Basic Visual Function and Cortical Thickness Patterns in Posterior Cortical Atrophy

Manja Lehmann1, Josephine Barnes1, Gerard R. Ridgway1, John Wattam-Bell2, Elizabeth K. Warrington1, Nick C. Fox1 and Sebastian J. Crutch1

1Dementia Research Centre, UCL Institute of Neurology, University College London, London WC1N 3BG, UK and 2Visual Development Unit, Psychology and Language Sciences Division, University College London, London WC1E 6BT, UK

Address correspondence to Dr Sebastian Crutch. Email: s.crutch@drc.ion.ucl.ac.uk.

Posterior cortical atrophy (PCA) is characterized by a progressive decline in higher-visual object and space processing, but the extent to which these deficits are underpinned by basic visual impairments is unknown. This study aimed to assess basic and higher-order visual deficits in 21 PCA patients. Basic visual skills including form detection and discrimination, color discrimination, motion coherence, and point localization were measured, and associations and dissociations between specific basic visual functions and measures of higher-order object and space perception were identified. All participants showed impairment in at least one aspect of basic visual processing. However, a number of dissociations between basic visual skills indicated a heterogeneous pattern of visual impairment among the PCA patients. Furthermore, basic visual impairments were associated with particular higher-order object and space perception deficits, but not with nonvisual parietal tasks, suggesting the specific involvement of visual networks in PCA. Cortical thickness analysis revealed trends toward lower cortical thickness in occipitotemporal (ventral) and occipitoparietal (dorsal) regions in patients with visuoperceptual and visuospatial deficits, respectively. However, there was also a lot of overlap in their patterns of cortical thinning. These findings suggest that different presentations of PCA represent points in a continuum of phenotypical variation.

Keywords: Alzheimer’s disease, atrophy, basic visual processing, MRI, neuropsychology

Introduction

Research into neurodegenerative diseases is frequently grounded in the idea that diseases are defined by characteristic clinico-anatomical syndromes, such as the parietotemporal syndrome of Alzheimer’s disease (AD; Cummings 2004). However, this premise is moderated by the existence of phenotypic variation in which different patterns of behavioral and structural dysfunction result from a common pathology affecting different brain regions to different extents (e.g., amnestic, visual, and aphasic presentations of AD; Galton et al. 2000; Lambon Ralph et al. 2003). Investigating the clinical, cognitive, structural, functional and genetic similarities, and differences between these phenotypes offers the opportunity to understand more about the pathophysiological mechanisms of the disease as a whole. The current study uses behavioral and neuroimaging data to investigate individuals with posterior cortical atrophy (PCA).

PCA is a clinical syndrome characterized by a progressive, dramatic and relatively selective decline in higher-visual processing, and other posterior cortical functions (Benson et al. 1988; Tang-Wai et al. 2004). The syndrome has been labeled alternatively Benson’s syndrome or biparietal AD. The condition is most commonly associated with the histopathological features of AD, however, a minority of cases of PCA have been attributed to alternative etiologies including corticobasal degeneration, dementia with Lewy bodies, and prion disease (Tang-Wai, Josephs, Boeve, Dickson, et al. 2003; Tang-Wai, Josephs, Boeve, Petersen, et al. 2003; Renner et al. 2004). In those PCA patients with AD pathology, the distribution of that pathology has been shown to differ from typical AD, with a greater density of senile plaques and neurofibrillary tangles in occipital, posterior parietal, and temporo-occipital cortex and fewer pathological changes in more anterior areas such as prefrontal cortex (e.g., Levine et al. 1993; Ross et al. 1996; Hof et al. 1997). The exact prevalence and incidence of PCA are not known, but investigations of patients with probable AD suggest that posterior presentations may account for up to 5% of AD cases (Snowden et al. 2007) with age at onset most commonly reported as being in the 50s or 60s (Mendez et al. 2002; McMonagle et al. 2006). Some assessments of Apolipoprotein E (ApoE) status have indicated a lower prevalence of ε4 alleles in PCA than in typical AD patients (Schott et al. 2006; Snowden et al. 2007), although not all studies have detected a difference in allele distribution between PCA and typical AD (e.g., Mendez et al. 2002; Tang-Wai et al. 2004; Migliaccio et al. 2009).

As the term PCA suggests, the syndrome is associated with posterior tissue loss primarily of the occipital, parietal, and temporo-occipital cortices. To date, only 2 systematic evaluations of brain structure in PCA using automated methods have been conducted, with voxel-based morphometry (VBM) revealing greater right parietal atrophy and less left medial temporal and hippocampal atrophy in PCA patients compared with those with typical AD (Whitwell et al. 2007; Lehmann et al. 2009). In addition, direct cortical thickness comparisons between PCA and typical AD revealed thinner cortex in the right superior parietal lobe and relatively thicker cortex in the left entorhinal cortex in the PCA subjects (Lehmann et al. 2009). The principal behavioral factors distinguishing patients with PCA from those with typical AD are relatively spared episodic memory function in conjunction with prominent impairments of space perception, object perception, and other posterior cognitive functions. Indeed, it is noteworthy that with a relative preservation of episodic memory, many individuals with PCA do not meet all established criteria for dementia (e.g., Diagnostic and Statistical Manual of Mental Disorders). The most frequently cited neuropsychological deficits in PCA include agnosia, alexia, agraphia, acalculia, apraxia, and some or all of the features of Balint’s syndrome (simultanagnosia, oculomotor apraxia, optic ataxia, environmental agnosia; Mendez et al. 2002; Tang-Wai et al. 2004; Renner et al. 2004; Charles and Hills 2005; McMonagle et al. 2006).

Although PCA is often considered a relatively homogeneous syndrome, clinical experience indicates that a degree of heterogeneity exists in the behavioral and neuroimaging profiles of PCA patients. Extrapolating from basic
neuroscientific evidence of distinct cortical streams that process different kinds of visual information (Ungerleider and Mishkin 1982; Goodale and Milner 1992), it has been suggested that separate parietal (dorsal) and occipitotemporal (ventral) forms of PCA exist (Ross et al. 1996). A third, primary visual (striate cortex; caudal) form of PCA has also been proposed (Galton et al. 2000). However, these claims are based upon the observation of patterns of impairment in single cases. Furthermore, the most detailed neuropsychological study of PCA to date found evidence of object perception deficits, faces, and colors in a proportion of the patients tested, but overall the pattern of impairments was suggestive of greater impairment of the dorsal than ventral visual processing streams as no pure ventral stream syndromes were detected (McMonagle et al. 2006).

One limitation in understanding PCA and evaluating the relationship between PCA and typical AD is that very few studies have assessed the integrity of fundamental, basic visual processes supported by striate and extrastriate occipital cortex (e.g., basic form, color, motion, and location processing). Without testing these basic visual functions, it is difficult to determine whether higher-order object and space perception deficits are attributable to parietotemporal tissue loss, or in fact result from a more fundamental deafferentation of such areas owing to occipital lobe disease. A second limitation is that no studies reported to date have systematically evaluated both neuropsychological deficits and patterns of brain atrophy using quantitative, unbiased methods in a large group of patients.

The current study was designed to address these limitations, with the motivation that only with increasingly precise characterizations of AD-associated syndromes such as PCA can factors driving the distribution and spread of pathology underpinning typical and atypical clinical presentations be elucidated. The study investigated a relatively large sample of patients with PCA using the dual methodologies of detailed neuropsychological evaluation and systematic measurement of cortical thickness. The primary hypothesis was that higher-order visual deficits in PCA are associated with specific and separable patterns of basic visual processing. The secondary hypothesis was that different patterns of posterior behavioral dysfunction are associated with distinct patterns of anatomical change. These hypotheses were addressed by 1) characterizing the basic visual, space, and object perceptual processing abilities of patients with PCA; 2) identifying associations and dissociations between specific basic visual functions and measures of higher-order object and space perception; and 3) assessing whether PCA patients with predominant object and space perception impairments show greater cortical thinning in dorsal (superior parietal) and ventral (occipitotemporal) regions. It is demonstrated that the object and spatial agnosias commonly reported in PCA are underpinned by specific patterns of basic visual dysfunction, but that there is only modest support for the behavioral and anatomical distinction of dorsal and ventral phenotypes.

Methods and Materials

Subject Characteristics

The study involved 21 patients (12 females, 9 males, mean (standard deviation) age: 63.5 (7.7) years) with a clinical diagnosis of PCA owing to probable AD. Demographics and clinical data of the subjects are summarized in Table 1. A group of 20 healthy control subjects was included for comparison of the imaging data (11 females, 9 males, mean (standard deviation) age: 61.9 (10.6) years). The groups were matched for gender ($P = 1$), age ($P = 0.7$), and scanner distribution ($P = 0.7$). All clinically affected subjects had attended the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, London, United Kingdom. Written informed consent was obtained using procedures approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee.

All PCA patients fulfilled the clinical criteria proposed by Mendez et al. (2002) and Tang-Wai et al. (2004). In addition, patients were only included if there was evidence of fulfillment of a set of PCA-specific neuropsychological criteria at some stage in their clinical history (either at or prior to the current experimental investigations). These criteria required posterior cognitive dysfunction with concomitant memory preservation. Specifically an individual had to demonstrate relatively preserved episodic memory (>5th percentile on a recognition memory test; Warrington 1984; Warrington 1996), along with neuropsychological deficits (<5th percentile) in at least 2 of the following 4 posterior cortical functions: 1) object perception (Visual Object and Space Perception Battery object decision test; Warrington and James 1991), 2) space perception (VOSP number location test), 3) calculation (graded difficulty arithmetic test; Jackson and Warrington 1986), and 4) spelling (graded difficulty spelling test; Baxter and Warrington 1994). It should be noted that at the time of experimental investigations, some PCA patients had progressed to a more global pattern of impairment including mild memory impairment.

Background Neuropsychological Assessment

Each patient completed a background neuropsychological battery at the time of the current experimental investigations, including tests of general cognitive function, verbal recognition memory, word comprehension, naming from verbal description, cognitive estimates, calculation, spelling, gesture production, and auditory-verbal short-term memory. In addition, patients were administered tests of visual acuity, space perception, and object perception. The test details, scores, and percentage of patients failing each task are shown in Table 1. Verbal recognition memory, verbal comprehension, and visual acuity were generally well preserved, but the majority of patients showed deficits in calculation, praxis, and short-term memory. In particular, 95% of patients failed one or both space perception tasks, and 100% of patients failed at least 2 object perception tasks.

Experimental Investigations of Basic Visual Processing

The following detailed experimental investigations were administered in order to assess the contribution of basic form, color, motion, and location processing to the object and space perception deficits observed in the PCA cohort.

Form I: Form Detection

VOSP shape detection test (Warrington and James 1991) examining figure-ground discrimination. Stimuli ($N = 20$) were random black patterns, half with a degraded ‘X’ superimposed. Patients were requested to state whether an ‘X’ was present.

Form II: Form Coherence

Adapted from Braddick et al. (2000), the stimuli ($N = 80$) consisted of static arrays of 3000 randomly oriented short line segments. In half the arrays, a percentage of the line segments in an 11.8° central region were coherently oriented tangentially to concentric circles. In the remaining arrays, all line segments were arranged randomly. There were 4 levels of difficulty: 90%, 70%, 50%, and 30% coherence. Patients were requested to state whether a “circle” was present in each stimulus.

Form III: Form Discrimination

The stimuli ($N = 60$) for this boundary detection task, adapted from Efron (1968), were a square ($50 \times 50$ mm) or an oblong matched for total flux. There were 3 levels of difficulty: oblong edge ratio 1:1.63.
Table 1
Background neuropsychological assessment conducted at the time of the experimental investigations

| Patient number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | PCA Mean (SD) | N below 5th %ile | Normative Mean (SD) |
| Age            | 69 | 72 | 64 | 49 | 61 | 77 | 58 | 61 | 62 | 61 | 63 | 66 | 64 | 60 | 70 | 56 | 57 | 51 | 63 | 73 | 78 | 63.5 (7.7) | —            | —               |
| Gender         | M  | F  | M  | F  | M  | F  | F  | F  | M  | M  | F  | M  | M  | F  | F  | F  | M  | F  | M  | M  | 6.6 (5.0) | —            | —               |
| Disease duration (years) | 3.5 | 5.0 | 4.3 | 4.5 | 8.8 | 10.9 | 2.3 | 3.2 | 3.4 | 9.1 | 3.0 | 3.8 | 5.6 | 3.4 | 3.5 | 1.7 | 5.0 | 1.7 | 5.8 | 9.1 | 6.6 (5.0) | —            | —               |
| General function | MMSE (1/30)* | 27 | 26 | 26 | 26 | 25 | 24 | 24 | 24 | 22 | 21 | 21 | 21 | 21 | 21 | 19 | 19 | 19 | 18 | 17 | 15 | 21.5 (3.4) | —            | —               |
| Short RMT (words; /25)** | 22 | 22 | 21 | 20 | 20 | 24 | 24 | 19 | 21 | 17 | 22 | 22 | 19 | 23 | 20 | 23 | 19 | 17 | 15 | 14 | 18 | 20.1 (2.8) | 5 (24%)     | 23.5 (2.1)     |
| Concrete synonyms (/5)** | 22 | 24 | 18 | 20 | 20 | 22 | 24 | 25 | 24 | 20 | 14/17** | 24 | 24 | 23 | 22 | 22 | 16 | 19 | 14 | 18 | 22.3 (3.1) | 1 (5%)      | 20.8 (3.0)     |
| Naming (/20)** | 19 | 17 | 5 | 19 | 10 | 15 | 17 | 13 | 10 | 14 | 9/10** | 19 | 18 | 20 | 5 | 16 | 12 | 14 | 5 | 6 | 17 | 13.6 (5.1) | 12 (57%)    | 18.9 (1.5)     |
| Cognitive estimates** | 6 | 9 | 14 | 6 | 13 | 13 | 14 | 11 | 10 | 12 | 7 | 7 | 1 | 2 | 15 | 16 | 18 | 13 | 18 | 15 | 12.0 (6.6) | 15 (71%)    | 3.6 (1.9)      |

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.

**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 Shallice and Evans 1978
- f cortical visual screening test (CORVIST); James et al. 2001
- g Wechsler (unpublished data; N = 100)
- h Baxter and Warrington 1994
- i Wechsler 1987
- j Warrington and James 1991
- k Warrington and James 1998
- l English not first language.
- m Below mean normal performance.

(Level 1), 1.1.37 (Level II), and 1.1.20 (Level III). The task was to determine whether each shape presented was a square or an oblong.

**Color Discrimination**

The stimuli (N = 60) were pairs of matte color chips presented adjacently. The colors were selected from the Munsell color system and had fixed value and chroma (6/6). There were 3 difficulty levels based on varying the distance between hue pairs on the Munsell hue scale. The task was to determine whether the hues in each pair were the same or different.

**Motion Coherence**

Using the same experimental paradigm as the form coherence task, the stimuli (N = 80) were arrays of 3000 0.1° high-contrast dots drifting in random linear directions (5.12°/s). In half the arrays, the direction of motion of a percentage of dots in an 11.8° central region was coherently circular. In the remaining arrays, all the dots moved in random directions. There were 4 levels of difficulty: 90%, 70%, 50%, and 30% coherence. Patients were requested to state whether a "moving circle" was present in each stimulus.

**Point Localization**

The stimuli (N = 8) were A3 laminated white cards with a single, randomly positioned black dot (5 mm diameter). The position of each dot was revealed for 3 s before the stimulus was covered by a second blank A3 card, and participants were requested to mark the position of the dot on the blank sheet using a pen in their dominant hand. Target–response discrepancy was measured.

**Neuropsychological Data Analysis**

**Correlations**

Performance on each level of each experimental task was recorded as a raw score, and a total score calculated for multilevel tasks. In the calculation of total scores, performance at untestable levels and scores <10 were assigned a chance score of 10/20. Correlations were based on total scores.

**Dissociations**

Raw total scores were converted to rank scores, by ranking the order performance among the 21 PCA patients from 1 (=lowest performance) to 21 (=highest performance), using split-tied ranks where more than one patient achieved the same score. Rank score discrepancies were calculated between each pairwise combination of tests. To minimize the chance of discrepancies reflecting only minor variations in performance, only discrepancies of 10 or more ranking places were selected (e.g., patients who had the 4th best score on one test but only the 16th best score on another).

**Syndrome Subgroups**

Two behavioral subgroups were generated on the basis of object perception and space perception composite scores (the mean performance across the fragmented letters/object decision and number location/dot counting scores, respectively, transformed onto linear scales of 0–100 representing minimum and maximum values of the range of PCA group performance). The Object subgroup (N = 11) showed lower object than space perception composite scores, whilst the Space subgroup (N = 9) showed the reverse tendency (see Fig. 1).

**Brain Image Acquisition and Analyses**

Magnetic resonance brain images (MRI) were acquired from all patients and controls, however, one patient (no. 10, Space subgroup) had to be excluded due to an artifact on the scan. Therefore, 20 patients and 20 control subjects were included for the imaging analysis. Scans were acquired at 2 different scanners. The average time between psychological assessment and scan was 27.7 days (SD 72.2 days). Controls and patients were matched for scanner: 14 patients and 14 controls were scanned on a 1.5T GE Signa scanner using an inversion-recovery prepared fast spoiled Gradient-Recalled sequence (time echo [TE] = 5.4 ms, readout interval time repetition [TR] = 12 ms, and time to inversion [TI] = 650 ms). T1-weighted volumetric images were obtained with a 24-cm field of view and 256 x 256 matrix to provide 124 contiguous 1.5-mm-thick slices in the coronal plane. Six patients and 6 controls were scanned on a Siemens Trio TIM 3T scanner using an Magnetization Prepared Rapid Acquistion Gradient Echo sequence (TE = 2.9 ms, inversion interval TR = 2200 ms, and TI = 900 ms). T1-weighted volumetric images were obtained with 28.2-cm field of view.
view and 256 x 256 acquisition matrix to provide 208 contiguous 1.1-mm-thick slices in the sagittal plane. In the subgroup analysis, 8/9 scans in the Space subgroup and 6/11 scans in the Object subgroup were acquired on the 1.5T scanner.

**Cortical Thickness**

Cortical thickness measurements were made using the freely available software FreeSurfer, version 4.3.0. (http://surfer.nmr.mgh.harvard.edu/). The detailed procedure for the surface construction has been described and validated in previous publications (Dale et al. 1999; Fischl and Dale 2000). Cortical thickness was smoothed with a 20 mm full-width at half height Gaussian kernel to reduce local variations in the measurements for further analysis. Two modifications to the standard FreeSurfer processing stream were undertaken: a locally generated brain mask was used for skull stripping, and FreeSurfer ventricular segmentations were added to the white matter mask to improve cortical segmentation.

**Statistical Analysis**

Regional cortical thickness variations between the PCA group and the control group were assessed using a vertex-by-vertex general linear model, performed with the SurfStat software (http://www.stat.uchicago.edu/~worlsery/surfstat/). Cortical thickness (C) was modeled as a function of group, controlling for age (mean centered), gender, and scanner by their inclusion as covariates: $C = \beta_1$ (controls) + $\beta_2$ (PCA) + $\beta_3$ age + $\beta_4$ gender + $\beta_5$ scanner + $\varepsilon$ (where $\varepsilon$ is error). Maps were produced showing statistically significant differences with false discovery rate (FDR) correction at $P < 0.05$. A subgroup analysis was performed comparing cortical thickness between the controls and the 2 syndrome subgroups described above (Space and Object) using the following model: $C = \beta_1$ (Controls) + $\beta_2$ (Space) + $\beta_3$ (Object) + $\beta_4$ age + $\beta_5$ gender + $\beta_6$ scanner + $\varepsilon$. The comparisons between individual PCA subgroups were further corrected for average cortical thickness (mean centered) by inclusion as covariate. Statistical difference maps for comparisons with controls show FDR-corrected P values thresholded at a 0.05 significance level, whereas maps for the comparisons between individual subgroups present uncorrected statistical differences ($P < 0.05$) and percent differences.

**Support Vector Machine**

A linear support vector machine (SVM; Vapnik 1995; Vapnik 1998) was trained to classify the controls and PCA subjects, and the resultant SVM scores were subsequently labeled according to Space (dorsal) and Object (ventral) PCA subgroups. A second SVM was trained directly to separate Space and Object subgroups. These analyses were implemented with LIBSVM version 2.89 (Chang and Lin 2001) under MATLAB (version 7.2.0). SVMs identify an optimal separating hyperplane in this space such that subjects from each group lie as far as possible from the hyperplane, on opposite sides. Once the hyperplane has been defined, scores can be generated by projecting the points onto the normal of the hyperplane. We use the C-SVM formulation, employing a 2-level nested cross-validation to optimize the misclassification penalty parameter C using a leave-one-out procedure within the main leave-one-out loop (Wilson et al. 2009). This ensures an unbiased estimation of generalization accuracy by leaving each scan in turn entirely out of the training procedure.

**Results**

**Neuropsychological Analysis**

The raw scores for each patient and the mean and standard deviation scores for the PCA patient group for each experimental assessment of basic visual processing are shown in Table 2. All 21 patients (100%) failed at least 1 of the 6 experimental tests of basic visual processing (with 90% failing at least 2 tasks and 81% failing at least 3 tasks). Therefore, there was not a single case of higher-order object or space agnosia in the current sample to which a basic visual processing deficit did not potentially contribute.

**Correlations**

Pairwise correlations (and significance values) between each of the 6 experimental tests of basic visual processing and also between these experimental tasks and tests of general cognition, space perception, and object perception are shown in Table 3. The correlation matrix revealed 4 key findings:

1. Between the experimental tests of basic visual processing, only 4 correlations reached formal significance: between the color and the 3 tests of basic form processing (form...
2. Three tests (form detection, form coherence, and color) were significantly correlated with both higher-order object and space perception. However, form discrimination correlated significantly only with object perception, whilst point localization correlated significantly only with space perception.

3. None of the basic visual processing tasks correlated with nonvisual, dominant parietal functions (calculation and spelling), although these dominant parietal tasks were themselves very strongly correlated \((r = 0.63, P = 0.002)\).

4. None of the experimental tests were correlated significantly with recognition memory or mini-mental state examination (MMSE) score (with the exception of a spurious negative color-MMSE correlation).

**Dissociations**

Despite a degree of correlation between the different aspects of basic visual processing, the dissociation analysis revealed...
substantial evidence that the different components of basic visual processing are not uniformly impaired in patients with PCA. There was a significant between-subject variation in performance on the 6 basic visual processing tasks (Friedman 2-way analysis of variance $= 58.49$, $P < 0.0001$). The identities of patients showing pairwise rank score discrepancies of $\geq 10$ ranking points between relatively preserved and impaired performance are shown in Table 4. This dissociation matrix reveals numerous patterns of single and double dissociations, including double dissociations between static and moving stimulus processing (e.g., form vs. motion coherence), color and motion processing, and form discrimination and every other basic visual skill tested. The double dissociation between even elementary components of form processing (form detection vs. discrimination; form coherence vs. discrimination) is particularly noteworthy. However, not all skills dissociated: there were no dissociations in either direction between motion and location processing, consistent with the significant motion/location group correlation shown in the correlation matrix.

**Syndrome Subgroups**

Pairwise comparisons between the Object and the Space subgroups on each of the demographic and behavioral measures were conducted using Wilcoxon–Mann–Whitney rank sum statistics. There were no significant differences between the subgroups in terms of age, disease duration, MMSE, or on any of the individual neuropsychological tests.

**Cortical Thickness Analysis**

**PCA Versus controls**

Statistically significant differences in cortical thickness between PCA patients and controls are shown in Figure 2. The PCA group showed the greatest differences in thickness (PCA < controls) bilaterally in the occipital lobe, followed by the parietal lobe, posterior cingulate gyrus, and regions in the medial temporal lobe.

**Syndrome Subgroups (Object and Space) Comparisons**

Differences in cortical thickness between the 2 putative PCA subgroups (Space and Object) and the controls are shown in Figure 3. The Space (dorsal) subgroup compared with controls showed significantly lower cortical thickness predominantly bilaterally in the occipital lobe and the posterior parietal lobe, as well as the precuneus, occipitotemporal gyrus, and medial temporal lobe, with relative sparing of the orbitofrontal gyrus (Fig. 3A). Similar results were shown in the Object (ventral) subgroup versus controls comparison, however, cortical thinning showed more focal differences, including thinner cortex bilaterally in the inferior parietal lobe and fusiform gyrus, with relative sparing of medial occipital lobe and frontal lobe regions (Fig. 3B). Figure 4 presents differences in cortical thickness for the direct comparison between Object and Space subgroups. The Space subgroup compared with the Object subgroup showed reduced cortical thickness in the right occipital and medial temporal lobe and bilaterally in the inferior and superior parietal lobe (Fig. 4A). However, these differences did not survive FDR correction. No statistically significant differences were found in the Object subgroup compared with the Space subgroup.

The less widespread reduction in cortical thickness in the Object subgroup, despite matching for age and disease duration, suggested that this group overall had a relatively thick cortex (possibly owing to premorbid differences and/or lesser disease severity). This motivated the use of correction for average cortical thickness for the direct comparison between Object and Space subgroup. Figure 4B shows percent differences in cortical thickness over and above global thinning between the 2 subgroups. The Space subgroup compared with the Object subgroup showed reduced cortical thickness bilaterally in the occipital, inferior parietal, and medial temporal lobe. In contrast, the Object subgroup showed reduced cortical thickness in the right fusiform gyrus, right lateral inferior temporal lobe, and frontal lobe regions.

These cortical thickness maps provide some evidence that thickness of the cortex varies in a predictable manner between the 2 behaviorally defined subgroups, as seen most clearly in the right lateral percentage map in Figure 4B. More specifically, there was an indication of greater thinning in occipital and superior parietal (dorsal) regions in patients with greater impairment of Space perception, and greater thinning of inferior temporal (ventral) regions in patients with greater impairment of Object perception. However, putting issues of statistical power to one side, the scarcity of regions showing significant thickness differences between the 2 subgroups suggests substantial anatomical overlap, making a separation into distinct subgroups less clear.

**Support Vector Machine**

The classification analysis produced a near complete separation between the controls and the PCA patients (Fig. 5), with 97.5% accuracy (binomial 95% confidence interval 86.8–99.9%). In contrast, no clear separation into the 2 putative subgroups was found, with the SVM-weighted scores

<table>
<thead>
<tr>
<th>Relative impairment</th>
<th>Form detection</th>
<th>Form coherence</th>
<th>Form discrimination</th>
<th>Color</th>
<th>Motion</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative preservation</td>
<td>Form detection</td>
<td>19</td>
<td>3, 15, 19</td>
<td>1</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Form coherence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form discrimination</td>
<td>7, 9, 13</td>
<td>9</td>
<td>3, 16</td>
<td></td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td>9, 17, 21</td>
<td>17</td>
<td>3, 15</td>
<td>5</td>
<td>9, 15, 17</td>
<td>9</td>
</tr>
<tr>
<td>Motion</td>
<td>21</td>
<td>5</td>
<td>2, 3, 16</td>
<td></td>
<td>2, 5</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3, 15, 16</td>
<td></td>
</tr>
</tbody>
</table>

Dissociations were defined by a rank discrepancy $\geq 10$ points.
showing great overlap between subgroups. The SVM trained specifically to separate Object and Space subgroups yielded a low accuracy with confidence interval spanning chance performance.

**Discussion**

This study investigated basic visual function in a relatively large sample of patients with PCA using both detailed neuropsychological assessments and quantitative measures of cortical thickness. PCA is a degenerative condition characterized by progressive visual impairment. In this context, it is surprising that previous studies have failed to examine the integrity of basic visual functions or to consider their influence upon higher-order visual processing. Here, we argue that basic visual functions are disordered in the vast majority of PCA patients, and that the severity of deficit in these basic functions predicts the pattern of higher-order object and space perception observed. We also argue that the severity of space and object perception difficulties can partially predict the degree of cortical thinning in dorsal and ventral posterior cortical regions, but that the neuroimaging evidence garnered from the current study is insufficient to justify the specification of distinct PCA subtypes.

**Basic Visual Deficits Predict the Nature of Higher-Order Perceptual Deficits in PCA**

Two main related hypotheses were addressed in this study. The first hypothesis was that higher-order visual deficits in PCA are associated with specific and separable patterns of basic visual processing. Object and space perception problems are reported commonly in PCA, and yet it is unknown whether these problems constitute true visual agnosias or result from impaired sensory processing, because the integrity of basic visual processes (e.g., form, color, motion, and location) have not been assessed systematically in previous neuropsychological studies of PCA. Furthermore, although atrophy and pathological changes have been found in striate and extrastriate occipital cortex, it is unknown whether mechanisms supporting these fundamental components of vision are uniformly affected in PCA or can be selectively disrupted in line with models of the human visual system (e.g., Ungerleider and Mishkin 1982; Goodale and Milner 1992; Deyoe et al. 1996; Wandell et al. 2007).

The neuropsychological analysis revealed 5 points of note. First, every PCA patient was impaired on at least one basic visual processing task. Thus, no evidence of “pure” visual agnosia was found, with the data suggesting that basic visual processing disorders are factors in the object and space agnosias commonly reported in PCA patients. Second, there was significant heterogeneity within the basic visual processing capacities of the PCA patients, with only a limited number of between test correlations (motion-location and color-form, consistent with a broad dorsal/ventral division of visual processing; Goodale and Milner 1992; Zeki et al. 1993) and numerous single and double dissociations within individual patients (e.g., between processing of static and motion information and even between different elements of basic form perception). Third, the type of basic visual processing dysfunction exhibited by the PCA patients was shown to have a significant impact upon the nature of their higher-order visual dysfunctions: whilst form detection, form coherence, and color perception were correlated with both object and space perception, form detection predicted object but not space perception, and point localization predicted only space but not object perception. Together, these 2 findings provide the first evidence that the fundamental components of vision are not uniformly affected in PCA, and that higher-order visual deficits in PCA are associated with different patterns of basic visual processing impairment.

Fourth, in contrast to their influence on higher-order perceptual functions, basic visual processing dysfunction had no significant impact upon nonvisual parietal functions (e.g., calculation and spelling), despite the equivalent proximity of the critical cortical regions. Models of the evolution of AD and related disorders contrast pathological proliferation between contiguous brain regions with network-based progression, in which functional and anatomical connections between non-contiguous brain areas play an important role in determining the spread and development of tissue pathology (e.g., Palop et al. 2006; Seeley et al. 2009). The current evidence of associations between occipital dysfunction and some but not other forms of parietal dysfunction may thus support network models, and reflect network dysfunction and disconnection. Fifth, basic visual processing dysfunction did not correlate with recognition memory, MMSE or disease duration, providing some evidence that involvement of basic visual processing, held to depend primarily upon more posterior occipital regions, may reflect a different locus of pathology in some individuals rather than merely greater disease severity.

**Variation in Patterns of Cortical Thinning**

The second main hypothesis addressed in this study was that different types of behavioral dysfunction are associated with distinct patterns of structural change in posterior cortical regions. More specifically, it was hypothesized that PCA patients with predominant spatial perception problems (Space
subgroup) would be associated with greater posterior parietal cortical thinning, and that patients with predominant object perception problems (Object subgroup) would be associated with greater inferior temporal cortical thinning. In line with this hypothesis, the Space subgroup showed particular thinning in the occipital and inferior parietal lobes, and the Object subgroup showed particular thinning in the fusiform gyrus and inferior temporal lobe. Trends toward lower cortical thickness in ventral (Object Subgroup) and dorsal (Space subgroup) regions were apparent in independent subgroup-control comparisons (Fig. 3) and between-subgroup comparisons (Fig. 4).

However, whilst these neuroimaging findings provide some evidence for differential patterns of tissue loss in the dorsal and ventral regions of different PCA patients, the majority of differences detected between subgroups were only found as percent differences. Furthermore, the indirect comparisons between each subgroup and the control population (Fig. 3) showed multiple common areas of tissue loss across the subgroups. This observation was confirmed using automated SVMs, with SVM-weighted scores showing considerable overlap between subgroups (Fig. 5), while almost perfectly separating controls from patients. Thus overall the neuroimaging findings are indicative of a degree of heterogeneity within the PCA population but do not motivate a clinical characterization of distinct PCA subtypes.

Furthermore, previous neuropsychological analyses of PCA have claimed good evidence to support the description of caudal (occipital) and dorsal (parietal) subtypes of PCA but have failed to find convincing evidence for a ventral (occipito-temporal) subtype (McMonagle et al. 2006). In the current study, individual examples of a ventrally focused syndrome have been found (e.g., Patient 15 who failed all object perception tests and passed all space perception tests). However, this patient’s cognitive profile constituted merely the most extreme value on a continuous range of object-space difference scores, with several patients showing moderate, mild or no differences between object and space perception tasks (see Fig. 1). In our clinical experience, the majority of PCA patients complain of or exhibit both space and object processing difficulties from early in the disease course, but as

---

**Figure 3.** Regional variation of cortical thickness in (A) Space subgroup compared with controls and (B) Object subgroup compared with controls. The color scale represents FDR-corrected $P$ values at a 0.05 significance level. Red and yellow (positive values) represent lower cortical thickness in the PCA subgroups compared with controls, whereas dark and light blue (negative values) represent the reversed contrasts. A—anterior, P—posterior.

**Figure 4.** Regional variation of cortical thickness between Space and Object subgroups. A shows uncorrected $P$ values at a 0.05 significance level and B shows percent difference maps after correcting for average cortical thickness. Warmer colors show regions thinner in the Space subgroup compared with the Object subgroup, whereas cooler colors represent the opposite comparison. A—anterior, P—posterior.
consider how a population of patients varies on a particular continuous marker of topology (e.g., measures of basic visual function as a marker of occipital cortical loss) rather than dichotomizing the population into symptomatic categories (e.g., typical AD, PCA), the boundaries of which may be poorly defined. Such continuous rather than categorical techniques may be used to determine the role of molecular and environmental factors in driving the topological focus of pathology (e.g., anterior-posterior, superior-inferior, and unilateral-bilateral) and their interaction with other structural and physiological constraints. It should also be noted that the anterior-posterior and dorsal-ventral distinctions considered to date also fail to capture the pronounced asymmetry apparent in the neuropsychological and neuroimaging profiles of many individuals with PCA (e.g., Freedman et al. 1991; Snowden et al. 2007). Without considering this lateral dimension of pathological distribution, it will also be difficult to establish the relationship between PCA and atypical variants of AD and related disorders such as LPA, which is characterized by highly asymmetric atrophy of the dominant hemisphere (Gorno-Tempini et al. 2004; Rohrer et al. 2009).

**Continuous Variation within PCA**

The current study yields evidence of both similarities and differences among the PCA patients. At one level, the PCA cohort is collectively quite different from individuals with typical AD: relatively preserved memory, impaired perceptual skills, and predominant posterior deficits (e.g., Lehmann et al. 2009). At a more fine-grained level, detailed assessment reveals that PCA patients differ in the severity of their basic visual, object, and space perception deficits and the extent to which occipital, superior parietal, and inferior temporal cortical regions are affected. However, these more fine-grained differences do not reflect discrete, definable syndromic subtypes of PCA. Rather, the manual classification of neuropsychological profiles (Fig. 1) and the automated classification of cortical thickness patterns (Fig. 5) are more suggestive of continuous variation within the syndrome of PCA. The data in the present study are insufficient to support the existence of discrete dorsal and ventral sub syndromes within PCA, although patients at the outer limits of such continuous variability can indeed possess markedly different phenotypes (Galton et al. 2000). Instead, those putative subtypes are more likely to represent points in a continuously varying topological distribution of cortical dysfunction, which may in turn reflect the distribution of underlying pathology. A similar notion has recently been expressed in a study of progressive nonfluent aphasia (PNFA) to describe the relationship between putative PNFA subtypes such as progressive apraxia of speech and logopenic progressive aphasia (LPA); namely that individual patients with such phenotypes represent "points at the edges of a space of continuous variability within PNFA" (Knibb et al. 2009, p. 2744).

If PCA phenotypes do represent different points in a space of continuous variation, this has implications for studies investigating the factors that drive the variation both within and between the different "typical" and "atypical" presentations of AD and related disorders. It may be more appropriate to consider how a population of patients varies on a particular continuous marker of topology (e.g., measures of basic visual function as a marker of occipital cortical loss) rather than dichotomizing the population into symptomatic categories (e.g., typical AD, PCA), the boundaries of which may be poorly defined. Such continuous rather than categorical techniques may be used to determine the role of molecular and environmental factors in driving the topological focus of pathology (e.g., anterior-posterior, superior-inferior, and unilateral-bilateral) and their interaction with other structural and physiological constraints. It should also be noted that the anterior-posterior and dorsal-ventral distinctions considered to date also fail to capture the pronounced asymmetry apparent in the neuropsychological and neuroimaging profiles of many individuals with PCA (e.g., Freedman et al. 1991; Snowden et al. 2007). Without considering this lateral dimension of pathological distribution, it will also be difficult to establish the relationship between PCA and atypical variants of AD and related disorders such as LPA, which is characterized by highly asymmetric atrophy of the dominant hemisphere (Gorno-Tempini et al. 2004; Rohrer et al. 2009).

**Figure 5.** SVM-weighted scores for each subject. Left: illustration of separation between the controls and the PCA group; right: no separation between the 2 putative PCA subgroups (Space and Object).

**Limitations of the Current Study**

With regard to the neuropsychological aspects of the study several possible limitations should be considered. First, visual fields were not tested formally in the PCA patients. Many showed problems on informal clinical field assessment, but our clinical experience of PCA suggests that an inability to detect the presence or movement of a stimulus in the periphery during clinical examination is often more accurately attributed to visual disorientation and attentional problems rather than a field defect per se. Second, the division between visual processes labeled "basic" and "higher" is relative rather than absolute; we do not deny that for example that the boundary detection skills critical to the basic form detection task are also necessary for the higher-order fragmented letter task. Third, whilst the space and object perception tests (mainly from the VOSP) employed in the current study are routinely used in clinical and research practice, there is little direct evidence to demonstrate differential dependence upon dorsal and ventral visual streams. Therefore alternative tasks with greater or more demonstrable localizing power may yield a more accurate classification of "dorsal" and "ventral" subgroups.

From the neuroimaging and diagnostic perspectives, one limitation of the current study is that scans were obtained from 2 different scanners with different field strengths which may have an effect on thickness measures (Han et al. 2006). Without considering this lateral dimension of patholog- ical confirmation. A further issue, which applies to most studies of degenerative disease relates to controlling for the variable of disease severity when conducting between-group comparisons. Replication of this study with a larger cohort of patients may increase the power to detect differences between the behaviorally defined subgroups. Although all the patients in the current study have a clinical diagnosis of probable AD, another limitation of the current study is the lack of pathological confirmation. A further issue, which applies to most studies of degenerative disease relates to controlling for the variable of disease severity when conducting between-group comparisons. There were no significant differences between the 2 behaviorally defined subgroups on measures of general cognitive function, although measures such as the MMSE are of limited
utility in this population of patients. Furthermore, cortical thickness comparisons were corrected for mean cortical thickness in order to adjust for potential premorbid differences and/or differences in disease severity. Although the current study reports cross-sectional differences in cortical thickness, longitudinal studies using other imaging techniques such as VBM have related such differences to underlying cell loss rather than premorbid differences (Chetelat et al. 2005; Ruocco et al. 2008). However, changes in cortical thickness over time in AD and PCA remain to be studied.

Funding
Alzheimer’s Society to M.L.; J.B. is supported by an Alzheimer’s Research Trust Co-ordinating Centre and has also received equipment funded by the Alzheimer’s Research Trust. We are grateful to Professor Martin Rossor for his support of this work, and to Professor Rossor, Dr Jason Warren, Dr Cath Mummery, Dr Dennis Chan, and Dr Gordon Plant for allowing us to study patients under their care. We are also indebted to Professors Jan Atkinson and Oliver Braddick from the UCL Visual Development Unit for permitting the adaptation of form and motion coherence tests for use in this study. We would like to thank Mary Keilty, Katy Randlesome, and Sarah Connell for their help with gathering control data, and above all we are indebted to our patients for giving so generously of their time and energy. Conflict of Interest: None declared.

References


