Lateralized occipital degeneration in posterior cortical atrophy predicts visual field deficits

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**A B S T R A C T**

**Background:** Posterior cortical atrophy (PCA), the visual variant of Alzheimer’s disease, leads to high-level visual deficits such as alexia or agnosia. Visual field deficits have also been identified, but often inconsistently reported. Little is known about the pattern of visual field deficits or the underlying cortical changes leading to this visual loss.

**Methods:** Multi-modal magnetic resonance imaging was used to investigate differences in gray matter volume, cortical thickness, white matter microstructure and functional activity in patients with PCA compared to age-matched controls. Additional analyses investigated hemispheric asymmetries in these metrics according to the visual field most affected by the disease.

**Results:** Analysis of structural data indicated considerable loss of gray matter in the occipital and parietal cortices, lateralized to the hemisphere contralateral to the visual loss. This lateralized pattern of gray matter loss was also evident in the hippocampus and parahippocampal gyrus. Diffusion-weighted imaging showed considerable effects of PCA on white matter microstructure in the occipital cortex, and in the corpus callosum. The change in white matter was only lateralized in the occipital lobe, however, with greatest change in the optic radiation contralateral to the visual field deficit. Indeed, there was a significant correlation between the laterality of the optic radiation microstructure and visual field loss.

**Conclusions:** Detailed brain imaging shows that the asymmetric visual field deficits in patients with PCA reflect the pattern of degeneration of both white and gray matter in the occipital lobe. Understanding the nature of both visual field deficits and the neurodegenerative brain changes in PCA may improve diagnosis and understanding of this disease.

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1. Introduction

Posterior cortical atrophy (PCA) is a progressive neurodegenerative disease, often described as the visual variant of Alzheimer disease (AD). The disorder is characterized by an early presentation of higher order visual processing deficits and mild memory impairments, with memory dysfunction occurring with progression of the disease (Crutch et al., 2012).

The most commonly reported impairments in PCA are high-level visual problems such as alexia or visuospatial processing, however hemianopia has been reported in a number of studies. Reported incidence of hemianopia in PCA is between 10 and 20% in most studies (Schmidtke et al., 2005; McMonagle et al., 2006; Whitwell et al., 2007; Andrade et al., 2010), the highest being 80% (Kaeser et al., 2015). Tang-Wai et al. (2004) found hemianopia to be one of the most prevalent visual deficits in their cohort of PCA patients, with 35% exhibiting a homonymous field deficit, and a further 12.5% having less consistent field deficits. As such, they proposed that visual field deficits should be considered a core clinical feature in diagnosing PCA. However, in spite of the number of studies reporting hemianopia in PCA patients, the prevalence, and indeed the existence of visual field deficits in these patients remains controversial. Crutch et al. (2012) state that hemianopia is often misdiagnosed in PCA patients due to the presence of higher-level visual deficits such as hemispatial neglect, and older studies of the visual deficits in PCA patients have failed to report any visual field deficits (Benson et al., 1988; Victoroff et al., 1994). Mendez et al. (2002) actively screened out patients with visual field deficits when constructing a cohort in which to study the clinical characteristics of PCA, citing intact primary visual function as a core diagnostic feature. Indeed many studies investigating the visual deficits characteristic of PCA do not include visual field testing in their study battery, although field deficits may be incidentally reported. Where visual field loss has been accounted for, visual confrontation is often used (Benson et al., 1988;...
Andrade et al., 2010), which is not as sensitive as perimetry in detecting field deficits (Johnson and Baloh, 1991).

While recent studies have attempted to systematically quantify visual fields in PCA patients (Formaglio et al., 2009; Pelak et al., 2011), little is known of the pattern of degeneration underlying this visual deficit, and its relationship to homonymous hemianopia due to V1 damage. Neuroimaging in PCA has indicated bilateral loss of gray matter in the occipital, parietal, and posterior temporal lobes, and the right hemisphere appears to be more severely affected (Whitwell et al., 2007; Migliaccio et al., 2012a, 2012b), particularly in patients with more ‘dorsal’ symptoms (Migliaccio et al., 2012c). Similarly, case studies indicate white matter microstructure is also affected in the parietal and occipital lobes (Duning et al., 2009) and may be present throughout the major white matter pathways involved in visuo-spatial processing (Migliaccio et al., 2012c).

The aim of the present study was firstly to shed light on the pathological basis of the visual field defects in this group of patients and secondly to use the existence of the defect as a marker of asymmetry in the involvement of the two hemispheres. Comparisons between symmetrical structures in the same individual can prove more sensitive in revealing change than between cases and controls. Thus, we apply multimodal neuroimaging to test the hypothesis that asymmetric degeneration of gray and white matter in the occipital cortex underlies the lateralized visual field deficits present in these PCA patients.

2. Methods

2.1. Subjects

Ten patients with a diagnosis of PCA were recruited from the National Hospital for Neurology and Neurosurgery. For a diagnosis of PCA, patients needed to demonstrate progressive impairment of posterior cortical function with relative preservation of memory and other cognitive functions. The cases all fulfilled the diagnostic criteria proposed by Tang-Wai et al. (2004) with the exception that the presence of a visual field defect was a necessary condition for inclusion. The patients were all recruited from a neuro-ophthalmology clinic and therefore were often referred due to presence of a visual field deficit. Furthermore, all patients who attend the clinic have automated fields performed as part of standard work up, so deficits are more likely to be detected. Patient ages ranged from 53 to 77 years (median 70), and included six females and four males. All patients displayed an asymmetric visual field deficit, with eight having the greatest VF loss in the left hemisphere. The longest time since diagnosis of PCA was 6 years (P01), and the shortest was three months (P06), although in most cases PCA symptoms had been present for some time before diagnosis. Estimated time since onset of symptoms in each patient is given in Table 1. Prior to inclusion in the study, patients underwent neuropsychological assessment to ensure memory deficits did not exceed mild cognitive impairment. A summary of patient details is given in Table 1.

Data collected from ten healthy controls were used to compare with the PCA patients (age range 57–78, median age 73, 4 females). Four of these were scanned for a previous study, and six were scanned as part of Oxford Project to Investigate Memory and Ageing (OPTIMA). For the fMRI analyses, a slightly different set of control data was used as fMRI data was not collected in OPTIMA (n = 9, age range 31–74, median age 52, 4 females).

All participants gave written informed consent prior to participation, and the study was granted ethical approval from the Oxfordshire National Health Service Research Ethics Committee (08/H0605/156).

2.2. Perimetry

Patients with a diagnosis of PCA with no evidence of any other opthalmic or neurological disorder were screened for inclusion in the study. Humphrey visual fields (HVF) were acquired with a Zeiss Humphrey Field Analyzer, using central 24–2 threshold test and SITA-Standard strategy. Patients who demonstrated consistent homonymous visual field deficits were recruited for the study. Visual field examples are shown in Fig. 1. Half of the patients showed VF loss in both hemifields, although in all cases the deficit was greater in the left

![Fig. 1. Examples of visual field deficits in patients with PCA. In P02 and P10 the deficit is limited to a hemi-field, while in P03 and P04 both hemifields are affected to an extent. The shade of the box indicates the number of trials seen at each location after correction for generalised decreases in visual sensitivity with white being areas most sensitive to visual stimuli and black being locations with the greatest visual field loss.]
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