Published in final edited form as:

Neurobiol Aging. 2012 November ; 33(11): 2572–2584. doi:10.1016/j.neurobiolaging.2011.12.025.

Ventral and dorsal visual streams in posterior cortical atrophy: A DT MRI study

Raffaella Migliaccio^{a,b,c}, Federica Agosta^a, Elisa Scola^d, Giuseppe Magnani^e, Stefano F. Cappa^{f,g}, Elisabetta Pagani^a, Elisa Canu^a, Giancarlo Comi^e, Andrea Falini^d, Maria Luisa Gorno-Tempini^h, Paolo Bartolomeo^{b,c}, and Massimo Filippi^{a,e,*}

^aNeuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

^bINSERM, U975 Centre de Recherche de l'Institut du Cerveau et de la Moëlle Epinière (CRICM), Hôpital de la Salpêtrière, Paris, France

^cDepartment of Psychology, Catholic University, Milan, Italy

^dDepartment of Neuroradiology and CERMAC, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

^eDepartment of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

^fDepartment of Clinical Neurosciences, San Raffaele Turro Hospital, Milan, Italy

^gVita-Salute San Raffaele University and Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy

^hMemory and Aging Center, Department of Neurology, UCSF, 350 Parnassus Avenue, San Francisco, CA, USA

Abstract

Using diffusion tensor magnetic resonance imaging tractography, ventral (inferior longitudinal fasciculus) and fronto-occipital (inferior fronto-occipital fasciculus) and dorsal (fronto-parietal superior longitudinal fasciculus) visual pathways were assessed in 7 patients with posterior cortical atrophy (PCA), showing either predominantly ventral or additional dorsal cognitive deficits. Corpus callosum and corticospinal tracts were also studied. Gray and white matter atrophy was assessed using voxel-based morphometry. In all PCA patients, abnormal diffusivity indexes were found in bilateral inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, with a left-side predominance. Patients also had mild microstructural damage to the

*Corresponding author at: Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, via Olgettina 60, 20132 Milan, Italy. Tel.: +39-02-26433033; fax: +39-02-26435972. m.filippi@hsr.it (M. Filippi).

Disclosure statement

The remaining authors disclose no conflicts of interest.

Approval was received from the local ethical standards committee on human experimentation and written informed consent was obtained from all subjects prior to study enrollment.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2011.12.025.

corpus callosum. The 2 patients with more dorsal symptoms also showed right fronto-parietal superior longitudinal fasciculus abnormalities. Corticospinal tracts were normal, bilaterally. When studied separately, patients with ventral clinical impairment showed a pattern of atrophy mainly located in the ventral occipitotemporal regions, bilaterally; patients with both ventral and dorsal clinical deficits showed additional atrophy of the bilateral inferior parietal lobe. Magnetic resonance imaging patterns of abnormalities mirror closely the clinical phenotypes and could provide reliable ante mortem markers of tissue damage in PCA.

Keywords

Posterior cortical atrophy (PCA); Visual streams; Diffusion tensor MRI; Tractography; VBM

1. Introduction

Posterior cortical atrophy (PCA) is a rare neurodegenerative dementia whose clinical features have been described by Frank Benson in 1988 (Benson et al., 1988). Patients with PCA usually present with progressive high order visual and visuomotor deficits, including visual agnosia, environmental disorientation, elements of the Bálint syndrome, or Gerstmann syndrome, along with deficits in praxis and language. All these symptoms, as the definition of PCA suggests, reflect a severe and diffuse posterior cerebral damage. Consistent with their clinical presentation, PCA patients show hypometabolism (Nestor et al., 2003; Schmidtke et al., 2005) and gray matter (GM) atrophy in parieto-occipital and posterior temporal cortices (Migliaccio et al., 2009; Whitwell et al., 2007).

Biological and pathological studies have suggested that an Alzheimer's disease (AD) type of pathology is the most likely cause of PCA (Renner et al., 2004; Tang-Wai et al., 2004). However, in this condition the distribution of pathological changes is atypical compared with that of classic AD, because PCA is characterized by a preponderance of neurofibrillary tangles and senile plaques in occipital, parietal, and middle/inferior temporal cortices (Hof et al., 1997; von Gunten et al., 2006). Given its early age of onset, usually before 65 years, and because of the lack of memory deficits as the core early symptom, PCA has been defined as a "nontypical form of AD with an early age of onset" (Migliaccio et al., 2009).

A classification of PCA into dorsal and ventral subtypes has been suggested by McMonagle et al. (2006), which reflects the classic dichotomy of higher order visual processing in the ventral "what" and dorsal "where" pathways (Ungerleider and Mishkin, 1982). According to the model proposed by Goodale and Milner (1992), the dorsal and ventral streams are both able to process information about objects and their locations, but each stream elaborates this information in different ways. The ventral stream carries out information about perceptual features, allowing the creation of long-term representations necessary to identify and recognize objects. The dorsal stream processes information about objects and their locations in a moment-to-moment way, and mediates the visual control of skilled actions. As a consequence, the ventral PCA subtype is characterized by deficits in the processing of visual objects (e.g., object, face, color, and written word recognition), while the dorsal subtype by deficits in the processing of spatial location (spatial awareness and reaching movements) (Mendez, 2001; Ross et al., 1996). Recently, a structural magnetic resonance imaging (MRI)

study has shown a tendency toward a lower cortical thickness in occipitotemporal and occipitoparietal cortices in PCA patients with predominant visuo-perceptual and visuospatial deficits, respectively (Lehmann et al., 2011).

Anatomically, the inferior longitudinal fasciculus (ILF), connecting the occipital and temporal lobes, and the inferior fronto-occipital fasciculus (IFOF), connecting occipitoparietal and frontal regions, are considered components of the ventral stream (Ffytche et al., 2010). The dorsal stream corresponds to inferior and superior parietal brain regions connected with the frontal lobes by the long-range white matter (WM) bundle called superior longitudinal fasciculus (SLF) (Ffytche et al., 2010). Diffusion MRI measures the effect of tissue microstructure on the random translational motion of water molecules in biological tissues (Basser et al., 1994; Pierpaoli et al., 1996). A full characterization of diffusion can be provided by diffusion tensor (DT)-based methods. From the DT, 2 scalar measures are most frequently derived. The first, mean diffusivity (MD), is calculated as 1/3 of the tensor matrix trace and reflects the average diffusion in all 3 spatial directions. The other, fractional anisotropy (FA), is derived from the eigenvalues of the tensor matrix and measures the extent to which diffusion is nonuniform in the 3 orthogonal directions. Tractography algorithms use this information to track WM pathways by inferring the continuity of fiber paths from a voxel to another, that is, the direction of maximum diffusivity in a particular voxel is followed into an adjacent one (Basser et al., 2000).

DT MRI tractography is contributing significantly to the study of various neurodegenerative dementias, such as late-onset AD (Pievani et al., 2010; Stricker et al., 2009) and frontotemporal lobar degeneration (Agosta et al., 2010; Matsuo et al., 2008; Zhang et al., 2009). To the best of our knowledge, only 3 single case studies (Duning et al., 2009; Yoshida et al., 2004) have investigated the pattern of WM damage in PCA patients using DT MRI. In 1 study (Duning et al., 2009), using a region of interest (ROI)-based approach, the cognitive deterioration of a PCA patient (over a period of 15 months) was associated with diffusivity changes of the occipitoparietal WM rather than with overall GM and WM atrophy progression. In the second study (Yoshida et al., 2004), a FA reduction in the splenium of the corpus callosum (CC), possibly reflecting neuronal loss in posterior brain regions, has been detected. More recently, we described a PCA patient with left visual neglect, optic ataxia, left limb apraxia, and mild visuospatial episodic memory impairment. In this patient, we showed a bilateral posterior GM atrophy with right predominance and, using DT MRI tractography, a WM damage to the right hemisphere fasciculi only, suggesting that selective visuospatial deficits typical of PCA are not necessarily a result of cortical damage only (Migliaccio et al., 2011). There are currently no group studies assessing the long-range WM tracts in PCA patients using DT MRI tractography.

In the present study, we obtained DT MRI tractography from 7 patients with PCA to investigate WM integrity of the 2 major cortical visual pathways, i.e., the dorsal and ventral streams. To investigate the relationship between microstructural WM abnormalities and the pattern of brain atrophy, patients also underwent structural MRI in order to perform a voxel-based morphometry (VBM) assessment. We hypothesized that PCA patients would show an impairment of the dorsal, the ventral visual, or both streams, and that this would mirror the corresponding clinical phenotypes. Because neurodegenerative diseases are likely to target

large-scale, distributed brain networks (Seeley et al., 2009), the demonstration of a damage to WM pathways of the functional visual streams in PCA patients, which corresponds to the disease clinical manifestations, would be important to gain additional insights into the more general question of a selective vulnerability of brain networks to neurodegenerative processes.

2. Methods

2.1. Subjects

Seven PCA patients were consecutively enrolled. Patients were selected by a team of experienced neurologists and the diagnosis was based on clinical history, neurological examination, and neuropsychological testing, according to published criteria (McMonagle et al., 2006) modified by Alladi et al., 2007. Medical records were further reviewed to establish the clinical symptoms at presentation and describe the clinical history of each patient. Subjects were excluded if they had: (1) a family history of dementia; (2) significant medical illnesses or substance abuse that could interfere with cognitive functioning; (3) any other major systemic, psychiatric or neurological illnesses; and (4) other causes of focal or diffuse brain damage, including lacunae, and extensive cerebrovascular disorders on routine MRI scans. Thirteen age- and sex-matched healthy subjects served as controls (Table 1). VBM was used to investigate patterns of GM and WM atrophy in PCA patients relative to a larger control group of 29 age- and sex-matched healthy subjects (19 women, 10 men; mean age: 59 ± 4.9 years). Approval was received from the local ethical standards committee on human experimentation and written informed consent was obtained from all subjects prior to study enrollment.

2.2. Cognitive testing

All patients underwent a neuropsychological screening battery (Supplementary Table 1). Neuropsychological assessment was performed by an experienced neuropsychologist blinded to the MRI results, and evaluated: (1) global cognitive functioning with the Mini Mental State Examination (MMSE) (Folstein et al., 1975); (2) memory function with the story recall (Carlesimo et al., 2002) or Rey's word list immediate and delayed recall tests (Carlesimo et al., 1996; Mauri et al., 1997); (3) executive functions with attentional matrices (Spinnler and Tognoni, 1987) and verbal (Orsini et al., 1987) and visual (Spinnler and Tognoni, 1987) digit span task; (4) language functions with the phonological and semantic fluency (Novelli et al., 1986) and Token test (De Renzi and Vignolo, 1962); and (5) visuospatial abilities with the Rey's figure copy test (Caffarra et al., 2002).

To identify deficits related to the ventral stream, e.g., visual agnosia, the following tests were used: object identification and recognition (Riddoch and Borb, 1993), masked object recognition, face recognition and identification (Benton et al., 1994; Spinnler and Tognoni, 1987), and a figure completion test (Spinnler and Tognoni, 1987). Clinical evaluation of reading abilities was also conducted (sub-tests of the Aachen Aphasia Test [AAT] (Luzzatti et al., 1987) and "Batteria per l'analisi dei deficit afasici [BADA]" (Miceli et al., 1994). Cases 1, 2, and 4 also performed the Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991), which is sensitive to visual perceptual and spatial

impairment, and the Birmingham Object Recognition Battery (BORB) (Riddoch and Borb, 1993), which is sensitive to deficits in object recognition. Simultanagnosia, often resulting from both ventral and dorsal stream impairment, was assessed using the overlapping figure test (Gainotti et al., 1986). Finally, cases 1–4 and 7 underwent a paper-and-pencil battery (Azouvi et al., 2006) sensitive to signs of visual neglect, and a clinical evaluation of optic ataxia and ocular apraxia, as previously described (Kas et al., 2011).

2.3. MRI acquisition

Using a 3.0-T scanner, DT sequences were acquired. A T2-weighted spin echo (to investigate other cause of focal or diffuse brain damage) and 3-D T1-weighted (to assess the atrophy) sequences were also acquired. See Supplementary Appendix 1 for further details.

2.4. MRI analysis

All MRI analysis was performed by a single experienced observer, who was unaware of subjects' identity. DT MRI preprocessing is described in Supplementary Appendix 1.

2.4.1. Fiber tracking—Fiber tracking was performed using the Diffusion Tool-kit based on the interpolated streamline method and Track-Vis software (Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Boston, MA, USA; version 05.1) (Wedeen et al., 2008). Fiber tracts were launched from every voxel in the brain and terminated when entering a voxel with a FA lower than 0.15, or in case of a voxel-to-voxel deflection angle greater than 45°. The trajectories of the ILF, IFOF, and the frontoparietal SLF (so called branches II and III) bilaterally, and the CC were obtained. The corticospinal tracts (CST) were also tracked as “internal control” bundles. By cross-referencing neuroanatomical (Dejerine, 1895; Schmahmann and Pandya, 2006) and previous DT MRI tractography works (Catani and Thiebaut de Schotten, 2008; Glasser and Rilling, 2008), ROIs were defined manually on the axial, coronal, and sagittal FA images of each subject, and were used as target regions for tracking. ROIs were delineated as follows (Supplementary Fig. 1):

- **ILF ROIs:** a 2-ROI approach was used. The first ROI was drawn on axial FA slices around the WM of the anterior temporal lobe. The second ROI was drawn on axial FA slices around the occipital WM lying posterior to the splenium of the CC. In order to include the entire occipital lobe, coronal, and sagittal FA maps were used as reference to identify the parieto-occipital sulcus.
- **IFOF ROIs:** a 2-ROI approach was used. The first ROI was drawn around the occipital lobe using the same criteria used for ILF. The second ROI was drawn around the external/extreme capsule.
- **Frontoparietal SLF ROI:** a single ROI was drawn on the coronal slice of the color-coded map to define all fibers oriented in an anterior-posterior direction (green on the color maps), running lateral to the corona radiata and medial to the cortex. Because all SLF bundles pass through this bottleneck, it is an ideal region to define the main body of the tract. All tracts that did not reach the frontal lobe were removed because they represent either erroneous tracts or tracts that were not of

interest for the present study. Then, a second ROI was drawn on sagittal FA slices around the entire descending temporal portion of the SLF, corresponding approximately to the posterior third of the superior temporal gyrus, bordered caudally and dorsally by the angular and supramarginal gyri, respectively. The rostral border of the temporal ROI was defined as the position of the Heschl's gyrus. This ROI was then used as an exclusion ROI to isolate the frontoparietal component of SLF.

- CC ROIs: a single ROI was drawn around the CC on a midsagittal slice.
- CST ROIs: a 2-ROI approach was used. The first ROI was drawn around the cerebral peduncle, and the second around the internal capsule.

2.4.2. Anatomical verification of ROIs and tracts—Anatomical verification on structural images allows a more accurate anatomical localization of ROIs and tracts than when using the native diffusion space (Basser et al., 2000). Extracerebral tissue was removed from the T1-weighted and b0 images, using the brain extraction tool of the MRICro (University of South Carolina, SC, USA; version 1.34) (Rorden et al., 2007). Then, using statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/spm) running on Matlab 7.2.1 (Math-Works, Natick, MA, USA), T1-weighted images were registered linearly to the b0 images. On the resulting T1-weighted images, the anatomical localization of each subject's ROIs was verified. Finally, all tracts were overlaid on the transformed anatomic magnetic resonance images, and visually checked for consistency with known anatomy.

2.4.3. Deriving tract-specific DT metrics—Maps of MD and FA, as well as axial diffusivity (axD, i.e., the largest eigenvalue) and radial diffusivity (radD, i.e., the average of the smallest eigenvalues), were derived from the DT. WM thresholding and cerebrospinal fluid (CSF) masking were obtained as follows. WM maps, as obtained in the VBM analysis (see below), were normalized to single subject's FA space, applying the transformation matrices calculated in the previous steps for T1-weighted images. Then, WM maps were thresholded at a value > 0.75 and used to mask DT MRI maps. The same procedure was applied to the CSF maps for exclusive masking. Finally, mean DT MRI metrics were obtained for each WM tract. To explore visually the topographical distribution of diffusivity abnormalities in each pathway, WM tracts were also rendered as maps of FA values in both hemispheres for all subjects. Figs. 1 and 2 show the anatomy and the pattern of damage to both dorsal and ventral WM pathways in illustrative patients.

2.4.4. Voxel-based morphometry—VBM was performed using SPM8 (Wellcome Department of Imaging Neuroscience) and the Diffeomorphic Anatomical Registration Exponentiated Lie Algebra (DARTEL) registration method (Ashburner, 2007). A detailed description of VBM analysis is provided in Supplementary Appendix 1.

2.5. Statistical analysis

Demographic and clinical variables were compared between groups using a χ^2 test for categorical variables and the Mann-Whitney *U*-test for continuous variables. For each DT

MRI metric, comparisons between PCA patients and controls were performed using linear mixed-effect model analysis (McCulloch et al., 2008), adjusted for subjects' age. These models contain predictors for Group, Tract, and the Tract $\times$ Group interaction. Random intercepts were estimated to account for correlation among measures from the same subjects. The coefficients of Group and the Tract $\times$ Group interaction assess the tract-specific group differences for each DT MRI variable studied. Following the Wald's approach, we tested if these coefficients were all 0, providing an overall, multivariate test of the hypothesis that the group-specific means of a given variable were the same for each tract. If this hypothesis was rejected at $\alpha = 0.05$, then tract-specific differences for each DT MRI variable were assessed by using the Fisher's least significant difference. If we did not reject the null hypothesis of the multivariate test, we did not proceed to the second stage of the analysis. Results are reported as estimated means along with their standard error. To investigate the DT MRI pattern of damage in individual patients, a test for comparing an individual case with a small control sample was used (Crawford and Garthwaite, 2002). Statistical analysis was performed using SAS Release 9.1 (SAS Institute, Cary, NC, USA).

GM and WM maps were compared between patients and controls using an analysis of variance (ANOVA) model in SPM8 (Wellcome Department of Imaging Neuroscience), adjusting for subject's age, gender, and total intracranial volume. The following sets of linear contrasts were performed to identify regional GM and WM atrophy: (1) all patients versus controls; (2) each subgroup, ventral and ventral plus dorsal, separately versus controls; (3) each subgroup versus the other. Regions showing a more severe atrophy in each subgroup were identified by masking the relevant contrast from Set 2 (ventral vs. controls, and ventral plus dorsal vs. controls) with the appropriate contrast from Set 3 (ventral vs. ventral plus dorsal and vice-versa). A significance threshold of $p < 0.05$ corrected for multiple comparisons (family-wise error [FWE]) was adopted.

3. Results

3.1. Demographic, clinical, and cognitive data

There were no significant differences in age, gender, education, and handedness between patients and controls (Table 1). The clinical profiles of the 7 PCA patients are summarized in Table 1, where they are listed in a decreasing order of disease severity established on clinical and cognitive results and their symptoms are categorized in terms of clinical ventral and dorsal symptoms and signs. Neuropsychological assessment scores are reported in Supplementary Table 1.

All patients had, as early and major complaints, deficits in recognizing objects and faces, as well as reading difficulties. In particular, the visual agnosia, along with alexia, was the earliest symptom in all but 1 patient. Prosopagnosia was present in 3 patients at disease onset, and it was invariably present in all of them later on in the course of the disease. Two patients showed additional dorsal symptoms and signs: case 7 showed a left visual neglect at disease onset, and case 2 showed an optic ataxia during follow-up (Table 1). Among the elements of Gerstmann syndrome, finger agnosia and acalculia were present in 4 patients, and left-right disorientation in 2. Visuospatial memory deficits also occurred during disease evolution; in 2 cases only, they were already detectable at presentation. Language deficits

and ideomotor apraxia were presented in 3 patients during the disease course. Case 1 was the patient with the longest clinical history and a more focal clinical picture with isolated difficulties in reading and writing for about 7 years. Cases 2 and 3 were characterized by the presence of visuospatial working memory deficits at disease onset. Mild executive deficits were present in patients 3, 4, and 5. Depression, irritability, and apathy were present in patients 3, 4, 5, and 6.

Based on clinical and cognitive profiles, we separated the patients into 2 subgroups depending on the predominance of ventral symptoms (i.e., patients 1, and 3–6) or the presence of additional dorsal symptoms (i.e., patients 2 and 7).

3.2. DT MRI findings

Visual assessment of each tract in each subject showed a consistent and similar pattern across patients and controls. Figs. 1 and 2 show the ILF, IFOF, and frontoparietal SLF, bilaterally in representative PCA cases. The anatomy of CC for a normal subject and all patients is shown in Supplementary Fig. 2.

Table 2 shows the estimated means (and standard error) of the DT MRI metrics of patient and control groups. All PCA patients had significantly higher MD, axD, and radD, and lower FA in the left ILF and IFOF compared with controls (p values from < 0.001 to 0.005). Relative to controls, PCA patients also had significantly higher MD and radD and lower FA in the right ILF and IFOF (p values from < 0.001 to 0.03), and higher MD, axD, and radD in the CC (p values from < 0.001 to 0.01) (Table 2). The comparison between all PCA patients and controls did not show differences in the fronto-parietal SLF (except for a slightly significantly higher MD on the right side, $p = 0.04$), and CST, bilaterally. When DT MRI measures were assessed separately in the 2 subgroups, patients with dorsal symptoms (i.e., cases 2 and 7) had significantly lower FA and higher MD and radD in the right frontoparietal SLF compared with the other PCA patients.

3.3. Voxel-based morphometry

VBM results are shown in Fig. 3. When compared with controls, PCA patients showed GM atrophy in posterior temporal, parietal, and occipital regions, bilaterally. In particular, GM loss occurred bilaterally in the middle and inferior occipital, ventral occipitotemporal, inferior parietal, posterior middle and inferior temporal lobes, and the hippocampi. Atrophy also occurred in the right superior parietal gyrus, the right thalamus, the left calcarine cortex, the cuneus, the precuneus, the superior temporal gyrus, and the posterior cingulum (Supplementary Table 2). WM atrophy was detected in the ventral occipitotemporal region, bilaterally, close to the damaged GM areas.

In PCA patients showing predominant ventral symptoms (i.e., cases 1 and 3–6) compared with healthy controls, GM atrophy was mainly found in ventral regions, namely in ventral occipital (x, y, z : $-21, -53, -7$, T -score 13.3; and $25, -60, -9$, T -score 10.2) and temporal (x, y, z : $-32, -65, -7$, T -score 11.5; and $29, -60, -9$, T -score 10.2) regions, bilaterally. In patients showing additional dorsal symptoms (i.e., cases 2 and 7) relative to healthy controls, GM atrophy was mainly located in the right inferior parietal lobe (supramarginal gyrus, x, y, z : $67, -37, 41$, T -score 11.0), and bilateral inferior parietal lobule (x, y, z : $40, -47, 44$, T -

score 11.0; $-43, -51, 43$, T -score 7.58), as well as in the ventral occipital ($x, y, z: -22, -53, -7$, T -score 7.9; and $25, -78, 12$, T -score 7.5) and temporal ($x, y, z: -25, -56, -9$, T -score 6.3; and $26, -57, -9$, T -score 9.0) regions, bilaterally. When we assessed the areas mostly affected in each subgroup (Supplementary Fig. 3), GM atrophy was centered on the left ventral temporal regions ($x, y, z: -32, -65, -7$, T -score 11.5) in the ventral PCA group, and on the right inferior parietal lobe ($x, y, z: 64, -37, 41$, T -score 11.0) in the ventral plus dorsal one. WM atrophy occurred in occipitotemporal regions in the ventral subgroup, and mainly in occipital areas in the ventral plus dorsal subgroup (data not shown).

4. Discussion

We investigated clinical, cognitive, and anatomical profiles of 7 patients affected by PCA, a rare form of focal neurodegenerative dementia. Impaired “ventral” functions, such as recognition of faces and objects as well as reading deficits, dominated the clinical picture of all our PCA patients from onset. Additionally, in 2 cases (i.e., cases 2 and 7), left visual neglect and optic ataxia were also present. DT MRI tractography and volumetric study demonstrated a selective damage to the ventral visual network (occipitotemporal regions and ILF and IFOF), especially in the left hemisphere. In the 2 patients with additional dorsal stream deficits, damage to the dorsal network (parietal areas and frontoparietal SLF) was also detected, with right side predominance. We will discuss these findings in relation to the clinical features experienced by these PCA patients and in the framework of the current models of disconnection syndromes.

The left ILF carries visual information from occipital areas to the temporal lobe (Catani et al., 2003) and is likely to play an important role in visual object recognition (Ffytche et al., 2010), and naming (Ffytche et al., 2010; Shinoura et al., 2010), and reading (Epelbaum et al., 2008). A right-handed patient with a brain tumor showed a marked deterioration in an object naming task and DT MRI demonstrated an interruption of the left ILF (Shinoura et al., 2010). All our PCA patients had diffusivity abnormalities to the left ILF and impaired object recognition as the major clinical complaint; such a finding is clearly exemplified by case 3, a road laborer, who began with difficulties in recognizing and, as a consequence, in interpreting road signs. In patients affected by semantic dementia with anterior temporal atrophy, ILF damage has been suggested to be responsible for a disconnection between damaged temporal regions and spared posterior visual cortex (Agosta et al., 2010). Taken together, these findings suggest that the integrity of the left ILF is crucial to couple the visual inputs with their semantic connotation, and consequently to recognize and name objects correctly. The ILF is also considered to have an important role in linking object representations to their lexical labels (Mummery et al., 1999), and is believed to be involved in reading skills. For example, a left ILF disconnection has been described in a patient with pure alexia (Epelbaum et al., 2008), in agreement with the early interpretation of this condition proposed by Jules Dejerine (Dejerine, 1895). Indeed, Dejerine documented the presence of ILF damage in 1 of his pure alexia patients and hypothesized its causal role in the disconnection between visual areas and reading centers. In our sample, all patients had reading difficulties, either at onset (all but 1), or during the course of the disease. Interestingly, alexia was the only complaint, along with writing deficits, reported by patient 1 for at least 7 years. The involvement of both left and right ventral cerebral regions has

been suggested as a possible substrate of prosopagnosia (Barton et al., 2010; Benson et al., 1974; Kay and Levin, 1982; Kleinschmidt and Cohen, 2006; Sorger et al., 2007; Takahashi et al., 1995; Thomas et al., 2009). In this framework, the damage to the ILF (Fox et al., 2008; Ishai, 2008) can disconnect face-processing areas located in the inferior occipital and fusiform gyri from more anterior regions in the temporal and frontal lobes (Alexander et al., 2007; Giussani et al., 2009; Rapsak et al., 2001; Simon et al., 2011), which in turn may result in deficits in the ability to recognize known faces.

The IFOF mediates long-range interactions between the ventral visual stream and the ventrolateral frontal and orbitofrontal cortex (Martino et al., 2010). In patients with strokes in the ventral portions of the right hemisphere, damage to the IFOF has been suggested to be the lesional correlate of signs of left visual neglect (Urbanski and Bartolomeo, 2008). Intraoperative electrical stimulation of the left IFOF induced semantic paraphasias, independently of which part of the fasciculus was stimulated (Duffau et al., 2005; Martino et al., 2010). Recently, fiber dissection of the IFOF in 14 postmortem human hemispheres (Martino et al., 2010) identified a deep and ventral subcomponent of IFOF connecting the frontal lobe with the posterior portion of the inferior occipital gyrus and posterior basal temporal region, 2 areas known to be involved in semantic processing. Taken together, these findings support a functional role of the left IFOF in the semantic network (de Zubicaray et al., 2011; Martino et al., 2010), and of the right IFOF in processes related to spatial awareness and memory recognition (Thomas et al., 2008; Urbanski and Bartolomeo, 2008; Wimber et al., 2010). In our cases, damage to the left IFOF might have contributed, along with ILF damage, to the genesis of visual agnosia, alexia, and prosopagnosia, while the damage to the right IFOF, which was less severe than that seen in the corresponding tract of the left hemisphere, might have contributed to prosopagnosia and left visual neglect.

The frontoparietal SLF, connecting the parietal lobes with frontal areas, was relatively spared in our sample, in agreement with the clinical and cognitive features of PCA patients. Nevertheless, 2 patients (i.e., cases 2 and 7) showed in their history signs of a more dorsal involvement, especially to the right hemisphere. For patient 2, the clinical picture included optic ataxia. For patient 7, PCA symptoms started with left visual neglect. Neglect signs are relatively frequent in neurodegenerative conditions (Andrade et al., 2010; Bartolomeo et al., 1998). Relative to other PCA patients, these 2 cases showed additional GM atrophy in supramarginal/inferior parietal regions and altered diffusivity of the right frontoparietal SLF. Right parietal and frontal cortical areas are likely involved in the detection of locations (Doricchi et al., 2008) and motion of objects in preparation for movement (Pisella et al., 2000, 2008). Our results are also in agreement with previous studies (Bartolomeo et al., 2007; Battaglia-Mayer et al., 2001; Rizzolatti and Matelli, 2003; Thiebaut de Schotten et al., 2005), which have linked neglect and optic ataxia to damage to the right frontoparietal connections.

Recent neuroimaging studies of normal subjects suggest that the attentional orienting may rely on a somewhat differing neural substrate. Discrete loci in the parietal lobe have been identified as the neural source for goal-directed (superior parietofrontal portions) and stimulus-driven (inferior parietofrontal portions) attentional orienting (Behrmann et al., 2004; Corbetta and Shulman, 2002; Corbetta et al., 2000; Serences et al., 2005). In our PCA

sample, both of these anatomic regions were damaged: the superior parietal in the right hemisphere and the inferior parietal bilaterally (see Supplementary Table 2). However, signs of left visual neglect (which results from dysfunction of these networks) were detected in only 1 patient (case 7). Interestingly, this patient also showed a disconnection of the frontoparietal SLF, which highlights the important contribution of WM damage in the emergence of neglect.

In the present study, 5 patients showed elements of the Gerstmann syndrome (Rusconi et al., 2009). For a long time, the presence of left GM parietal damage has been considered as the main cause of the Gerstmann's syndrome. Since the first descriptions, Josef Gerstmann considered that this syndrome, characterized clinically by 4 different elements (acalculia, finger agnosia, left-right disorientation, and agraphia), was the result of a single parietal lesion damaging a "common functional denominator," which would subserve these 4 cognitive abilities. Recently, Rusconi et al. (2009) have conducted a study on normal subjects where activated areas after 4 different functional MRI paradigms, each assessing 1 of the 4 clinical deficits of the syndrome, were used as seed regions for fiber tracking. The results of this study suggest that Gerstmann's tetrad is not due to an individual cortical lesion, but rather to an intraparietal WM disconnection. On the contrary, the long-range intrahemispheric tracts connecting the parietal lobe with frontal regions, including the frontoparietal SLF, were not found to be involved. In agreement with this finding, we did not find damage to the left frontoparietal SLF in our PCA patients with Gerstmann's syndrome.

PCA patients showed a higher MD of the CC compared with controls. Moreover, visual assessment of the CC in each patient showed a loss of fibers in the posterior part of the tract (Supplementary Fig. 2), which might result from a bilateral posterior neuronal degeneration (Yoshida et al., 2004). Damage to the CC could contribute to the appearance of limb ideomotor apraxia (Catani and ffytche, 2005), visual neglect (Heilman and Adams, 2003), and prosopagnosia (Devinsky and Laff, 2003), all of which occurred in our sample. As expected, there was no damage to the CST, which were used as "internal control bundles". As a consequence, this strengthens the robustness of DT MRI abnormalities found in the other tracts.

Consistent with their clinical presentation, the pattern of GM atrophy in our PCA patients included a large area involving posterior brain regions, centered on the occipitoparietal cortices and the posterior part of the temporal lobes (Fig. 3), as well as the hippocampus, bilaterally. This picture is in agreement with previous studies showing GM loss in the occipital, parietal, and temporal cortices (Galton et al., 2000; Migliaccio et al., 2009; Whitwell et al., 2007), positron emission topography studies have reported a prominent hypometabolism in the same posterior brain areas (Bokde et al., 2005; Nestor et al., 2003; Schmidtke et al., 2005). In the present study, the lateralization of the atrophy is left-sided for the occipitotemporal regions, and right-sided for the parietal regions, reflecting the clinico-anatomical categorization proposed in the pathologic study by Alladi and collaborators (Alladi et al., 2007), namely in the biparietal and occipitotemporal variants.

The pattern of WM atrophy was less distributed than that of GM and limited to the occipitotemporal ventral regions, which most likely correspond to the posterior segments of

the ILF and IFOF, bilaterally. The pattern of eigenvalue abnormalities observed in our patients (i.e., increase of both axD and radD) is likely to reflect the concomitant presence of axonal and myelin pathology in WM tracts (Pierpaoli et al., 2001). The same pattern of predominantly proportional tensor variations in all 3 spatial dimensions rather than in 1 given direction has been described previously in patients with typical AD (Stricker et al., 2009). Our results, showing such similarities between PCA and AD, are consistent with previous studies (Alladi et al., 2007; Migliaccio et al., 2009) that considered PCA as an atypical clinical manifestation of AD.

The main limitation of this study is the small patient sample, but it has to be underlined that PCA is a rare disorder. Moreover, even if small in size, our sample was homogenous in terms of clinical profile, because all PCA patients complained of ventral symptoms at disease onset, and it was adequate to show significant microstructural changes in critical brain regions. The occurrence of more dorsal symptoms and signs in 2 cases allowed us to speculate that the involvement of the ventral and dorsal visual streams is related to the visual and spatial deficits of PCA. Moreover, although the neuropsychological battery was similar among subjects, not all patients had exactly the same cognitive tests. Finally, this is a cross-sectional study and, thus, it cannot fully address the temporal sequences of brain abnormalities in PCA. Within this framework, our results should be interpreted with caution. Future larger studies, including a standardized neuropsychological evaluation, are warranted to confirm our findings. Finally, DT MRI measures may have been influenced by partial volume effects from the CSF. However, contamination from the CSF was minimized by deriving DT MRI metrics from WM tracts after CSF masking and WM thresholding. The use of thin slices (2.5 mm) should also have reduced the contribution of partial volume effects.

In conclusion, this is the first study using a combined structural and DT MRI tractography approach to assess in vivo the long-range ventral and dorsal WM pathways in patients with PCA. Our results show that the pattern of abnormalities detectable in PCA patients mirror closely the clinical and cognitive phenotypes of this condition, thus suggesting that MRI has the potential to provide reliable ante mortem markers of tissue damage in PCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Raffaella Migliaccio was funded by a fellowship of the European Neurological Society. We thank Alessandra Marcone, Monica Falautano, and Francesca Caso for their help in selecting and evaluating patients, Stefania Sala for her support in the MRI analysis, and Massimiliano Copetti for his assistance in the statistical analysis.

F. Agosta: funding for travel from Teva Pharmaceutical Industries, Ltd; speaker honoraria from Bayer Schering Pharma, Sanofi Aventis, and Sero Symposia International Foundation. S.F. Cappa: speakers' bureaus, Janssen Pharmaceuticals and Novartis; royalties for the books entitled "*Cognitive Neurology*" (Imperial College Press) and "*Cognitive Neurology. A textbook*" (Oxford University Press). G. Comi: speakers' bureaus, Teva Pharmaceutical Industries, Ltd, Sanofi-Aventis, Merck Sero, Bayer Schering Pharma, Boehringer Ingelheim Italia, and Novartis; speaker honoraria from Sanofi-Aventis, Merck Sero SA, Sero Symposia International Foundation, Bayer Schering Pharma, Novartis, Biogen-Dompè, and Merz Pharmaceuticals, Gmb. H.P. Bartolomeo: editorial board of *Cortex*. M. Filippi: scientific advisory boards, Teva Pharmaceutical Industries, Ltd; funding for travel from Bayer

Schering Pharma, Biogen-Dompé, Merck Serono, and Teva Pharmaceutical Industries, Ltd; editorial boards of *American Journal of Neuroradiology*, *BMC Musculoskeletal Disorders*, *Clinical Neurology and Neurosurgery*, *Erciyes Medical Journal*, *Lancet Neurology*, *Magnetic Resonance Imaging*, *Multiple Sclerosis*, and *Neurological Sciences*; consultant to Bayer Schering Pharma, Biogen-Dompé, Genmab, A/S, Merck Serono, and Teva Pharmaceutical Industries, Ltd; speakers' bureaus for Bayer Schering Pharma, Biogen-Dompé, Merck Serono, Teva Pharmaceutical Industries, Ltd; research support from Bayer-Schering, Biogen-Dompé, Merck Serono, Teva Pharmaceutical Industries, Ltd, Fondazione Italiana Sclerosi Multipla (FISM), and Fondazione Mariani.

References

- Agosta F, Henry RG, Migliaccio R, Neuhaus J, Miller BL, Dronkers NF, Brambati SM, Filippi M, Ogar JM, Wilson SM, Gorno-Tempini ML. Language networks in semantic dementia. *Brain*. 2010; 133:286–299. [PubMed: 19759202]
- Alexander MP, Stuss DT, Picton T, Shallice T, Gillingham S. Regional frontal injuries cause distinct impairments in cognitive control. *Neurology*. 2007; 68:1515–1523. [PubMed: 17470755]
- Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, Hodges JR. Focal cortical presentations of Alzheimer's disease. *Brain*. 2007; 130:2636–2645. [PubMed: 17898010]
- Andrade K, Samri D, Sarazin M, de Souza LC, Cohen L, Thiebaut de Schotten M, Dubois B, Bartolomeo P. Visual neglect in posterior cortical atrophy. *BMC Neurol*. 2010; 10:68. [PubMed: 20698982]
- Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage*. 2007; 38:95–113. [PubMed: 17761438]
- Azouvi P, Bartolomeo P, Beis JM, Perennou D, Pradat-Diehl P, Rousseaux M. A battery of tests for the quantitative assessment of unilateral neglect. *Restor Neurol Neurosci*. 2006; 24:273–285. [PubMed: 17119304]
- Bartolomeo P, Dalla Barba G, Boissé MF, Bachoud-Lévi AC, Degos JD, Boller F. Right-side neglect in Alzheimer's disease. *Neurology*. 1998; 51:1207–1209. [PubMed: 9781564]
- Bartolomeo P, Thiebaut de Schotten M, Doricchi F. Left unilateral neglect as a disconnection syndrome. *Cereb Cortex*. 2007; 17:2479–2490. [PubMed: 17272263]
- Barton JJ, Sekunova A, Sheldon C, Johnston S, Iaria G, Scheel M. Reading words, seeing style: the neuropsychology of word, font and handwriting perception. *Neuropsychologia*. 2010; 48:3868–3877. [PubMed: 20863841]
- Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B*. 1994; 103:247–254. [PubMed: 8019776]
- Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med*. 2000; 44:625–632. [PubMed: 11025519]
- Battaglia-Mayer A, Ferraina S, Genovesio A, Marconi B, Squatrito S, Molinari M, Lacquaniti F, Caminiti R. Eye-hand coordination during reaching. II. An analysis of the relationships between visuomanual signals in parietal cortex and parieto-frontal association projections. *Cereb Cortex*. 2001; 11:528–544. [PubMed: 11375914]
- Behrmann M, Geng JJ, Shomstein S. Parietal cortex and attention. *Curr Opin Neurobiol*. 2004; 14:212–217. [PubMed: 15082327]
- Benson DF, Davis RJ, Snyder BD. Posterior cortical atrophy. *Arch Neurol*. 1988; 45:789–793. [PubMed: 3390033]
- Benson DF, Segarra J, Albert ML. Visual agnosia-prosopagnosia. A clinicopathologic correlation. *Arch Neurol*. 1974; 30:307–310. [PubMed: 4816835]
- Benton, AL.; Sivan, AB.; Hamsher, K.; Varney, NR.; Spreen, O. Contributions to Neuropsychological Assessment. New York: Oxford University Press; 1994.
- Bokde AL, Teipel SJ, Drzezga A, Thissen J, Bartenstein P, Dong W, Leinsinger G, Born C, Schwaiger M, Moeller HJ, Hampel H. Association between cognitive performance and cortical glucose metabolism in patients with mild Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2005; 20:352–357. [PubMed: 16192725]
- Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A. Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurol Sci*. 2002; 22:443–447. [PubMed: 11976975]

- Carlesimo GA, Buccione I, Fadda L, Graceffa A, Mauri M, Lorusso S, Bevilacqua G, Caltagirone C. Standardizzazione di due test di memoria: Breve Racconto e Figura di Rey. *Nuova Riv Neurol.* 2002; 12:1–13.
- Carlesimo GA, Caltagirone C, Gainotti G. The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. *Eur Neurol.* 1996; 36:378–384. [PubMed: 8954307]
- Catani M, ffytche DH. The rises and falls of disconnection syndromes. *Brain.* 2005; 128:2224–2239. [PubMed: 16141282]
- Catani M, Jones DK, Donato R, Ffytche DH. Occipito-temporal connections in the human brain. *Brain.* 2003; 126:2093–2107. [PubMed: 12821517]
- Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex.* 2008; 44:1105–1132. [PubMed: 18619589]
- Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nat Neurosci.* 2000; 3:292–297. [PubMed: 10700263]
- Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci.* 2002; 3:201–215. [PubMed: 11994752]
- Crawford JR, Garthwaite PH. Investigation of the single case in neuropsychology: confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia.* 2002; 40:1196–1208. [PubMed: 11931923]
- De Renzi E, Vignolo LA. The token test: A sensitive test to detect receptive disturbances in aphasics. *Brain.* 1962; 85:665–678. [PubMed: 14026018]
- de Zubizaray GI, Rose SE, McMahon KL. The structure and connectivity of semantic memory in the healthy older adult brain. *Neuroimage.* 2011; 54:1488–1494. [PubMed: 20807579]
- Dejerine, J. *Anatomie des centres nerveux.* Paris: Rueff; 1895.
- Devinsky O, Laff R. Callosal lesions and behavior: history and modern concepts. *Epilepsy Behav.* 2003; 4:607–617. [PubMed: 14698693]
- Doricchi F, Thiebaut de Schotten M, Tomaiuolo F, Bartolomeo P. White matter (dis)connections and gray matter (dys)functions in visual neglect: gaining insights into the brain networks of spatial awareness. *Cortex.* 2008; 44:983–995. [PubMed: 18603235]
- Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. *Brain.* 2005; 128:797–810. [PubMed: 15705610]
- Duning T, Warnecke T, Mohammadi S, Lohmann H, Schiffbauer H, Kugel H, Knecht S, Ringelstein EB, Deppe M. Pattern and progression of white-matter changes in a case of posterior cortical atrophy using diffusion tensor imaging. *J Neurol Neurosurg Psychiatry.* 2009; 80:432–436. [PubMed: 19289480]
- Epelbaum S, Pinel P, Gaillard R, Delmaire C, Perrin M, Dupont S, Dehaene S, Cohen L. Pure alexia as a disconnection syndrome: new diffusion imaging evidence for an old concept. *Cortex.* 2008; 44:962–974. [PubMed: 18586235]
- Ffytche DH, Blom JD, Catani M. Disorders of visual perception. *J Neurol Neurosurg Psychiatry.* 2010; 81:1280–1287. [PubMed: 20972204]
- Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12:189–198. [PubMed: 1202204]
- Fox CJ, Iaria G, Barton JJ. Disconnection in prosopagnosia and face processing. *Cortex.* 2008; 44:996–1009. [PubMed: 18597749]
- Gainotti G, D’Erme P, Monteleone D, Silveri MC. Mechanisms of unilateral spatial neglect in relation to laterality of cerebral lesions. *Brain.* 1986; 109:599–612. [PubMed: 3730807]
- Galton CJ, Patterson K, Xuereb JH, Hodges JR. Atypical and typical presentations of Alzheimer’s disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain.* 2000; 123:484–498. [PubMed: 10686172]

- Giussani C, Roux FE, Bello L, Lauwers-Cances V, Papagno C, Gaini SM, Puel M, Démonet JF. Who is who: areas of the brain associated with recognizing and naming famous faces. *J Neurosurg.* 2009; 110:289–299. [PubMed: 18928357]
- Glasser MF, Rilling JK. DTI tractography of the human brain's language pathways. *Cereb Cortex.* 2008; 18:2471–2482. [PubMed: 18281301]
- Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends Neurosci.* 1992; 15:20–25. [PubMed: 1374953]
- Heilman KM, Adams DJ. Callosal neglect. *Arch Neurol.* 2003; 60:276–279. [PubMed: 12580716]
- Hof PR, Vogt BA, Bouras C, Morrison JH. Atypical form of Alzheimer's disease with prominent posterior cortical atrophy: a review of lesion distribution and circuit disconnection in cortical visual pathways. *Vision Res.* 1997; 37:3609–3625. [PubMed: 9425534]
- Ishai A. Let's face it: it's a cortical network. *Neuroimage.* 2008; 40:415–419. [PubMed: 18063389]
- Kas A, de Souza LC, Samri D, Bartolomeo P, Lacomblez L, Kalafat M, Migliaccio R, Thiebaut de Schotten M, Cohen L, Dubois B, Habert MO, Sarazin M. Neural correlates of cognitive impairment in posterior cortical atrophy. *Brain.* 2011; 134:1464–1478. [PubMed: 21478188]
- Kay MC, Levin HS. Prosopagnosia. *Am J Ophthalmol.* 1982; 94:75–80. [PubMed: 7091286]
- Kleinschmidt A, Cohen L. The neural bases of prosopagnosia and pure alexia: recent insights from functional neuroimaging. *Curr Opin Neurol.* 2006; 19:386–391. [PubMed: 16914978]
- Lehmann M, Barnes J, Ridgway GR, Wattam-Bell J, Warrington EK, Fox NC, Crutch SJ. Basic visual function and cortical thickness patterns in posterior cortical atrophy. *Cereb. Cortex.* 2011; 21:2122–2132.
- Luzzatti C, Willmes K, Bisiacchi P, De Bleser R, Mazzucchi A, Posteraro L, Taricco M, Faglia L. L'Aachener Aphasia test (AAT). II. Qualità psicometriche della versione italiana del test. *Arch. di Psicol. Neurol e Psichiatr.* 1987; 48:480–519.
- Martino J, Brogna C, Robles SG, Vergani F, Duffau H. Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex.* 2010; 46:691–699. [PubMed: 19775684]
- Matsuo K, Mizuno T, Yamada K, Akazawa K, Kasai T, Kondo M, Mori S, Nishimura T, Nakagawa M. Cerebral white matter damage in frontotemporal dementia assessed by diffusion tensor tractography. *Neuroradiology.* 2008; 50:605–611. [PubMed: 18379765]
- Mauri M, Carlesimo G, Graceffa A. Standardizzazione di due nuovi test di memoria: apprendimento di liste di parole correlate e non correlate semanticamente. *Arch Psicol Neurol Psichiatr.* 1997; 58:621–645.
- McCulloch, CE.; Searle, SR.; Neuhaus, JM. *Generalized, Linear, and Mixed Models.* second ed. Hoboken, NJ: Wiley; 2008.
- McMonagle P, Deering F, Berliner Y, Kertesz A. The cognitive profile of posterior cortical atrophy. *Neurology.* 2006; 66:331–338. [PubMed: 16476930]
- Mendez MF. Visuospatial deficits with preserved reading ability in a patient with posterior cortical atrophy. *Cortex.* 2001; 37:535–543. [PubMed: 11721864]
- Miceli, G.; Laudanna, A.; Burani, C.; Capasso, R. B.A.D.A A Battery for the Assessment of Aphasic Disorders [in Italian]. CEPSAG; Rome: 1994.
- Migliaccio R, Agosta F, Rascovsky K, Karydas A, Bonasera S, Rabinovici GD, Miller BL, Gorno-Tempini ML. Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum. *Neurology.* 2009; 73:1571–1578. [PubMed: 19901249]
- Migliaccio R, Agosta F, Toba MN, Samri D, Corlier F, de Souza LC, Chupin M, Sharman M, Gorno-Tempini ML, Dubois B, Filippi M, Bartolomeo P. Brain networks in posterior cortical atrophy: A single case tractography study and literature review. *Cortex.* 2011 In press. 10.1016/j.cortex.2011.10.002
- Mummery CJ, Patterson K, Wise RJ, Vandenberghe R, Price CJ, Hodges JR. Disrupted temporal lobe connections in semantic dementia. *Brain.* 1999; 122:61–73. [PubMed: 10050895]
- Nestor PJ, Caine D, Fryer TD, Clarke J, Hodges JR. The topography of metabolic deficits in posterior cortical atrophy (the visual variant of Alzheimer's disease) with FDG-PET. *J Neurol Neurosurg Psychiatry.* 2003; 74:1521–1529. [PubMed: 14617709]

- Novelli G, Papagno C, Capitani E, Laiacona N, Vallar G, Cappa SF. Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normalis. *Arch Psicol Neurol Psichiatr.* 1986; 47:477–506.
- Orsini A, Grossi D, Capitani E, Laiacona M, Papagno C, Vallar G. Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. *Ital J Neurol Sci.* 1987; 8:539–548. [PubMed: 3429213]
- Pierpaoli C, Barnett A, Pajevic S, Chen R, Penix LR, Virta A, Basser P. Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *Neuroimage.* 2001; 13:1174–1185. [PubMed: 11352623]
- Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. *Radiology.* 1996; 201:637–648. [PubMed: 8939209]
- Pievani M, Agosta F, Pagani E, Canu E, Sala S, Absinta M, Geroldi C, Ganzola R, Frisoni GB, Filippi M. Assessment of white matter tract damage in mild cognitive impairment and Alzheimer's disease. *Hum Brain Mapp.* 2010; 31:1862–1875. [PubMed: 20162601]
- Pisella L, Gréa H, Tilikete C, Vighetto A, Desmurget M, Rode G, Boisson D, Rossetti Y. An “automatic pilot” for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. *Nat Neurosci.* 2000; 3:729–736. [PubMed: 10862707]
- Pisella L, Ota H, Vighetto A, Rossetti Y. Optic ataxia and Balint's syndrome: neuropsychological and neurophysiological prospects. *Handb Clin Neurol.* 2008; 88:393–415. [PubMed: 18631703]
- Rapcsak SZ, Nielsen L, Littrell LD, Glisky EL, Kaszniak AW, Laguna JF. Face memory impairments in patients with frontal lobe damage. *Neurology.* 2001; 57:1168–1175. [PubMed: 11591831]
- Renner JA, Burns JM, Hou CE, McKeel DW Jr, Storandt M, Morris JC. Progressive posterior cortical dysfunction: a clinicopathologic series. *Neurology.* 2004; 63:1175–1180. [PubMed: 15477534]
- Riddoch, MJ.; Humphreys, GW. BORB: the Birmingham Object Recognition Battery. Lawrence Erlbaum Associates; Hove, UK: 1993.
- Rizzolatti G, Matelli M. Two different streams form the dorsal visual system: anatomy and functions. *Exp Brain Res.* 2003; 153:146–157. [PubMed: 14610633]
- Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. *J Cogn Neurosci.* 2007; 19:1081–1088. [PubMed: 17583985]
- Ross SJ, Graham N, Stuart-Green L, Prins M, Xuereb J, Patterson K, Hodges JR. Progressive biparietal atrophy: an atypical presentation of Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 1996; 61:388–395. [PubMed: 8890778]
- Rusconi E, Pinel P, Eger E, LeBihan D, Thirion B, Dehaene S, Kleinschmidt A. A disconnection account of Gerstmann syndrome: functional neuroanatomy evidence. *Ann Neurol.* 2009; 66:654–662. [PubMed: 19938150]
- Schmahmann, JD.; Pandya, DN. *Fiber Pathways of the Brain.* New York: Oxford University Press; 2006.
- Schmidtke K, Hüll M, Talazko J. Posterior cortical atrophy: variant of Alzheimer's disease? A case series with PET findings. *J Neurol.* 2005; 252:27–35. [PubMed: 15654552]
- Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron.* 2009; 62:42–52. [PubMed: 19376066]
- Serences JT, Shomstein S, Leber AB, Golay X, Egeth HE, Yantis S. Coordination of voluntary and stimulus-driven attentional control in human cortex. *Psychol Sci.* 2005; 16:114–122. [PubMed: 15686577]
- Shinoura N, Suzuki Y, Tsukada M, Yoshida M, Yamada R, Tabei Y, Saito K, Koizumi T, Yagi K. Deficits in the left inferior longitudinal fasciculus results in impairments in object naming. *Neurocase.* 2010; 16:135–139. [PubMed: 19937506]
- Simon SR, Khateb A, Darque A, Lazeyras F, Mayer E, Pegna AJ. When the brain remembers, but the patient doesn't: Converging fMRI and EEG evidence for covert recognition in a case of prosopagnosia. *Cortex.* 2011; 47:825–838. [PubMed: 20850714]
- Sorger B, Goebel R, Schiltz C, Rossion B. Understanding the functional neuroanatomy of acquired prosopagnosia. *Neuroimage.* 2007; 35:836–852. [PubMed: 17303440]
- Spinnler H, Tognoni G. Standardizzazione e taratura Italiana di test neuropsicologici. *Ital J Neurol Sci.* 1987; 1–120.

- Stricker NH, Schweinsburg BC, Delano-Wood L, Wierenga CE, Bangen KJ, Haaland KY, Frank LR, Salmon DP, Bondi MW. Decreased white matter integrity in late-myelinating fiber pathways in Alzheimer's disease supports retrogenesis. *Neuroimage*. 2009; 45:10–16. [PubMed: 19100839]
- Takahashi N, Kawamura M, Hirayama K, Shiota J, Isono O. Prosopagnosia: a clinical and anatomical study of four patients. *Cortex*. 1995; 31:317–329. [PubMed: 7555009]
- Tang-Wai DF, Graff-Radford NR, Boeve BF, Dickson DW, Parisi JE, Crook R, Caselli RJ, Knopman DS, Petersen RC. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology*. 2004; 63:1168–1174. [PubMed: 15477533]
- Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Lévy R, Dubois B, Bartolomeo P. Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. *Science*. 2005; 309:2226–2228. [PubMed: 16195465]
- Thomas C, Avidan G, Humphreys K, Jung KJ, Gao F, Behrmann M. Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. *Nat Neurosci*. 2009; 12:29–31. [PubMed: 19029889]
- Thomas C, Moya L, Avidan G, Humphreys K, Jung KJ, Peterson MA, Behrmann M. Reduction in white matter connectivity, revealed by diffusion tensor imaging, may account for age-related changes in face perception. *J Cogn Neurosci*. 2008; 20:268–284. [PubMed: 18275334]
- Ungerleider, L.; Mishkin, M. Two Cortical Visual Systems. In: Ingle, DJ.; Goodale, MA.; Mansfield, RJW., editors. *Analysis of motor behavior*. Cambridge, MA: Cambridge MIT Press; 1982. p. 549-586.
- Urbanski M, Bartolomeo P. Line bisection in left neglect: the importance of starting right. *Cortex*. 2008; 44:782–793. [PubMed: 18489959]
- von Gunten A, Bouras C, Kövari E, Giannakopoulos P, Hof PR. Neural substrates of cognitive and behavioral deficits in atypical Alzheimer's disease. *Brain Res Rev*. 2006; 51:176–211. [PubMed: 16413610]
- Warrington EK, James M. A new test of object decision: 2D silhouettes featuring a minimal view. *Cortex*. 1991; 27:370–383. [PubMed: 1743033]
- Wedeer VJ, Wang RP, Schmahmann JD, Benner T, Tseng WY, Dai G, Pandya DN, Hagmann P, D'Arceuil H, de Crespigny AJ. Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage*. 2008; 41:1267–1277. [PubMed: 18495497]
- Whitwell JL, Jack CR Jr, Kantarci K, Weigand SD, Boeve BF, Knopman DS, Drubach DA, Tang-Wai DF, Petersen RC, Josephs KA. Imaging correlates of posterior cortical atrophy. *Neurobiol Aging*. 2007; 28:1051–1061. [PubMed: 16797786]
- Wimber M, Heinze HJ, Richardson-Klavehn A. Distinct frontoparietal networks set the stage for later perceptual identification priming and episodic recognition memory. *J Neurosci*. 2010; 30:13272–13280. [PubMed: 20926653]
- Yoshida T, Shiga K, Yoshikawa K, Yamada K, Nakagawa M. White matter loss in the splenium of the corpus callosum in a case of posterior cortical atrophy: a diffusion tensor imaging study. *Eur Neurol*. 2004; 52:77–81. [PubMed: 15256828]
- Zhang Y, Schuff N, Du AT, Rosen HJ, Kramer JH, Gorno-Tempini ML, Miller BL, Weiner MW. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. *Brain*. 2009; 132:2579–2592. [PubMed: 19439421]

Fig. 1.

An illustrative reconstruction of the ventral stream pathways, namely the inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF), in a normal control (A) and in posterior cortical atrophy patient 1 (B), who had a long clinical history of isolated deficits in reading and writing, followed by an impairment in object and space perception and face recognition. White matter tracts are rendered as maps of fractional anisotropy (FA), and shown on the native T1-weighted image. The color scale represents the FA values from lower (yellow) to higher values (red).

Fig. 2.

An illustrative reconstruction of the frontoparietal superior longitudinal fasciculus (SLF) in 2 posterior cortical atrophy patients (i.e., cases 6 and 2). White matter tracts are rendered as maps of fractional anisotropy (FA), and shown on the native T1-weighted image of each patient. The color scale represents the FA values from lower (yellow) to higher values (red). On the left side, case 6 shows a preserved frontoparietal SLF (mean FA = 0.44). On the right side, case 2, having experienced optic ataxia after 2.5 years after disease onset, shows a diffusely damaged frontoparietal SLF (mean FA = 0.39).

Fig. 3.

(A) Regions of gray matter (GM) atrophy in posterior cortical atrophy patients compared with healthy controls, overlaid on the 3-D rendering of the Montreal Neurological Institute (MNI) standard brain. (B) GM (blue) and white matter (yellow) regions of atrophy in patients compared with controls are shown on the axial sections of the MNI standard brain. Results are displayed in neurological convention, at the threshold of $p < 0.05$ corrected for multiple comparisons (family-wise error).

Table 1
Demographic and clinical characteristics of each posterior cortical atrophy in patients and healthy controls

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Controls, <i>n</i> = 13
Age, y	62	62	57	65	59	66	55	62 (5.2)
Gender	F	F	M	F	F	F	F	6 F/7 M
Education	10	12	5	13	13	8	11	14 (6.3)
Handedness	R	R	R	R	R	R	R	13 R
Years from first symptom	7	2.5	3	4	5	4	3	
MMSE	26	16	17	15	17	—	11	
Ventral symptoms								
Visual agnosia	+	++	++	++	++	++	++	
Prosopagnosia	+	++	+	++	+	++	+	
Alexia	++	++	++	++	++	++	+	
Dorsal symptoms								
Neglect							++	
Optic ataxia		+						
Other symptoms								
Gerstmann's syndrome		+(L/R, FiA)	+(Ac, FiA)	+(Ac)	+(Ac, FiA)	+(L/R, FiA)	+(Ac)	
Visual-spatial memory deficits	+	++	++	+	+	+	+	
Language deficits				+		+	+	
Ideomotor apraxia			+		+	+	+	

Age and education for controls is mean (SD).

Key: +, present later in the disease course;

++, present at disease onset;

Ac, acalculia; F, female; FiA, finger agnosia; L/R, left/right disorientation; M, male; MMSE, Mini Mental State Examination; R, right.

Table 2

Diffusion tensor MRI metrics for white matter tracts in posterior cortical atrophy patients and healthy controls

	MD [$\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$]	FA	axD [$\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$]	radD [$\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$]
χ^2, p	50.9, < 0.001	37.8, < 0.001	25.0, < 0.001	39.1, < 0.001
Tract, F, p	28, < 0.001	57.2, < 0.001	51.4, < 0.001	5.7, < 0.001
Group, F, p	25.4, < 0.001	5.4, 0.02	20.2, < 0.001	20.7, < 0.001
Group $\times$ Tract, F, p	4.6, < 0.001	4.6, < 0.001	1.4, 0.21	3.4, 0.002
Percent of variance not accounted for by the fixed effects	34.2	66.0	6.1	34.4

	Controls	PCA	Controls	PCA	Controls	PCA
ILF						
L	0.80 (0.01)	0.93 (0.01)**	0.46 (0.01)	0.41 (0.01)**	1.24 (0.01)	1.34 (0.02)*
R	0.81 (0.01)	0.88 (0.01)**	0.45 (0.01)	0.41 (0.01)*	1.27 (0.02)	1.23 (0.01)
I/O						
L	0.79 (0.01)	0.88 (0.01)**	0.49 (0.01)	0.45 (0.01)*	1.26 (0.01)	1.33 (0.02)*
R	0.80 (0.01)	0.85 (0.01)*	0.49 (0.01)	0.45 (0.01)*	1.27 (0.01)	1.28 (0.02)
F-P SLF						
L	0.76 (0.01)	0.78 (0.01)	0.42 (0.01)	0.42 (0.01)	1.11 (0.01)	1.13 (0.02)
R	0.77 (0.01)	0.80 (0.01)*	0.43 (0.01)	0.41 (0.01)	1.14 (0.01)	1.17 (0.02)
CST						
L	0.78 (0.03)	0.77 (0.06)	0.54 (0.02)	0.50 (0.01)	1.28 (0.05)	1.17 (0.15)
R	0.80 (0.05)	0.75 (0.05)	0.55 (0.02)	0.50 (0.02)	1.3 (0.08)	1.28 (0.11)
CC	0.84 (0.01)	0.92 (0.01)**	0.51 (0.01)	0.50 (0.01)	1.38 (0.01)	1.45 (0.02)*

Numbers are estimated means $\pm$ standard errors. χ^2 and p values refer to the overall multivariate Wald test which jointly test Group and Group $\times$ Tract effects (see Methods for further details). Tract (F, p), Group (F, p) and Group $\times$ Tract (F, p) refer to the overall F -tests from the mixed-model.

Key: axD, axial diffusivity; CC, corpus callosum; CST, corticospinal tracts; F-P SLF, fronto-parietal superior longitudinal fasciculus; FA, fractional anisotropy; I/O, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; L, left; MD, mean diffusivity; MRI, magnetic resonance imaging; PCA, posterior cortical atrophy; R, right; radD, radial diffusivity.

* $p < 0.05$ versus healthy controls according to the Fisher's least significant difference test (see text for further details).

** $p < 0.001$ versus healthy controls according to the Fisher's least significant difference test (see text for further details).