the effect of test instructions upon scene perception, the results revealed significant differences between the three groups. These differences were most evident when comparing the search task with the other non-search conditions. Across tasks without a search component, PCA patients exhibited lower between-task and between-observer similarity ratings than tAD patients and controls (i.e. were less consistent in where they were looking). By contrast, when comparing search and non-search tasks, it was controls who exhibited the lowest between-task similarity ratings, suggesting they were much better able than PCA or tAD patients to respond appropriately by looking at different target regions of the scene that were relevant to the current task. However, PCA patients continued to show the lowest

between-observer similarity ratings suggesting more varied, inconsistent performance among these individuals. These differences were reflected in significant group by task interaction effects. PCA patients also had a significant tendency to fixate upon more salient parts of the scenes than controls irrespective of the viewing task.

The research objectives of this study of naturalistic scene perception in posterior cortical atrophy were reciprocal. Understanding task-related effects upon these patients' viewing behaviour sheds light on the mechanisms by which high level cognitive schemes interact with low level perception. On the other hand, the experimental manipulations also help us to better understand how PCA patients perceive the real world, and to explain some of the characteristic features and inconsistencies of their everyday perception. These two complementary goals are considered in more detail below.

5.4.1 High- and low-level influences on scene perception

Scene perception is a complex process in which eye movements are influenced by knowledge structures (top-down control), image features (bottom-up processes) and the interaction between these mechanisms. The experimental paradigm used in the current study was designed to manipulate knowledge-driven control whilst holding image features constant. The pattern of results obtained (as outlined above) suggest that PCA patients exhibit a loss of the capacity to adapt their eye movement behaviour to current task demands. The fact that this loss of task-appropriate adaptation was most evident when contrasting search with non-search tasks may indicate that PCA patients have greater difficulty engaging particular more active modes of real-world scene perception relative to more passive viewing conditions. The loss of the capacity to adapt eye movement behaviour to current task demands is unlikely to be explained by basic oculomotor dysfunction (because saccade gain was controlled for, and all between-task comparisons employed a within-subjects design), failure to understand the test instructions (which were simplified from the original Yarbus paradigm), stimulus properties (as the identical scenes were viewed under each task condition), or a non-specific 'dementia' effect (as PCA performance diverged from that of typical AD patients in a number of respects).

Although the primary experimental manipulation was of task knowledge (i.e. test instructions), other forms of knowledge are known to influence eye movement control. These include scene schema knowledge (e.g. vegetation is usually at the edge rather than centre of carriageways) and short-term episodic scene knowledge (e.g. the tree was in the top left corner; see Henderson & Ferreira, 2004). PCA patients' well-preserved semantic knowledge of the world means there is no reason to suspect deficits in scene schema knowledge. However, short-term episodic scene knowledge may well have been compromised by a combination of factors including visuoperceptual and visuospatial deficits (see background neuropsychology in the appendix [Table A-1]); leaving an unreliable or incomplete trace of feature identity and location within the scene. Such an impairment of short-term episodic scene knowledge could account for several features of the PCA patients' performance, including the significant increase in time taken for PCA patients to fixate within a target area for the first time during the search task. As the search task was the third task administered, participants had two prior opportunities (during encoding and recognition) to view the (familiar) scenes and to construct a short-term episodic trace of the scene which, for controls, could support the rapid re-fixation of task-relevant target areas. This argument is strengthened by the particular disparity of the proportion of fixations in target areas between PCA patients and both controls and tAD patients when searching familiar scenes (for which a short-term episodic trace would have been established) relative to novel scenes (for which no such trace was available).

Finally, a better understanding of the interactions between knowledge-driven and image feature control of eye movements remains a critical area in eye movement research. Although the current experiment was designed to hold image features constant by means of the comparison of task performance across identical scenes, a computer-based image saliency map was used to probe for any differences in saliency-biases across different viewing tasks. However, no statistical interaction was found between the salience of image features and the task demands (PCA patients showed a greater tendency to focus on high salience regions irrespective of task). Whilst this result may simply reflect the primacy of basic visual function in determining PCA patients' scene perception, the current paradigm could be adapted to involve two search tasks in which the salience or other visual properties of the targets are varied.

5.4.2 Real-world scene perception in PCA

Despite visual dysfunction being the primary feature of the PCA syndrome, there is very little understanding of how individuals with the condition actually perceive the world. The current study provides evidence that PCA scene perception is characterized (in contrast to controls) by saliency-dependence, a reduced ability to fixate task-relevant areas and reduced consistency between observers. In particular, two features of the observed performance may help explain why patients and carers frequently report variability and inconsistency in everyday vision (e.g. completely failing to perceive the saltcellar on the table in front of them when asked to pass the salt, and then picking up and using it appropriately soon after). First, between-task consistency of fixations and scan paths was abnormally high, reflecting inability to adjust flexibly to environmental contingencies. Some goal-oriented or externally-directed conditions (e.g. actively searching for a particular object) may place much heavier demands on this capacity than other more passive or self-directed conditions (e.g. observing the object during free-viewing). Second, between-observer consistency was abnormally low; this may be because inconsistencies in the basic visual processing of item features leads to the formation and retrieval of distorted or irrelevant higher level scene schema.

A detailed functional account of PCA patients' real-world perception as it relates to everyday tasks is critical for improving clinical management. One clinically-relevant extension of the current study would be to progress from scene pictures to more naturalistic settings in which the influence of not only external test instructions but the behavioural goals of the observer can be examined. Analyses of eye movements during naturalistic actions (e.g. making a sandwich, driving, playing cricket) have revealed the crucial role of prior knowledge (see Hayhoe & Ballard, 2005 for a review). Whilst we have assumed that scene schema knowledge for the simple tasks and static scene photographs in the current study (e.g. knowing grass is more likely to be found on the ground than on walls) is relatively preserved, it remains to be seen whether relevant prior knowledge is available or can be successfully transformed into computations for the planning and guidance of eye movements in more dynamic situations (e.g. anticipating the bounce point of a ball, or the moment of contact when reaching out to grasp a door handle). Understanding patients' perception of naturalistic settings rather

than scene depictions will also involve consideration of a wider range of eye movements and control circuits (e.g. the predictive component of the pursuit system; Barnes & Collins, 2008; Tabata et al., 2008). Better appreciation of gaze control mechanisms in natural vision will form a critical basis for attempts to develop strategies and aids to reduce the widespread impact of dementia-related visual dysfunction upon activities of daily living and quality of life not just in PCA but in typical Alzheimer's disease and Dementia with Lewy Bodies more generally.

6 A carer questionnaire in Posterior Cortical Atrophy

6.1 Introduction

The presenting features in PCA are quite different from the episodic memory impairments for recent events typically seen in Alzheimer's Disease. Early clinical symptoms include difficulties with reading, locating objects, or judging distance often resulting in problems when driving. Other skills that rely on parietal and occipital function such as spelling and calculation can also be impaired early. In contrast to these impairments, people with PCA tend to have relatively preserved insight and episodic memory. This characterisation of PCA has been informed by clinical experience, clinical studies, and neuropsychological investigations, but there has been very little work to directly compare PCA and tAD patients over a wide range of symptoms and stages of disease, or to relate the cognitive changes observed in PCA directly to their impact upon the everyday lives of patients and carers.

There are a number of difficulties in assessing symptoms in people at later stages of the disease. Often, neuropsychological testing becomes unsuitable even in the moderate stages, and as symptoms become more severe and mobility becomes more difficult, it is not feasible for patients to attend a research centre. In these circumstances, a carer questionnaire provides a good opportunity to assess a wide range of symptoms and behaviours, and allows data to be collected for a longer period of time, giving potential to improve our understanding of disease progression in the moderate and severe stages of PCA.

One carer questionnaire, the Cambridge Behavioural Inventory (CBI) is well suited to address this problem. It has domains addressing a wide range of cognitive functions, neuropsychiatric symptoms and everyday skills, and has been used in a number of previous studies to discriminate between different dementias. Distinct CBI profiles have been demonstrated for Parkinson's disease, Huntington's disease, Alzheimer's disease and behavioural variant frontotemporal dementia (Wedderburn et al., 2008). The CBI has high test-retest reliability (Nagahama et al., 2006), and there is a good correlation between the neuropsychiatric items of the CBI and the neuropsychiatric inventory (Cummings et al., 1994). The original CBI has been revised to retain the most

informative questions for a comparison of typical Alzheimer's disease with frontotemporal dementia (Wear et al., 2008). This shorter revised questionnaire (named the CBI-R) has 45 rather than 81 questions.

The CBI and CBI-R do not fully meet the requirements for a questionnaire in PCA, as there are a number of cognitive domains that we know to be affected in PCA which are not included in the questionnaire. Visual perception and understanding of quantity are both known to be affected in PCA, and we therefore added domains with questions assessing these symptoms. We also know that some PCA patients develop language impairments (Crutch, Lehmann, et al., 2013) and motor symptoms (e.g. myoclonus and limb rigidity, see motor symptoms chapter of this thesis) so added questions to address these domains.

A very frequently asked question by patients and carers regards the staging of PCA – they want to know how quickly symptoms are likely to develop and spread to other cognitive domains, and what level of care will be needed at different stages of the disease. Recently, attempts have been made to provide and validate this kind of predictive information (Razlighi et al., 2013), raising the possibility of giving carers better information about time to death, institutionalization and need for full-time care. This information is valuable as it can be used to plan changes in financial and living arrangements and we are keen to develop a similar approach for patients with PCA.

In this chapter we investigate whether the CBI-R can discriminate between tAD and PCA, allowing us to investigate whether the features identified by systematic survey match those often described from clinical experience. We also extend the CBI to include further domains (e.g. vision and language) revealing how patterns of cognitive and oculomotor differences between PCA and tAD are reflected in their independence and difficulties in everyday function.

6.2 Methods

6.2.1 Participants

PCA and tAD patients met the respective clinical criteria (Dubois et al., 2007, 2010; Mendez et al., 2002; Tang-Wai et al., 2004). Whilst all PCA patients were recruited at the Dementia Research Centre, data for the tAD group was obtained from two centres

in order to improve sample size (Dementia Research Centre, UCL and the Hodges group, Neuroscience Research Australia). Participants without a contemporary MMSE score (within 1 year of the questionnaire), with a very low MMSE (5 or less), or for whom disease duration information was not available, were removed from the analysis. The project was approved by the NRES Committee London - Queen Square. The CBI-R was completed by a relative or carer of the patient.

The PCA patients (N=32) and the tAD patients (N=71) were matched for age (mean [SD] PCA: 64.7 [8.3] years; tAD: 67.3 [7.5] years, p=0.11) and disease duration (mean [SD] PCA: 4.5 [2.0] years; tAD: 4.3 [2.3] years, p=0.72) but the PCA patients had lower MMSE scores on average (mean [SD] PCA 16.4 [4.8], tAD 21.6 [5.1], p<0.001).

6.2.2 Extension of the questionnaire

After consultation with an expert neuropsychologist and neurologist (SC and NR), new items were added to the CBI in the following categories; movement and body, language, vision/space, and quantity. These additional questions are listed in the Appendix (Table A-2). The intention was to increase the range of symptoms assessed by the questionnaire to include symptoms that might be expected to be present in people with PCA. The extended CBI was administered only to the PCA patients (N=32) and tAD patients (N=21) at the Dementia Research Centre.

Whilst the two DRC patient groups were matched for disease duration (PCA mean [sd] 4.5 [2.0]; tAD 5.7 [2.2]; p=0.053) they were not matched for MMSE (PCA 16.4 [4.8], tAD 20.67 [5.5]; p=0.005) or age (PCA 64.7 [8.3], tAD 69.3 [6.3] p=0.034). The difference in age partially reflects the tendency of patients with atypical phenotypes to have an earlier age at onset.

6.2.3 Data analysis

The questionnaire was given to a friend or relative of each patient, who was asked to respond to each item of the questionnaire by marking whether the behaviour occurred never (0), a few times per month (1), a few times per week (2), daily (3), or constantly (4). For everyday skills and self care, an alternative scale was used: completely independent (0), only prompting needed (1), mild assistance required (2), moderate assistance required (3), or complete help required/completely unable (4). A score of 3

or 4 for an item was categorised as severe. Logistic regression was carried out on the severe/not severe categorisation (to replicate the analysis techniques used in previous studies of the CBI; Wear et al., 2008, Wedderburn et al., 2008), and included age, MMSE, gender and disease duration as covariates, with patient group the independent variable. Separate analyses were carried out at the domain level and the single item level.

Looking at all items in all participants, approximately 2% of data was missing (no response or marked 'not applicable'). Where one or more responses were present within a domain, the value of a missing item was imputed as the mean of the items that were present for that domain.

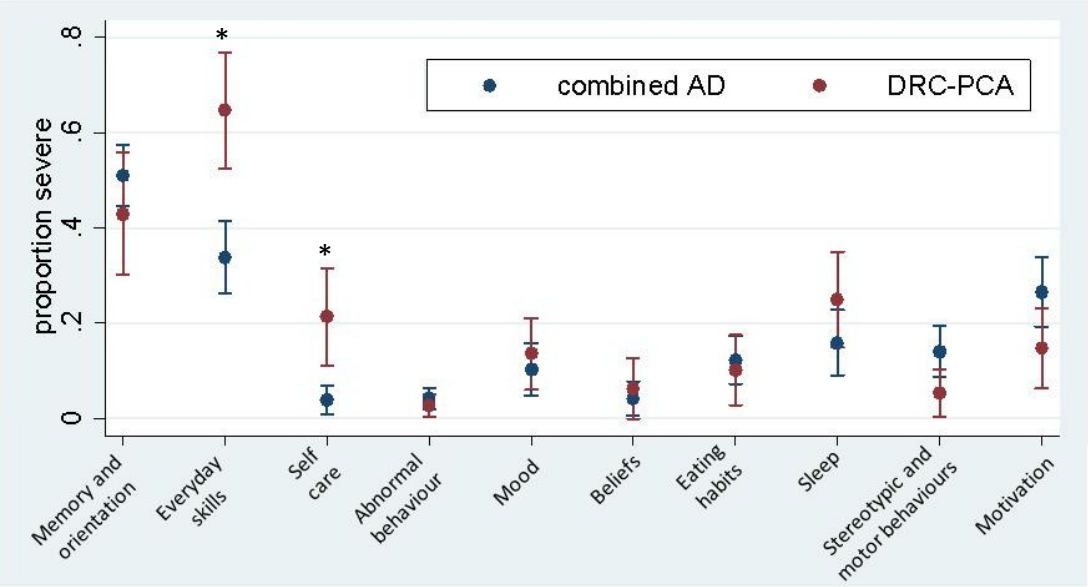
6.3 Results

6.3.1 CBI-R

PCA patients were more severely impaired than the combined tAD group in domains of everyday skills (mean proportion severe PCA=65%, tAD=34%; $\chi^2(1, N=103) = 15.48$, $p<0.001$, odds ratio = 3.79) and self-care (mean PCA=21%, tAD=4%; $\chi^2(1, N=103) = 12.45$ $p<0.001$, odds ratio = 7.01), whilst the tAD group show a trend to greater impairment in stereotypic and motor behaviours (mean PCA=5%, tAD=14%, $\chi^2(1, N=103) = 3.73$, $p=0.053$, odds ratio = 0.34), and motivation (mean PCA=15%, tAD=27%, $\chi^2(1, N=103) = 3.35$, $p=0.067$, odds ratio = 0.46). The majority of domains in which there was no group difference were not severe in either group, with the exception of memory and orientation, in which both groups had relatively high but similar severity (see Figure 6-1 for means and confidence intervals). Applying the Bonferroni correction raised the statistical threshold to $p<0.005$, and therefore the differences in the domains of everyday skills and self-care remained statistically significance.

In the analysis of individual items, 12 items showed significant differences between groups (see Table 6-1). Of these items, the tAD group had more severe deficits than PCA patients in three – two were from the memory domain, the other from motivation. Applying the Bonferroni correction raised the statistical threshold to $p<0.0011$; at this threshold only difficulties with writing and difficulties dressing remained significantly different between patient groups.

Figure 6-1 Mean proportion of severe deficits in each domain of the CBI-R in the combined AD and the PCA patient groups. Bars show 95% confidence intervals. Notable differences are more severe deficits in everyday skills and self care in PCA patients, and a trend towards more severe deficits in stereotypic and motor behaviour, and motivation in tAD patients. Significant group differences are indicated with an asterisk.



6.3.2 Extended CBI (DRC data only)

We also analysed results from the additional categories we added to the CBI (see Figure 6-2). PCA patients had more severe deficits in the 'vision/space' domain (mean PCA = 52%, tAD = 25%; $\chi^2(1, N=53) = 8.09$, p=0.003, odds ratio = 3.61), and the 'quantity' domain (mean PCA = 62%, tAD = 34%; $\chi^2(1, N=53) = 5.45$, p=0.014, odds ratio = 3.49), but the groups did not differ in the movement and body domain (mean PCA = 17%, tAD = 10%; $\chi^2(1, N=53) = 1.56$, p=0.157, odds ratio = 2.02) as severe impairment was not frequent in either group, or language domain (mean PCA = 33%, tAD = 32%, $\chi^2(1, N=53) = 0.02$, p=0.771, odds ratio = 1.16), where both groups had a moderate proportion of severe impairment. None of the additional domains remained significant after Bonferroni correction for multiple comparisons.

In an item-level analysis, 6 questions in the vision/space and quantity domains showed significantly more severe impairment in PCA than tAD, as shown in Table 6-1. No individual items remained significantly different between groups after Bonferroni correction.

Figure 6-2 Mean proportion of severe deficits in domains added to the CBI for the DRC-AD and DRC-PCA groups. Bars show 95% confidence intervals. The vision and quantity domains are more severe in PCA than tAD.

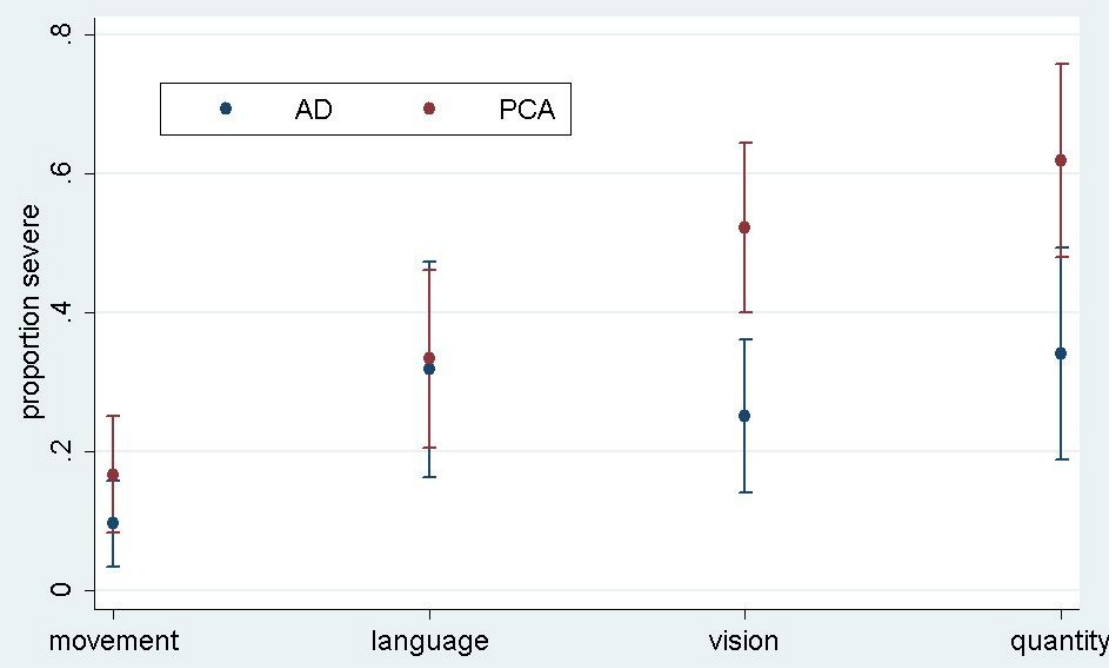


Table 6-1 Individual item analysis. A: Individual items in the CBI-R. B: Individual items added to the CBI, in which there was a significant difference between the PCA and tAD groups. Domains coloured red denote PCA worse than AD, blue denotes AD worse than PCA. Comparisons that survived Bonferroni correction for multiple corrections are indicated with an asterisk.

A. CBI-R individual items

Domain	Question	p-value
Everyday skills	Has difficulties writing (letters, Christmas cards, lists etc.)	<0.001*
Self care	Has difficulties dressing self	<0.001*
Everyday skills	Has difficulties using the telephone	0.002
Everyday skills	Has difficulties making a hot drink (e.g. tea/coffee)	0.003
Memory and orientation	Has poor day-to-day memory	0.007
Everyday skills	Has problems handling money or paying bills	0.007
Memory and orientation	Asks the same questions over and over again	0.014
Sleep	Sleeps more by day than before (cat naps etc.)	0.020
Everyday skills	Has difficulties using electrical appliances	0.025
Motivation	Fails to maintain motivation to keep in contact with friends or family	0.034
Eating habits	Table manners are declining e.g. stuffing food into mouth	0.035
Self care	Has problems bathing or showering self	0.042

B. Additional individual items from extended questionnaire (DRC participants only)

Domain	Question	p value
Vision / space	Has difficulty reading	0.002
Quantity	Has difficulty using and understanding numbers	0.009
Quantity	Has difficulty estimating volume or size	0.019
Vision / space	Has difficulty locating objects that are right in front of them	0.025
Vision / space	Has difficulty perceiving distances and depth	0.027
Vision / space	Has difficulty identifying objects	0.049

6.4 Chapter conclusions

This pilot study demonstrates the ability of the CBI-R to differentiate between typical AD and posterior cortical atrophy, with PCA patients showing greater impairment in everyday skills and self-care whilst the tAD group trend towards greater impairment in stereotypic and motor behaviours, and motivation. In the additional questions developed to extend the CBI, PCA patients showed more severe impairments in vision/space and understanding of quantity, whilst both groups showed moderate but similar levels of impairment in language.

It is notable that the groups did not differ in the memory and orientation domain of the CBI-R, with both patient groups showing a relatively high proportion of severe deficits, compatible with previous findings in the CBI-R with typical AD patients (Wedderburn et al., 2008). One would expect PCA patients to have relatively preserved memory due to the clinical criteria for PCA (Mendez et al., 2002; Tang-Wai et al., 2004), however their high score may be explained by the fact that the memory and orientation domain included behaviours such as losing or misplacing objects and becoming confused in unusual surroundings, which could result from visual deficits rather than memory deficits. This explanation is consistent with the finding in the individual item analysis that two memory related items in the memory and orientation domain (poor day-to-day memory, asks the same question over and over again) were more severely impaired in tAD than PCA, as would be expected.

Our study also points towards relatively spared motivation in PCA; maintaining enthusiasm and interest in activities and contact and affection with family members. This may relate to what carers describe as a maintained sense of purpose, and in this sense there may be parallels between the PCA patients in this study, and patients with Parkinson's disease who also showed less severe deficits than typical AD patients in the motivation domain of the CBI-R (Wedderburn et al., 2008). Differences in motivation between PCA and typical AD have not previously been investigated. Patients with typical AD are noted to have high scores in assessments of apathy (Landes et al., 2001; Robert et al., 2002) which is likely to relate to motivation as probed in the current study. The results from this study suggest that PCA patients may not show such apathy, and whilst the effects are not large, they warrant assessment

using more detailed measures of this symptom. The association of apathy in Alzheimer's disease with frontal atrophy (Apostolova et al., 2007) provides further indirect evidence suggesting that apathy may be not be as important a feature in PCA compared to tAD (given the relative sparing of frontal cortices in PCA). PCA patients also showed a trend towards less severe impairments in another frontal domain; stereotypic and motor behaviours. Frontal variant fronto-temporal dementia patients score highly in this domain (Wedderburn et al., 2008) which includes items such as fixed ideas, rituals and hoarding. The lower scores in PCA patients likely reflect relatively spared high-order cognition and executive function.

The additional questions that were added to the CBI in the domains of 'vision and space' and 'quantity' proved informative as they revealed further differences between the PCA and tAD groups, whilst moderate deficits in the 'language' domain in both groups suggests an area of commonality. Although the finding that PCA patients are more impaired in behaviours requiring use of vision or number understanding is far from novel (see Crutch et al., 2012 review), this addition to the questionnaire allows further comparison to typical AD to be made. The additional movement domain, addressing symptoms such as shaking (aimed at picking up tremor or myoclonus), slowness, and stiffness did not reveal differences between groups, and only a low proportion of patients had severe deficits in this domain. A detailed study of PCA patients who show motor symptoms is presented in the next chapter.

We hope that extending the questionnaire to these domains will also allow us to capture the wide spectrum of phenotypes in early onset Alzheimer's disease (Migliaccio et al., 2009; Ridgway et al., 2012), and also investigate changes in cognitive and psychiatric features of the disease over a longer time period than is possible through intensive neuropsychological examination. In particular, the preserved insight reported in PCA patients and its relationship with psychiatric features such as mood and anxiety is an interesting and important feature that remains little studied.

The challenge of matching different patient groups for disease severity presents a potential weakness of this study. Whilst the PCA and combined tAD group were matched for age and disease duration, the PCA patients had lower MMSE scores. Future studies may be able to determine whether this is due to a more rapid decline in

PCA, or a result of items within the MMSE being heavily dependent upon visual abilities (see Van Der Vlies et al., 2009). Matching tAD and PCA groups in terms of age presents a further challenge as younger patients are more likely to have atypical phenotypes (Koedam et al., 2010).

In conclusion, the striking deficits in everyday skills, along with greater impairments in self care illustrate the particular challenges that face PCA patients, and the people who care for them. We hope that this work is a first step towards a better understanding of these difficulties, and that we will learn more about how they evolve over time and relate to other cognitive and psychiatric factors, as larger sample sizes and longitudinal data are collected.

7 Beyond visual deficits: motor features in posterior cortical atrophy and associated atrophy patterns

7.1 Introduction

Although commonly considered a selective visual syndrome, a number of patients with PCA develop sensorimotor signs, often asymmetric (McMonagle et al., 2006; Seguin et al., 2011; Tang-Wai, Josephs, Boeve, Dickson, et al., 2003; Whitwell et al., 2010), which are more typically seen in corticobasal syndrome (CBS; Boeve et al., 2003). However, a physical examination within normal limits is considered supportive of PCA in the original criteria (Mendez et al., 2002). Another proposed criteria excludes early Parkinsonism but recognises that it may subsequently develop and does not state how early on its presence is acceptable (Tang-Wai et al., 2004). The prevalence of motor features in PCA is currently unclear, as are other potential differences between PCA patients with and without such signs. Therefore there is a need for a clearer description of the relationship and overlap between PCA and other related syndromes, particularly corticobasal syndrome (CBS).

The aim of the current study was to compare the clinical and neuroimaging profiles of PCA patients with and without features of CBS. The core clinical features of CBS are progressive asymmetrical limb rigidity and apraxia (Boeve et al., 2003). There may be additional cortical signs such as myoclonus, alien limb phenomena and cortical sensory loss and extrapyramidal signs including tremor, bradykinesia and dystonia; all of which contribute to clumsiness and loss of function of the affected limb. Historically, these clinical features were considered to be diagnostic of CBD (a four-repeat tau neurodegenerative disease; Dickson et al., 2002; Rebeiz et al., 1968), however, clinicopathological studies have demonstrated that CBD can cause a variety of different phenotypes including progressive supranuclear palsy (PSP), frontotemporal dementia, and PCA (Armstrong et al., 2013; Josephs et al., 2006; Kertesz et al., 2000; Lee et al., 2011). Furthermore, it has become apparent that CBD pathology is found at autopsy in less than half of the patients who are clinically diagnosed during life (Boeve et al., 1999; Josephs et al., 2006; Lee et al., 2011). Increasingly, AD is recognized as an important cause of CBS but alternative pathologies include PSP, Pick's disease,

frontotemporal lobar degeneration (FTLD) with TDP inclusions, dementia with Lewy bodies (DLB) and Creutzfeldt-Jakob disease (Boeve et al., 1999; Hu et al., 2009; Josephs et al., 2006; Ling et al., 2010; Shelley et al., 2009). The term 'CBS' was therefore coined to refer purely to the constellation of clinical features, in recognition that they may be caused by diverse underlying pathologies (Boeve et al., 2003; Kertesz et al., 2000).

Cognitive function was initially reported to be relatively well preserved until late in the disease with initial diagnostic criteria listing early dementia an exclusion criterion (Lang et al., 1994; Rebeiz et al., 1968). More recent studies however report cognitive symptoms early in the course of CBS or even predating the emergence of motor features (Graham et al., 2003; Grimes et al., 1999; Kertesz et al., 2000; Murray et al., 2007; Schneider et al., 1997). Although no consensus yet exists for the diagnosis of CBS, proposed criteria have subsequently included cognitive dysfunction as a supportive feature (Boeve et al., 2003) or have given equal weight to the cognitive and motor aspects of the disorder (Mathew et al., 2012). In addition to limb apraxia, the characteristic cognitive manifestations of CBS are frontal dysfunction and language impairment (typically nonfluent aphasia), but also dysgraphia, dyscalculia and visuospatial deficits (Graham et al., 2003; Mathew et al., 2012). The relationship between CBS, FTLD and primary progressive aphasia (PPA) has been the subject of a number of studies (Josephs et al., 2006; Kertesz et al., 2000), however the overlap between CBS and PCA has received comparatively little attention. We aimed to investigate how frequently the core features of CBS were observed in a relatively large cohort of PCA patients and whether there was a neuroimaging correlate of these signs. In line with previous evidence of an association between CBS and perirolandic atrophy irrespective of underlying pathology (Lee et al., 2011), we hypothesised that PCA patients with motor features would show greater atrophy of contralateral sensorimotor cortices.

7.2 Methods and Materials

7.2.1 Subject characteristics

The study was conducted at the Dementia Research Centre (DRC), University College London Institute of Neurology, at the National Hospital for Neurology and

Neurosurgery. The majority of subjects in this study had attended our Specialist Cognitive Disorders Clinic for their clinical assessment. The DRC database was interrogated to identify individuals with a clinical diagnosis of PCA and at least one MRI brain scan and a neurologist then reviewed their clinical notes. Subjects were only included in this study if they met the original proposed clinical criteria for PCA (Mendez et al., 2002) and had a clearly documented neurological examination within a year of their MRI scan. A total of 44 individuals with PCA were identified, along with 30 healthy controls. Informed consent was obtained from all subjects according to the Declaration of Helsinki and the study had local ethics committee approval.

The same neurologist reviewed all the clinical assessment notes to ascertain the age at symptom onset, mini-mental state examination (MMSE) (Folstein et al., 1975) score and presence of limb rigidity, apraxia, myoclonus, tremor, dystonia and alien limb phenomenon at time of scanning. Not all patients were consistently examined for cortical sensory signs or bradykinesia so these features were not considered for the purpose of this study. If the motor signs affected one side only or one side more than the other, this asymmetry was documented. Limb rigidity is a core feature shared by all three of the existing diagnostic criteria for CBS (Boeve et al., 2003; Lang et al., 1994; Mathew et al., 2012) and was used to define group membership for this study. Patients were classified as PCA+CBS if prominent limb rigidity was present or PCA-CBS if absent. They were not included in the PCA+CBS group if a very subtle increase in limb tone was only evident on testing with synkinesis.

Six patients had undergone lumbar puncture (LP). CSF was analysed for 14-3-3 protein positivity and total tau and amyloid beta ($A\beta_{1-42}$) concentrations (Innotest platforms, Innogenetics, Ghent, Belgium). According to our laboratory's local reference ranges, a CSF profile is considered to show 85% sensitivity for a clinical diagnosis of AD when tau >307pg/ml and $A\beta_{1-42}$< 325pg/ml (unpublished data). Two patients had come to post-mortem and a third patient had undergone brain biopsy. DNA was available for 40 of the PCA patients, which was analysed to establish *Apolipoprotein E* (*APOE)* genotype.

7.2.2 Neuropsychological Assessment

Detailed neuropsychological assessment was available for 21/31 (67%) PCA-CBS and 9/13 (69%) PCA+CBS patients. This included tests of visuospatial processing (number

location and dot counting from the Visual Object and Space Perception battery (VOSP; Warrington & James-Galton, 1991), visuoperceptual processing (fragmented letters and object decision from the VOSP), calculation (Graded Difficulty Arithmetic test Jackson & Warrington, 1986), spelling (Baxter Graded Difficulty Spelling test; Baxter & Warrington, 1994), naming from verbal description and praxis (gesture production in the dominant upper limb, a subset of five of the traditional gesture tasks from Crutch et al., 2007).

The limb apraxia subtest of the Apraxia Battery for Adults (ABA-2,3A) (Dabul, 2000) was recently introduced into our clinical assessment protocol to provide a standardised assessment of limb praxis. Therefore this subtest was available for only the eight most recently assessed patients (four PCA+CBS, four PCA-CBS). In this assessment, ten different actions are verbally described and the subject is scored out of five to record how accurately they perform each gesture. We conducted the assessment separately for the right and left upper limb to give a total score out of 50 for each limb, from which the difference between scores for left and right could be calculated.

7.2.3 MRI Acquisition

T1-weighted volumetric MR brain scans were acquired on a 3.0T Siemens TIM Trio scanner (N=43, Siemens, Erlangen) using a magnetisation prepared rapid gradient echo (MPRAGE) sequence and on 1.5T GE Signa units (N=31, General Electric, Milwaukee) using a spoiled gradient recalled (SPGR) sequence. The proportion of patients scanned on each scanner was balanced across groups (see Table 7-1).

7.2.4 Voxel-based Morphometry (VBM) processing

VBM was carried out using SPM8 (Statistical Parametric Mapping, version 8; Wellcome Trust Centre for Neuroimaging, London, UK). Scans were segmented into grey and white matter using SPM8's new segment toolbox with default settings (Ashburner & Friston, 2005; Weiskopf et al., 2011). Segmentations were produced with rigid alignment to standard space (Montreal Neurological Institute (MNI) space) and resampled to 1.5mm isotropic voxels for use with DARTEL (Ashburner, 2007). DARTEL then iteratively registered the grey and white matter segments to an evolving estimate

of their group-wise average (Ashburner & Friston, 2009). The native space tissue segments were then normalized to MNI space using the DARTEL transformations, modulated to account for local volume changes. A 6mm full width at half maximum (FWHM) Gaussian smoothing kernel was applied. Total intracranial volume (TIV) for each participant was estimated using Jacobian integration of deformation fields (Ridgway et al., 2011). An explicit mask was applied to include only voxels for which the intensity was at least 0.1 in at least 80% of the images (Ridgway et al., 2009).

7.2.5 Cortical thickness processing

Cortical thickness measurements were made using FreeSurfer version 5.1.0 (http://surfer.nmr.mgh.harvard.edu/). The detailed procedure has been described and validated in previous publications (Fischl & Dale, 2000; Dale et al., 1999). Two modifications to the standard FreeSurfer processing stream were made: a locally generated brain mask was used to improve skull stripping, and FreeSurfer ventricular segmentations were added to the white matter mask to improve cortical segmentation.

7.2.6 Whole-brain analysis of VBM and cortical thickness data

A general linear model (GLM) was used to assess group differences in grey and white matter volume in the VBM analysis (implemented in SPM) and cortical thickness in the FreeSurfer analysis (implemented using SurfStat (http://www.math.mcgill.ca /keith/surfstat/) (Chung et al., 2010) and a locally-developed Matlab toolkit). Volume and cortical thickness were modelled as a function of group (controls, PCA–CBS, PCA+CBS), adjusting for age, gender, TIV (all mean centred) and scanner. Statistical significance of differences between groups was tested using family-wise error (FWE) correction at $p<0.05$. Maps showing statistically significant differences between the controls and patient groups as well as maps showing percent differences between the two patient groups were generated.

7.2.7 Cortical region of interest (ROI) analysis

Cortical thickness values were extracted for 34 brain areas in the left and right hemisphere using FreeSurfer's Desikan parcellation (Desikan et al., 2006). These areas were grouped into five larger regions – central, frontal, parietal, temporal and occipital

(see Appendix Table A-3). To investigate differences in laterality of cortical thickness between patient groups in all five regions, six linear regressions were performed (using Stata 12 - StataCorp, 2011), one for each ROI, and one for all ROIs combined. Cortical thickness was the dependent variable and group, hemisphere and their interaction were the independent variables of interest. Robust standard errors were used to account for repeated measures by patient. Age, gender, scanner and TIV were included as additional covariates for adjustment. Wald tests were carried out to elucidate the main effects of group and laterality and their interaction.

In order to compare the size of the effect of differences between PCA+CBS and PCA–CBS groups, Cohen's d was calculated for this comparison in each of the cortical ROIs in the right and left hemisphere.

7.2.8 Subcortical ROI analysis

The Multi-Atlas Propagation and Segmentation (MAPS) technique was used to investigate volumes of the subcortical structures of interest in this study; namely the thalamus, caudate and putamen. This segmentation method was previously developed for hippocampal segmentation (Leung et al., 2010) and has been used in brain extraction (Leung et al., 2011). In MAPS, the target T1-weighted image is compared to all the atlases in a template library, comprising 30 MRI scans of healthy individuals which have been manually segmented into 83 anatomical structures (Hammers et al., 2003). Multiple best-matched atlases were used to segment the target image and an optimal segmentation was created by fusing the multiple segmentations. Leave-one-out cross-validation comparing the automated and manual segmentations of the template library was used to determine the optimal number of best-matched atlas (7 for putamen and thalamus, 9 for caudate) and label-fusion algorithm (simultaneous truth and performance level estimation (STAPLE)) (Warfield et al., 2004). We used the optimised parameters to generate individual ROIs from MAPS for each subject. Linear regression analysis was used to test the effect of group, laterality and their interaction in the same way as for the cortical thickness ROIs. Similarly, effect sizes were calculated using Cohen's d for the comparison between PCA+CBS and PCA-CBS.

7.3 Results

7.3.1 Clinical

The control and PCA groups were matched for age and gender (see Table 7-1 for demographics and clinical data). The patient sub-groups were matched for age at scan, disease duration (time between symptom onset and scan) and MMSE score. There was no significant difference in *ApoE e4* allele frequency between the two PCA subgroups and two patients in each group were *e4* homozygous.

Of the 44 PCA patients, 13 met inclusion criteria for PCA+CBS and 31 for PCA-CBS. In all patients with limb rigidity (PCA+CBS) the rigidity was asymmetrical, and in all 13 the left arm was predominantly affected. All 13 PCA+CBS patients demonstrated apraxia, which was considered to be asymmetrical (all left worse than right) in 92% of them. In the PCA-CBS group, apraxia was observed in 39% and was described as asymmetrical in 17% of those with apraxia. Therefore, although limb apraxia occurred in both groups, it was seen significantly more frequently ($p<0.001$) and was more frequently asymmetrical ($p<0.001$) in the PCA+CBS than PCA-CBS group. On the ABA-2,3A test, the mean score in the four PCA-CBS patients tested was 43/50 for both left and right upper limb, which is considered indicative of mild apraxia (Dabul, 2000), with a mean difference in scores between left and right of 2. In the four PCA+CBS patients tested, the mean score was 34/50 for the right (moderate apraxia) and 21/50 (severe apraxia) for the left upper limb, with a mean difference in scores between left and right of 13. Although the sub-group of patients assessed with this battery was small, the PCA+CBS group demonstrated significant asymmetry in the severity of their apraxia between left and right upper limb ($p=0.02$), which was significantly worse than the degree of asymmetry observed in the PCA-CBS group ($p = 0.01$).

Myoclonus was observed in both the PCA+CBS (77%) and PCA-CBS (45%) group but was more frequently asymmetrical in the PCA+CBS group ($p=0.04$). 80% of those with myoclonus in the PCA+CBS group had asymmetric myoclonus, which was only or more prominent on the left. In the PCA-CBS group, asymmetry was observed in 29% of those with myoclonus but half of this sub-group demonstrated worse myoclonus on the left and half demonstrated worse on the right. In the PCA+CBS group, three subjects (23%) had a resting tremor of the left hand and two subjects (15%) had alien limb

phenomena affecting the left upper limb. None of the subjects in the PCA-CBS group had a rest tremor or signs of alien limb. No subjects were documented to have dystonia. Two of the PCA+CBS subjects had symptoms of rapid eye movement (REM) sleep behaviour disorder; both manifested myoclonus and one had signs of alien limb. No subject reported visual hallucinations. However, one PCA+CBS subject had experienced extracampine hallucinations earlier on in his illness. He described feeling a presence on his left, with involuntary drifting of his left arm, which began two years after his cognitive symptoms and resolved three years later. No symptoms or signs of alien limb were evident at his assessment, six years into his illness, although he did have left upper limb rigidity, apraxia, myoclonus and a resting tremor. The time of onset of motor features was not clearly documented or not known for the majority of patients. However, 3/13 PCA+CBS subjects had reported difficulty using the left hand from the onset of their illness.

One PCA+CBS and one PCA-CBS patient underwent post-mortem pathological examination. Both had AD with Braak & Braak stage VI neurofibrillary pathology (the most severe grading, and considered diagnostic) (Braak & Braak, 1995), which involved visual cortex. The PCA+CBS case (the individual with extracampine hallucinations described above) additionally had Lewy body pathology (LBP) in limbic and brainstem structures, and mild amyloid angiopathy. The PCA-CBS case showed severe amyloid angiopathy but no LBP. Another PCA+CBS patient underwent a right frontal lobe biopsy, which demonstrated AD pathology with amyloid angiopathy but no LBP.

CSF total tau and $A\beta_{1-42}$ concentrations were analysed for six other patients (two PCA+CBS, four PCA-CBS, see Table 7-2). All subjects with complete CSF analysis had increased concentrations of total tau supporting an underlying diagnosis of neurodegeneration. The majority (5/6) also had low concentrations of $A\beta_{1-42}$ and a raised tau/$A\beta_{1-42}$ ratio >1, supportive of a diagnosis of AD (Bian et al., 2008; Blennow & Hampel, 2003). The only patient with a particularly high $A\beta_{1-42}$ concentration for AD (patient 1), nonetheless had a tau/$A\beta_{1-42}$ ratio >1 and was in the PCA-CBS group. This individual had a typical clinical presentation for PCA but was only very mildly affected (MMSE 29/30) at the time of his LP. None of the patients had a positive CSF 14-3-3 protein level.

Table 7-1 Subject characteristics and clinical data

	Controls (N=30)	**PCA + CBS (N=13)**	**PCA –CBS (N=31)**	***p* value**
Gender (male, female)	13, 17	7, 6	12, 19	0.71
Age in years, mean (S.D.)	63.9 (6.2)	63.8 (8.0)	63.4 (6.2)	0.94[b]
MMSE, mean (S.D.)	29.3 (0.8)	17.4 (6.3)	18.9 (6.4)	0.49[c]
Disease duration in years, mean (S.D.)	N/A	4.9 (2.1)	5.3 (2.8)	0.66[c]
Scanner (3.0T, 1.5T)	18, 12	7, 6	18, 13	0.95[a]
ApoE, no. (percentage) with e*4* allele / no. with DNA sample)	N/A	5/11 (45%)	12/29 (41%)	1.00[a]
Neurological signs				
Limb rigidity*	N/A	13 (100%)	0	N/A
Alien limb phenomena*	N/A	2 (15%)	0	N/A
Tremor*	N/A	3 (23%)	0	N/A
Myoclonus* - asymmetrical	N/A	10 (77%) 8 (80%)	14 (45%) 4 (29%)	0.10[a] 0.04[a]
Apraxia* - asymmetrical	N/A	13 (100%) 12 (92%)	12 (39%) 2 (17%)	<0.001[a] <0.001[a]
Limb apraxia subtest (3A) of Apraxia battery for adults (ABA-2A)	-	**PCA + CBS (N=4)**	**PCA –CBS (N=4)**	***p* value**
Right upper limb score**, mean (S.D)	-	34.4 (12.3)	42.75 (10)	0.32[c]
Left upper limb score**, mean (S.D)	-	21.3 (13.3)	42.75 (7.3)	0.05[c]
Difference between left and right scores, mean (S.D) *p* value for paired samples t-test comparing left and right upper limb scores	-	13 (5.9) 0.02	2 (2.3) 1.00	0.01[c]

(a) Fisher's exact test (b) one way ANOVA (c) two sample unpaired t-test comparing PCA+CBS against PCA–CBS

** Numbers indicate the number (percentage) of patients in each group documented as manifesting the sign on clinical examination. Where indicated, the number (percentage) of these subjects in whom the sign was asymmetrical i.e. observed only or more prominently on one side than the other, is recorded on the line below. The remaining signs were asymmetrical in all cases.*

Limb rigidity was the feature used to define membership of the PCA+CBS group and affected the left upper limb in all cases

*** Maximum score 50, with lower scores indicating more severe apraxia*

Table 7-2 CSF results for patients who underwent LP

	Patient1	**Patient2**	**Patient3**	**Patient4**	**Patient5**	**Patient6**
Group	PCA-CBS	PCA -CBS	PCA -CBS	PCA -CBS	PCA +CBS	PCA +CBS
Total tau (pg/ml)	931	Insufficient	488	660	630	566
$A\beta_{1-42}$ (pg/ml)	625	105	135	343	243	205
Tau:Aβ ratio	1.49	n/a	3.61	1.92	2.59	2.75

7.3.2 Neuropsychology

There were no significant differences between the PCA+CBS and PCA–CBS groups on any neuropsychological test, including assessments of visual function and naming. There was, however, a trend towards worse performance in gesture production in the PCA+CBS (mean 8.6, SD 4.16) than PCA–CBS group (mean 11.6, SD 4.13, p=0.08 between groups).

Table 7-3 Neuropsychology scores

	PCA-CBS Mean (SD)	PCA+CBS Mean (SD)	t test (p value)	Normative mean (SD)	PCA-CBS number (%) below 5th %ile	PCA+CBS number (%) below 5th %ile
Interval between MRI and psychology (months)	3.2 (4.3)	3.1 (6.0)	0.93	-	-	-
General function						
sRMT words (/25)[a]	19.2 (2.8)	20.3 (2.6)	0.30	23.5 (2.1)	17 (81.0)	5 (55.6)
sRMT faces (/25)[a]	18.6 (5.6)	15.5 (4.7)	0.30	22.8 (1.9)	4 (19.1)	4 (44.4)
Concrete Synonyms (/25)[b]	19.4 (5.7)	20.8 (4.6)	0.54	20.8 (3.0)	3 (14.2)	1 (11.1)
Naming from description (/20)[c]	13.3 (6.8)	12.4 (4.7)	0.72	18.9 (1.5)	11 (52.4)	7 (77.8)
Gesture production (/15)	11.6 (4.1)	8.6 (4.2)	0.08	-	-	-
Non-visual parietal						
Calculation (adap. GDA, /26)[d]	9.24 (5.2)	9.3 (5.2)	0.96	20.7 (3.1)	19 (90.5)	8 (88.9)
Spelling (Baxter, /20)[e]	8.05 (6.7)	7.4 (7.2)	0.83	19.5 (6.5)	10 (47.6)	5 (55.6)
Visual function						
Figure-ground (/20)[f]	15.3 (3.7)	15.0 (4.0)	0.83	19.9 (0.3)	17 (81.0)	8 (88.9)
Fragmented letters (/20) [f]	3.7 (4.6)	1.1 (1.6)	0.11	18.8 (1.4)	17 (81.0)	9 (100)
Object decision (/20) [f]	10.6 (5.3)	9.6 (4.3)	0.61	17.7 (1.9)	14 (66.7)	9 (100)
Usual views (/20)[g]	13.7 (7.1)	7.8 (5.7)	0.16	19.7 (0.5)	6 (28.6)	4 (44.4)
Unusual views (/20) [g]	4.9 (4.8)	2.3 (1.9)	0.32	17.1 (3.0)	9 (42.9)	4 (44.4)
Number location (/20) [f]	3.1 (3.4)	1.4 (2.0)	0.20	9.40 (1.1)	15 (71.4)	9 (100)
Dot counting (/20) [f]	4.0 (3.7)	3.0 (3.6)	0.53	9.90 (0.2)	17 (81.0)	8 (88.9)

Note: Mean and standard deviation of raw scores for the PCA patient group and relevant normative data. Normative data samples: a) Warrington, 1996; b) Warrington et al., 1998; c) Randlesome (unpublished data N = 100); d) Crutch (unpublished data); e) Baxter & Warrington, 1994; f) Warrington & James-Galton, 1991; g) Warrington & Taylor, 1973.

7.3.3 Voxel-based morphometry results

7.3.3.1 Grey matter

The PCA+CBS group showed lower grey matter volume in occipital and parietal lobe regions compared with controls (peak in right lateral occipital cortex, MNI [52,-64.5,15]), with some additional lateral temporal lobe involvement. On visual inspection, differences appeared greater in the right hemisphere than the left (Figure 7-1). A similar pattern of reduced grey matter volumes in occipital and parietal lobe regions was found in the PCA-CBS group compared with controls (peak in right lateral occipital cortex, MNI [52,-61.5,22.5], however asymmetry between hemispheres was less pronounced. The direct comparison of PCA+CBS versus PCA–CBS did not produce statistically significant differences after correcting for multiple comparisons (FWE $p<0.05$). However, percent difference maps revealed regions of lower grey matter volume on the right in the PCA+CBS group, particularly in the fronto-parietal operculum, supramarginal gyrus and middle part of the cingulate gyrus, with lower left occipital volume suggested in the PCA-CBS group (Figure 7-1).

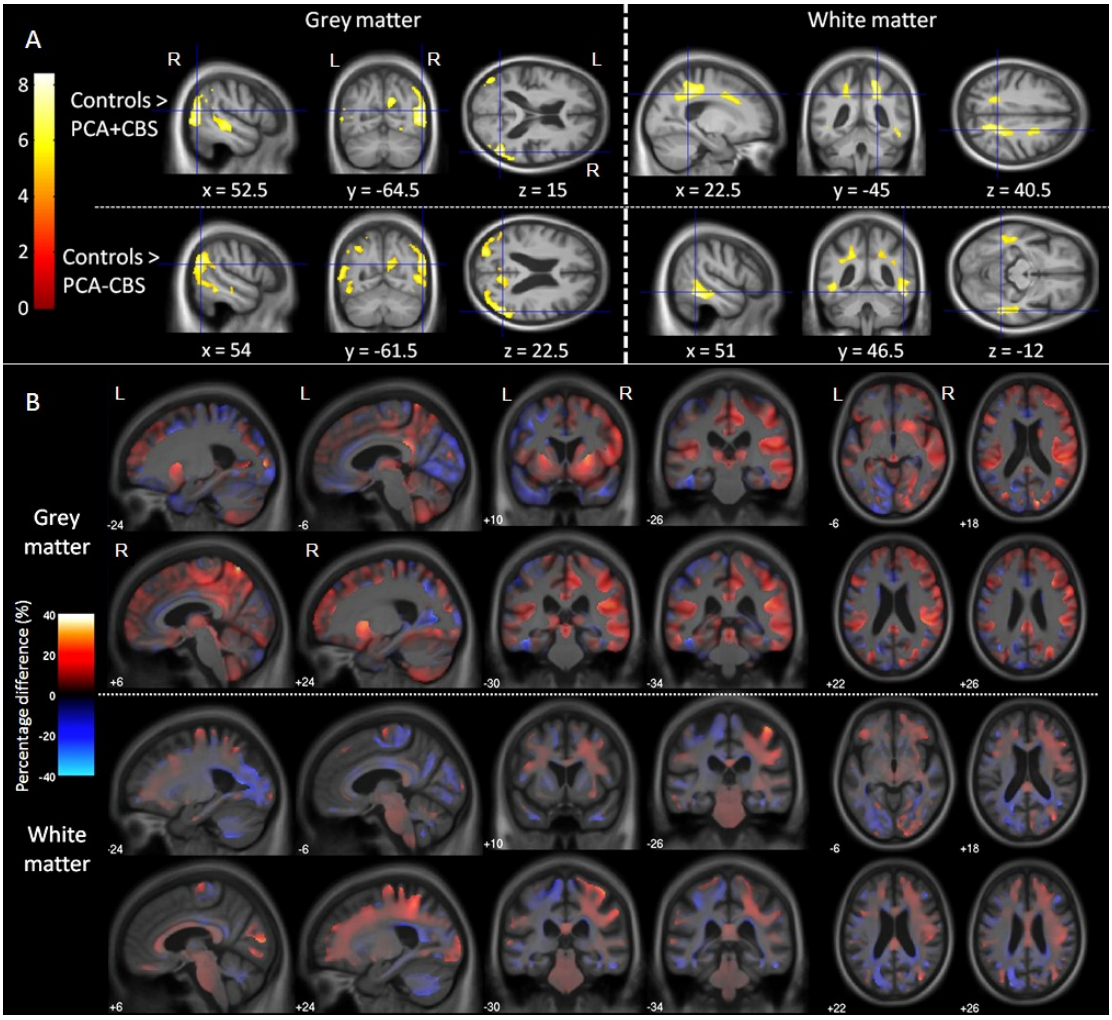
7.3.3.2 White matter

Effects in the white matter reflected those seen in the grey matter (see Figure 7-1). The PCA+CBS group showed lower white matter volume in bilateral parietal cortex compared to controls and also in the right frontal cortex. Again, visual inspection suggested a greater spatial extent of white matter involvement in the right hemisphere. The PCA-CBS group showed reduced white matter volume in parietal and temporal regions compared to controls but with less pronounced asymmetry. The direct PCA+CBS versus PCA–CBS comparison did not produce statistically significant differences after correcting for multiple comparisons (FWE $p<0.05$). However, percent difference maps revealed regions of lower white matter volume in the right hemisphere in the PCA+CBS group, particularly extending antero-posteriorly between the frontal and parietal cortices, with lower left occipital volume suggested in the PCA-CBS group.

Figure 7-1 Results from voxel-based morphometry analysis

A. Differences in grey and white matter volume between controls and PCA+CBS, and between controls and PCA–CBS. T scores are shown for statistically significant lower grey matter in the patient groups compared with controls (FWE corrected at p<0.05). Images shown in neurological convention (right on right). Cross hairs and coordinates (in MNI space) indicate t score global maxima (this is in the right hemisphere for both comparisons).

B. Percent difference maps for differences in grey and white matter between PCA+CBS and PCA-CBS. Warmer colours show regions of lower volume in PCA+CBS compared with PCA–CBS, whilst cooler colours show regions for the opposite contrast. Images shown in neurological convention (right on right), coordinates are in MNI space.



7.3.4 Cortical thickness analysis

7.3.4.1 Whole-brain cortical thickness results

Comparing the two patient groups with controls revealed reduced cortical thickness predominantly in occipital and parietal lobes, including the posterior parietal lobe, precuneus, posterior cingulate gyrus, as well as fusiform gyrus (Figure 7-2). On visual inspection, lower cortical thickness was found bilaterally in the PCA–CBS group,

whereas the PCA+CBS group showed greater involvement in right hemisphere regions. The direct comparison of PCA+CBS and PCA-CBS did not reveal any statistically significant results after FWE correction. However, percent difference maps revealed trends towards lower cortical thickness in left occipitoparietal regions of the PCA-CBS group, whereas the PCA+CBS group showed lower cortical thickness in the right hemisphere, including the motor cortex (Figure 7-2).

7.3.4.2 Regional and lateralisation cortical thickness results

Mean cortical thickness of each region in the left and right hemisphere for each group is presented in Figure 7-3. Combining all regions and both hemispheres, pairwise comparisons revealed lower global cortical thickness than controls (mean 2.26mm, SD 0.25) in the PCA+CBS (mean 1.99mm, SD 0.27; $\beta = 0.26$, $t(41) = 7.07$, $p<0.001$) and PCA-CBS group (mean 2.02mm, SD 0.30; $\beta = 0.24$, $t(59) = 8.93$, $p<0.001$), but no evidence for an overall difference in cortical thickness between PCA+CBS and PCA-CBS ($\beta = 0.01$, $t(42) = 0.35$, $p=0.73$). This effect was comparable when looking at each cortical ROI separately and is evident in Figure 7-3 (see Table A-4 in the appendix for p values and mean differences for pairwise comparisons).

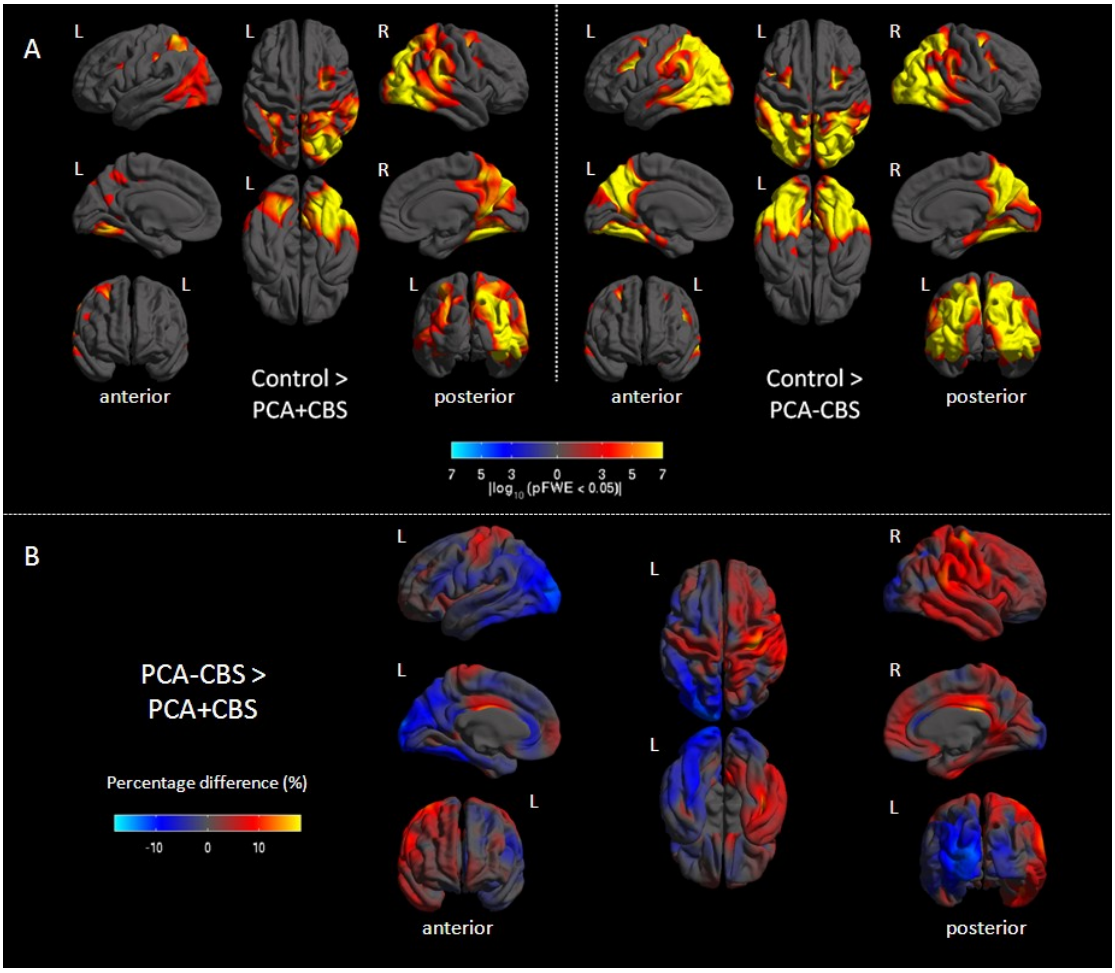
There was, however, a significant interaction between hemisphere and group in every region (parietal $F(2,71)=27.90$, $p<0.001$; temporal $F(2,73)=7.12$, $p=0.002$; occipital $F(2,71)=8.89$, $p<0.001$; central $F(2,71)=8.02$, $p<0.001$) except frontal cortex ($F(2,71)=0.67$, $p=0.514$). Thus in all regions other than frontal cortex, the difference in cortical thickness between left and right hemispheres depended upon patient group. Pairwise comparisons revealed that this was driven by more loss in right hemisphere regions in the PCA+CBS than PCA-CBS and control groups. In some regions (parietal, occipital, temporal) this constituted a reversal of the asymmetry seen in controls, whilst in others (all cortical ROIs combined and central) there was asymmetry in PCA+CBS whilst there was no left-right difference in controls. There was no evidence for a difference in the laterality of cortical thickness between controls and the PCA-CBS group in any cortical ROI.

7.3.5 Subcortical volumetric analysis

In the subcortical ROIs, averaging over the three structures studied (caudate, putamen and thalamus) and both hemispheres, volume was greater in controls (mean= 5235mm^3, SD=1262) than PCA-CBS (mean= 4726mm^3, SD=1032; β = 508, t(59) = 5.68, p<0.001) and greater in controls than PCA+CBS (mean=4387mm^3, SD=1032; β = 807, t(41) = 7.37, p<0.001). The PCA+CBS group had significantly lower overall volumes than the PCA-CBS group (β = 299, t(41) = 2.67, p=0.009). There was an interaction between hemisphere and group (F(2,71)=36.45, p<0.001). Pairwise comparisons revealed that this was driven by smaller subcortical volumes on the left than right in the PCA-CBS and control groups, but no difference between left and right in the PCA+CBS group. This pattern reflects reduced volume on the right in the PCA+CBS group (see Figure 7-3 and Table A-4 for all subcortical ROI pairwise comparisons).

Caudate volume was greater in controls than in PCA+CBS and PCA-CBS, who did not differ from each other. Left and right caudate volume did not differ in any group. Putamen and thalamus volume differed significantly between groups; PCA+CBS < PCA–CBS < controls. Evidence for a left-right difference in putaminal volume was absent in PCA+CBS, weak in controls and strong in PCA–CBS, with control and PCA-CBS groups both showing greater volumes on the right. Evidence for a difference in the magnitude of putaminal asymmetry was absent for controls versus PCA–CBS, weak for controls versus PCA+CBS and strong for PCA+CBS versus PCA–CBS. Evidence for a left-right difference in thalamic volume was absent in PCA+CBS but strong in control and PCA–CBS groups, with both showing greater volumes on the right. The magnitude of thalamic asymmetry did not differ between controls and PCA-CBS but both groups were significantly more asymmetrical than PCA+CBS.

Figure 7-2 Results from cortical thickness analysis



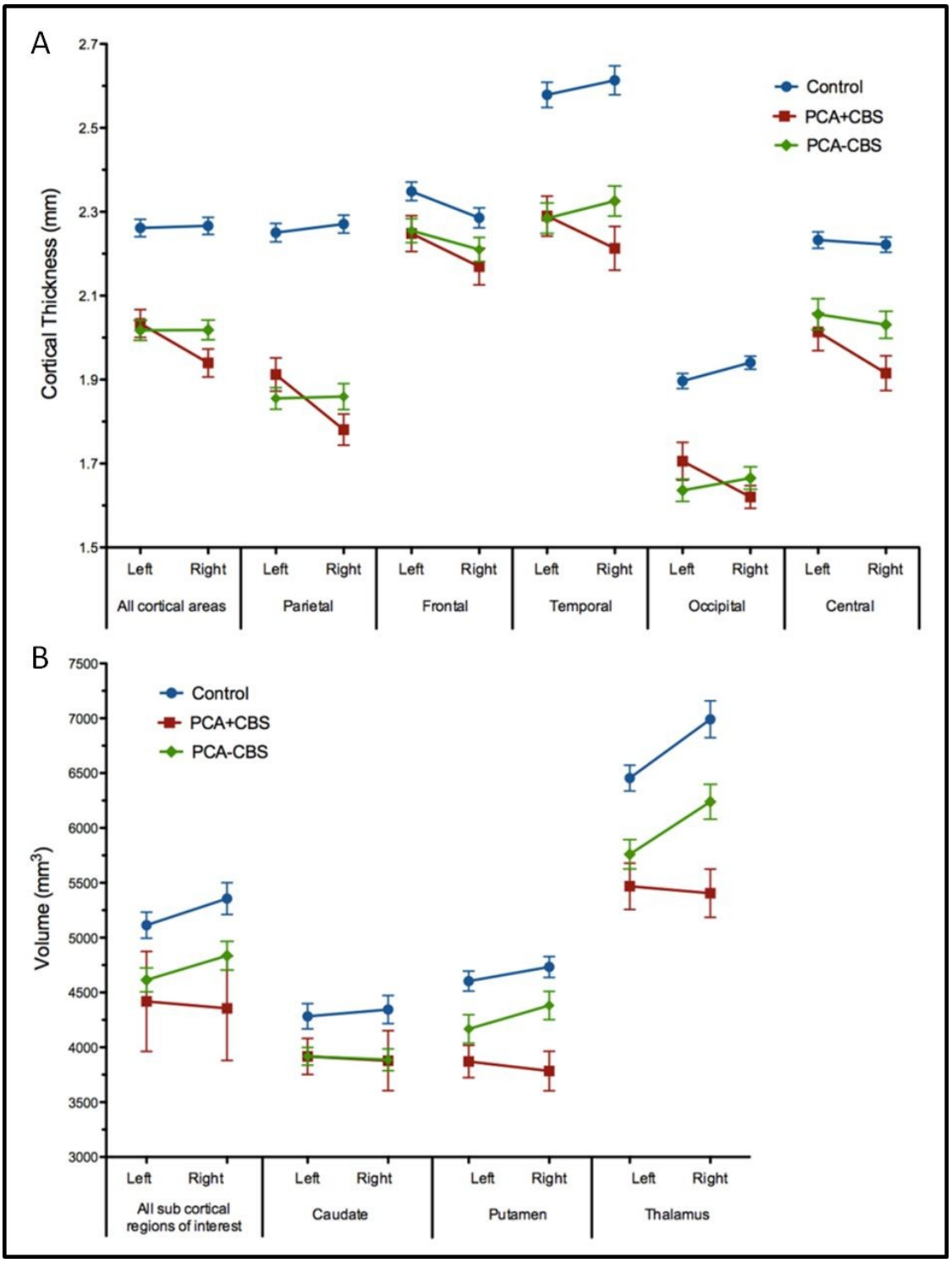
A. Differences in cortical thickness between controls and PCA+CBS, and between controls and PCA–CBS. The colour scale represents FWE corrected p values (p<0.05), with warmer colours representing regions with lower cortical thickness in the patient groups compared with controls, and cooler colours showing the opposite contrast (which yielded no statistically significant results).

B. Difference in cortical thickness between PCA–CBS and PCA+CBS. The colour scale represents percent differences in cortical thickness with warmer colours showing regions where PCA+CBS has lower cortical thickness compared with PCA-CBS, whilst cooler colours represent areas for the opposite contrast.

7.3.6 Effect size analysis

Large effect sizes for the difference between PCA+CBS and PCA–CBS were found in the right thalamus and right putamen. Medium effect sizes were found in the right parietal, right temporal and right central ROIs. Small effect sizes were found in right frontal, left parietal, left central and bilateral occipital regions, left putamen and left thalamus (Table A-5). These effect sizes represent greater atrophy in the PCA+CBS group than the PCA-CBS group except for the left parietal and left occipital regions where atrophy was greater in the PCA-CBS group.

Figure 7-3 Mean cortical thickness and subcortical volume for each patient group in each region of interest. Error bars indicate standard error.



7.4 Chapter conclusions

This study demonstrates the overlap of the PCA and CBS syndromes, revealing significant differences in the clinical and neuroimaging profiles of PCA patients with and without the core clinical features of CBS. All patients participating in the study met the originally proposed clinical criteria for PCA, of which 13 (30%) also showed prominent asymmetrical limb rigidity. Limb apraxia occurred in both the PCA+CBS and PCA-CBS groups but was seen more frequently, and was more often asymmetrical, in the PCA+CBS group. This difference in asymmetry of apraxia between the groups was confirmed in the sub-group who underwent standardised assessment with the ABA-2,3A. Myoclonus was also seen in both groups but was more often asymmetrical in the PCA+CBS group. Rest tremor and alien limb phenomena were only observed in the PCA+CBS group. Other than a trend towards greater impairment on gesture production tests of praxis, no significant difference in neuropsychological measures was observed between the PCA+CBS and PCA-CBS groups.

Neuroimaging analyses revealed overlapping but distinct patterns of tissue loss in the PCA+CBS and PCA-CBS groups. Both grey and white matter volume and cortical thickness techniques revealed more asymmetry in the PCA+CBS than the PCA-CBS group compared to controls, with more pronounced atrophy and reductions in thickness in the right hemisphere in the PCA+CBS group. The regions found to show the greatest difference in VBM between these groups were the fronto-parietal operculum, supramarginal gyrus and middle part of the cingulate gyrus, all anterior to the maxima identified in the patient-control comparisons. These differences could not be attributed to age or disease duration and suggest a greater spatial extent of atrophy in the PCA+CBS than PCA-CBS group. The cortical thickness analysis showed a similar trend towards right-sided atrophy, and particularly emphasised the involvement of the perirolandic sensory and motor cortices (bilaterally but more on the right) in the PCA+CBS group. Subcortical region of interest volumetric analysis revealed lower volumes of putamen and thalamus in the PCA+CBS group compared to the PCA-CBS group and healthy controls, an effect that was strongest in the right hemisphere.

Asymmetry, with greater atrophy in the right hemisphere, was a prominent and distinctive feature of the PCA+CBS group and may underlie the left upper limb motor

features that were observed in these patients. The results are consistent with the hypothesis that CBS signs in PCA reflect atrophy of contralateral sensorimotor cortices. The data extend the hypothesis by demonstrating that such signs are also associated with greater tissue loss in subcortical structures, namely the putamen and thalamus. The thalamus and putamen have been found to undergo significant atrophy in AD (de Jong et al., 2008), however their differential involvement in atypical AD phenotypes has not, to our knowledge, been systematically evaluated. Thalamic and basal ganglia volume loss on MRI has also been identified in CBS, however does not appear to differentiate between CBS cases with underlying CBD or AD pathology (Josephs et al., 2010). In our study, the control and PCA-CBS groups both showed greater volumes in the right thalamus and putamen. This normal asymmetry was lost in the PCA+CBS group, implying that these structures had undergone a greater degree of atrophy in the right hemisphere. It seems likely that the prominent motor features in the PCA+CBS group reflect dysfunction of a whole network of areas involved in the planning, coordination and execution of movement. This includes the primary motor and somatosensory cortices, premotor and supplementary motor areas and the posterior parietal and deep subcortical structures with which they connect.

It was striking that the asymmetric motor features affected the left side in all subjects in the PCA+CBS group. Interestingly, the right side was involved more than the left in a series of CBS patients presenting with language, behavioural or motor symptoms, with left hemispheric atrophy a frequent finding (Kertesz et al., 2000). A predominantly right-sided pattern of cortical atrophy has been reported in prior imaging studies of PCA (Lehmann, Crutch, et al., 2011; Whitwell et al., 2007), whereas our data showed no difference in the symmetry of cortical thickness between controls and the PCA-CBS group in any cortical ROI. This perhaps suggests that asymmetry in PCA group studies may be driven by the subset of subjects with additional features of CBS.

There is significant pathological overlap in the aetiology of PCA and CBS, with both potentially being caused by underlying AD, CBD, DLB or CJD. Some clinicopathological studies investigating CBS patients with underlying AD or CBD have indicated that behavioural/frontal symptoms such as early personality change predict CBD pathology whilst impairment of visuospatial skills and memory, young age at onset and

myoclonus are associated with AD. Contrary to the traditional view, it is in fact CBD that often appears to present without motor symptoms (with a frontal cognitive/behavioural syndrome) (Lee et al., 2011) or with motor features that are symmetrical (Hassan et al., 2010). In our cohort, AD pathology was confirmed in the two PCA+CBS patients who underwent post-mortem examination and was suggested by an AD-like CSF profile in the two other PCA+CBS patients who underwent LP. The pathological overlap in the aetiology of PCA and CBS emphasises the need for improved clarity as to the clinical overlap between the two syndromes. Considering current clinical criteria for PCA (Mendez et al., 2002; Tang-Wai et al., 2004) and CBS , considerable overlap is evident meaning that some patients may fulfil criteria for both syndromes. This is particularly apparent in more recent CBS criteria, which have emphasised early cognitive change in executive function, language, memory and/or visuospatial processing. For example, the modified Bak and Hodges (Cambridge) criteria for CBS could be met by PCA patients with insidious onset and no levodopa response (mandatory criteria), limb apraxia and language impairment (major features) and a combination of at least two of alien limb phenomenon, cortical sensory loss, dyscalculia and visual dysfunction (Mathew et al., 2012). Whilst typically considered a progressive visual syndrome, anomia and phonological processing deficits are common early features in PCA (Benson et al., 1988; Crutch, Lehmann, et al., 2013; McMonagle et al., 2006). Conversely, patients fulfilling CBS criteria may also fulfil PCA criteria, which either have no exclusion criteria (Mendez et al., 2002) or exclude only early Parkinsonism (Tang-Wai et al., 2004). Thus individuals diagnosed with CBS who have visual complaints and signs such as myoclonus, limb apraxia, alien limb phenomenon and cortical sensory loss would still meet current criteria for PCA (Rajagopal et al., 2012).

Clarifying the relationship between PCA and CBS would have a number of implications for diagnosis, management and research. First, although the presence of linguistic and executive dysfunction in CBS patients may not distinguish underlying pathologies (Lee et al., 2011), the presence of cortical visual dysfunction and other posterior cortical deficits may weight the diagnostic probabilities towards AD. Consistent with this view, Rabinovici and Miller (2012) have speculated that some features within the modified Cambridge criteria for CBS such as visuospatial dysfunction and myoclonus may be

predictive of AD. Second, the current evidence of CBS-like motor features in a substantial proportion of PCA patients argues against any tendency to withhold currently available AD therapeutic treatments such as acetylcholinesterase inhibitors to PCA patients with these signs. Conversely, CBS patients presenting to movement disorders specialists should be examined closely for posterior cortical deficits and, if the phenotype suggests AD, offered appropriate treatment. The vast majority of patients with PCA have underlying AD (Renner et al., 2004), and there is no evidence to date that the co-occurrence of CBS-like signs makes that diagnosis any less likely. In fact, the pathological and CSF data in this study, although limited, were consistent with an underlying diagnosis of AD in all of the PCA+CBS patients for whom this information was available. Third, although a syndromic classification could be adequate for some types of research study (e.g. brain–behaviour correlations or behavioural interventions), other investigations will need direct consideration of probable underlying pathology (e.g. clinical trials of protein-specific therapies). Finally, the identification of CBS-like signs in patients who fulfil criteria for PCA has a bearing upon how inclusively or exclusively PCA should be defined in any future consensus criteria; for instance, should the term PCA only be applied to patients with predominant visual dysfunction (as specified by existing clinical criteria) or should the syndrome encompass patients with progressive deterioration in other cognitive domains such as calculation, spelling, and praxis (Aharon-peretz et al., 1999; De Renzi, 1986; Seguin et al., 2011; Snowden et al., 2007). Including patients with impairments in cognitive domains other than vision seems logical, given that the term PCA refers to the locus of focal atrophy rather than a particular set of clinical features.

In this study we hypothesised that PCA patients with motor features would show greater atrophy of contralateral sensorimotor cortices, in line with previous evidence of atrophy in CBS patients (with various underlying pathologies; Lee et al., 2011). Whilst the regional cortical thickness analyses revealed differences between the patient groups, the whole-brain voxel-based morphometry analysis did not show such differences, after correction for multiple comparisons. A more sensitive technique in voxel-based morphometry is to identify a region based on *a priori* knowledge, and apply a small volume correction, so that the comparison is only carried out in this region rather than the whole brain. This has the advantage of being more sensitive to

differences in that region, but the disadvantage that differences in other regions may not be identified. Although we had a specific hypothesis, we felt that it did not constitute sufficient *a priori* knowledge to justify use of a small volume correction. The use of such a correction would mean that any effects in the rest of the brain would not be identified, and the strength of the a priori knowledge did not seem sufficient to risk neglecting effects in the rest of the brain.

To our knowledge, this is the first study to compare directly the clinical and neuroimaging features of PCA patients with and without the core motor features of CBS. One limitation of the study is the relatively small number of subjects, which may explain the finding that although volumetric and cortical thickness asymmetries were evident at the level of control-patient comparisons and between-patient group percentage effect maps, direct comparisons between the two groups did not survive correction for multiple comparisons. However this is a common problem when studying relatively rare degenerative conditions (Whitwell et al., 2007) and may be rectified with larger samples (Lehmann, Crutch, et al., 2011). Another limitation of the study was that detailed neuropsychological data and a standardised clinical assessment of limb apraxia were only available in a subset of patients. Although the neuropsychological results revealed a trend towards lower performance in gesture production in the PCA+CBS group, further study should investigate the cognitive correlates of PCA with features of CBS in more detail. Despite only having been performed in a small subgroup of patients, the apraxia battery demonstrated significantly more asymmetry and a greater severity of left upper limb apraxia in the PCA+CBS compared to PCA-CBS group. This highlights the value of applying standardised clinical assessment tools to investigate neurological signs, such as the ABA-2 to evaluate apraxia, and the importance of assessing the left and right side separately in a condition like PCA. The retrospective nature of this study, with reliance on the recording of neurological signs by a number of different clinicians, were limitations which we attempted to overcome by only including patients with a clearly documented full neurological examination. Larger cohorts of patients, with clinico-pathological correlation, will be required to further investigate the insights raised by this study. Multi-centre collaboration may be needed to achieve this, particularly if the potential genetic factors underlying phenotypic heterogeneity in PCA are to be

evaluated. The recent establishment of an international PCA Working Party represents a positive step in taking such collaboration forwards (Crutch et al., 2012).

8 Summary and conclusions

8.1 Summary

In this thesis I described studies undertaken with two broad objectives in mind; understanding the consequences of PCA in everyday activities (particularly scene perception), and understanding different forms of heterogeneity in the symptoms that people with PCA experience. In Chapter 2 the impairments that PCA patients experienced when viewing photographs of scenes were established (poor accuracy and increased response times when categorising scenes). Descriptions of scenes were characterised by paucity of detail and occasional perceptual errors (notably, errors were consistent with the overall perception of the scene). Strong associations were demonstrated between performance on this higher-level test of perception, and much more basic aspects of form, colour and space perception.

Chapter 3 expanded upon clinical observations of oculomotor abnormalities, another basic aspect of the visual system impaired in PCA. Patients showed impairments such as a high frequency of intrusive saccades during fixation, hypometric saccades and low pursuit gain. Whilst not all patients showed deficits in these tasks, the prevalence of oculomotor abnormalities using this methodology was much higher than had previously been reported in clinical studies of PCA. The evidence for associations of oculomotor abnormalities with measures of disease severity (MMSE and disease duration) was mixed, perhaps suggesting that both disease severity and heterogeneity within the PCA group contribute to inter-individual variation in performance. The impairments in oculomotor function described in this chapter were important to take into account in the following chapters investigating scene perception through eyetracking.

Chapter 4 described a pilot study, establishing that eye tracking could reveal interesting differences between the fixation patterns of patients with PCA, typical AD and healthy controls. This demonstrated that fixation patterns may contribute to explaining impairments in categorising and describing scenes. This was extended in Chapter 5, demonstrating that PCA patients have a particular impairment in adapting their eye movement behaviour to task requirements, and show a bias to fixate regions

of low-level visual salience regardless of task. These findings may help explain why patients and carers frequently report variability and inconsistency in everyday vision.

Taking a more direct approach to investigating the consequences of PCA for everyday life, Chapter 6 described the extension of a carer questionnaire to include domains typically affected in PCA (vision and understanding of quantity), in addition to domains that have been reported to be impaired in some but not all PCA patients (language and movement). This approach revealed significantly greater impairments in everyday skills and self-care (tasks that require visual perception, motor control and co-ordination) amongst the PCA group compared to typical AD. PCA patients also showed more severe impairments in vision and understanding of quantity, whilst both groups showed moderate but similar levels of impairment in language.

The final chapter revealed an aspect of heterogeneity within the PCA syndrome, finding that a subset of PCA patients had motor symptoms (e.g. limb rigidity, tremor and alien limb phenomena), despite being at a similar stage of disease severity. These symptoms were associated with greater atrophy of the contralateral motor cortex; the findings raise questions about the criteria for PCA and shed light on heterogeneity within the syndrome.

8.2 Characterising the PCA phenotype

An important issue in PCA research is the extent to which there is heterogeneity within the syndrome, this is well recognised and there is a considerable effort to improve the definition of PCA through an international working group that I have been able to take part in (Crutch et al., 2013). All PCA patients involved in this study met the current standard criteria for PCA (Mendez et al., 2002; Tang-Wai et al., 2004). Whilst further attempts to define subtypes of PCA have been made, the extent of heterogeneity and whether discrete subgroups or continuous variation between extremes best capture this heterogeneity remains unresolved.

In this thesis I have taken a number of different approaches with regards to this, reflecting a compromise between the wish to ensure all patients within a study have similar profile, and a pragmatic requirement to recruit a sufficient number of patients

who have this relatively rare syndrome. Chapters 2 and 4 use standard clinical criteria, whilst Chapters 3, 5, 6 and 7 use further criteria such as a specific neuropsychological profile (Chapter 5) or severity measure (Chapter 6) to ensure participants within the patient group are comparable.

The empirical studies in this thesis further our characterisation of the PCA phenotype in a number of ways. Firstly, Chapter 3 investigated oculomotor abnormalities in patients with PCA. A number of previous studies have commented on ocular apraxia in PCA, testing it using standard qualitative clinical assessments. The systematic and sensitive approach used in Chapter 3 revealed a much higher proportion of PCA patients to have oculomotor dysfunction than was previously acknowledged (previous studies reported approximately 10%-50% of patients to have ocular apraxia, in the present study 11/16 [68.7%] of patients had hypometric saccades). In addition, impairments in fixation stability and smooth pursuit in PCA patients were described for the first time. These findings improve the characterisation of PCA, and have implications for the interpretation of patients' performance on other tests which purport to measure higher visual functions. Just as it has been demonstrated that higher visual functions depend on more basic functions such as form and motion processing (Lehmann, Barnes, et al., 2011), basic aspects of oculomotor function are likely to influence performance in more complex visual tasks that require eye movements, although this is rarely acknowledged.

Secondly, Chapter 7 of this thesis improved the characterisation of the motor features experienced by PCA patients, and the associated atrophy pattern. Interestingly, whilst a number of studies have suggested that there is a tendency towards greater right than left hemisphere atrophy in PCA (Lehmann, Crutch, et al., 2011), voxel-based morphometry and cortical thickness analysis in the present study suggested that this effect could be driven by a subgroup of patients with more prominent motor features (such as limb rigidity, myoclonus and asymmetrical apraxia) in whom atrophy is particularly asymmetric. This study is also important in understanding characterisation of PCA in that it describes how patients may fit diagnostic criteria for corticobasal syndrome, serving as a reminder that it is important to fully investigate motor features even in syndromes thought to be predominantly cognitive, and also to investigate

cognitive features in syndromes thought to be primarily characterised by motor abnormalities, as there could be overlap between syndromes (this is true in other areas of neurodegeneration, such as the ALS/FTD overlap).

Thirdly, both of the above studies shed further light on the heterogeneity between patients with the PCA syndrome. Only a subset of patients had motor features (despite being matched for disease duration and severity to those who did not). Similarly, not all patients showed oculomotor deficits, and variation in oculomotor performance was only partially explained by differences in disease duration and severity. Whether these differences are driven by genetic influences, developmental or other environmental differences is currently unknown, but improving our awareness of them paves the way for future studies that could reveal more about the causes of different patterns of neurodegeneration and different symptoms in people with Alzheimer's disease and other neurodegenerative conditions.

8.3 What does studying PCA reveal about normal cognitive function?

Previous studies have used eye tracking during scene perception with single cases of PCA patients to investigate the processes that underlie this task. By showing that a PCA patient with visual agnosia has a scan path that diverges from that of controls in later fixations, Mannan et al., (2009) claim that the initial eye movements when scanning a scene are driven by low-level bottom up features. They suggest that the diverging pattern at later fixations is due to the top-down influence that healthy participants exert at this stage, but does not exist in their patient with agnosia due to PCA. Foulsham et al., (2011) present a separate case of PCA in which the evidence suggested top-down processes influenced perception throughout the process of scanning a scene, as using a bottom-up salience model did not fully predict fixation patterns even at the earliest stages of scene scanning. These examples demonstrate how the cognitive deficits of PCA patients can help to test hypotheses about the cognitive processes underlying a task, in this case scene perception. In Chapter 4 of this thesis we demonstrated that the difference in the fixation locations of PCA

patients and healthy controls was similar across the viewing period, a finding more consistent with the notion that top-down strategies are important even at the earliest stages of scanning the scene. In Chapter 5 of this thesis, we attempted to extend these studies by investigating scan paths under different task conditions and analysed using a number of techniques, to allow further investigation of top-down and bottom-up influences. We also accounted for PCA patients' basic impairment in saccade amplitude, and demonstrated a particular impairment in knowledge-driven control in the PCA patients.

However, there are limitations to how useful cases or groups of PCA patients can be in understanding healthy cognitive function. Unlike other degenerative diseases where detailed study has allowed great insights into cognitive function (e.g. the study of semantic dementia and semantic processing), PCA patients have relatively diffuse atrophy meaning that it is difficult to pinpoint specific neural substrates for cognitive performance. Furthermore, it is likely that a range of cognitive impairments of both low level visual processing (e.g. form, motion, colour) and higher level deficits (e.g. object processing, spatial localisation) contribute to performance. The eye tracking studies presented in Chapter 3 of this thesis suggest that basic oculomotor abnormalities may also play a part in their performance on many visual tasks. In sum it is important to consider the different impairments that may contribute to patients' performance, and it may be difficult to draw strong inferences about the exact cognitive impairments responsible for failing a particular task in this group.

8.4 Living with and managing PCA

This thesis considerably expands our knowledge of what it means to live with PCA. The most direct measure of the impact of PCA was carried out in the carer questionnaire, revealing that people with PCA have very severe impairments in their ability to carry out everyday tasks, and care for themselves. Tasks such as dressing, writing, using the telephone, and showering were particularly impaired, even more so than in a group of patients with typical AD. These findings reinforce the anecdotal reports given by carers of people with PCA and this quantitative approach, whilst losing the detail and depth of individual reports from patients, allows the implications of PCA in everyday life to be

measured and aggregated across patients for the first time. PCA patients were not more impaired than tAD in every category, with a trend towards spared motivation and fewer stereotypic and motor behaviours. These aspects of spared function relate strongly to the descriptions of patients' relatively intact sense of self and drive given by carers.

It is likely that patients' poor vision and coordination are responsible to a large extent for their impairments in everyday tasks, one of which – scene perception – was investigated in detail in this thesis. Patients' scene perception was characterised by a bias towards regions with high salience, and a reduced ability to modulate fixation patterns when required by task demands, suggesting a particular impairment in goal-oriented visual behaviour such as searching for a particular object. Knowing that visually salient areas tend to capture patients' attention provides a potential for intervention. Marking objects that need to stand out (e.g. door handles, stair rails, toilet seats) with high contrast, bright colours is likely to improve the ability of patients to notice them and be able to interact with them. Indeed, many patients and carers in the PCA support group report using such techniques successfully. This thesis also describes a more direct approach to understanding scene perception in PCA by asking patients to describe a number of scenes (Chapter 2 experiment 2). This more qualitative analysis gave a feel for the visual experience of PCA, suggesting a slow, cumulative process by which features are put together in attempt to form a coherent percept. As patients with PCA tend to have relatively unimpaired verbal communication, and intact insight they are often able to describe their experience quite eloquently. Although patients' descriptions of their experience were not investigated in detail in this thesis, our understanding of what it is like to have PCA will be furthered in future work at the DRC through the use of structured interviews with patients and their carers.

There are also practical implications of the abnormalities in eye movements and motor function described in Chapters 3 and 7 of this thesis. Deficits in fixation stability have been related to perceived motion of static stimuli (Crutch et al., 2011), impairments in saccades relate to a difficulty in disengaging fixation from one locus and moving it to a new place of interest, whilst impairments in smooth pursuit likely lead to difficulties

when tracking moving objects (e.g. cars driving along a road). The motor symptoms described in Chapter 7, such as limb rigidity and myoclonus have a clear impact on function, reducing mobility and making tasks requiring fine motor manipulation incredibly difficult. This study has implications for the clinical management of PCA, for example arguing against any tendency to withhold AD therapeutic treatments to PCA patients with these motor signs.

Thus visual perception adversely affects performance in everyday tasks, as a result of a combination of basic-level visual processing impairments, eye movement control deficits, and higher-order visual processing impairments. Motor function also contributes, in some patients more than others, to a reduction in abilities and independence in the home.

8.5 Limitations and weaknesses

In drawing conclusions from the research presented in this thesis, it is helpful to consider the limitations of the studies. The primary limitation is that in most patients, we do not know the underlying pathology. Techniques such as amyloid imaging and analysis of amyloid beta 1-42 and tau in the cerebrospinal fluid would allow greater certainty that the PCA patients tested have Alzheimer's disease (Baumann et al., 2010; Rosenbloom et al., 2011). However as the majority of the patients tested for this thesis did not have these investigations, we must assume that their underlying pathology would reflect that described in previous studies of PCA, where the majority have Alzheimer's disease, but some have Lewy Body Disease, or corticobasal degeneration. The extent to which this is a limitation differs depending on the inferences that we attempt to make from the studies. For example, one could argue that this is only a minor limitation for the studies of scene perception and the carer questionnaire, where the primary interest is the cognitive phenotype and the consequences for everyday life of the syndrome (regardless of the underlying pathology). However, for the studies of eye movements and motor features it would be very beneficial to have information about the underlying pathology in all rather than just a subset of patients, in order to demonstrate more conclusively that these features are present in people with PCA due to AD, and investigate whether people with PCA due to other

pathologies such as CBD or LBD differ with regard to these features. Of course, post mortem examination of brain tissue is the only way of definitively ascertaining the underlying pathology. Whilst CSF analysis and amyloid imaging can strongly indicate that a patient has Alzheimer's disease, they cannot rule out coexisting Lewy Body Dementia.

Another limitation to the studies in this thesis concerns the heterogeneity within the PCA syndrome, and the extent to which we can extrapolate our findings at the group level to each individual patient. Whilst between group differences are demonstrated in the scene eye tracking and carer questionnaire experiments, there may be heterogeneity between PCA patients that these studies were not able to show. This heterogeneity is directly addressed in the study of oculomotor function, where the number of patients falling outside the normal range of controls was identified. It was notable that for each metric, there were some PCA patients who performed within normal limits, and that associations with MMSE and disease duration were present but weak, suggesting that both disease severity and heterogeneity in symptoms contribute to the differences between patients. The study of motor features also directly investigated heterogeneity, revealing differences in both clinical presentation and atrophy patterns between two subgroups of PCA patients.

Finally, as mentioned in previous chapters, the typical AD patients who took part tended to be older than the PCA patients, reflecting the relatively young age at onset of PCA (Crutch et al., 2012). Where appropriate, age was included as a covariate in statistical analyses so that age differences did not account for statistical differences between groups.

8.6 Future directions

There are a number of specific ways in which the research presented in this thesis could be taken forward to improve our knowledge of PCA. One particularly interesting possibility that presents itself from the scene perception analysis in Chapter 5 is that areas of low-level salience should attract attention of patients with PCA to objects. If objects which patients need to interact with are given high salience (for example with

colour contrast) we would expect this to make them easier to notice and therefore use. This could be tested in laboratory conditions by manipulating low-level salience of target objects and testing whether this improves visual search for these targets, but could also be tested in more naturalistic settings such as a patients' homes. Indeed, the data from this study has contributed to the design of a new study testing the effectiveness of different visual cues in the Pedestrian Accessibility Movement Environment Laboratory (PAMELA) at UCL.

Both of the more clinical aspects of this paper (the oculomotor abnormalities and motor features) could be improved by collecting further data on patients where markers of the underlying pathology were available. It would be of interest to see whether PCA patients with likely AD pathology differ from those who do not show evidence of AD pathology. This may become possible as more patients undertake amyloid imaging or CSF samples and the availability of neurodegeneration biomarkers, particularly markers of amyloid deposition continues to improve.

Whilst the carer questionnaire reinforced and quantified our knowledge of the experience of PCA patients in everyday life, it would be very informative to undertake longitudinal data collection in this sample. Particularly given the fact that there is likely to be variability in the way that different people rate items on the questionnaire, longitudinal data will allow a better understanding of how the profile of cognitive impairment changes over the course of PCA, right from the earliest to the latest stages. This would provide invaluable information about the disease course that could inform our understanding of disease progression, but could also be relayed back to those patients and carers who would like to have a better understanding of how the disease affects people at different stages.

In studying the neurological basis of patients' impairments, both in the associations with oculomotor performance and differences between PCA patients with and without motor features, the emphasis has been on the changes in grey matter that could underlie their performance. However, the importance of brain networks for understanding impaired function and disease progression in neurodegeneration has grown in recognition in recent years (Buckner et al., 2005; Seeley et al., 2009; Warren et al., 2012). Measuring changes in structural connectivity using diffusion tensor

imaging could be very informative in understanding how changes to network connections contribute to these impairments, and how the disease progresses over time, giving a more comprehensive view of the neurological underpinnings of PCA. This forms the basis for my post-doctoral research project funded by Alzheimer's Research UK, investigating whether cortical atrophy is associated with changes in the optic radiations, and whether the effects of Alzheimer's disease spreading along this pathway can be measured with retinal imaging.

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Appendices

A1. Division of labour

The work described in this thesis was conducted by TJS in collaboration with other researchers based at the Dementia Research Centre and affiliated institutions. Contributions made by others are detailed below. Collaborators not affiliated with the Dementia Research Centre are marked with superscript numbering.

Chapter 2 Scene perception in PCA: a study of categorisation and description
Experimental design: TJS, EKW, SC
Construction of tests: TJS
Data collection: TJS (majority of data), KY
Data analysis: TJS in consultation with CF & LK
Writing: TJS, SC

Chapter 3 Abnormalities of fixation, saccade and pursuit in PCA
Experimental design: TJS, SC, DK[1]
Construction of tests: TJS
Data collection: TJS
Data analysis: TJS in consultation with DK[1]
Writing: TJS

Chapter 4 Perception of scenes in Posterior Cortical Atrophy: a pilot eyetracking study
Experimental design: TJS, SC
Construction of tests: TJS
Data collection: TJS
Data analysis: TJS
Writing: TJS, SC

Chapter 5 Reduced modulation of scanpaths in response to task demands in PCA
Experimental design: TJS, SC
Construction of tests: TJS
Data collection: TJS
Data analysis: TJS in consultation with YP[2]
Writing: TJS, SC

Chapter 6 A carer questionnaire in PCA
Experimental design: TJS
Construction of tests: TJS
Data collection: TJS (the majority of data collected at DRC), KY , HG (note that data also used from Neuroscience Research Australia)
Data analysis: TJS in consultation with JN
Writing: TJS

Chapter 7 Beyond visual deficits: motor features in PCA and associated atrophy patterns
Experimental design: TJS, NR
Construction of tests: SC, NR (neuropsychology and clinical tests)
Data collection: SC, NR
Data analysis: TJS (cortical neuroimaging and psychology), NR (clinical data), SK (subcortical neuroimaging)
Writing: TJS, NR, SC, ML

CF, **Chris Frost**; DK, **Diego Kaski**; EW, **Elizabeth Warrington**; HG, **Hannah Golden**; JN, **Jennifer Nicholas**; KY, **Keir Yong**; LK, **Lois Kim**; ML, **Manja Lehmann**; NF, **Nick Fox**; NR, **Natalie Ryan**; SC, **Sebastian Crutch**; SK, **Shiva Keihaninejad**; TJS, **Tim Shakespeare**; YP, **Yoni Pertzov**.

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2. Until October 2013: Institute of Cognitive Neuroscience, UCL, London, UK (October 2013 onwards: Psychology Department, Hebrew University of Jerusalem).

A2. Primary author publications

Shakespeare, T. J., Crutch, S. J., & Fox, N. C. (2012). Posterior cortical atrophy: advice for diagnosis and implications for management. *Neurodegenerative Disease Management*, *2*(6), 599–607.

Shakespeare, T. J., Ryan, N. S., Petrushkin, H., & Crutch, S. J. (2012). Identifying cortical visual dysfunction in posterior cortical atrophy. *Optometry in Practice*, *13*(4), 159–162.

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A3. Abbreviations

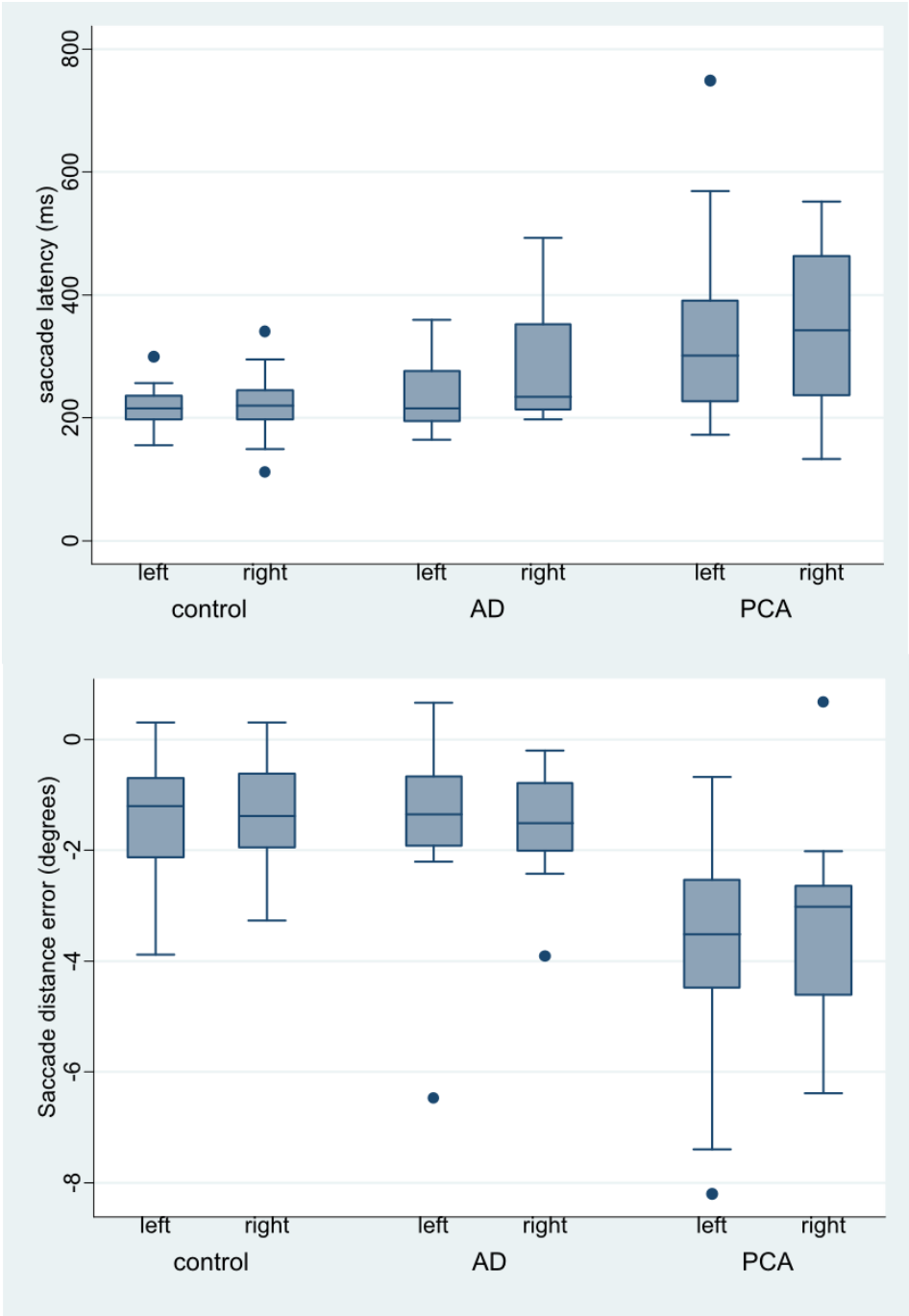
AAO	Age at onset	MPRAGE	Magnetisation prepared rapid gradient echo
AD	Alzheimer's disease	MMSE	Mini-mental state examination
ANOVA	Analysis of variance	MNI	Montreal Neurological Institute
ApoE	Apolipoprotein E	MAPS	Multi-Atlas Propagation and Segmentation
BA	Brodmann area	NP	Neuritic plaques
CBI	Cambridge Behavioural Inventory	NFT	Neurofibrillary tangles
CBI-R	Cambridge Behavioural Inventory revised	NRES	NHS Research Ethics Committees
CSF	Cerebrospinal fluid	NT	Not tested
CERAD	Consortium to Establish a Registry for Alzheimer's Disease	PPA	Parahippocampal place area
CORVIST	Cortical visual screening test	PiB	Pitsburgh compound B
CBD	Corticobasal Degeneration	PET	Positron emission tomography
CBS	Corticobasal syndrome	PM	Post mortem
CJD	Creutzfeldt-Jakob disease	PCC	Posterior cingulate cortex
DRC	Dementia Research Centre	PCA	Posterior Cortical Atrophy
DLB	Dementia with Lewy bodies	PPC	Posterior parietal cortex
DARTEL	Diffeomorphic Anatomical registration Through Exponentiated Lie Algebra	PSP	Progressive Supranuclear Palsy
EOAD	Early onset Alzheimer's disease	RMT	Recognition Memory Test
EOG	Electro-oculography	RGB	Red, green, blue (an additive colour model)
FWE	Family-wise error	ROI	Region of interest
FTLD	Frontotemporal lobar degeneration	RSC	Retrosplenial cortex
FWHM	Full width at half maximum	sRMT	Short Recognition Memory Test
fMRI	functional Magnetic Resonance Imaging	STAPLE	Simultaneous truth and performance level estimation
GLM	General linear model	SPGR	Spoiled gradient recalled
GEE	Generalised estimating equations	SD	Standard deviation
GBVS	Graph-based visual salience	SPM	Statistical Parametric Mapping
IT	Inferior temporal cortex	TDP	TAR DNA-binding protein 43
IQ	Intelligence quotient	TIV	Total intracranial volume
LOAD	Late onset Alzheimer's disease	tAD	typical (memory-led) Alzheimer's disease
LOC	Lateral occipital complex	UCL	University College London
LBP	Lewy body pathology	UT	Untestable
LP	Lumbar Puncture	VOSP	Visual Object and Space Perception battery
MRI	Magnetic Resonance Imaging	VBM	Voxel-based morphometry

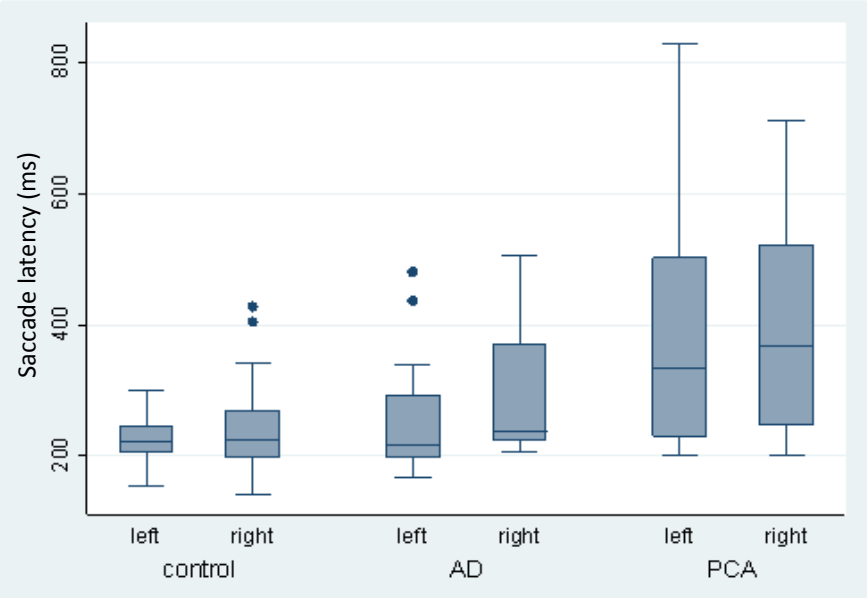
A4. Left-right differences in saccade amplitude and latency (Chapter 3)

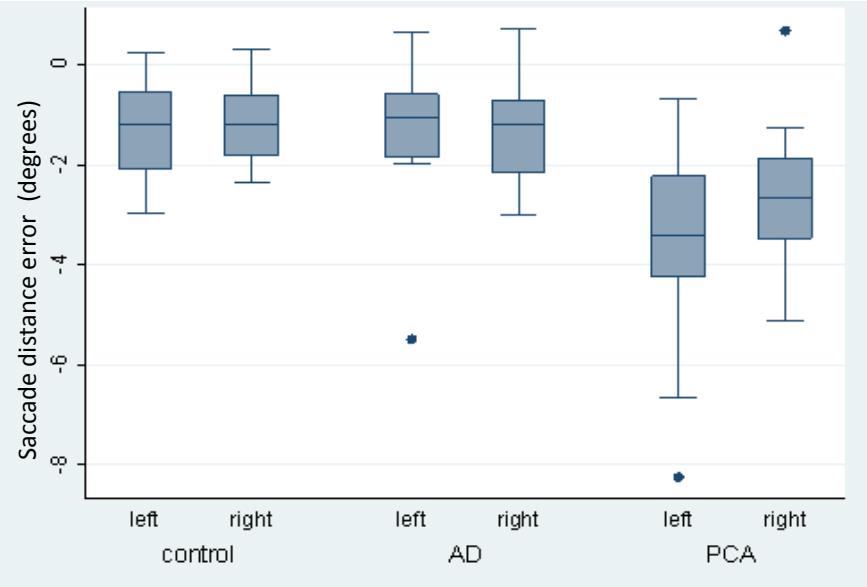
Saccade latency and saccade amplitude error for targets presented on the left, and targets presented on the right are shown in Figure A-1, for each patient group. The interaction between participant group and stimulus direction (left vs right) was tested separately for each pair of participant groups. For saccade latency, there was no interaction between stimulus direction and patient group looking at PCA and controls ($p=0.37$), typical AD and controls ($p=0.18$) and PCA and typical AD ($p=0.78$). Similarly for saccade amplitude error, there was no interaction between stimulus direction and patient group when looking at PCA and controls ($p=0.58$), typical AD and controls ($p=0.80$), and PCA and typical AD ($p=0.51$). This suggests that any bias towards better performance on one side than the other did not differ between groups.

At the individual level, 4 PCA patients and 2 typical AD patients and 2 healthy controls showed a bias towards lower amplitude of saccades on the left (bias greater than 2 SD from control performance), whilst 2 PCA patients showed a bias towards lower amplitude of saccades on the right. In terms of saccade latency, 1 typical AD patients, 1 controls and 4 PCA patient showed a bias towards longer latency on the right (again greater than 2 SD from control performance), whilst 3 PCA patients showed a greater bias to the left. Only one participant (a PCA patient) showed a consistent left-right bias greater than 2 SD from control performance in both amplitude and latency of saccades, with both measures worse for targets presented on the left than on the right.

Figure A-1 Box plots of saccade latency and amplitude error for targets on the left and right.

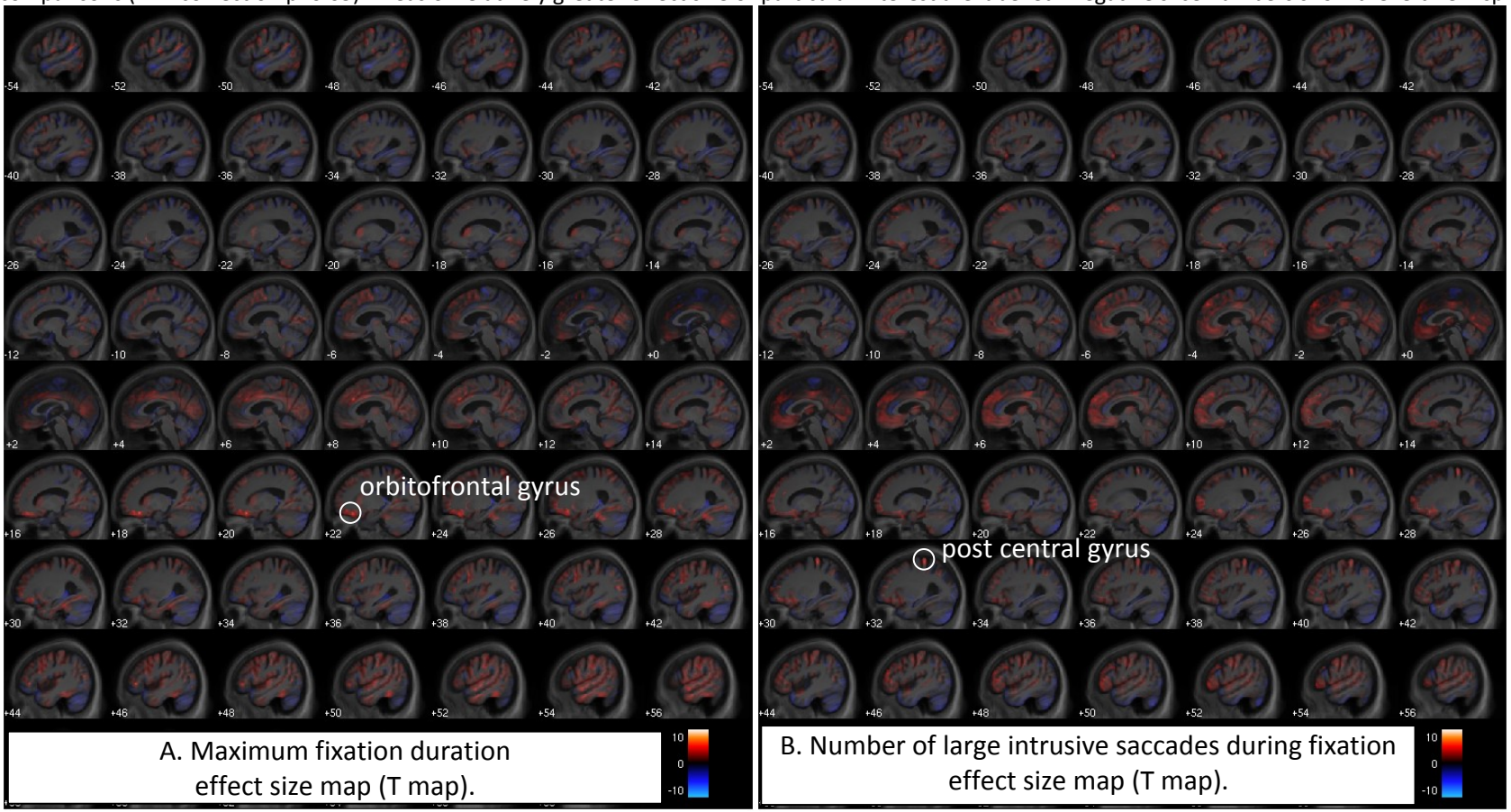


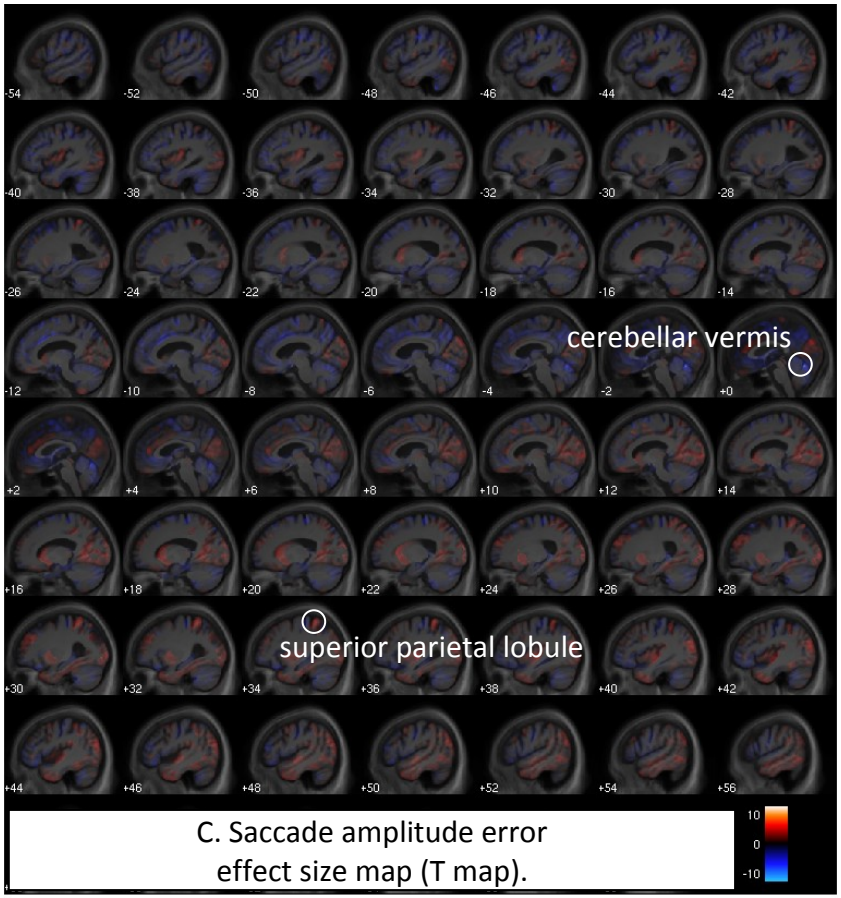

Saccade latency (ms)
200
400
600
800
left
right
left
right
left
right
control
AD
PCA


Saccade distance error (degrees)
0
-2
-4
-6
-8
left
right
left
right
left
right
control
AD
PCA

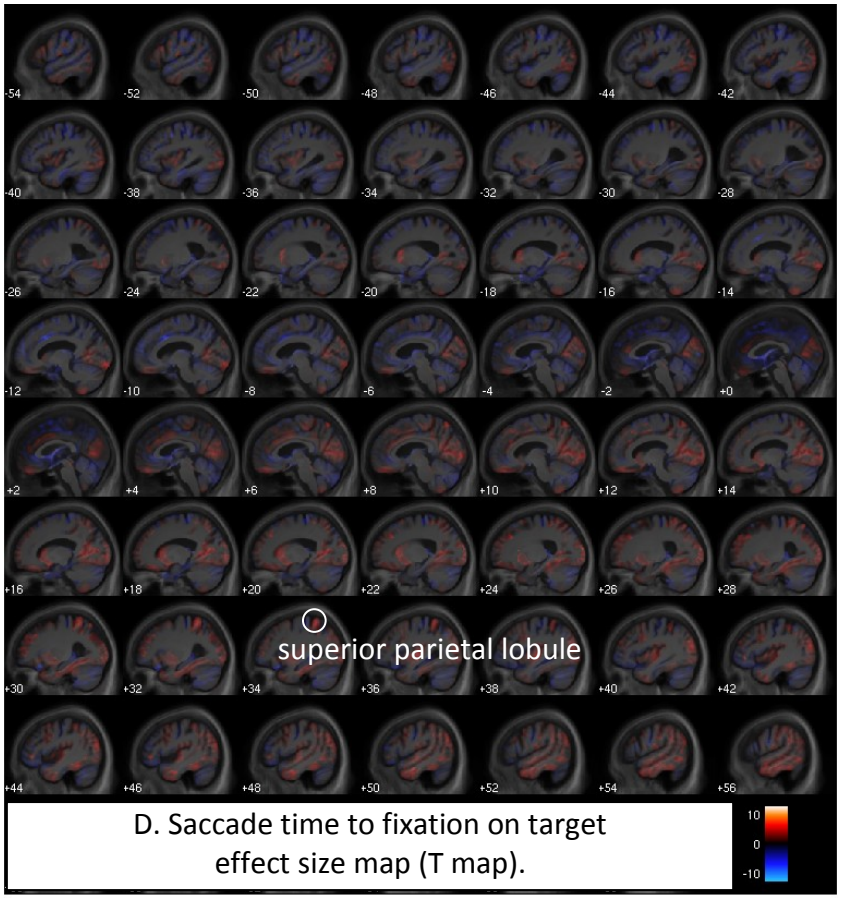
A5. Associations between oculomotor task performance and grey matter volume (Chapter 3)

Figure A-2 T value effect size maps showing the association of oculomotor task performance with grey matter atrophy in PCA patients, overlaid on the group average T1. Hot colours represent areas where worse performance is associated with greater atrophy and cold colours better performance. No areas survived correction for multiple comparisons (FDR correction p<0.05). Areas of relatively greater effect size or particular interest are labelled. Negative slice numbers show the left hemisphere.

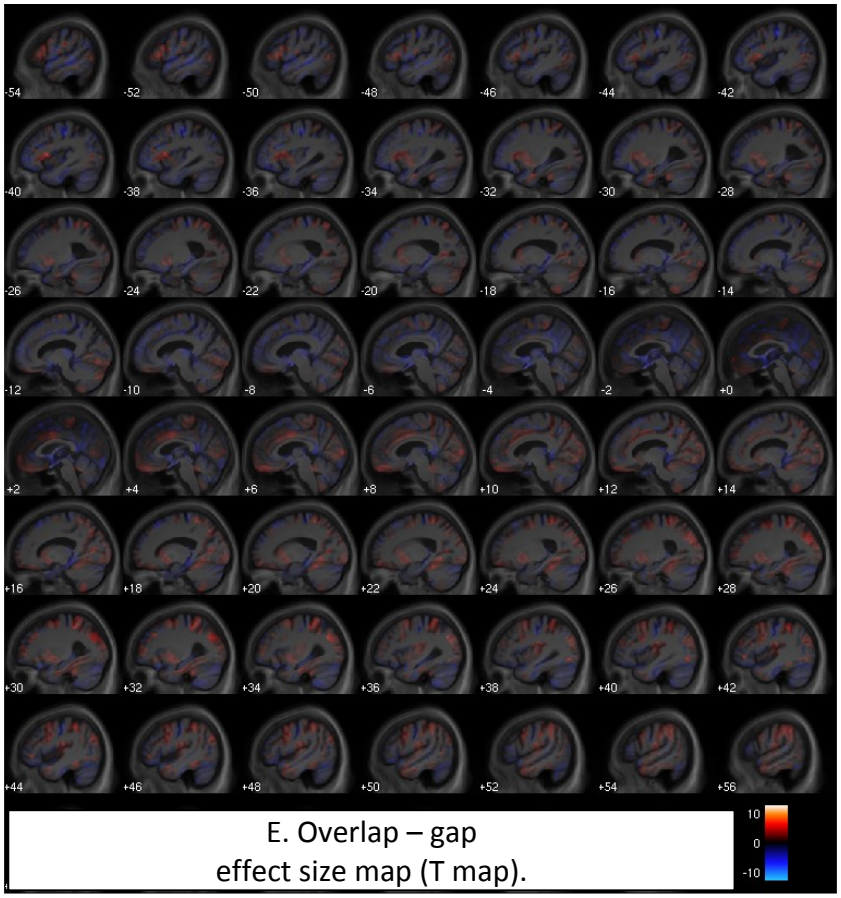




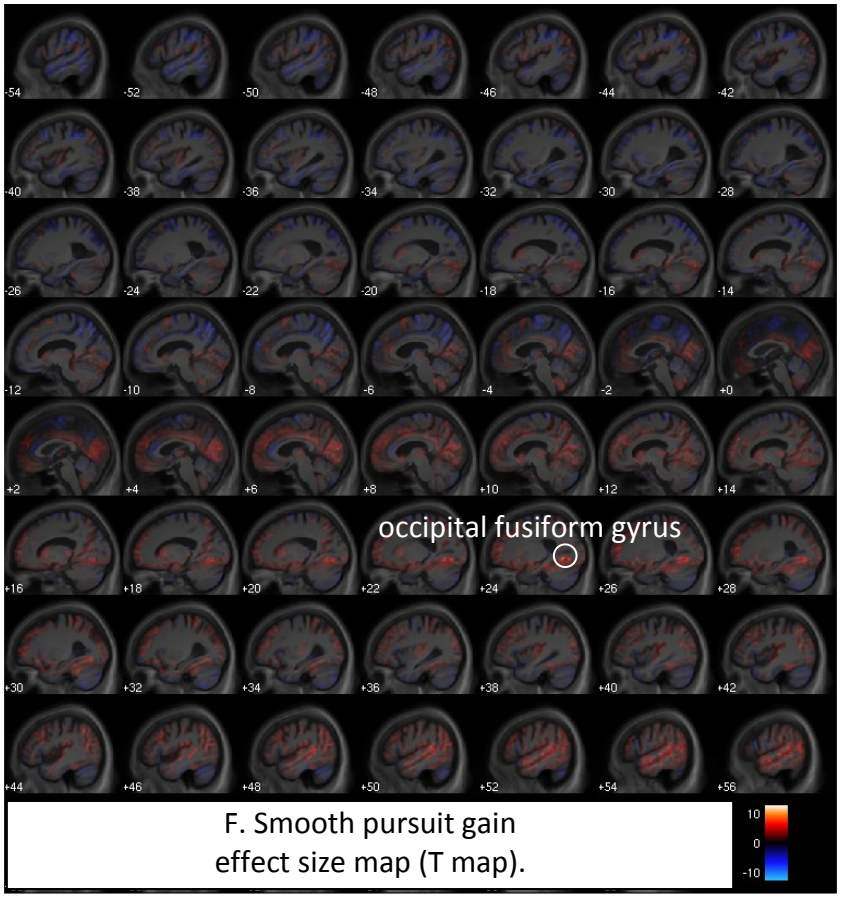
C. Saccade amplitude error effect size map (T map).



D. Saccade time to fixation on target effect size map (T map).



E. Overlap – gap
effect size map (T map).



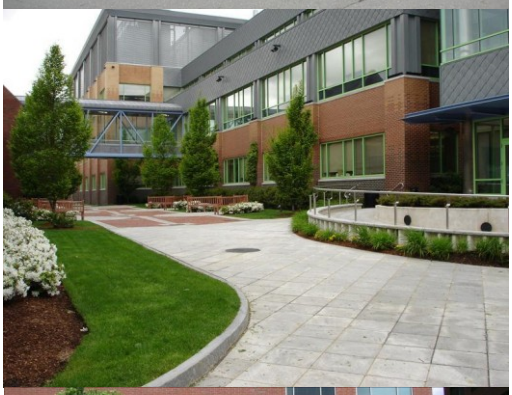
F. Smooth pursuit gain
effect size map (T map).

A6. Scene stimuli (Chapter 5)

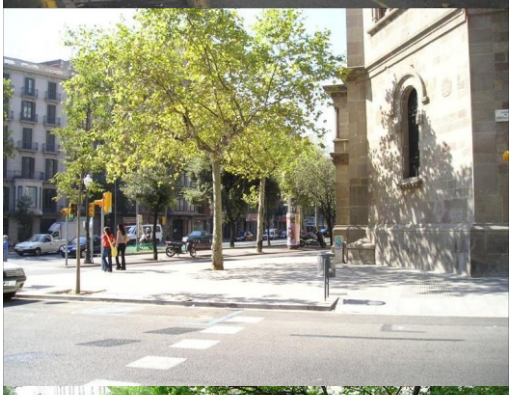
Figure A-3 Photographic stimuli from Chapter 5 These 30 photographic images of street scenes were selected from a readily available previously studied dataset (Ehinger et al., 2009).

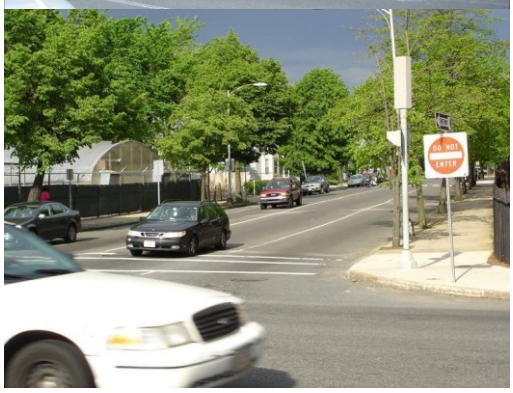


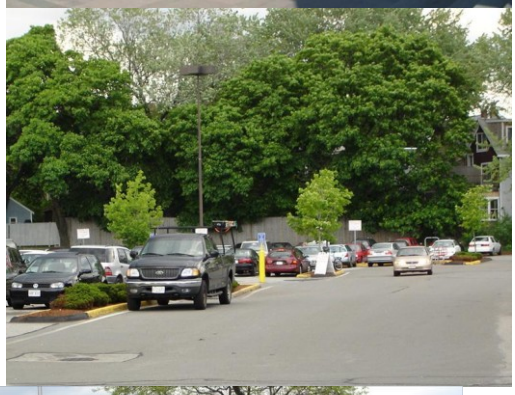


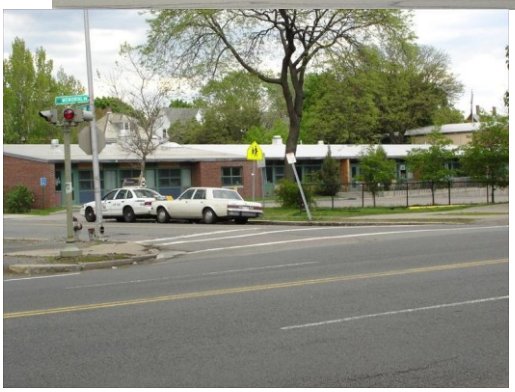







A7. Background psychology (Chapter 5)

Table A-1 Background neuropsychology for chapter 5

Patient number:	1	2	3	4	5	6	7	PCA Mean (SD)	*N* below 5th %ile	Normative Mean (SD)
Age	63.2	58.6	51.8	70.4	53.8	56.4	57.9	58.9 (6.3)	-	-
Gender	M	F	F	F	F	F	M	5f, 2m	-	-
Disease duration (years)	7	3	5	2	2	2	2	3.4 (1.9)	-	-
MMSE (/30)[a]	23	24	22	26	18	24	21	22.6 (2.6)	-	-
sRMT words (/25)[b]	20	25	24	25	21	21	20	22.3 (2.3)	0	23.7 (1.8)
sRMT faces (/25)[b]	23	15	19	22	25	22	22	21.1 (3.2)	2	22.8 (1.9)
Naming from description (/20)[c]	10	18	15	19	4	NT	17	13.8 (5.8)	3	18.9 (1.5)
Calculation (/26)[d]	19	9	9	17	9	16	9	12.6 (4.5)	4	20.7 (3.1)
Spelling (/30)[e]	7	16	7	18	5	8	5	9.4 (5.3)	5	19.5 (6.5)
Object decision (/20)[f]	14	9	12	16	16	14	7	12.6 (3.5)	5	17.7 (1.9)
Number location (/10)[f]	7	0	0	2	6	3	0	2.6 (2.9)	7	9.4 (1.1)
Concrete Synonyms (/30)[g]	16	23	21	24	23	NT	23	21.7 (2.9)	0	20.8 (3.0)

Raw scores for each patient are presented, with mean and standard deviation scores for the PCA patient group and relevant normative data. NT = not tested.
Normative data samples: a mini-mental state examination(Folstein et al. 1975); b Short Recognition Memory Test (Warrington 1996); c Randlesome (unpublished data N = 100); d Crutch (unpublished data); e Baxter spelling test (Baxter and Warrington 1994); f Visual Object and Space Perception battery (Warrington and James 1991); g Synonyms test (Warrington et al., 1998).

A8. Questions in the CBI (Chapter 6)

Table A-2 Questions in the CBI. Questions in the original CBI are blue, questions added to extend the CBI for use in patients with PCA are in red, and include care questions at the end of the questionnaire. Those questions that were included in the CBI-R are indicated in the third column, along with the CBI-R category. Participants were asked to rate the frequency of the behaviour over the last month 0 = never 1 = a few times per month 2 = a few times per week 3 = daily 4 = constantly. For everyday skills and self care, an alternative scale was used: 0 = completely independent 1 = only prompting needed 2 = mild assistance required 3 = moderate assistance required 4 = complete help required/completely unable.

Category	Question	In CBI-R?	CBI-R Category
memory	Forgets to pass on phone messages	-	-
memory	Has poor day-to-day memory (e.g. about conversations, trips etc.)	yes	memory and orientation
memory	Asks the same questions over and over again	yes	memory and orientation
memory	Loses or misplaces things	yes	memory and orientation
memory	Forgets the names of familiar people	yes	memory and orientation
memory	Forgets the names of objects and things	yes	memory and orientation
orientation and attention	Has difficulties completing activities once started	-	-
orientation and attention	Shows poor concentration when reading or watching television	yes	memory and orientation
orientation and attention	Forgets what day it is	yes	memory and orientation
orientation and attention	Forgets what time of day it is	-	-
orientation and attention	Gets the present mixed up with past situations	-	-
orientation and attention	Becomes confused or muddled in unusual surroundings	yes	memory and orientation
orientation and attention	Gets lost inside the house	-	-
everyday skills	Has difficulties using electrical appliances (e.g. TV, radio, cooker, washing machine)	yes	everyday skills
everyday skills	Has problems preparing meals	-	-
everyday skills	Has difficulties writing (letters, Christmas cards, lists etc.)	yes	everyday skills
everyday skills	Has difficulties using the telephone	yes	everyday skills
everyday skills	Has difficulties making a hot drink (e.g. tea/coffee)	yes	everyday skills
everyday skills	Has difficulties shopping	-	-

Category	Question	In CBI-R?	CBI-R Category
everyday skills	Has problems handling money or paying bills	yes	everyday skills
everyday skills	Has difficulties with household chores	-	-
self care	Has difficulties travelling to places by self (either driving or on public transport)	-	-
self care	Has difficulties grooming self (e.g. shaving or putting on make-up)	yes	self care
self care	Has difficulties dressing self	yes	self care
self care	Has problems feeding self without assistance	yes	self care
self care	Has problems bathing or showering self	yes	self care
self care	Has difficulties using toilet by self	-	-
self care	Wets self with urine	-	-
mood	Cries	yes	mood
mood	Appears sad or depressed	yes	mood
mood	Is anxious or fearful	-	-
mood	Is very restless or agitated	yes	mood
mood	Is very irritable	yes	mood
mood	Has rapid shifts between different emotions	-	-
mood	Appears inappropriately cheerful	-	-
mood	“Talks big” e.g. claims more wealth than true	-	-
mood	Finds humour or laughs at things others do not find funny	yes	abnormal behaviour
mood	Can become very frustrated	-	-
mood	Is embarrassed of their own abilities, for instance when having	-	-
beliefs	Is suspicious or accusative	-	-
beliefs	Sees things that are not really there (visual hallucinations)	yes	beliefs
beliefs	Hears voices that are not really there (auditory hallucinations)	yes	beliefs
beliefs	Has odd or bizarre ideas that cannot be true	yes	beliefs
beliefs	Believes that additional people are living in the house	-	-
beliefs	Thinks that a family member has been replaced by an impostor	-	-

Category	Question	In CBI-R?	CBI-R Category
beliefs	Thinks that people on the TV are actually in the room	-	-
challenging behaviour	Has temper outbursts	yes	abnormal behaviour
challenging behaviour	Threatens to harm self/others or property	-	-
challenging behaviour	Is uncooperative when asked to do something	yes	abnormal behaviour
challenging behaviour	Disturbs others by shouting or yelling	-	-
disinhibition	Shows socially embarrassing behaviour	yes	abnormal behaviour
disinhibition	Makes tactless or suggestive remarks	yes	abnormal behaviour
disinhibition	Displays suggestive behaviour (e.g. touching inappropriately)	-	-
disinhibition	Acts impulsively without thinking	yes	abnormal behaviour
disinhibition	Talks to total stranger as if they know them	-	-
eating habits	Prefers sweet foods more than before	yes	eating habits
eating habits	Wants to eat the same foods repeatedly	yes	eating habits
eating habits	Her/his appetite is greater, s/he eats more than before	yes	eating habits
eating habits	Table manners are declining e.g. stuffing food into mouth	yes	eating habits
eating habits	Eats non-edible foodstuffs or things not normally eaten	-	-
sleep	Sleep is disturbed at night	yes	sleep
sleep	Sleeps more by day than before (cat naps etc.)	yes	sleep
stereotypic and motor behaviours	Is rigid and fixed in her/his ideas and opinions	yes	stereotypic and motor behaviours
stereotypic and motor behaviours	Develops routines from which s/he can not easily be discouraged e.g. wanting to eat or go for walks at fixed times	yes	stereotypic and motor behaviours
stereotypic and motor behaviours	Exhibits rituals e.g. takes the same route across the kitchen, only steps on certain floor tiles	-	-
stereotypic and motor behaviours	Clock watches or appears pre-occupied with time	yes	stereotypic and motor behaviours
stereotypic and motor behaviours	Appears pre-occupied with counting, numbers, puzzles or jigsaws	-	-

Category	Question	In CBI-R?	CBI-R Category
stereotypic and motor behaviours	Takes, hides or hoards things, or packs away special items	-	-
stereotypic and motor behaviours	Repeatedly uses the same expression or catch phrase	yes	stereotypic and motor behaviours
stereotypic and motor behaviours	S/he immediately repeats words and sentences that you or others have just said (echolalia)	-	-
stereotypic and motor behaviours	Paces around without purpose	-	-
stereotypic and motor behaviours	Rummages around excessively	-	-
stereotypic and motor behaviours	S/he fidgets (e.g. bounces, taps feet/hands) a lot	-	-
motivation	Shows less enthusiasm for his or her usual interests	yes	motivation
motivation	Shows little interest in doing new things	yes	motivation
motivation	Requires nagging to start activities and chores	-	-
motivation	Shows no interest in attending social functions	-	-
motivation	Fails to maintain motivation to keep in contact with friends or family	yes	motivation
motivation	Withdraws from others, fails to start conversations	-	-
motivation	Appears indifferent to the worries and concerns of family members	yes	motivation
motivation	Shows reduced affection	yes	motivation
insight/awareness	Shows insight into changes in behaviour and personality	-	-
insight/awareness	shows insight into memory problems	-	-
insight/awareness	shows insight into visual language or other problems	-	-
movement and body	Has abnormal movement of limbs e.g. shaking. On both sides, on their left or on the right (circle as appropriate)	-	-

Category	Question	In CBI-R?	CBI-R Category
movement and body	Slower with their movements. On both sides, on their left or on the right (circle as appropriate)	-	-
movement and body	Limbs are stiff. On both sides, on their left or on the right (circle as appropriate)	-	-
movement and body	Can lose balance or not be aware of where their body is in the space around them	-	-
movement and body	Experiences dizziness	-	-
movement and body	Has severe headaches	-	-
language	Has difficulty finding the right word	-	-
language	Has trouble comprehending words or objects, or has lost the meaning of some words	-	-
language	The amount of speech they produce is significantly reduced	-	-
language	Mispronounces words, or says words that aren't real	-	-
language	Has developed stuttering or repeating sounds	-	-
vision/space	Has difficulty locating objects that are right in front of them	-	-
vision/space	Has difficulty reading	-	-
vision/space	Has difficulty perceiving distances and depth	-	-
vision/space	Has difficulty recognising people's faces	-	-
vision/space	Has difficulty identifying objects	-	-
vision/space	Has unusual experiences of colour, or lack of colour	-	-
vision/space	Has difficulty perceiving motion, perhaps not realising when things are moving, or seeing movement in things that are still.	-	-
quantity	Has difficulty using and understanding numbers	-	-
quantity	Has difficulty estimating time and duration (e.g. thinking things will take much longer or shorter than they will)	-	-
quantity	Has difficulty estimating volume or size (e.g. in comparing the size of two objects)	-	-

A9. Desikan regions (Chapter 7)

Table A-3 Division of 34 Desikan regions into 5 groups.

Region of interest	Desikan region	Region of interest	Desikan region
central	paracentral	parietal	inferiorparietal
central	postcentral	parietal	isthmuscingulate
central	precentral	parietal	precuneus
central	posteriorcingulate *	parietal	superiorparietal
frontal	caudalanteriorcingulate	parietal	supramarginal
frontal	caudalmiddlefrontal	temporal	bankssts
frontal	frontalpole	temporal	entorhinal
frontal	lateralorbitofrontal	temporal	fusiform
frontal	medialorbitofrontal	temporal	inferiortemporal
frontal	parsopercularis	temporal	insula
frontal	parsorbitalis	temporal	middletemporal
frontal	parstriangularis	temporal	parahippocampal
frontal	rostralanteriorcingulate	temporal	superiortemporal
frontal	rostralmiddlefrontal	temporal	temporalpole
frontal	superiorfrontal	temporal	transversetemporal
occipital	lateraloccipital		
occipital	lingual		
occipital	pericalcarine		
occipital	cuneus		

** The region labelled posterior cingulate in the Desikan atlas (Desikan et al., 2006) is directly inferior to the paracentral lobule, rather than the posterior-most end of the cingulate, and was therefore placed in the central region of interest.*

A10. Table of p values (Chapter 7)

Table A-4 P values for linear regression effects and post hoc pairwise comparisons in cortical thickness and subcortical volume ROI analysis. Table shows p value (mean difference) for each of the pairwise comparisons performed. Shading indicates p<0.05.

P value (difference)	PCA-CBS vs Control[1]	PCA+CBS vs Control[1]	PCA+CBS vs PCA-CBS[2]	L vs R in controls[3]	L vs R in PCA+CBS[3]	L vs R in PCA-CBS[3]	L vs R in controls compared to PCA+CBS[4]	L vs R in controls compared to PCA-CBS[4]	L vs R in PCA+CBS compared to PCA-CBS[5]
Cortical ROIs									
All	<0.001 (-0.25)	<0.001 (-0.33)	0.730 (-0.03)	0.388 (0.00)	<0.001 (-0.09)	0.963 (0.00)	<0.001 (0.10)	0.849 (0.00)	<0.001 (0.10)
Parietal	<0.001 (-0.40)	<0.001 (-0.41)	0.978 (-0.01)	0.043 (0.02)	<0.001 (-0.13)	0.864 (0.00)	<0.001 (0.15)	0.570 (0.02)	<0.001 (0.14)
Frontal	0.013 (-0.08)	0.030 (-0.11)	0.826 (-0.02)	<0.001 (-0.06)	0.007 (-0.08)	0.006 (-0.04)	0.630 (0.02)	0.413 (-0.02)	0.297 (0.03)
Temporal	<0.001 (-0.29)	<0.001 (-0.34)	0.611 (-0.05)	0.008 (0.03)	0.006 (-0.08)	0.228 (0.04)	<0.001 (0.11)	0.863 (-0.01)	0.008 (0.12)
Occipital	<0.001 (-0.27)	<0.001 (-0.26)	0.455 (0.01)	<0.001 (0.04)	0.004 (-0.09)	0.155 (0.03)	<0.001 (0.13)	0.520 (0.01)	0.002 (0.11)
Central	<0.001 (-0.18)	<0.001 (-0.26)	0.240 (-0.08)	0.309 (-0.01)	<0.001 (-0.10)	0.242 (-0.03)	<0.001 (0.09)	0.550 (0.01)	0.013 (0.07)
Subcortical ROIs									
All	<0.001 (-509)	<0.001 (-848)	0.009 (-339)	<0.001 (242)	0.426 (-63)	<0.001 (221)	<0.001 (305)	0.761 (21)	0.006 (284)
Caudate	0.002 (-411)	0.002 (-417)	0.998 (-6)	0.614 (62)	0.86 (-39)	0.666 (-31)	0.689 (101)	0.514 (93)	0.973 (8)
Putamen	0.002 (-393)	0.002 (-841)	0.004 (-448)	0.084 (129)	0.304 (-87)	0.003 (214)	0.057 (216)	0.406 (-85)	0.008 (301)
Thalamus	<0.001 (-723)	<0.001 (-1,286)	0.005 (-563)	<0.001 (535)	0.464 (-63)	<0.001 (480)	<0.001 (598)	0.697 (56)	<0.001 (543)

1. Negative means represent reduced thickness in the PCA-CBS and PCA+CBS group than control group,

2. Negative means represent reduced thickness in the PCA+CBS group compared to the PCA-CBS group.

3. Negative means represent reduced thickness in the right hemisphere.

4. Positive means represent greater asymmetry (right thinner than left) in the PCA+CBS compared to control and PCA-CBS groups.

5. Positive means represent greater asymmetry (right thinner than left) in the PCA+CBS compared to PCA-CBS group.

A11. Table of effect sizes (Chapter 7)

Table A-5 Cohen's d measure of effect size for PCA+CBS vs. PCA-CBS (the two groups differ by d of a standard deviation, e.g. a d of 0.5 means they differ by half a SD, and is considered a medium effect size). Dark shading indicates large effect size, light shading indicates small effect size. The warm colours are used when thickness or volume is lower in PCA+CBS than PCA-CBS, cold colours show the opposite.

all cortical areas		**parietal**		**frontal**		**temporal**		**occipital**		**central**	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
0.06	0.28	0.40	0.51	0.04	0.26	0.03	0.58	0.45	0.36	0.23	0.70

all subcortical areas		**caudate**		**putamen**		**thalamus**	
Left	Right	Left	Right	Left	Right	Left	Right
0.20	0.41	0.00	0.01	0.47	0.88	0.39	1.00

PCA+CBS less than PCA-CBS		
large	medium	small
PCA-CBS less than PCA+CBS		
large	medium	small