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Neural correlates of cognitive impairment in posterior cortical atrophy

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With the prospect of disease-modifying drugs that will target the physiopathological process of Alzheimer's disease, it is now crucial to increase the understanding of the atypical focal presentations of Alzheimer's disease, such as posterior cortical atrophy. This study aimed to (i) characterize the brain perfusion profile in posterior cortical atrophy using regions of interest and a voxel-based approach; (ii) study the influence of the disease duration on the clinical and imaging profiles; and (iii) explore the correlations between brain perfusion and cognitive deficits. Thirty-nine patients with posterior cortical atrophy underwent a specific battery of neuropsychological tests, mainly targeting visuospatial functions, and a brain perfusion scintigraphy with ^{99m}Tc-ethyl cysteinate dimer. The imaging analysis included a comparison with a group of 24 patients with Alzheimer's disease, matched for age, disease duration and Mini-Mental State Examination, and 24 healthy controls. The single-photon emission computed tomography profile in patients with posterior cortical atrophy was characterized by extensive and severe hypoperfusion in the occipital, parietal, posterior temporal cortices and in a smaller cortical area corresponding to the frontal eye fields (Brodmann areas 6/8). Compared with patients with Alzheimer's disease, the group with posterior cortical atrophy showed more severe occipitoparietal hypoperfusion and higher perfusion in the frontal, anterior cingulate and mesiotemporal regions. When considering the disease duration, the functional changes began and remained centred on the posterior lobes, even in the late stage. Correlation analyses of brain perfusion and neuropsychological scores in posterior cortical atrophy highlighted the prominent role of left inferior parietal damage in acalculia, Gerstmann's syndrome, left–right indistinction and limb apraxia,

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whereas damage to the bilateral dorsal occipitoparietal regions appeared to be involved in Bálint's syndrome. Our findings provide new insight into the natural history of functional changes according to disease duration and highlight the role of parietal and occipital cortices in the cognitive syndromes that characterize the posterior cortical atrophy.

Keywords: PCA; Alzheimer's disease; SPECT; cerebral perfusion; neuropsychological correlations

Abbreviations: MMSE = Mini-Mental State Examination; PCA = posterior cortical atrophy; SPECT = single photon emission computed tomography

Introduction

Posterior cortical atrophy (PCA) was first used by Benson *et al.* (1988) to describe a progressive dementing syndrome in which the onset is characterized by early, higher order visual deficits. Patients develop features of Bálint's syndrome (ocular apraxia, optic ataxia and simultanagnosia), Gerstmann's syndrome (acalculia, agraphia, finger agnosia and left–right disorientation), visual agnosia and transcortical sensory aphasia, whereas episodic memory is preserved or only mildly impaired.

Neuropathological studies demonstrated that the primary cause of PCA is Alzheimer's disease followed, more rarely, by corticobasal degeneration, dementia with Lewy bodies or prion disease (Renner *et al*., 2004; Tang-Wai *et al*., 2004; McMonagle *et al*., 2006; Alladi *et al*., 2007). In cases of Alzheimer's disease pathology, PCA and typical Alzheimer's disease can be distinguished by the distribution of these pathological changes; patients with PCA have a higher density of neurofibrillary tangles in the occipital regions and fewer in the prefrontal cortex, hippocampus and subiculum (Hof *et al*., 1997; Galton *et al*., 2000; Tang-Wai *et al*., 2004). Thus, the term 'atypical focal cortical presentation of Alzheimer's disease' was proposed, as well as 'visual variant of Alzheimer's disease' (Levine *et al*., 1993; Kramer and Miller, 2000; Alladi *et al*., 2007). With the prospect of disease-modifying drugs that will target the physiopathological process of Alzheimer's disease, it is crucial to increase our understanding of PCA. Little is known about the topography and the natural progression of PCA. Indeed, the rarity of the disease makes it difficult to create a clinical cohort. In a longitudinal follow-up of 19 patients with PCA, McMonagle *et al*. (2006) reported early and prominent visuospatial deficits with latter, but variable, agnosia and posterior language deficit (alexia, agraphia and transcortical aphasia), whereas memory and frontal lobe functions remained relatively spared. This cognitive profile suggests that PCA symptoms remain mainly posterior, in accordance with the neurofibrillary tangles topography observed in PCA (Hof *et al*., 1997; Galton *et al*., 2000; Tang-Wai *et al*., 2004). In case reports, other authors reported marked deteriorations in other cognitive domains, including memory, leading to global cognitive impairment (Levine *et al*., 1993; Della Sala *et al*., 1996). The question of diffuse versus focal posterior clinical evolution in PCA remains open.

Functional neuroimaging, using PET or single photon emission computed tomography (SPECT), offers reliable and sensitive methods to investigate *in vivo* the cerebral perfusion or metabolic defects in dementia disorders, even at early stages (Habert *et al*., 2011). Both hypoperfusion and hypometabolism display synaptic dysfunction or neuronal loss and provide information about the topography and the severity of lesions, regardless of the underlying pathological process. Only a few studies of patients with PCA have been published. PET studies have reported a prominent hypometabolism in the parietal associative cortex, with a variable involvement of the adjacent temporal and occipital associative cortices, while the frontal and mesiotemporal regions were relatively spared (Bokde *et al*., 2001; Nestor *et al*., 2003; Schmidtke *et al*., 2005). However, these studies are hampered by the small number of subjects (no more than 10 patients) and by the succinct exploration of neuropsychological deficits. Brain perfusion SPECT use has only been reported in single cases of patients with PCA (Ross *et al*., 1996; Galton *et al*., 2000; Goethals and Santens, 2001).

Therefore, we aimed first to use brain SPECT to study the profile of brain hypoperfusion in a large group of patients with PCA, compared with normal controls and patients with Alzheimer's disease. In addition, we analysed the patterns of perfusion decrease in patients with PCA according to the duration of the symptoms. Second, we analysed the neural bases of the PCA syndrome by studying the correlations between the SPECT data and the scores of a specific battery of neuropsychological tests, which mainly explore visuospatial functions. The method of clinico/imaging correlations allows the study of the anatomical correlates of a cognitive process assessed by a specific test in patients with neurodegenerative disorders (Desgranges *et al*., 2002), but has not yet been used in patients with PCA.

Materials and methods

Subjects

Thirty-nine subjects (61.1 ± 7.8 years old, 37 right-handed, two left-handed) with a clinical diagnosis of PCA were admitted to the Centre of Cognitive and Behavioural Disorders (Pitié-Salpêtrière Hospital, Paris, France) between 2002 and 2008 (Table 1). The diagnosis of PCA was based on the clinical criteria from (McMonagle *et al*., 2006) (details in Table 2). Ophthalmological assessment excluded primary causes of visual disorder for all patients. Patients with parkinsonian signs, symptoms suggestive of dementia with Lewy bodies or severe depression or, more generally, patients with medical conditions that could interfere with cognitive performance were excluded. All patients were clinically followed for at least 24 months to confirm that visuospatial dysfunctions remained the main cause of cognitive impairment, in accordance with the diagnosis of PCA.

Table 1 General demographic features of the study groups

	PCA	Alzheimer's disease	Controls	*P*-value
Number of subjects	39	24	24	NS
Gender (male/female)	10/29	14/10	7/17	$P < 0.05$[a]
Age (years)	61.1 ± 7.8 (47.9–80.3)	65.1 ± 12.1 (42.0–82.9)	69 ± 6.9 (52–81)	$P < 0.05$[b]
Education level (years)	10.5 ± 5 (2–15)	7.8 ± 5.1 (2–15)	10.6 ± 4.1 (3–15)	$P < 0.05$[a]
Onset age (years)	57.4 ± 7.7 (45–74)	62.4 ± 11.1 (40–80)		NS
Duration (years)	3.8 ± 2.1 (0.6–12.6)	3.7 ± 2.0 (1.2–8.1)		NS
MMSE (/30)	18.1 ± 5.0 (6–27)	19.4 ± 5.0 (10–26)	28.8 ± 0.7 (28–30)	$P < 0.05$[b]

Values are mean ± SD (min–max).
a PCA versus Alzheimer's disease (Mann–Whitney U-test).
b PCA versus controls (Mann–Whitney U-test); NS = not significant.

Table 2 Inclusion criteria for PCA

Inclusion criteria for PCA (adapted from McMonagle *et al.*, 2006)
(i) Insidious onset and gradual progression of cognitive impairment.
(ii) Presentation with prominent visuospatial impairment in the absence of ophthalmologic impairment.
(iii) Evidence of complex visual disorder on examination: elements of Bálint's syndrome (optic ataxia, ocular apraxia and simultanagnosia), and/or Gerstmann's syndrome (acalculia, agraphia, left–right disorientation and finger agnosia), visual agnosia or spatial neglect.
(iv) Proportionately less memory loss or reduced verbal fluency.
(v) Absence of focal lesion (brain tumour, haematoma or stroke) on brain scan or MRI.

All imaging and clinical data were generated during routine clinical workup in the Neurology Department and were extracted for the purpose of this study. Therefore, according to French legislation, explicit informed consent was waived. However, the regulation concerning electronic filing was followed, and both patients and their relatives were informed that individual data could be used in clinical research studies.

For the purpose of imaging analysis, we also studied 24 patients with probable Alzheimer's disease, diagnosed according to NINCDS–ADRDA criteria (McKhann *et al.*, 1984), who were matched to the group with PCA for age, disease duration and Mini-Mental State Examination (MMSE) score. All of the patients with Alzheimer's disease were described in a previous study (Habert *et al.*, 2011). Twenty-four healthy subjects, also previously described (Le Ber *et al.*, 2006), were used as controls (Table 1).

Posterior cortical atrophy neurological and neuropsychological assessment

Neurological assessment was performed by trained clinicians (M.S., L.C.d.S., M.K., L.L. and B.D.) with expertise in the field of dementia. Clinical features of memory deficits, visuospatial deficit, visual agnosia, environmental disorientation, body schema distortion, spatial neglect or any feature suggestive of Bálint's or Gerstmann's syndromes were considered present if clearly documented by history or on examination. All patients were tested by the same neuropsychologist (D.S.) using a standardized neuropsychological battery. The battery consisted of two series of tests and took ~2 h. The first series included the MMSE (Folstein *et al.*, 1975), the Free and Cued Selective Reminding Test (Van der Linden, 2004), the Frontal Assessment Battery (Dubois *et al.*, 2000), picture naming test and word generation tasks for category and letter fluency (Kremin, 1999). Visual and verbal direct and backward span (Wechsler, 1981) were employed to assess working memory, defined as the capacity for the temporary storage and manipulation of the information that is necessary for the realization of a given complex cognitive task (Baddeley, 2003). Patients who scored 1.5 standard deviations (SD) below the norm were considered to have a working memory deficit.

The second series, the 'posterior neuropsychological battery', included the following:

(i) Copy of the Rey figure to examine visuoconstructive function (Liberman *et al.*, 1994) (maximum score = 36);
(ii) A limb apraxia battery (Peigneux and Van der Linden, 2000) (maximum score = 32);
(iii) The Cookie Theft picture from the Boston Diagnostic Aphasia Examination (Goodglass, 1983) and the five series of overlapping figures (Gainotti *et al.*, 1991) to assess simultanagnosia, defined as the inability to perceive two or more objects simultaneously (maximum score = 25);
(iv) Assessment of ocular apraxia [defined as the inability to voluntarily direct one's gaze to a particular point (Charles and Hillis, 2005)]. The patient was seated in front of the examiner at a distance of 50 cm and was asked to move his eyes towards a moving target after staring at the examiner's nose. The four visual quadrants were evaluated (maximum score = 4);
(v) Assessment of optic ataxia [defined as the impairment of goal-directed hand movements towards visually presented targets (Trillenberg *et al.*, 2007)]: The patient was seated in front of the examiner at a distance of 50 cm and asked first to stare at the examiner's nose, then to use a designated hand (left or right) to touch a moving target without moving his eyes from the examiner's nose. The examiner moved the target through

the four visual quadrants. One point was given for each time the patient could reach the target with his hand (maximum score = 8);

(vi) Right–left distinction and body schema assessment. The patient was asked to indicate 12 body parts on both himself and the examiner (maximum score = 24);

(vii) Digital gnosia (defined as the ability to recognize the fingers of the hand). First, the patient was asked to show each of the five fingers when named by the examiner. Next, they were asked to name each one of the five fingers showed by the examiner (maximum score = 10);

(viii) Mental calculation. The patient was asked to perform a series of seven subtractions, seven additions and six multiplications (maximum score = 20);

(ix) Agraphia. The 'agraphia score' (out of 11) was established by asking the patient to write a dictated sentence composed of 11 frequently used French words.

Finally, we defined the sum of the simultanagnosia, visual praxia and optic ataxia scores (out of 37) as the Bálint's syndrome score and the sum of the agraphia, acalculia, digital agnosia and right–left distinction scores (out of 65) as the Gerstmann's syndrome score.

All patients with PCA underwent the first series of tests, and 30 out of 39 patients underwent the posterior neuropsychological battery.

Subgroups of patients with posterior cortical atrophy according to disease duration

The patients with PCA were divided in two groups based on the estimated disease duration. A cut-off of 3 years was chosen, based on the median length of disease duration, to define two groups of equal size: (i) a short disease duration group, with a disease duration $\leqslant 3$ years (19 patients); and (ii) a long disease duration group with a disease duration >3 years (20 patients, mean 5.1 ± 2.1 years, range 3.3–12.6). The majority of long disease duration patients had disease duration between 3.3 and 6.5 years. One patient had 8-year disease duration and another had 12.6-year disease duration. We also isolated seven patients within the short disease duration group with a very short ($\leqslant 2$ years) disease duration (Supplementary Table 1). All statistical analyses of demographic and neuropsychological data were performed with STATISTICA 5.5 A (© StatSoft). Descriptive statistics were used to characterize each group. Differences in medians between groups were compared using the Mann–Whitney U-test.

Brain perfusion single photon emission computed tomography study

All subjects underwent a brain perfusion SPECT within 3 months of diagnosis. Thirty minutes after the injection of ^{99m}Tc-ethyl cysteinate dimer (925 MBq) 120 projections were acquired in a 128×128 matrix with a three-headed gamma-camera equipped with parallel high resolution collimators (Irix, Philips). Projections were reconstructed using an iterative algorithm, post-filtered (low pass filter: order = 4, cut-off frequency = 0.4 cm^{-1}), then corrected for attenuation using the Chang method ($\mu = 0.12\ cm^{-1}$). Reconstructed volumes were spatially normalized to the Montreal Neurological Institute space with Statistical Parametric Mapping software (SPM2, Welcome Department of Cognitive Neurology, University College, London), using a SPECT perfusion template. A 12-parameter affine transformation was used, followed by a non-linear estimation of the deformations required for an optimal registration. Normalized images were smoothed using an isotropic Gaussian kernel of 12 mm. The dimensions of the resulting voxel were $2 \times 2 \times 2$ mm^3. To take into account the presence of severely hypoperfused regions in patients with Alzheimer's disease and patients with PCA, differences in global cerebral activity were removed between subjects by scaling the voxel values of each individual image to the cerebellar activity, and the analyses performed with a grey matter threshold set at 40% of whole brain mean activity (Nestor *et al.*, 2003).

Statistical analysis of neuroimaging data

A first set of analyses was designed to define the brain perfusion profile in the overall population of 39 patients with PCA. A second set aimed to explore the relationship between the brain perfusion and neuropsychological scores, especially the scores pertaining to visuospatial functions.

Brain perfusion profile in posterior cortical atrophy and Alzheimer's disease

The first analysis was designed to compare the extent of hypoperfused brain regions in the group with PCA with the healthy controls, using a two-sample *t*-test. Then, the group with PCA was compared with the Alzheimer's disease age-matched group to investigate regions of hypoperfusion common to Alzheimer's disease and PCA and those specific to PCA. Second, to explore the natural progression of PCA, brain hypoperfusion was evaluated in patients with PCA at different stages of the disease by comparing the groups with very short, short and long disease duration and healthy control groups two by two, using a two-sample *t*-test. We also correlated brain perfusion with the duration of symptoms, measured in years.

All Statistical Parametric Mapping T-maps were obtained using a statistical significance threshold of $P < 0.001$, corrected for multiple tests using the False Discovery Rate method. To decrease the risk of false positive results, clusters of <100 voxels were not considered. Age was entered as a nuisance variable. The Montreal Neurological Institute coordinates were converted into Talairach coordinates using WFU PickAtlas software (http://www.fmri.wfubmc.edu/download.htm). Further analyses using anatomical volumes of interest obtained from the AAL software (Tzourio-Mazoyer *et al.*, 2002) were also performed to study between-group differences in brain perfusion. Comparisons between the groups were performed with a Mann–Whitney test. Volumes of interest were also used to calculate asymmetry indexes between left (L) and right (R) cortical perfusion as follows: $(L - R) \times 200\%/(L + R)$.

Brain perfusion correlation with neuropsychological scores in posterior cortical atrophy

Voxel-based correlations were studied independently of age, educational level and MMSE, except for constructive apraxia and mental calculation scores. For the latter, MMSE was not set as a nuisance variable because it evaluates constructive praxis and mental calculation *per se*. T-maps were obtained at a height threshold of $P < 0.005$ uncorrected, which is an accepted procedure in correlation analyses considering the number of subjects (Desgranges *et al.*, 1998). The minimal cluster size was set at 100 voxels. Individual adjusted normalized regional activities values were extracted from the eligible clusters

to calculate correlation coefficients using MarsBaR software (Brett, 2002).

Results

Clinical and cognitive characteristics of the posterior cortical atrophy cohort

The clinical and cognitive characteristics of this population are detailed in Tables 1 and 3. The mean disease duration at the time of SPECT was 3.8 ± 2.1 years (0.6–12.6 years).

Comparison between posterior cortical atrophy, Alzheimer's disease and control groups

The group with PCA was younger than the control group (U-test, $P < 0.001$) but did not differ in educational level or gender distribution. The groups with PCA and Alzheimer's disease were similar for age and MMSE scores, duration of disease and age of onset (U-test, all $P > 0.5$). Performances on the episodic verbal memory test were significantly higher in the PCA than the Alzheimer's disease group: free recall was 16.6 ± 8.6 for patients with PCA and 11.1 ± 7.1 for patients with Alzheimer's disease; total recall (free + cued recall) was 35.5 ± 11.2 for patients with PCA and 28.2 ± 9.7 for patients with Alzheimer's disease (U-test, all $P = 0.05$).

Cognitive characteristics of patients with posterior cortical atrophy

The most frequent neurological signs were working memory impairment (100%), with visual memory more impaired than the verbal modality; limb apraxia (95%) and simultanagnosia (92%). Overall, 31% of patients presented a complete Bálint's syndrome and 36% had a complete Gerstmann's syndrome. Others findings included visual agnosia and aphasia, predominantly characterized by reading and writing deficits (Table 3).

Comparison between short and long disease duration posterior cortical atrophy

No significant differences in demographics, neurological symptoms or neuropsychological performances were observed between groups with short and long disease duration PCA (Supplementary Table 1).

Single photon emission computed tomography analysis

Comparison between patients with posterior cortical atrophy, patients with Alzheimer's disease and control subjects

Comparing the group with PCA to the healthy controls revealed extensive and severe hypoperfusion in the parietooccipitotemporal cortex and the middle and posterior cingulum, and involvement of the bilateral pulvinar ($P < 0.001$ corrected) (Fig. 1 and Table 4). The distribution of the hypoperfusion over the posterior cortex was bilateral and symmetrical, with the most severe decrease in

Table 3 Neurological characteristics and neuropsychological scores of patients with PCA

Neurological symptoms	Number of affected subjects	(%)
Working memory deficit	39	100
Visual symptoms		
Simultanagnosia	36	92
Optic ataxia	19	49
Ocular apraxia	15	38
Complete Bálint's syndrome	12	31
Limb apraxia	37	95
Gerstman's syndrome		
Agraphia	28	72
Acalculia	25	64
Digital agnosia	20	51
Right–left indistinction	20	51
Complete Gerstmann's syndrome	14	36
Aphasia	21	54
Alexia	14	36
Neuropsychological tests (maximal score)	**Mean score ± SD**	**Range**
Global cognitive efficiency		
MMSE (30)	18.2 ± 5.3	6–27
Time and spatial orientation (10)	7.1 ± 2.3	2–10
Executive functions		
Frontal assessment battery (18)	10.4 ± 3.7	3–17
Verbal episodic memory (FCSRT)		
Immediate recall (16)	10.3 ± 4.2	1–16
Total free recall (48)	16.6 ± 8.6	2–36
Total free and cued recall (48)	35.5 ± 11.2	9–48
Working memory		
Direct and backward verbal span	7.2 ± 1.7	3–10
Direct and backward visual span	3.8 ± 2.3	0–8
Total verbal and visual spans	11 ± 3.6	3–17
Language		
Categorial fluency	8.7 ± 5.13	2–20
Letter fluency	5.9 ± 4.6	0–13
Pictures naming (12)	10 ± 1.58	8–12
Visuo-constructive function		
Rey copy[a] (36)	17.2 ± 12.5	4–35
Limb apraxia		
Imitation of meaningless gestures (20)	10.4 ± 4.3	4–18
Pantomime of familial gestures on verbal command (12)	9.6 ± 2.7	4–12
Gerstmann's syndrome (65)	47.7 ± 13.5	18–63
Right–left indistinction (24)	20.6 ± 3.9	11–24
Agraphia (11)	6.6 ± 4	0–11
Digital Agnosia (10)	7.4 ± 2.8	1–10
Acalculia (20)	13.3 ± 5.6	1–20
Balint's syndrome (37)	24.7 ± 8.7	2–36
Optic ataxia (8)	5 ± 2.8	0–8
Simultanagnosia (25)	15.9 ± 6.9	2–23
Ocular apraxia (4)	3.3 ± 1.1	0–4

a Data were available for 12/39 patients because 27 patients could not or refused to perform the test due to the severity of visual impairment.
FCRT = Free and Cued Selective Reminding Test; SD = standard deviation.

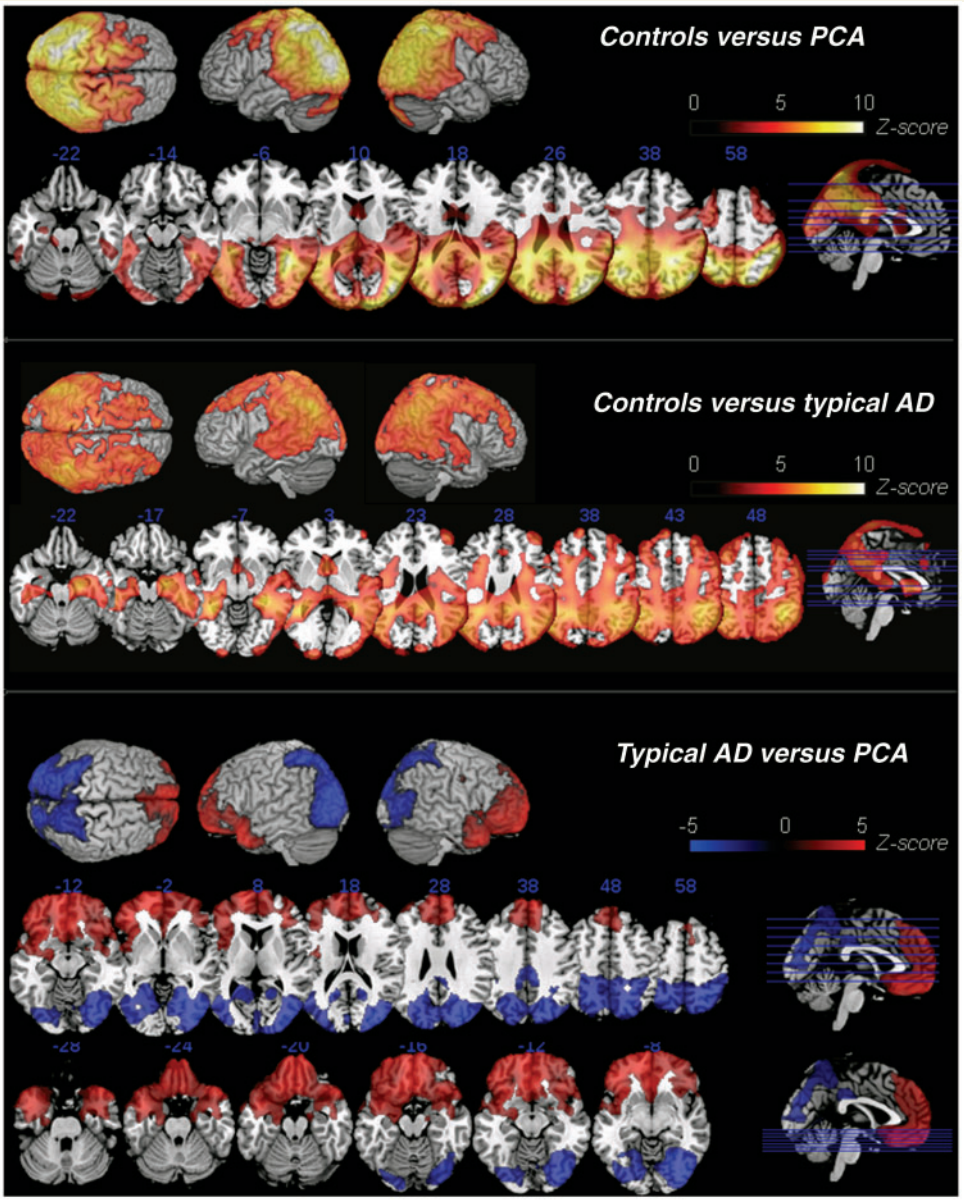

Figure 1 Comparisons of brain perfusion among patients with PCA, patients with Alzheimer's disease (AD) and controls, using Statistical Parametric Mapping. (*Top*) *Z*-score hypoperfusion maps of patients with PCA compared with controls. The maps were projected onto a surface rendering and axial views of the customized MRI template. Axial slices are shown in accordance with radiological convention (right is left). The group with PCA showed an extensive and symmetrical hypoperfusion in the occipital, parietal and posterior temporal cortices ($P < 0.001$ false discovery rate corrected). (*Middle*) *Z*-score hypoperfusion maps of patients with Alzheimer's disease compared with controls. Patients with Alzheimer's disease showed extensive hypoperfusion throughout the posterior associative cortex, as well as in the prefrontal cortex and the bilateral hippocampus ($P < 0.001$ false discovery rate corrected). (*Bottom*) *Z*-score hypoperfusion maps of patients with PCA compared with patients with Alzheimer's disease. The maps were projected onto surface rendering and axial views of the customized MRI template. The hypoperfusion in the parieto-occipital cortex was more severe in patients with PCA than in patients with Alzheimer's disease (blue, $P < 0.05$ corrected). Conversely, significantly higher perfusion (red) was observed in the frontal, anterior cingulate, inferior and medial temporal regions of patients with PCA compared with patients with Alzheimer's disease. Axial slices are shown in accordance with radiological convention.

the inferior parietal cortex [Brodmann area (BA) 40]. The frontal cortex was also hypoperfused, with a cluster running along the middle and superior frontal gyri (from BA 6 and 8 to BA 9), including the bilateral frontal eyes fields (BA 6/8) and spreading to the opercular part of the left frontal cortex (BA 44). At $P < 0.05$ corrected, the T-map revealed a hypoperfusion of the bilateral hippocampus. These results were confirmed by the volumes of interest analysis (Supplementary Fig. 1). The calculation of asymmetry indexes showed that occipital and parietal hypoperfusions were prominent on the right side in 19 patients and on the left side in 17 patients, and were symmetrical in three patients.

Table 4 SPM results for patients with PCA compared with controls and patients with Alzheimer's disease

Cluster-level			Coordinates (mm)				Location
$P_{corrected}$	K_E	$P_{uncorrected}$	*T*	*x*	*y*	*z*	
PCA minus controls							
0.000	111 735	0.000	11.30	−34	48	56	Left inferior parietal lobule (BA 40)
			10.95	−26	−55	58	Left superior parietal lobule (BA 7)
			10.77	34	−44	48	Right inferior parietal lobule (BA 40)
Alzheimer's disease minus controls							
0.000	92 521	0.000	7.34	−34	−43	−2	Left hippocampus
			7.31	36	−46	48	Right inferior parietal lobule (BA 40)
			7.27	32	−31	−5	Right hippocampus
PCA minus Alzheimer's disease							
0.000	28 441	0.000	6.34	−30	−82	22	Left middle occipital gyrus (BA 19)
			6.09	−26	−58	−0.4	Left lingual gyrus (BA 19)
			5.91	−22	−72	39	Left precuneus (BA 7)
Alzheimer's disease minus PCA							
0.000	33 597	0.000	6.23	12	48	−6	Right anterior cingulate (BA 32)
			6.16	2	52	−20	Right orbital gyrus (BA 11)
			5.98	18	68	−5	Right superior frontal gyrus (BA 10)

Coordinates are in millimetres relative to the anterior commissure, corresponding to the atlas of Talairach and Tournoux. Statistical maps were thresholded for significance at $P < 0.001$, false discovery rate corrected with a cluster extent of 100 voxels. K_E = number of voxels per cluster.

Compared with controls, patients with Alzheimer's disease showed extensive hypoperfusion throughout the bilateral temporo-parietooccipital cortex, including the posterior cingulate and the precuneus, and extending to the dorsolateral prefrontal cortex. Bilateral hippocampal gyri were significantly hypoperfused ($P < 0.001$ corrected).

Comparison between patients with posterior cortical atrophy and patients with Alzheimer's disease

To allow broad visualization of the regional perfusion differences between patients with PCA and patients with Alzheimer's disease, results were displayed on T-maps thresholded at $P < 0.05$, corrected. Compared with the Alzheimer's disease group, the group with PCA had significantly decreased perfusion in the associative posterior cortex (Fig. 1 and Table 4). The hypoperfused regions were mainly on the left-side, and they extended along the dorsal visual associative cortex (dorsal BA 18/19) to the superior parietal lobe (BA 7), the precuneus, the median occipital cortex and the middle cingulum. The T-maps revealed hypoperfusion in the bilateral temporal cortex (BA 37/21) and the occipitotemporal junction (BA 19/39). Conversely, the patients with Alzheimer's disease showed much more hypoperfusion in the bilateral dorsolateral (BA 46/45/10), ventrolateral and orbital (BA 47/11) prefrontal cortices, the mesial prefrontal and anterior cingulate cortices, the anterior temporal cortex and the hippocampus (Fig. 1 and Table 4). Similar results were obtained with volumes of interest analyses (Supplementary Fig. 1).

Comparison between very short, short and long disease duration and control subjects

When compared with controls, the very short disease duration subgroup showed a bilateral hypoperfusion in the posterior associative cortex, more prominent in the left inferior parietal cortex and the precuneus ($P < 0.001$ corrected; Fig. 2). It extended to the dorsal occipital cortex, the posterior cingulum and the left superior frontal cortex (BA 6). Compared with controls, the patients with short disease duration PCA had extensive and severe hypoperfusion in the bilateral posterior cortex (parietal, inferior and median occipital cortex and left posterior temporal cortex) and the middle and posterior cingulum. There was also involvement of the bilateral superior frontal cortex (BA 6), including the frontal eyes fields ($x = -24$, $y = 2.5$, $z = 51$ mm in the Talairach atlas). Finally, compared with controls, the patients with long disease duration PCA had more symmetrical hypoperfusion throughout the parietal, occipital and posterior temporal cortices. Despite the extension to the cingulate cortex, the anterior cingulum remained unaffected. Hypoperfusion of the bilateral frontal superior cortex (BA 6) was observed. No statistically significant difference in cortical perfusion was found among PCA subgroups. A significant negative correlation was found in the whole group with PCA, between the disease duration and the perfusion of the bilateral inferior parietal cortex, the bilateral temporooccipital junction and the right inferior occipital gyrus ($P < 0.005$).

Correlation between brain perfusion and neuropsychological scores in posterior cortical atrophy

Table 5 shows the significant positive correlations ($P < 0.005$) between perfusion and cognitive profile. Correlations were found between visual working memory scores and the perfusion of precuneus (Fig. 3), and between the limb apraxia scores and the perfusion of the left angular gyrus and precuneus (Fig. 4).

The Bálint scores were correlated to perfusion in the dorsal regions of the parietal and occipital lobes, the precuneus and the cuneus, with right predominance. Both ocular apraxia and optic ataxia were primarily related to hypoperfusion of the bilateral superior parietal cortex and the right precuneus. Right superior occipital cortex involvement was also detected with optic ataxia.

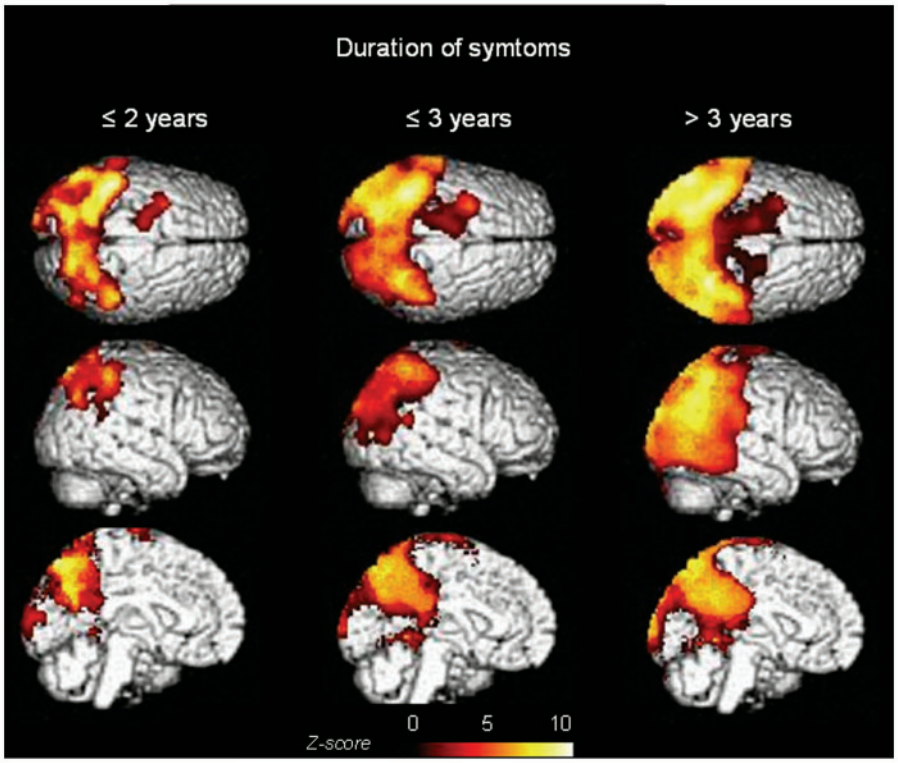

Figure 2 Brain hypoperfusion according to PCA duration. *Z*-score hypoperfusion maps of controls compared with subgroups with PCA with <3 years or >3 years disease duration, projected onto surface rendering of the MRI template. A third subgroup with very short disease duration ($\leqslant 2$ years) was also identified. Early hypoperfusions involved the parietal cortex (particularly the precuneus and the inferior parietal cortex), the dorsal occipital regions, the middle and posterior cingulum and the left superior frontal cortex ($P < 0.001$ corrected). After 3 years of duration, the hypoperfusion involved the whole parietal and occipital cortices, the posterior temporal cortex and the bilateral frontal superior cortex (BA 6).

Simultanagnosia was mostly related to the lateral occipital cortex (the bilateral middle and inferior occipital gyrus and right superior occipital cortex), with an extension toward the right cuneus, the precuneus and the temporooccipital junction (Fig. 5).

We found a significant relationship between the Gertsmann scores and parietal hypoperfusion confined to the left angular cortex. Right–left confusion scores were also correlated with left angular perfusion and the middle temporal cortex. Positive correlations with acalculia scores were found in larger areas: (i) the largest cluster mostly covered the left angular cortex and extended to the supramarginal cortex; (ii) the left precuneus, with an extension to the middle cingulum; and (iii) the posterior part of the left middle temporal cortex. These clusters were still significant at $P < 0.05$ corrected (Fig. 6).

No significant correlation was observed among digital agnosia, agraphia or verbal working memory scores.

Discussion

This study investigated the clinical, cognitive and functional neuroimaging features in a large cohort of 39 patients with PCA. The perfusion profile was characterized by extensive and severe hypoperfusion in the lateral and medial parietooccipitotemporal cortices. Interestingly, the hypoperfusion remained focused on the posterior regions even at the late stage of the disease. Strong correlations were found between specific neuropsychological battery scores and posterior cortical hypoperfusion.

The clinical features of the 39 patients with PCA were similar to those of previously described cohorts of PCA. A large proportion of patients (85%) had an onset before the age of 65 years (Mendez *et al*., 2002; Tang-Wai *et al*., 2004; McMonagle *et al*., 2006; Whitwell *et al*., 2007; Lehmann *et al*., 2009). The most common symptoms were limb apraxia (95%), simultanagnosia (92%), agraphia (72%) and elements of Bálint's and/or Gerstmann's syndromes, while a full syndrome was observed in a third of the patients (Renner *et al*., 2004; Tang-Wai *et al*., 2004; McMonagle *et al*., 2006). Interestingly, working memory impairment (visuospatial, rather than verbal) was a consistent sign, whereas episodic memory deficit was only mild and always overshadowed by visuospatial dysfunction.

Single photon emission computed tomography perfusion profile in posterior cortical atrophy

We found extensive hypoperfusion of the bilateral posterior cortex, most prominent in the lateral and medial parietooccipital regions but extending to the posterior temporal cortex, the middle

Table 5 Coordinates of significant cluster maxima for the positive correlations between perfusion and neuropsychological scores and negative correlations with disease duration in the group with PCA

Anatomical regions	Brodmann area	Coordinates *x y z* (mm)	*Z*-scores (*n* voxels)	Correlation coefficient, (*P*-value)
Correlations with visuospatial working memory score				
Left precuneus	5/7	−8 −37 48	3.46 (530)	0.56 (<0.005)
Correlations with limb apraxia score				
Left angular gyrus	39	−57 −60 36	3.72 (1734)	0.60 (<0.001)
Left precuneus	7	−10 −40 50	3.28 (251)	0.58 (<0.01)
Correlations with acalculia score				
Left angular gyrus	39	−53 −41 1	3.87 (1121)	0.63 (<0.001)
Left precuneus/middle cingulum	7/31	−10 −41 43	3.73 (529)	0.48 (<0.05)
Left middle temporal gyrus	21	−42 −60 45	3.93 (451)	0.53 (<0.01)
Correlations with right–left confusion score				
Left angular gyrus	7	−38 −65 51	3.19 (136)	0.56 (<0.01)
Left middle temporal gyrus	37/21	−65 −58 5	3.56 (134)	0.63 (<0.001)
Left superior frontal gyrus	8	−14 49 43	3.42 (120)	0.63 (<0.01)
Correlations with Gerstmann's score				
Left angular gyrus	39	−48 −62 42	3.04 (342)	0.57 (<0.01)
Correlations with ocular apraxia score				
Left superior parietal lobule	7	−30 −55 69	3.86 (102)	0.65 (<0.001)
Right precentral gyrus	6	24 −17 65	3.28 (107)	0.61 (<0.001)
Right precuneus	7	6 −55 64	2.94 (210)	0.60 (<0.001)
Correlations with simultanagnosia score				
Right inferior occipital gyrus/middle occipital gyrus	18	36 −82 −3	3.34 (2570)	0.55 (<0.01)
Left middle occipital gyrus	18	−34 −83 4	3.18 (407)	0.53 (<0.01)
Correlations with optic ataxia score				
Right precuneus	7	8 −53 62	4.06 (597)	0.64 (<0.001)
Left superior parietal lobule	5/7	−30 −39 66	3.74 (469)	0.61 (<0.001)
Right superior occipital gyrus	19	30 −78 37	3.31 (506)	0.57 (<0.01)
Correlations with Bálint's score				
Right precuneus/superior parietal lobule	7	8 −53 62	3.52 (378)	0.62 (<0.001)
Right cuneus	18	14 −103 7	3.57 (277)	0.51 (<0.01)
Left superior parietal lobule	7	−30 −53 69	3.02 (130)	0.59 (<0.01)
Right precentral gyrus	6	22 −18 74	3.14 (116)	0.57 (<0.01)
Right superior occipital gyrus	19	24 −74 31	2.88 (346)	0.51 (<0.01)
Right fusiform gyrus	19	34 −62 −4	2.82 (103)	0.43 (<0.05)
Correlations with disease duration (years)				
Right supramarginalis gyrus	40	55 −53 34	3.47 (1803)	−0.48 (<0.005)
Left angular gyrus	39	−51 −66 35	3.29 (154)	−0.38 (<0.05)
Left middle temporal gyrus	37	−42 −52 10	3.21 (1355)	−0.42 (<0.01)
Right inferior occipital gyrus	18	30 −86 −11	3.00 (115)	−0.46 (<0.005)

Coordinates are in millimetres relative to the anterior commissure, corresponding to the Talairach atlas. Statistical maps were thresholded for significance at $P < 0.005$, with a cluster extent of 100 voxels.

and the posterior cingulum and the bilateral pulvinar, in agreement with previous PET studies (Bokde *et al*., 2001; Nestor *et al*., 2003; Schmidtke *et al*., 2005). In addition, we found hypoperfusion in the superior frontal cortex, especially the frontal eyes field areas, even at the early stage of the disease (Nestor *et al*., 2003; Schmidtke *et al*., 2005; Whitwell *et al*., 2007). The frontal eyes fields are known to be involved in the generation of voluntary eye movements (Nestor *et al*., 2003; Schmidtke *et al*., 2005; Whitwell *et al*., 2007). The deafferentation process, caused by the Wallerian degeneration of projecting fibres from posterior visual association areas, is a likely explanation for this phenomenon. Functional imaging studies using various paradigms to investigate saccadic eye movements in healthy volunteers have found associated activations in both the dorsal stream (BA 19 and BA 7) and frontal eyes fields (Kimmig *et al*., 2001, 2008; Nagel *et al*., 2006). In line with this hypothesis, early in the course of disease, we observed frontal involvement on the side with the greatest parietooccipital hypoperfusion. The frontal hypoperfusion became bilateral in later stages of the disease, when posterior hypoperfusion became severe and symmetrical.

Compared with patients with Alzheimer's disease, patients with PCA showed more severe hypoperfusion in the occipitoparietal regions, in accordance with MRI studies assessing regional cortical atrophy (Whitwell *et al*., 2007; Lehmann *et al*., 2009; Migliaccio *et al*., 2009). Additionally, the hypoperfusion was more severe in the parietooccipital cortex than the temporooccipital cortex, consistent with the hypothesis that damage in the dorsal visual stream could distinguish PCA from Alzheimer's disease, whereas damage

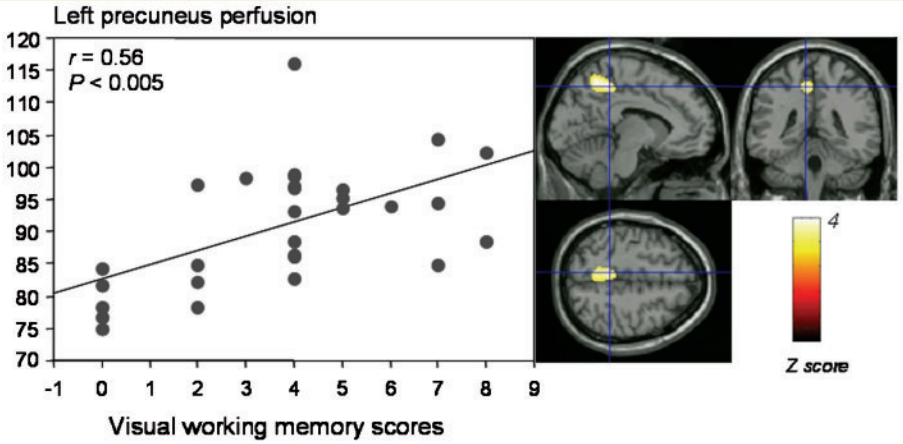

Figure 3 Correlation between brain perfusion and visual working memory scores in PCA. Plots of the normalized perfusion values in the left precuneus ($x = -8$, $y = -37$, $z = 48$ in the Talairach atlas) of patients with PCA for the cluster obtained from correlations with visual working memory scores.

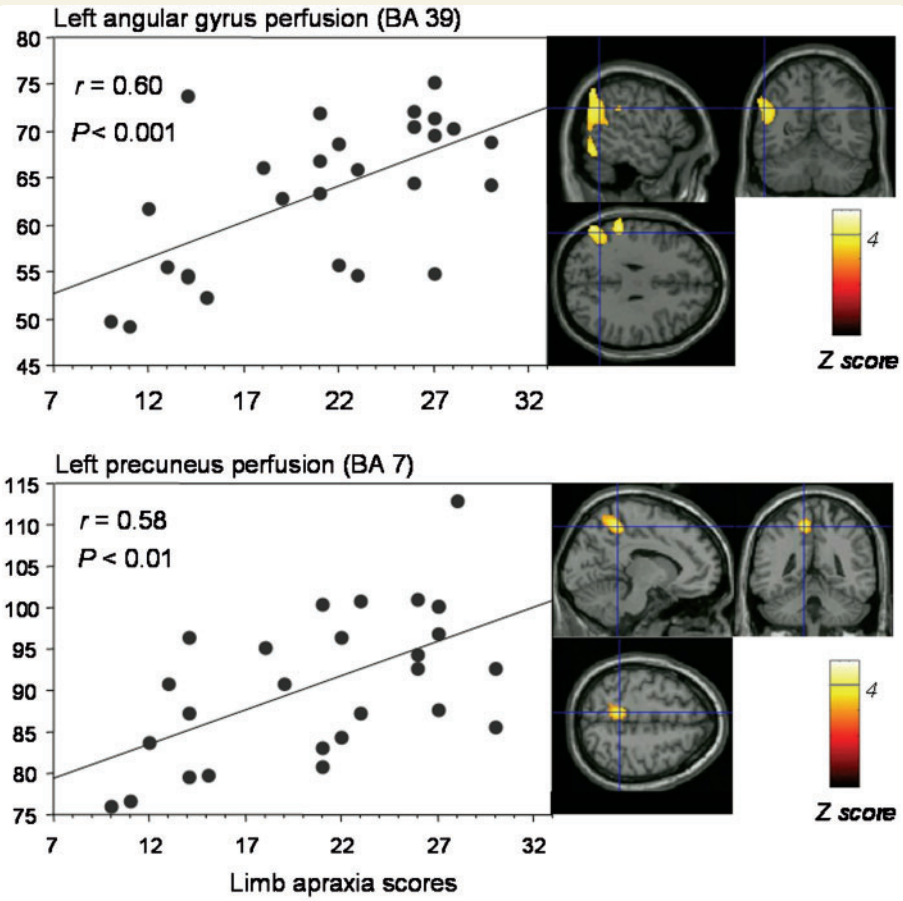

Figure 4 Correlation between perfusion and apraxia scores in PCA. Correlations between perfusion and limb apraxia scores in patients with PCA ($P < 0.005$ uncorrected, cluster extent of 100 voxels). Plots of the normalized brain SPECT perfusion values (expressed as a percentage of mean cerebellar activity) in the left precuneus ($x = -10$, $y = -40$, $z = 50$ in the Talairach atlas) and left angular gyrus ($x = -57$, $y = -60$, $z = 36$) were obtained from correlations with limb apraxia scores.

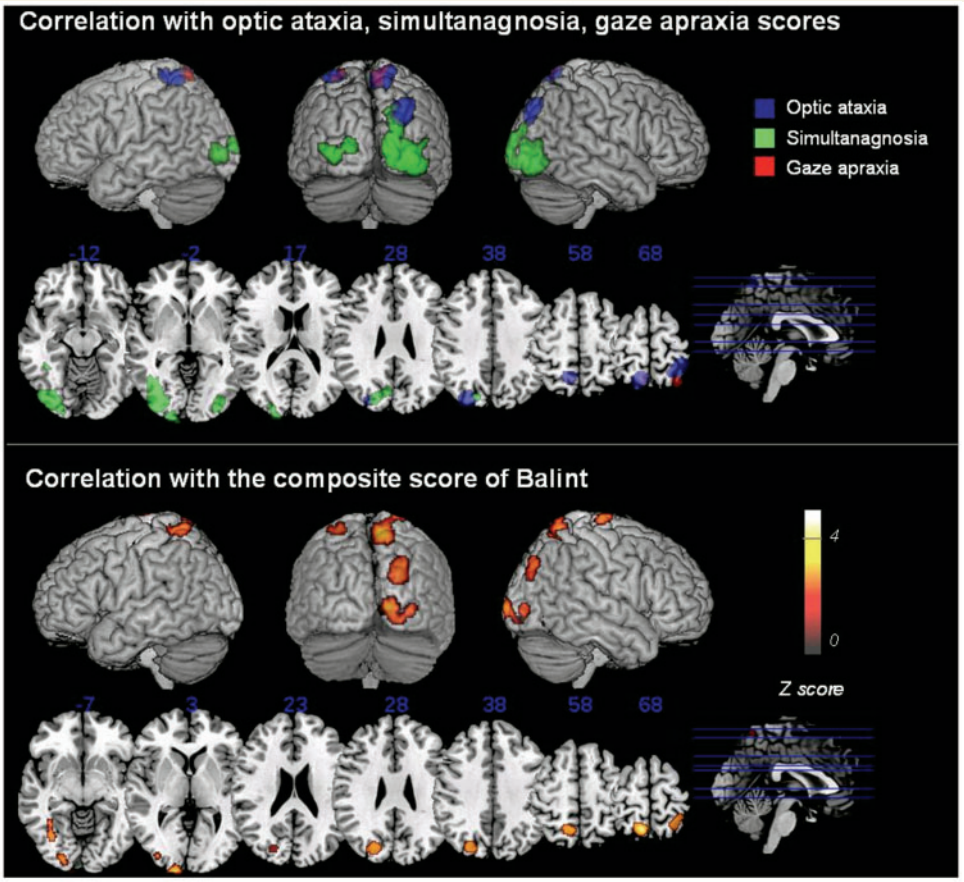

Figure 5 Correlation between cerebral perfusion and simultanagnosia, optic ataxia, gaze apraxia and Bálint's syndrome scores. (*Top*) Positive correlations between cerebral perfusion and optic ataxia (blue), simultagnosia (green) and ocular apraxia (red) scores (all $P < 0.005$ uncorrected). (*Bottom*) Positive correlation between the scores for Balint's syndrome and cerebral perfusion. Transaxial slices are shown according to radiological convention.

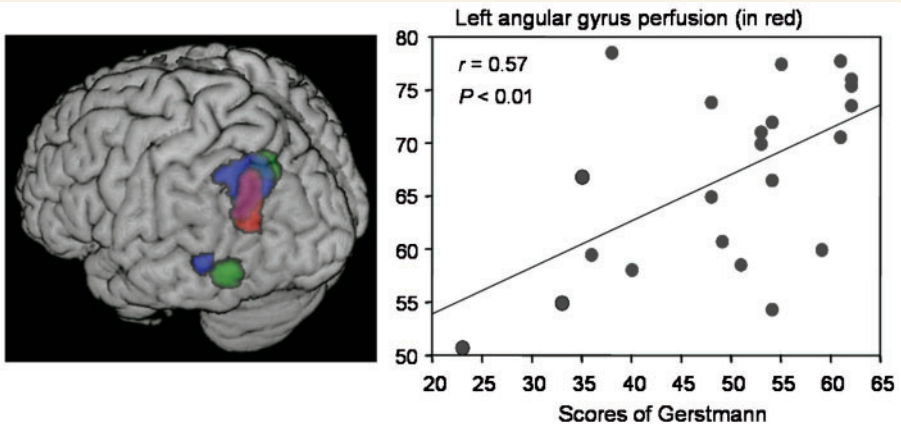

Figure 6 Correlation between cerebral perfusion and acalculia (blue), right–left confusion (green) and Gerstmann's syndrome (red) scores. (*Left*) Cortical areas were significantly correlated with the scores of mental calculation (blue), right–left confusion (green) and Gerstmann's syndrome (red) in patients with PCA ($P < 0.005$ uncorrected). (*Right*) Plots of the normalized perfusion values in the left angular region of patients with PCA for the single cluster (in red) obtained from correlation with the scores for Gerstmann's syndrome ($x = -48$, $y = -62$, $z = 42$ in the Talairach atlas).

in the inferior parietal lobule was common to both conditions (Charles and Hillis, 2005; McMonagle *et al*., 2006). The group with PCA showed significantly higher perfusion in mesiotemporal and anterior prefrontal regions, especially the orbitofrontal cortex, than the patients with Alzheimer's disease. This finding is consistent with the relative preservation of episodic memory (Charles and Hillis, 2005; McMonagle *et al*., 2006) and insight (Schmitz *et al*., 2006; Rosen *et al*. 2010) at the initial and intermediate stages of PCA.

Little is known about the natural progression of the degenerative process in PCA. When considering the disease duration, the most severe hypoperfusion was observed in the dorsal parietal cortex in the disease's early stage, while temporooccipital hypoperfusion appeared later. This result is in agreement with the only clinical longitudinal study of patients with PCA ($n = 19$ patients), which showed early visuospatial deficits with later visual agnosia and alexia (McMonagle *et al*., 2006). These results suggest that PCA remains a focal posterior disorder. Given that the most frequent underlying pathology found in autopsy studies is Alzheimer's disease (Tang-Wai *et al*., 2004; Alladi *et al*., 2007), we expected to find a more widespread progression of cortical hypoperfusion. On the contrary, our findings showed that both the topography and the progression of cortical hypoperfusions differ between the two diseases. However, our results were obtained from a cross-sectional study, and therefore, any conclusions about the patterns of progression should be drawn with caution. Moreover, the majority of patients from the group with long disease duration PCA had a mean disease duration of 5 years, which may not be long enough to observe more global patterns of hypoperfusion. To verify this point, an individual analysis of the two patients with the longest disease durations (8 and 12.6 years) showed that hypoperfusion mainly remained predominant in the posterior regions (Supplementary Fig. 2). Future studies are needed to clarify this observation.

Anatomical correlates of posterior cortical atrophy syndrome

We also aimed to understand the neural basis of the major cognitive symptoms by studying the correlations between cognitive scores and hypoperfusion areas.

Limb apraxia was one of the most common features in our sample and the limb apraxia scores were mainly correlated with the perfusion of the left posterior parietal cortex. The left lateralization is consistent with other studies, supporting the theory that the left hemisphere specializes in generating movement (Moll *et al*., 2000; Tessari *et al*., 2007; Goldenberg, 2009; Goldenberg and Spatt, 2009). Moreover, recent studies have shown that apraxia is associated with damage to a network of brain regions, including the parietal cortex, the superior posterior temporal cortex and the white matter bundles connecting the frontal and parietal association areas (Johnson-Frey *et al*., 2005; Zadikoff and Lang, 2005; Tessari *et al*., 2007; Weiss *et al*., 2008; Ramayya *et al*., 2010). In our study, the apraxia scores pooled the imitation of meaningless and meaningful gestures and pantomimes of familiar gestures and were highly correlated with the left angular gyrus, suggesting that this region plays a crucial role in integrating praxis information, meaningless action imitation, meaningful action imitation and pantomime (Tessari *et al*., 2007; Weiss *et al*., 2008; Goldenberg and Spatt, 2009).

The Gerstmann score and its components (except digital agnosia) were significantly correlated with the perfusion of the left parietal lobe, especially the left angular gyrus. This finding is in accordance with neuropsychological studies conducted in patients undergoing open brain surgery, which showed a relationship between Gerstmann's syndrome elements and the left parietal cortex (Rusconi *et al*., 2010). It is of note that these regions overlap with cortical sites where electrical stimulation elicited elements of Gerstmann's syndrome (Rusconi *et al*., 2010). Among the symptoms of Gerstmann's syndrome, mental arithmetic is the most studied in the literature. Most of these data were obtained in patients with focal lesions or in experimental tasks in healthy volunteers, but never in patients with PCA. In our study, mental calculation scores were strongly correlated with perfusion of the left angular and supramarginalis cortices, in agreement with brain electrostimulation studies (Roux *et al*., 2003). In functional MRI studies in normal volunteers, arithmetic processing was mediated by left-hemisphere specialization of the anterior and posterior parts of the intra-parietal sulcus (Zago *et al*., 2008). Repetitive transcranial magnetic stimulation over the left angular gyrus in healthy subjects disrupted tasks requiring number magnitude processing (Rusconi *et al*., 2005). The left posterior parietal regions' role in calculation is also supported by studies of patients with acalculia (Martory *et al*., 2003) and with developmental dyscalculia (Barnea-Goraly *et al*., 2005). Additionally, our study showed a significant correlation between the perfusion of the left parietal lobe (BA 39) and left–right distinction scores, consistent with functional neuroimaging studies demonstrating the left posterior parietal regions' role in left–right orientation (Rusconi *et al*., 2009, 2010). Finally, recent data obtained by combining functional and structural neuroimaging of parietal lobe organization in the healthy brain, suggest that pure Gerstmann's syndrome might arise from the disconnection, via lesion, of separate but colocalized tracts in the subcortical parietal white matter (Rusconi *et al*., 2010). The study of white matter connections in patients with PCA would be of great interest in identifying the underlying network involved in the disease.

The Bálint's score was correlated with the perfusion of areas involving the superior parietal lobule, the superior occipital cortex, the cuneus, the precuneus and the precentral cortex. Within Bálint's syndrome, correlation patterns for ocular apraxia and optic ataxia were distinct from those of simultanagnosia. Within the framework of ventral- versus dorsal-route organization of the visual system, optic ataxia and ocular apraxia can be interpreted as deficits involving the dorsal pathway, while simultanagnosia can be interpreted as a deficit involving mainly the higher associative visual occipital areas. These results are in accordance with the neural correlates of optic ataxia with superior parietal lobule lesions, either unilateral or bilateral (Milner and Goodale, 1995; Trillenberg *et al*., 2007) and with recent functional MRI studies showing that the dorsal stream (the lateral occipitoparietal junction) was associated with orientation changes for graspable stimuli (Rice *et al*., 2007) and visually guided reaching-to-grasp

(Hinkley *et al*., 2009). On the other hand, simultanagnosia in PCA seems to reflect the severity of damage in the visual associative cortex without involving the parietal cortex (Himmelbach *et al*., 2009; Huberle *et al*., 2009).

Working memory has been classically assigned to prefrontal regions and the posterior parietal cortex (Koechlin *et al*., 2003; Champod and Petrides, 2007, 2010; Koechlin and Hyafil, 2007). Visual working memory scores, but not verbal ones, were correlated with perfusion in the precuneus, in accordance with this region's role in spatial attention, mental imagery and shifting attention between object features (Cavanna and Trimble, 2006; Kaiser *et al*., 2010). In our study, involvement of the precuneus was correlated with other cognitive processes, such as apraxia, acalculia, ocular apraxia, optic apraxia and Bálint's syndrome. This result could be explained by the role of the precuneus in oculomotor guidance and spatial control of motor activity (Cavanna and Trimble, 2006). These findings demonstrate the importance of the posterior parietal cortex in brain networks that mediate working memory.

Our data concerning the correlations study should be interpreted keeping in mind that the neuropsychological battery mainly targets visuospatial dysfunctions rather than visuoperceptual deficits. Additionally, our observations about the progression of PCA over time were based on patient groups with different disease durations. These observations should be confirmed by longitudinal studies with serial perfusion or metabolism imaging. Finally, because only a small number of patients had a T_1-weighted 3D acquisition suitable for partial volume effect correction, no correction was implemented during our Statistical Parametric Mapping analyses. This is a methodological limitation of this work considering the spatial resolution of SPECT and the presence of brain atrophy in PCA and patients with Alzheimer's disease. However, it has been demonstrated that correcting for brain atrophy does not modify the metabolic differences among patients with Alzheimer's disease, patients with PCA and controls (Bokde *et al*., 2001). In addition, considering that regional hypoperfusion and cortical atrophy may both contribute to the clinical symptoms of PCA, the results of the correlation analysis can be considered pertinent despite the absence of partial volume effect correction (Nestor *et al*., 2003).

Our findings provide new insight about the role of parietal and occipital cortices in the cognitive syndromes that characterize PCA. Correlation analyses of patients with PCA brain perfusion and neuropsychological scores demonstrated the prominent role of left inferior parietal damage in acalculia, Gerstmann's syndrome, left–right indistinction and limb apraxia, whereas damage to the bilateral dorsal occipitoparietal regions appeared to be involved in Bálint's syndrome. Our study also provides new information on the natural history of functional changes according to disease duration and suggests that PCA remains centred on the posterior lobes even in the late stage of the disease.

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Supplementary material

Supplementary Material is available at *Brain* online.

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