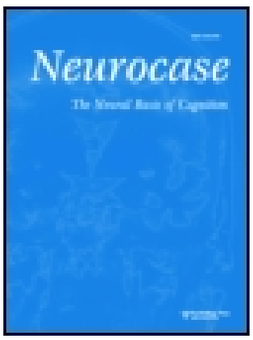

Routledge
Taylor & Francis Group

Neurocase
The Neural Basis of Cognition

ISSN: 1355-4794 (Print) 1465-3656 (Online) Journal homepage: http://www.tandfonline.com/loi/nncs20

Posterior cortical atrophy: a single case cognitive and radiological follow-up

Sol Esteves, Diana Andrea Ramirez Romero, Teresa Torralva, Macarena Martínez Cuitiño, Shannon Herndon, Blas Couto, Agustín Ibañez, Facundo Manes & María Roca

To cite this article: Sol Esteves, Diana Andrea Ramirez Romero, Teresa Torralva, Macarena Martínez Cuitiño, Shannon Herndon, Blas Couto, Agustín Ibañez, Facundo Manes & María Roca (2018): Posterior cortical atrophy: a single case cognitive and radiological follow-up, Neurocase, DOI: 10.1080/13554794.2017.1421667

To link to this article: https://doi.org/10.1080/13554794.2017.1421667

Published online: 08 Jan 2018.

NEUROCASE, 2018
https://doi.org/10.1080/13554794.2017.1421667

Routledge
Taylor & Francis Group

ARTICLE

Posterior cortical atrophy: a single case cognitive and radiological follow-up

Sol Esteves[a], Diana Andrea Ramirez Romero[a], Teresa Torralva[a], Macarena Martínez Cuitiño[a], Shannon Herndon[a,b], Blas Couto[c], Agustín Ibañez [c,d,e,f,g], Facundo Manes[d,g] and María Roca[g]

[a]Neuropsychological Research Laboratory, Institute of Cognitive and Translational Neuroscience (INCyT), INECO Foundation, Favaloro University, CONICET, Buenos Aires, Argentina; [b]Department of Psychiatry, School of Medicine, University of North Carolina Chapel Hill, Chapel Hill, USA; [c]Laboratory of Experimental Psychology and Neuroscience (LPEN), Institute of Cognitive and Translational Neuroscience (INCyT), INECO Foundation, Favaloro University, CONICET, Buenos Aires, Argentina; [d]Centre of Excellence in Cognition and its Disorders, Australian Research Council (ACR), Sydney, Australia; [e]Universidad Autónoma del Caribe, Barranquilla, Colombia; [f]Centre for Social and Cognitive Neuroscience (CSCN), School of Psychology, Universidad Adolfo Ibañez, Santiago de Chile, Chile; [g]National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina

ABSTRACT

Posterior cortical atrophy (PCA) is a rare neurodegenerative syndrome characterized by initial predominant visuoperceptual deficits followed by a progressive decline in other cognitive functions. This syndrome has not been as thoroughly described as other dementias, particularly from a neuropsychological evolution perspective with only a few studies describing the evolution of its cognitive progression. In this investigation we review the literature on this rare condition and we perform a 7-year neuropsychological and neuroradiological follow-up of a 64-year-old man with PCA. The subject's deficits initially appeared in his visuoperceptual skills with later affectation appearing in language and other cognitive functions, this being coherent with the patient's parieto-temporal atrophy evolution.

ARTICLE HISTORY
Received 28 March 2016
Accepted 18 December 2017

KEYWORDS
Posterior cortical atrophy; dementia; variant of Alzheimer's disease; cognitive and neuroradiological follow up

1. Introduction

Posterior cortical atrophy (PCA) is a rare early-onset dementia syndrome characterized by a progressive decline in visual processing skills and other functions related to parietal, occipital and occipito-temporal regions, in the absence of primary ophthalmologic causes (Crutch, Lehmann, Schott, Rabinovici, & Rossor et al., 2012). Although it has in some cases been classified as an early variant of Alzheimer's disease (AD), its clinico-pathological evaluation reveals a singular pattern that has led some authors to consider this disease as a distinct nosological entity (Borruat, 2013; Crutch et al., 2012; Crutch, Schott, Rabinovici, Murray, & Snowden et al., 2017). It was initially characterized by Frank Benson in 1988 (Benson, Davis, & Snyder, 1988) who described five patients that presented behavioral and physiological signs similar to a slow progressive dementia, but with a notable difference: these patients had early visual agnosia that would be followed by symptoms similar to the ones observed in Balint and Gertsmann's syndromes. Balint syndrome encompasses a triad of neuropsychological impairments: simultagnosia (inability to perceive the visual field as a whole), oculomotor apraxia (difficulty in fixating the eyes) and optic ataxia (inability to move the hand to a specific object by using visual guidance) (Hecaen & De Ajuriaguerra, 1954; Moreaud, 2003). Gertsmann's syndrome, on the other hand, is characterized by the presence of agraphia (deficiency in the ability to write), acalculia (loss of ability to perform simple arithmetic), finger agnosia (inability to distinguish the fingers of the hand) and left–right confusion (Ardila, 2014). Other symptoms that might be present in PCA include alexia, transcortical sensory aphasia, and in some cases environmental disorientation (Mizuno, Sartori, Liccione, Battelli, & Campo, 1996; Roca, Gleichgerrcht, Torralva, & Manes, 2010; Zakzanis & Boulos, 2001). In addition, these patients have memory, insight and judgment relatively preserved, the disruption of which are hallmark features of typical AD onset. Apathy, irritability, anxiety and depression are some of the psychiatric manifestations that can be found in PCA, which also have an impact on the patient's quality of life (Suarez-Gonzalez, Henley, Walton, & Crutch, 2015).

Further clinico-pathological studies found that this group of patients had senile plaques and neurofibrillary tangles similar to the ones found in AD, which led to its classification as an early variant of this disease (Bokde, Pietrini, Ibanez, Furey, & Alexander et al., 2001; Hof, Archin, Osmand, Dougherty, & Wells et al., 1993; Levine, Lee, & Fisher, 1993; Ross, Graham, Stuart-Green, Prins, & Xuereb et al., 1996). However, a shift was observed in the distribution of the pathological atrophy in the case of the PCA patients, compared to typical AD. In the former cases, the primary visual areas and certain visual association areas within the occipito-parieto-temporal junction and posterior cingulate cortex had very high densities of lesions, while these regions tend to be less affected in AD (Hof, Vogt, Bouras, & Morrison, 1997). Likewise, the prefrontal cortex had fewer lesions in PCA patients than are usually observed in typical AD (Alves, Soares, Sampaio, & Goncalves, 2013).

This evidence, together with the fact that on rare occasions PCA can also be associated with non-AD pathologies, such as

CONTACT María Roca mroca@ineco.org.ar

dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and prion disease, and that it has a distinct syndromic onset from the classic dementing syndromes, has led numerous authors to consider PCA as a distinct nosological entity with its own diagnostic criteria (Crutch et al., 2012; Mendez, Ghajarania, & Perryman, 2002; Tang-Wai & Mapstone, 2006).

The diagnosis of PCA will be built upon four main pillars: a detailed patient history, an accurate analysis of the behavior, the neuroimaging analysis and the neuropsychological testing (Ortner & Kurz, 2015). As the deficits frequently discovered are of a visuoperceptual nature, the classic neuropsychological assessment should be complemented with a battery of tests that allow the evaluation of these functions (Crutch & Warrington, 2007; Ortner & Kurz, 2015). Examples might include tests comprised of complex descriptions of photographs or scenes with a number of important stimuli such that the patient must identify all possible elements in the image and later give an impression of the overall scene. Tasks that involve color, shape, object, and face discrimination and recognition should also be included (Chan, Crutch, & Warrington, 2001), among others.

1.1 Epidemiology

Being that PCA is a rare disease and that there is a lack of scientific agreement regarding it as a distinct clinical entity, little can be said about its prevalence and incidence. However, a study revealed that 5% of the AD population first presented with a visual deficit, which could signify the overlap between classical AD and this distinct clinical syndrome (Snowden, Stopford, Julien, Thompson, & Davidson et al., 2007). The age of onset is usually earlier than in typical AD; beginning at 50 or 60 years (Crutch et al., 2012; Mendez et al., 2002). However, a delay in the recognition and diagnosis of PCA can occur when memory and insight are preserved and the patient wrongly attributes visual dysfunction to ophthalmologic causes (Tang-Wai, Graff-Radford, Boeve, Dickson, & Parisi et al., 2004). With regards to gender, some studies report twice as many women as men (Kas, De Souza, Samri, Bartolomeo, & Lacomblez et al., 2011; Migliaccio, Agosta, Rascovsky, Karydas, & Bonasera et al., 2009; Rosenbloom, Alkalay, Agarwal, Baker, & O'Neil et al., 2011; Snowden et al., 2007; Tang-Wai et al., 2004); while others report no difference in gender prevalence (McMonagle, Deering, Berliner, & Kertesz, 2006; Mendez et al., 2002).

1.2 Visuoperceptual difficulties

As it has been said before, PCA patients present with early visuoperceptual dysfunction, which includes visual object recognition and spatial deficits. Subjects also present with difficulties in the visual processing of form, color, movement and localization. The visuoperceptual difficulties might also include blurred or double vision, problems with depth perception, and difficulties seeing clearly in low light conditions or increased sensitivity to bright light (Crutch et al., 2012). In addition, some PCA patients can present with unusual symptoms, such as seeing abnormally colored objects after prior exposure to a colored stimulus (Chan et al., 2001); perception of movement in a static stimulus (Crutch, Lehmann, Gorgoraptis, Kaski, & Ryan et al., 2011); reverse size phenomena: an impairment in identifying larger visually presented objects relative to their smaller counterparts (Stark, Grafman, & Fertig, 1997); and room tilt illusion effects (Crutch et al., 2011). Defects in the visual field, unilateral neglect and visual hallucinations are not very common, though they have been described (Crutch et al., 2012; Stark et al., 1997). As the disease progresses, the visuospatial deficits begin to severely impair the patients, such that they may have trouble accurately reaching an object, recognizing familiar faces and orienting themselves in space. As a result, they might get lost while walking or driving in familiar places.

One of the most common perception deficits in PCA patients is ***simultagnosia*** (McMonagle et al., 2006), as it has been reported to be present in 82–92% of the patients (Kas et al., 2011; Mendez et al., 2002) who show great variability and abnormal fixation patterns in scene perception (Shakespeare, Yong, Frost, Kim, & Warrington et al., 2013). This manifestation, which is also a component of Balint's syndrome, is characterized by the inability to interpret a complex scene in its totality. Said in other words, it's the incapacity to perceive more than a single object at a time due to problems with processing multiple items and the relations between them (Chechlacz & Humphreys, 2014). Therefore, patients are typically poor at explicitly reporting and understanding global compound shapes, and instead tend to give detailed descriptions of the scene observed or describe individual parts of a complex scene (Mevorach, Shalev, Green, Chechlacz, & Riddoch et al., 2014).

Two types of simultagnosia have been described (Farah, 1990) depending on the localization of the lesions: dorsal and ventral. ***Dorsal simultagnosia*** is often a result of a bilateral parietal-occipital lesion and is usually accompanied by other symptoms, such as optic ataxia and oculomotor deficits. These patients present with difficulties in attending to more than one stimuli at the time, instead fixing their attention only on a single stimuli or a part of it (Holmes, 1918; Luria, 1959). ***Ventral simultagnosia***, on the other hand, is usually the result of occipito-temporal junction lesions (often in the left hemisphere) (Denburg, Jones, & Tranel, 2009). Patients with this kind of simultagnosia are limited in the amount of stimuli they are able to recognize at the same time (Kinsbourne & Warrington, 1962). Contrary to patients with dorsal simultagnosia, they do not fail in dot counting tasks, yet they do in tasks that require simultaneous perception of stimuli, such as during reading, when they tend to read letter by letter.

Reading difficulties are a common, early and disabling symptom of PCA, presenting in 80–95% of patients (Lehmann, Barnes, Ridgway, Wattam-Bell, & Warrington et al., 2011; McMonagle et al., 2006; Mendez et al., 2002; Yong, Rajdev, Shakespeare, Leff, & Crutch, 2015). Patients with PCA tend to read less accurately and slower than those who are normal or have typical AD, with worse performance when there is increased letter spacing, large font size and cursive script (Crutch et al., 2011; De Renzi, 1986; Yong, Shakespeare, Cash, Henley, & Nicholas et al., 2014). These impairments in reading may be due to several processes: visual disorientation may cause patients to get lost from one line to the next or to see words in false order (Mendez, 2001); visual crowding may

impair the identification of individual letters (Crutch & Warrington, 2007); unsteady eye fixation and involuntary eye movement can cause the letters to appear as if they are moving within a word or to disappear (Crutch et al., 2011); and reverse size phenomena may impair the perception of small versus large print (Crutch et al., 2011; Price & Humphreys, 1995). Some authors have suggested that PCA visual deficiencies begin with visual integration of letters, progress to whole scenes and culminate in Balint's syndrome (Mendez & Cherrier, 1998; Zakzanis & Boulos, 2001).

Also included as one of the most frequent signs of PCA is agraphia, though initially language and spatial word formations are preserved (Crutch et al., 2012). Visuospatial agraphia results from visuospatial defects that impair orientation and correct sequencing in writing (Ardila & Rosselli, 1993). A tendency to neglect one portion of the page when writing, inability to maintain horizontal writing (instead slanting lines upward or downward), and abnormal spacing between letters, syllables and words can also be observed (Yong et al., 2015). Apraxic agraphia can also be present, with patients showing deficits in written production, while maintaining motor and sensory functions, and oral spelling and typing (Magnin, Sylvestre, Lenoir, Dariel, & Bonnet et al., 2013; Ryan, Shakespeare, Lehmann, Keihaninejad, & Nicholas et al., 2014). The deficits in written production can also include inappropriate letter selection, mixing different types of letters (handwritten and print, uppercase and lowercase) and problems in copying letters and words (Funayama & Nakajima, 2015). Written spelling agraphia can also be present, which manifests by intact oral spelling and grapheme writing but failure at single word formations (Friedman & Alexander, 1989).

In addition, patients may present with optic ataxia, which implies a lack of coordination between visual input and motor output and results in the inability to reach and grab objects, such that patients over or under reach in the contra-lesional visual field and have difficulty pre-shaping the hand for grasping (Crutch, Lehmann, Warren, & Rohrer, 2013; Hecaen & De Ajuriaguerra, 1954). This symptom (also a component of Balint's syndrome) is usually present at some point during the progression of PCA, to the extent that it becomes a determinant sign in the diagnosis of the disease.

1.3 Other cognitive functions

Most PCA patients present with preserved language functions at the onset of their symptoms, though there have been cases reported with early language impairments, often in those with a mixed AD or logopenic presentation (Crutch et al., 2013; Migliaccio et al., 2009). When compared to healthy controls, PCA patients often show oral language dysfunction with prominent word retrieval difficulties. In addition, a study demonstrated that 8 out of 9 patients had anomia, reduced fluency, and phrase length-dependent phrase deficits, which led the authors to conclude that this syndrome frequently has co-existing logopenic features (Magnin et al., 2013). The relative preservation of the language skills in most patients, especially at early stages, has a fundamental role in enabling subjects to take advantage of psychological therapy and/or peer support meetings (Crutch et al., 2012).

Some PCA patients may also show asymmetrical limb rigidity and/or limb apraxia (a deficit in carrying out purposeful movements in the absence of primary sensory or motor impairments, or lack of motivation) (Funayama & Nakajima, 2015; Ryan et al., 2014). This disorder affects voluntary positioning and sequencing of the limbs; therefore, the patient may have trouble utilizing an object (a toothbrush to brush their teeth or a spoon to eat), getting dressed (dressing apraxia) or imitating a symbolic gesture (Buxbaum, Haaland, Hallett, Wheaton, & Heilman et al., 2008; Dovern, Fink, & Weiss, 2012; Ryan et al., 2014).

Gerstmann's syndrome is frequently present in these patients. This disorder includes agraphia, acalculia (deficits in performing simple arithmetic), finger agnosia (a deficiency in distinguishing, naming or recognizing the fingers) and left/right disorientation (Ardila, 2014).

Although various studies indicate that episodic memory and executive functions are generally conserved during the initial stages of the disease (Aharon-Peretz, Israel, Goldsher, & Peretz, 1999; Crutch et al., 2012; Mendez et al., 2002), an alteration in working memory can be present (Migliaccio et al., 2009). However, they deteriorate progressively over the course of the disease. In certain cases, patients report mild memory loss as the first symptom, but this is rapidly overshadowed by the marked visuospatial dysfunction (McMonagle et al., 2006). .

Abnormal odor identification is reported in some cases, with 30% of the PCA population losing complete olfaction (Borruat, 2013).

1.4 Neuroimaging and neuropathology

In PCA, patterns of bilateral posterior cerebral atrophy due to amyloid deposition as found in AD (Formaglio, Costes, Seguin, Tholance, & Le Bars et al., 2011) are usually observed, which predominantly affect the temporal, occipital and parietal lobes, specifically the primary visual cortex and the visual association cortex. These regions are often involved in visual perception and in the interpretation of sensory information in the brain. In contrast, the anterior temporal and prefrontal cortices are only mildly atrophic (Lehmann et al., 2011; Whitwell, Jack, Kantarci, Weigand, & Boeve et al., 2007), which is contrary to the medial temporal loss seen in the classic AD presentation.

Further, damage in dorsal areas of the parietal and occipital lobes, specifically the right superior occipital cortex, can explain the Balint-like symptoms of ocular apraxia and optical ataxia. Changes in the posterior hippocampus and posterior aspects of the temporal lobes, particularly on the right, can account for topographical memory and spatial navigation deficits, which may lead to environmental disorientation (Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998; Maguire, Gadian, Johnsrude, Good, & Ashburner et al., 2000; Whitwell et al., 2007).

A recent brain perfusion single photon emission computed tomography study in PCA patients shows decreased activity in the lateral occipital cortex and the temporal-occipital junction, which correlates with simultagnosia (Kas et al., 2011). In addition, studies (Lehmann et al., 2011; McMonagle et al., 2006;

Migliaccio, Agosta, Scola, Magnani, & Cappa et al., 2012) have found that lower cortical thickness in occipito-temporal regions is correlated with visuoperceptual deficits; and a lower cortical thickness in occipitoparietal regions is correlated with a visuospatial predominance of deficits (Lehmann et al., 2011; Mendez, 2001). This is in accordance with the widely accepted model of neural processing of vision proposed by Goodale and Milner (Goodale & Milner, 1992), which argues that visual processing is directed by two main streams: the ventral "what" and dorsal "where" pathways. According to this model, both streams process information about objects and their locations, but each pathway elaborates on the information in a different way. The ***ventral stream*** provides a detailed representation of the visual world, including perceptual features, which enables creation of long-term representations necessary to identify and recognize objects. The ***dorsal stream***, on the other hand, provides information about objects and their locations, transforming visual information into the required coordinates for skilled motor actions. Lesions in the ventral pathway result in deficits in the processing of visual objects (including objects, faces, colors, and written word recognition), while damage in the dorsal pathway is associated with deficits in spatial awareness and guidance of actions (Mendez, 2001). Pathological evidence on how symptoms progress in these two streams is still sparse. Some authors (McMonagle et al., 2006) argue that dorsal stream symptoms are more predominant initially in PCA patients and that as the disease progresses, it later implicates the ventral stream. Others (Lehmann et al., 2011) suggest a more heterogeneous pattern of visuoperceptual deficits concurrent with an overlap of dorsal and ventral cortical loss, and therefore they suggest that, rather than two discrete subsyndromes within PCA (dorsal and ventral), these subtypes represent points along a continuum of phenotypical variation.

Other pathologies that usually underlie PCA also present with focal cortical neural loss as seen in CBD (mostly in frontal, parietal and/or temporal regions) (Crutch et al., 2017; Tang-Wai, Josephs, Boeve, Dickson, & Parisi et al., 2003; Wadia & Lang, 2007), DLB (where patterns of hypometabolism were found to overlap with those of PCA in regions involving the lateral occipital lobe, lingual gyrus, cuneus, precuneus, posterior cingulate, inferior parietal lobe, supramarginal gyrus, striatum, and thalamus) (Whitwell, Graff-Radford, Singh, Drubach, & Senjem et al., 2017) and prion disease (where MRI-diffusion weighted imaging shows ribbon-like abnormalities in the cerebral cortex and/or hyperintensity in the caudate and putamen or thalamus) (Depaz, Haik, Peoc'h, Seilhean, & Grabli et al., 2012; Macfarlane, Wroe, Collinge, Yousry, & Jager, 2007).

1.5 Genetics

Genetic studies on PCA tend to be scarce, and due to the rarity of the disease, most of them have small sample sizes (Carrasquillo, Barber, Lincoln, Murray, & Camsari et al., 2016; Carrasquillo, Khan, Murray, Krishnan, & Aakre et al., 2014; Tang-Wai et al., 2004). Some studies have found a highly significant association between *apolipoprotein E* (*APOE*) *ε4* (the most common risk factor for late-onset AD) and increased risk for PCA, as well as AD (Carrasquillo et al., 2014) (meaning that some of the genetic risk factors for AD are shared with PCA); yet others have found either no association between *APOE ε4* and PCA (Snowden et al., 2007), or that a variation in or near *APOE* alters PCA risk, but with smaller effect than for typical AD (Schott, Crutch, Carrasquillo, Uphill, & Shakespeare et al., 2016; Schott, Ridha, Crutch, Healy, & Uphill et al., 2006; Van Der Flier, Schoonenboom, Pijnenburg, Fox, & Scheltens, 2006). A recent genome-wide association study genotyped 302 PCA patients from 11 different centers and calculated the PCA risk at 21 loci with known AD and DLB association; three candidate loci—*semaphorin 3C (SEMA3C), contactin associated protein like 5 (CNTNAP5)*, and *family with sequence similarity 46 member A (FAM46A*) —achieved genome-wide significance as potential genes of interest in PCA (Schott et al., 2016). This result may explain a phenotypic diversity in AD's variations.

In rare instances mutations in *presenilin-1* (*PSEN1)* (Sitek, Narozanska, Peplonska, Filipek, & Barczak et al., 2013) and *presenilin-2* (*PSEN2* (Carrasquillo et al., 2016; Tremolizzo, Susani, Mapelli, Isella, & Bertola et al., 2015); also a cause of autosomal dominant forms of early-onset AD (Lanoiselee, Nicolas, Wallon, Rovelet-Lecrux, & Lacour et al., 2017)); *granulin* (*GRN* (Caroppo, Belin, Grabli, Maillet, & De Septenville et al., 2015); associated with typical AD and frontotemporal lobar degeneration (Galimberti & Scarpini, 2012; Perry, Lehmann, Yokoyama, Karydas, & Lee et al., 2013)); *microtubule associated protein tau (MAPT* (Wojtas, Heggeli, Finch, Baker, & Dejesus-Hernandez et al., 2012); associated with frontotemporal dementia (Che, Zhao, Huang, Li, & Ren et al., 2017; Zhang, Xing, Tan, Tan, & Yu, 2016) and identified as a risk factor for progressive supranuclear palsy (Hoglinger, Melhem, Dickson, Sleiman, & Wang et al., 2011)); *prion protein* (*PRNP* (Guerreiro, Bras, Wojtas, Rademakers, & Hardy et al., 2014); also present in Creutzfeldt-Jakob Disease, kuru, fatal familial insomnia, and Gerstmann-Sträussler syndrome among others (Solomon, Schepker, & Harris, 2010)) and *triggering receptor expressed on myeloid cells 2* (*TREM2* (Carrasquillo et al., 2016); known to cause autosomal recessive forms of dementia (Guerreiro, Lohmann, Brás, Gibbs, & Rohrer et al., 2013; Paloneva, Manninen, Christman, Hovanes, & Mandelin et al., 2002)), have been detected in subjects with PCA. One study of a family with an early and long-standing prion dementia manifesting with PCA was found to be associated with this syndrome and to have a 5-octapeptide insertion into the prion protein gene (Depaz et al., 2012).

1.6 Treatment

To date, there is no medicine available that would stop the progression of cognitive dysfunction in dementia, though there are a few drugs in the market that have shown some benefits at slowing its decline (Maguire et al., 1998). The standard pharmacological therapy used in PCA is based on cholinesterase inhibitors, resembling the intervention used in early stages of AD, vascular dementia and in DLB (Maguire et al., 2000; Mendez, 2001). However, some patients could experience a loss of therapeutic benefit due to drug tolerability. A recent study showed global cognitive benefits in PCA patients taking donepezil, though no

improvement was found in visuospatial functions (Maguire et al., 1998). The use of rivastigmine has also demonstrated positive behavioral, cognitive and functional effects on the activities of daily life (Bokde et al., 2001). The results from plant-based interventions are controversial; for example while some laboratories have found a small but significant effect on cognitive function in AD using gingko biloba (Oken, Storzbach, & Kaye, 1998), others report no effectiveness of the plant in reducing the overall incidence rate of dementia (Birks & Grimley, 2007; DeKosky, Williamson, Fitzpatrick, Kronmal, & Ives et al., 2008). Anti-depressants in patients with low-mood or levodopa in patients with parkinsonism have also been administered (Crutch et al., 2012).

It should be taken into account that most pharmacological approaches serve to relieve the symptoms that coexist with dementia, yet no treatment exists to palliate the disease in its totality, given the complexity and multiplicity of neurodegenerative diseases. Instead, treatment must be analyzed on an individual basis and complemented with non-pharmacological strategies in order to increase its effectiveness (Buxbaum et al., 2008; Crutch et al., 2017). The treatment implemented in PCA patients focuses mainly on interventions to support activities of daily life and the accomplishment of personal independence. In spite of contradictory results, growing evidence supports the improvement of at least certain aspects of the disease when treated in this manner (Roca et al., 2010). The treatment should include cognitive rehabilitation, compensatory strategies and psychoeducation with additional caregiver education and support (Ortner & Kurz, 2015).

Previous studies have accounted for the benefits due to non-pharmacological treatment (Alves, Magalhaes, Arantes, Cruz, & Goncalves et al., 2015; Kim, 2015; Perez, Tunkel, Lachmann, & Nagler, 1996; Roca et al., 2010). For example, a rehabilitation program for Balint's syndrome and PCA patients that aimed to reduce visual perception errors showed that in at least 50 percent of the strategies, the patient was able to transfer, apply and generalize what he learned in therapy to new situations in his daily life. For cases in which the deterioration was severe, the rehabilitation focused more on repetition than on learning new material (Perez et al., 1996). Another study presented the case of a patient with PCA who took part in a cognitive rehabilitation program that included psychoeducation, compensatory strategies, and cognitive exercises. After the intervention, subtle differences were found in visuoperceptual tasks, yet worsening in other skills that were not the focus of the treatment was also observed (Roca et al., 2010). The selected exercises also aimed to strengthen the preserved functions in the patient in order to facilitate his deficits, which resulted in an improvement in his everyday functioning. In addition to the cognitive rehabilitation, psychoeducation interventions are also known to play a central role in the treatment, as they result in a better understanding of the disease and have been correlated with a decrease in anxiety levels as much for the patient as for the caregivers (Videaud, Torny, Cartz-Piver, Deschamps-Vergara, & Couratier, 2012).

While these types of interventions show positive results, they are not sufficient due to the progressive nature of the disease.

In this study, we describe the progression of the disease throughout 7 years in a patient, correlating the neuropsychological profile with its neural substrate provided by structural neuroimaging.

2. Longitudinal tracking of a patient with PCA

Although extensive literature has shown the neuropsychological deficits related to PCA, few have reported the progression of the disease and its neurological and cognitive implications. One of these studies, written by Kennedy et al. (Kennedy, Lehmann, Sokolska, Archer, & Warrington et al., 2012) described the case of a 61-year-old man suffering from PCA in a 5-year-longitudinal study. In this case, the decline in visuoperceptual, visuospatial and literacy impairments were accompanied by inferior temporal and posterior atrophy which spread to occipital cortices and subsequently to more anterior regions. Also, Chan et al. (Chan, Lynch, De May, Horton, & Miller et al., 2015) portrayed the case of a 63 year old prodromal PCA patient and reported a five year follow up, highlighting the insidious evolution of the disease and the importance of an early diagnosis. However, the PCA diagnosis was made in the final year of evaluation, and thus no information was provided on how the condition evolved thereafter.

2.1 Methods and materials

We describe the case of a right-handed 64-year-old man who attended a consultation at the Center for Memory Studies after undergoing ophthalmologic exams that indicated normal eye function. Although the patient, who had 12 years of education, had no formal higher education, he showed elevated premorbid intellectual functioning (Word Accentuation Test – Buenos Aires: 41 out of 44 points, 70th percentile). He belonged to an urban middle-class family, worked as a businessman most of his life and retired at the age of 60. The subject had no significant past medical or surgical history. Pertinent family history reveals that his paternal grandmother was diagnosed with a neurodegenerative disease at age 55, and his maternal grandmother developed AD at age 87. Unfortunately, no genetic information on this patient is available.

In the consultation he presented with memory and attention difficulties, which he did not report as progressive. Additionally, he mentioned difficulty with locating objects in space (particularly in the left hemispatial field), recognizing familiar places, episodes of spatial disorientation, and reading difficulties.

In the first neuropsychological evaluation he presented with letter-by-letter reading and deficits in his visuoperceptual skills. The BORB battery assessment indicated that the patient was below average in the precategory dimension of visual perception in tasks related to length, size, orientation, position

and superimposed images. A voxel-based morphometry (VBM) analysis was performed at 28 and 86 months post diagnosis.

2.2 Longitudinal evaluation

All evaluations and neuroimages were gathered over a 7-year period. The patient underwent several neuropsychological evaluations, and the neuroimages taken during his consultations were subsequently analyzed.

2.3 Neuropsychological evaluation

The patient was evaluated on nine separate occasions during a period of 7 years. In all evaluations, his performance was compared with people of the same age and education level. The patient's score was considered low when it was between one and two standard deviations below the median and deficient when it was more than two standard deviations below. In tests with a learning effect, the alternative versions were used when available (e.g. Rey Auditory Verbal Learning Test and Logical Memory). The sessions lasted one hour and a half, and the patient was evaluated each time by an experienced neuropsychologist.

Cognitive evaluations were composed of the following tests: Ineco Frontal Screening (IFS), Mini Mental State Examination (MMSE), Addenbrooke's Cognitive Examination – Revised Version (ACE–R) Rey Auditory Verbal Learning Test (RAVL), Logical Memory, Complex Rey Figure, Abbreviated Version of the Boston Naming Test (20 items), Token Test, Semantic and Phonological Verbal Fluency Test, Trail Making Test (TMT; Parts A and B) and Digit Span Task Forward and Backward. As described later, the patient could always understand and carry out the tests except during the final evaluation.

2.4 Neuroradiological evaluation

The patient was evaluated with Magnetic Resonance Imaging (MRI) on seven different occasions over the 7-year-period. In most cases, the MRI exam occurred in the same month as the cognitive evaluation, except during the third year in which the MRI exam occurred 9 months prior and also during the fifth year in which the MRI exam occurred 7 months after the neuropsychological evaluation. These MRI scans were evaluated in a qualitative fashion (see Table 1) by two clinical neuroimaging experts (FM and BC), who included a detailed description of sagittal and axial sections in T1 weighted, T2 weighted and fluid attenuated inversion recovery (FLAIR) sequences, and T2 weighted coronal sections. Furthermore, a quantitative longitudinal assessment of volume change (in percent of total brain volume) between two available time points was performed using the FSL (Smith, Jenkinson, Woolrich, Beckmann, & Behrens et al., 2004) tool SIENA (Smith, De Stefano, Jenkinson, & Matthews, 2001). This analysis inputted the MRIs scanned at 28 months after diagnosis and 86 months after diagnosis, given that these were the only two available scans in raw digital format suitable for the analysis. SIENA first extracted brain and skull images from the two-time-point whole-head input data. The two brain images were then aligned to each other (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) (using the skull images to constrain the registration scaling); both brain images were resampled into the space halfway between the two. Next, tissue-type segmentation was carried out in order to find brain/non-brain edge points, and then perpendicular edge displacement (between the two timepoints) was estimated at these edge points. Finally, the mean edge displacement was converted into a (global) estimate of percentage brain volume change between the two timepoints. In a second pipeline, we addressed specific atrophy sites of both MRI timepoints by performing a VBM analysis on the T1 images of the patient and two samples of gender and age-matched healthy controls. Two control samples were used to compare the data, the first at 28 months and the second at 86 months. Sample 1 consisted of 6 male subjects, with a mean age of 63.33 years (SD = 4.32 years; t = 0.35, p = .36) and with a mean formal education of 14.33 years (SD = 3.45 years; t = −0. 51, p = .31). Sample 2 consisted of 7 male subjects, with an average age of 69.2 years (SD = 5.58 years; t = 0.30, p = .38) and with a mean formal education of 13.6 years (SD = 3.45 years; t = −0. 43, p = .33). Images were preprocessed for VBM analysis using DARTEL Toolbox and following procedures previously

Table 1. Qualitative analysis of the neuroradiologic progression of patient's atrophy.

MRI	*Initial assessment*	*10 m*	*19 m*	*28 m*	*49 m*	*77 m*	*86 m*
Axial	b-PCG, b-PPC, b-SPL	l-PoCG ++	l-PPC ++		l-PPC ++ l-PCG ++ l-PHC l-Ins l-STG		
Sagital	b-PCG, b-PPC, b-SPL	l-PoCG	MOC r-Cu	b-Cunei b-PreCu	b-PPC ++ b-MOC + b-Cunei + b-PreCu + r-PHC	r-Cu ++ r-PreCu ++ r-MOC + l-PPC l-PreCu l-Cu l-MOC l-Ins	b-PoCG b-PPC ++ b-SPL ++ b-MOC + r-Sylvian/ Ins b-HC
Coronal	b-PCG, b-PPC, b-SPL	b-PPC l-SPL	PPC l-SPL	b-PPC b-SPL	r-Sylvian/ Ins l-HC	b-PPC l-SPL	

m: months after initial assessment; b-: bilateral; l-: left; r-, Right; PoCG: post-central gyrus; PPC: posterior parietal cortex; SPL: superior parietal lobule; Cu: cuneus; PHC: para-hippocampal cortex; STG: superior temporal gyrus; MOC: medial occipital cortex; PreCu: precuneus; Ins: insula; HC: hippocampus.

described (Ashburner & Friston, 2000). Subsequently, the images were modulated, smoothed with a 12 mm full-width half-maximum kernel (as suggested in other reports (Good, Johnsrude, Ashburner, Henson, & Friston et al., 2001)) and normalized to MNI space. Finally, these images were analyzed with general linear models in SPM-8 2nd level analyses (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Statistical analysis was performed by creating multiple linear regression (MLR) designs in SPM, comparing the patient's to the controls' gray matter that had been segmented, smoothed and normalized to MNI images, as well as entering the differences in total intracranial volume (TIV) and age as covariates of no interest. The statistical threshold was set at the voxel level $p < 0.001$, corrected for multiple comparisons with Bonferroni test.

3. Results

Both neuropsychological and neuroradiological results are provided in Figure 1 and Figure 3. A detailed description of the evolution of the neuropsychological profile is described later.

3.1 Neuropsychological evolution

3.1.1 Initial evaluation

In the first assessment, the patient was oriented to time and space, though he presented slight difficulties in the general and executive screening tests (ACE: 88/100; IFS: 18/30), with errors predominating in the visuospatial functions tested by the Cube Copy and the Clock Drawing tasks. The patient also showed severe deficiencies in this domain when performing the Complex Rey Figure ($z = -4.1$).

Regarding the attention domain, the patient performed well on auditory attention tasks (digit span forward, ($z = 0$); and serial calculations), but he demonstrated significant difficulties with tasks that required control of his visual attention, such that a greater amount of time was needed for completion (TMT Part A: $z = -7.41$, TMT Part B, $z = -1.39$).

In regards to verbal memory, the patient demonstrated difficulties with the immediate paragraph recall ($z = -1.38$), but he was able to remember all the words from a list (RAVL; immediate recall), indicating adequate storage and memory conservation. In respect to long-term visual memory, his performance was below average ($z = -1.29$), which appeared to be related to his initial difficulty with copying the complex figure (ROCF).

Line bisection tests were also used to analyze in further detail his complaint reported during the consultation. During these tests the patient had difficulty localizing the stimuli in space, although the errors did not appear to favor one hemifield over the other.

In respect to the patient's language ability, he demonstrated normal scores on tests that measured naming, comprehension of complex grammatical structures, and phonological verbal fluency, and he obtained low scores in the semantic verbal fluency task ($z = -1.02$). Regarding his written skills, the patient presented with a good initial performance, as can be seen in Figure 2. In reference to executive function, the patient demonstrated a normal performance in the programming of motor series, the capacity to respond in the presence of conflicting instructions, and verbal inhibitory control, but he manifested difficulties with motor inhibitory control, working memory exercises ($z = -2.1$) and cognitive flexibility.

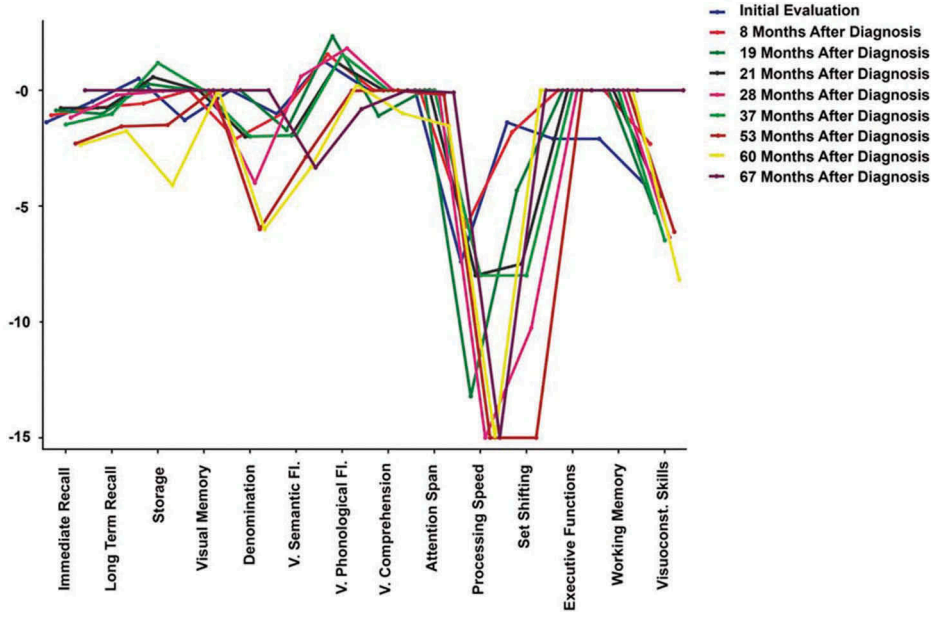

Figure 1. *Z* scores of the tests assessed throughout the 9 evaluations. (*Z*-scores below −15 were noted as −15 in the figure for visual purposes). The tests evaluated for each domain are: Immediate Recall: RAVLT, Immediate Recall; Long Term Recall: RAVLT: Long Term Recall; Storage: RAVLT: Recognition; Visual Memory: Complex Rey Figure: Visual Memory; Denomination: Boston Test; Verbal Semantic Fluency: Verbal Semantic Fluency; Verbal Phonological Fluency: Verbal Phonological Fluency; Verbal Comprehension: Token Test; Attention Span: Digit Span Task Forward; Processing Speed: Trail Making Test A; Set Shifting: Trail Making Test B; Executive Functions: Ineco Frontal Screening; Working Memory: Digit Span Task Backward; Visuoconstructive Skills: Complex Rey Figure, Copy. (RAVLT: Rey Auditory Verbal Learning Test).

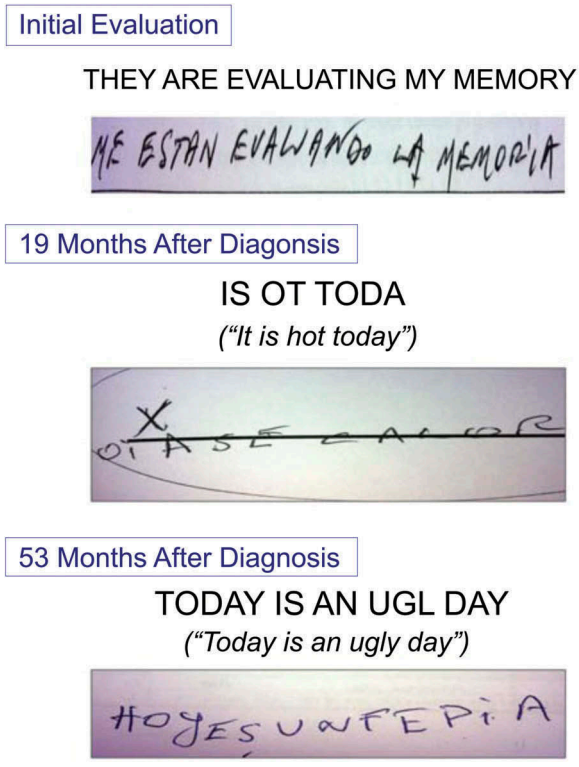

Figure 2. Progressive deterioration in writing during the initial evaluation; 19 months and 53 months after diagnosis. In italics: what patient meant to write.

3.1.2 Evaluation at 8 months after diagnosis

The next evaluation occurred 8 months after diagnosis. The patient displayed a small improvement in working memory, cognitive flexibility, constructive praxis ($z = -2.32$), processing speed (particularly in tasks with visual stimuli), and other processes that showed a deficit during the first evaluation. This initial improvement can be attributed to the patient's enrollment in a treatment program that included cognitive rehabilitation and pharmacological strategies described in the paper by Roca et al. (Roca et al., 2010). Apart from these improvements, however, the patient demonstrated major language difficulties during the evaluation, manifesting significant anomia and difficulty with verbal semantic fluency.

3.1.3 Evaluation at 19 months after diagnosis

The third evaluation occurred 19 months after diagnosis. During this evaluation, the patient exhibited greater difficulty with higher order functions (Copy of the Rey Complex Figure, $z = 5.29$) and also with visual attention processing (Trail Making Test A and B, $z = -13.21$ and $z = -4.33$, respectively), indicating a progression of the visuospatial symptoms. The patient's scores on executive function tasks remained unchanged from the prior evaluation, with the only exceptions being inhibitory control tasks, which were observed as being affected, and language skill tasks, which revealed further naming and verbal semantic fluency difficulties ($z = -1.72$), as shown in Figure 2. Also, orthographic errors, some graphemic omissions, sentence misalignment and difficulties in respecting the space between words were found. The patient scored within the normal range in tests of delayed memory ($z = -1.02$) and recognition phase ($z = 0.27$), indicating continued memory conservation.

3.1.4 Evaluation at 21 months after diagnosis

The fourth evaluation occurred 21 months after diagnosis, and it indicated difficulties largely related to visuoperceptual skills (copy of the Complex Rey Figure) ($z = -4.58$). There was also evidence of decreased performance in the patient's language skills, but the changes that occurred since the previous exam 12 months prior were not significant. The patient also started to report calculation problems. Simple arithmetic deficits were observed including difficulties with addition and subtraction. Memory impairment first appeared during this evaluation, with the patient demonstrating a less specific recall of learned information, as evidenced by intrusion errors during the recognition phase of the Rey Auditory Verbal Learning Test. Given the rise in visuoperceptual difficulties, tests such as the WCST could not be assessed and thus were not administered.

3.1.5 Evaluation at 28 months after the diagnosis

In the fifth evaluation, occurring 28 months after diagnosis, increased deficits were observed in the majority of the cognitive domains, but the patient's visuospatial difficulties continued to predominate as the main symptom (copy Complex Rey Figure) ($z = -6.48$). Notably, his performance decreased on visual attention, language, and executive function tasks.

3.1.6 Evaluation at 37 months after diagnosis

The sixth evaluation occurred 37 months after diagnosis. The patient demonstrated marked difficulty in most tests assessed, with language predominating as the most troubled, specifically in the naming test (Boston test) ($z = -4$). Errors in this test highly exceeded those expected by his perceptual difficulties, evidenced by the fact that the patient did not benefit from semantic cues and that naming was equally impaired both in simple and complex perceptual stimuli. Mistakes stood out in reading, anomia, and expressive language, causing the formal evaluation of the patient to become much more difficult. Figure 2 also shows the progression of his writing difficulties. The visuoperceptual functions were also largely compromised, and as a result, the patient needed additional time to execute tasks requiring visual search. The remaining cognitive functions that were evaluated also showed deficits. From this moment on, difficulties with the storage of information in memory tasks became much more evident (immediate recall (RAVLT; $z = -2.3$), delayed memory (RAVLT; $z = -1.56$) and recognition (RAVLT; $z = -1.5$)).

3.1.7 Evaluation at 53 months after diagnosis

The seventh evaluation illustrated marked difficulties in the majority of the cognitive areas evaluated, depicting a patient with moderate to severe cognitive deterioration. Consequently, the progressive deterioration of functions involving visuoperception and language (verbal semantic fluency) ($z = -3.34$) continued. The deterioration in writing progressed with a more evident difficulty in separating words, graphemic omissions and a difficulty in identifying the end of a word. However, the use of mixed letters was not produced in this

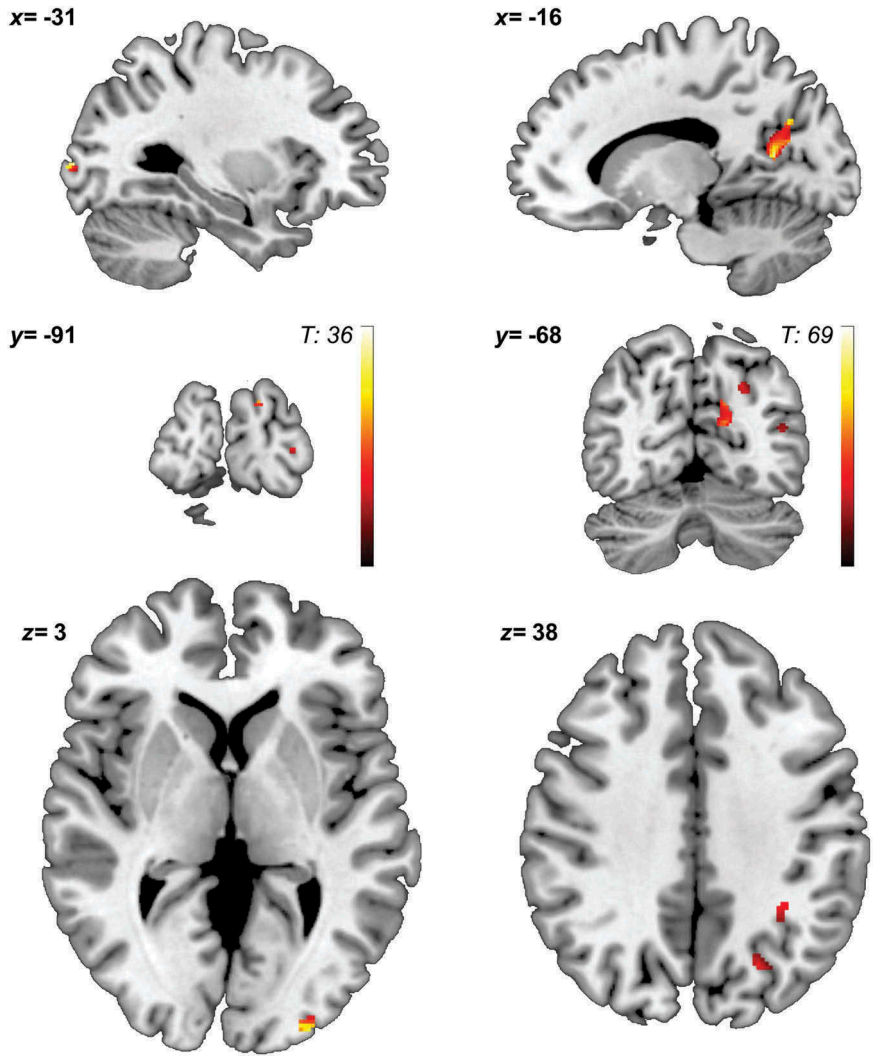

Figure 3. Sagittal, coronal and axial slices showing the VBM results of patient's atrophy compared to controls. Scans on the left, at 28 and right, at 86 months after diagnosis. *T*-score in color coded scale, $p < .005$ corrected for multiple comparisons. Overlapped over MNI T1 template.

case. Sentence misalignment could not be assessed because a blank page was presented to the patient (Figure 2). Furthermore, the patient's memory deficits persisted (immediate recall: $z = -2.36$, delayed memory: $z = -1.76$), due to difficulty acquiring new information and long-term recall. Deficiencies in the storage of information also become more evident during this evaluation and the patient's performance in the recognition phase of the memory task was highly affected ($z = -4.1$). Another prominent change was that for the first time the patient confused the month and date that he was in, implicating a compromise in his orientation to time.

3.1.8 Evaluation at 60 months after diagnosis

During this evaluation, the patient showed a global cognitive deterioration as he scored deficiently in the general screening tasks, obtaining 31/100 on ACE and 16/30 on IFS. The patient was orientated to space while his disorientation to time continued; however, at subsequent visits this latter disorientation did not clearly decline. While his comprehension was relatively conserved, errors stood out in expressive language and the use of visual information for even the simplest tasks. As a result, the initial difficulties observed in the figure copies (Complex Rey Figure) ($z = -8.18$) and the recognition of global scenes were augmented to such a degree that the patient started having errors in the recognition of simple forms, unique letters, colors and drawings. The patient demonstrated significant errors in the cube copy, counting dots, construction of a clock, and the copy of intersecting infinity loops.

3.1.9 Evaluation at 67 months after diagnosis

For the final evaluation, the patient showed an increased global cognitive deterioration and only a few tests could be evaluated. Although he presented with an adequate space orientation, his time disorientation continued. The patient showed a more severe deficit in verbal phonological fluency than in the previous assessment ($z = -0.81$), though he maintained the previous verbal semantic fluency scores ($z = -3.34$). He was also severely slower on graphomotor tasks such as the Trail Making (A) ($z = -37$). In general terms, it can be said that every cognitive domain was critically compromised.

3.2 Neuroradiological progression

From a qualitative point of view, the neuroradiologic atrophy described in Figure 1 was initially evidenced in the posterior parietal cortex (PPC), postcentral gyrus and superior parietal lobule (the complete lateral aspects of bilateral parietal lobes). The scan at 10 months of diagnosis showed a progression of the affectation of these same structures, predominantly in the left hemisphere, whereas at 19 months from diagnosis the medial wall of the posterior hemispheres was additionally atrophied, including medial occipital lobe and right cuneus. In addition to the bilateral PCC and superior parietal lobule neurodegeneration, the bilateral cuneus and precuneus showed decreased volume in the scan at 28 months post-diagnosis. In the scan at the 60-month follow-up, greater atrophy was identified in the bilateral precunei, cunei, medial occipital, right parahippocampus, bilateral hippocampus, and insula, as well as in right Sylvian sulcus. At 77 months post-diagnosis, the scan showed evidence of atrophy in bilateral medial posterior structures as well as bilateral PPC and superior parietal lobules. Finally, the scan at 86 months post-diagnosis showed incremental atrophy in the postcentral gyri, PPC, superior parietal lobules and medial occipital gyri, right Sylvian sulcus and insula, and bilateral hippocampi.

The quantitative analysis performed with SIENA resulted in a 1.3 percent total brain volume change between the scans at 86 months and 28 months after diagnosis.

The VBM analysis showed significant left hemisphere atrophy compared to age and gender matched controls. For the 5th time-point (28 months after the first evaluation), the patient's atrophy centers specifically in the middle occipital cortex (Brodmann Area [BA] 18; $x = -28.5$, $y = -93$, $z = 4.5$ mm; T score = 34; $p < 0.001$) and the superior occipital cortex (BA 19; $x = -13.5$, $y = -91.5$, $z = 27$ mm; T score = 21; $p < 0.005$) (see Table 2; Figure 3).

However, for the 7th time-point (86 months after first evaluation), the VBM showed atrophy specifically in the posterior cingulate cortex (BA 30/31; $x = -14$, $y = -62$, $z = 12$ mm; T score = 69; $p < 0.001$), the precuneus (medial continuation of BA 7; $x = -15$, $y = -69$, $z = 29$ mm; T score = 51; $p < 0.001$), the cuneus (BA 17; $x = -15$, $y = -69$, $z = 20$ mm; T score = 41; $p < 0.001$), the inferior parietal lobule including one voxel in the supramarginal gyrus (BA 40; $x = -30$, $y = -47$, $z = 41$ mm; T score = 43; $p < 0.001$), the superior parietal lobule (BA 7; $x = -29$, $y = -71$, $z = 33$ mm; T score = 21; $p < 0.005$), the middle temporal gyrus (BA 39; $x = -44$, $y = -71$, $z = 17$ mm; T score = 30; $p < 0.005$) and the mid occipital cortex (BA 18; $x = -33$, $y = -89$, $z = 3$ mm; T score = 40; $p < 0.005$) (see Table 3; Figure 3).

Table 2. VBM results at 28 months after initial evaluation.

Anatomical region	Brodmann Area	x (mm)	y (mm)	z (mm)	p (FWE-cor)	T score
Middle occipital L	**18**	−28.5	−93	4.5	0.0009	34.57
Superior occipital L	**19**	−13.5	−91.5	27	0.004	21.22

Table 3. VBM results at 86 months after initial evaluation.

Anatomical region	Brodmann Area	x (mm)	y (mm)	z (mm)	p (FWE-cor)	T score
Posterior cingulate L	**30/31**	−14	−62	12	0.00006	69.73
Precuneus L	**31**	−15	−69	29	0.0002	51.19
Cuneus L	**17**	−15	−69	20	0.0004	41.23
Parietal inferior L (*supramarginal*)		−30	−47	41	0.0004	43.13
Parietal superior L	**7**	−23	−66	39	0.006	21.86
Middle temporal gyrus L	39	−44	−71	17	0.001	30.47
OccipitalmMid gyrus L	19	−33	−89	3	0.0005	40.44

4. Discussion

PCA is a rare and degenerative early-onset disease whose main symptom is the deficiency in higher visual function with memory storage and executive functions relatively conserved. Although it has often been considered an atypical variant of AD, the initial manifestation of PCA with visuoperceptive dysfunction and memory conservation has led some authors to consider it a different nosological entity (Crutch et al., 2012; Kennedy et al., 2012). In addition, the neuroimaging depicts an inverse pattern of atrophy, showing volume reduction in posterior parietal and occipital regions in PCA and in temporal areas in AD (Lehmann, Barnes, Ridgway, Ryan, & Warrington et al., 2012).

Few studies have described the progression of PCA. While some of the studies focused mainly on the neuroimaging (Lehmann et al., 2012; Schmidtke, Hull, & Talazko, 2005) or individual cognitive symptoms, in the present investigation we describe the follow up of a patient over a period of 7 years, both in neuroimaging findings and in a complete battery of neuropsychological tests. During this period the patient underwent nine neuropsychological evaluations, and the neuroimages taken during his consultations were subsequently analyzed.

At diagnosis, the patient presented with early onset deficits related to the visuoperceptual function in the absence of ophthalmological deficiencies, which are in accordance with the PCA diagnosis. The patient also exhibited difficulties localizing the stimuli in space and demonstrated significant complications in other domains that required visual input, such as visual memory and visual attention tasks, but he performed well when the tasks lacked visual stimuli. The patient had sufficient memory storage, helping lead to the differential diagnosis between PCA and typical AD. The subject also presented with normal language abilities, and showed generally conserved executive functions. The neuroimages at the time of the diagnosis confirmed the presence of a focal pattern of atrophy in posterior regions (i.e., postcentral gyrus, PPC and superior parietal lobule), which are congruent with his difficulties identifying objects in space and deficiencies in perception and spatial relationships.

Eight months after the initial examination, the patient showed some improvements, particularly in visuoperceptual tasks, which could be explained by the cognitive rehabilitation he underwent after the first evaluation. This program included psychoeducation and the use of both compensatory strategies and cognitive exercises of visual search and attention (Roca et al., 2010). Some improvements were also evident in his

initial slight difficulties on working memory and executive functions that could be related to a possible decrease of the anxiety and affective symptoms expected by the uncertainty of his diagnosis.

As the disease progressed, the visuoperceptual deficits became more evident, and the patient demonstrated an increasing difficulty with visuospatial and visual attention processing. Even though some components of both kinds of simultagnosia (dorsal and ventral) could be inferred, ventral simultagnosia, with its characteristic letter-by-letter reading, was prominent, functionally implying a ventral stream involvement. However, neuroimaging findings did not show compromise of such stream until later on in the disease, possibly indicating an initial lag between imaging findings and symptoms onset. The presence of dorsal and ventral symptoms concomitantly suggests that, at least in this patient, such symptoms seem to represent parts of the same continuum rather than to define a subcategory within the disease presentation (Lehmann et al., 2011).

In concordance with previous literature (Crutch et al., 2012), a gradual loss of his language was also evidenced early in the course of the disease, with logopenic-like (impaired single-word retrieval in spontaneous speech and naming (Gorno-Tempini, Hillis, Weintraub, Kertesz, & Mendez et al., 2011)) and marked anomias as the hallmark of his language profile. Only as the disease progressed did language and naming difficulties became more prominent, affecting even words of common use. This occurred congruently with the MRI findings that showed a predominance of left hemisphere atrophy, depicted by a reduction of left PPC volume and a preponderance of left superior parietal lobule atrophy. Even though phonological verbal fluency has been predominantly reported in PCA patients (Crutch et al., 2012), our patient presented with spared results in this test up until his final evaluation. Unexpectedly, semantic verbal fluency was maintained during the initial stages of the disease, with no comprehension or other semantic deficits observed until progression later on.

Consistent with literature currently available, our patient also showed progressive agraphia with a growing tendency to produce orthographic errors, omission and misalignment of graphemes on the page line and lack of respect for the space between words. The use of different types of letters (handwritten and print, uppercase and lowercase) previously reported in PCA was not evident in our patient. At 21 months after diagnosis he also developed progressive acalculia, although neither of the other two Gerstmann Syndrome's manifestations (finger agnosia and right/left disorientation) ever appeared.

Later on, the visuoperceptual deficits continued to get worse and memory impairments first appeared. The progression of the disease led to greater disabilities in the patient, making it difficult to evaluate some domains, such as thought cognitive flexibility. Again, the appearance of symptoms preceded the neuroimaging findings which by this time showed the spread of the atrophy to the medial occipital right cuneus, an area mainly involved in basic visual processing.

In the latter evaluations, the patient continued to deteriorate in almost all cognitive domains, with visuospatial functions still dominating as the most afflicted. Language skills and memory difficulties became even more profound, which coincided with the atrophy now evident in medial temporal structures. The deterioration continued to such an extent that it affected the acquisition of new information and orientation to time. At the time of the final evaluation, the patient presented with severe cognitive deterioration, scoring very low on general screening tasks. The widespread pattern of gray matter loss in the patient became more global, and expanded to temporal areas including the hippocampus and parahippocampus (both areas related to memory skills), right Sylvian fissure, medial areas of the occipital lobule, and insular cortex, which likely account for the broad cognitive decline observed.

The progression of neuropsychological and neuroimaging findings in our patient seem to be in accordance with recent theories, which suggest that different neurodegenerative syndromes cause circumscribed atrophy within diverse healthy human intrinsic functional connectivity networks, rather than affecting contiguous brain regions (Pievani, Filippini, Van Den Heuvel, Cappa, & Frisoni, 2014; Seeley, Crawford, Zhou, Miller, & Greicius, 2009). Coherent with this view, the pattern of atrophy in our patient compromised different functional networks. Initially, atrophy developed from the visual network (middle and superior occipital gyri, cuneus) through the most lateral-posterior nodes of the default-mode network (DMN, including posterior and superior parietal lobule); next, it affected the medial nodes of the DMN (precuneus, posterior cingulate cortex), and later the anterior ventral nodes (hippocampus and parahippocampus); extending finally to specific nodes of the salience network (insula and Sylvian fissure corresponding to the fronto-opercular node). Hence, outlined both from the qualitative and quantitative (VBM) analyses, the patient's pathology spread from posterior-to-anterior and dorsal-to-ventral functionally related areas, which follow networks known to underlie the neuropsychological deficits detected.

The main limitation of this study is the fact that it is a single case analysis, which can be understood due to the singularity of this disease. Neuropsychiatric standardized information, such as the presence of depression, anxiety, apathy, irritability and hallucinations, would also have added to a more global image of PCA. Regarding the neuroimaging assessment, the time correlation between neuropsychology and imaging would have benefited from a narrower time window between each evaluation and each scan. Also, quantitative analysis was only possible for two of the images given the availability of raw data. Future research could benefit from a more detailed multidimensional approach encompassing neuropsychological, neuropsychiatric, neuroradiological and behavioral dimensions.

In summary, our research portrays how the cognitive impairments of PCA progress from mainly visuoperceptual deficiencies to deficits in other domains such as language, time orientation and memory acquisition. The longitudinal neuropsychological and neuroimaging follow-up adds important information regarding the relationship between onset of symptoms and neuroanatomical findings on MRI, as clinical manifestations were evident long before the structural MRI showed congruent changes in areas related to those

symptoms. Therefore, complementary methods, such as connectivity analysis, should be studied for their efficacy to detect early brain changes.

We have observed how PCA and AD remain two different nosological categories with neurocognitive and brain atrophy preference at early stages, and portrayed how, as the illness advances, the cognitive and behavioral symptoms become more uniform as the atrophy patterns spread to other areas in the brain.

Even though several studies have described the cognitive profile of PCA, very few investigations have performed a longitudinal follow up of these patients, making the clinical evolution uncertain both for professionals, patients and caregivers (Chan et al., 2015; Kennedy et al., 2012; Lehmann et al., 2012; Schmidtke et al., 2005). The present study provides a 7 year follow up of a patient's neuropsychological and neuroimaging evolution, permitting a better understanding of the disease progression, which could help lead to a better design of pharmacological and non-pharmacological interventions.

Acknowledgments

Study was supported by grants from CONICET and INECO Foundation.

Disclosure statement

The authors do not have any conflict of interest.

Funding

This work was supported by the INECO Foundation; National Scientific and Technical Research Council (CONICET).

ORCID

Agustín Ibañez http://orcid.org/0000-0001-6758-5101

References

Aharon-Peretz, J., Israel, O., Goldsher, D., & Peretz, A. (1999). Posterior cortical atrophy variants of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *10*, 483–487. doi:10.1159/000017194

Alves, J., Magalhaes, R., Arantes, M., Cruz, S., Goncalves, O. F., & Sampaio, A. (2015). Cognitive rehabilitation in a visual variant of Alzheimer's disease. *Applied Neuropsychology. Adult*, *22*, 73–78. doi:10.1080/23279095.2013.831865

Alves, J., Soares, J. M., Sampaio, A., & Goncalves, O. F. (2013). Posterior cortical atrophy and Alzheimer's disease: A meta-analytic review of neuropsychological and brain morphometry studies. *Brain Imaging and Behavior*, *7*, 353–361. doi:10.1007/s11682-013-9236-1

Ardila, A. (2014). A proposed reinterpretation of Gerstmann's syndrome. *Archives of Clinical Neuropsychology : the Official Journal of the National Academy of Neuropsychologists*, *29*, 828–833. doi:10.1093/arclin/acu056

Ardila, A., & Rosselli, M. (1993). Spatial agraphia. *Brain and Cognition*, *22*, 137–147. doi:10.1006/brcg.1993.1029

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry–The methods. *Neuroimage*, *11*, 805–821. doi:10.1006/nimg.2000.0582

Benson, D. F., Davis, R. J., & Snyder, B. D. (1988). Posterior cortical atrophy. *Archives of Neurology*, *45*, 789–793. doi:10.1001/archneur.1988.00520310107024

Birks, J, & Grimley, E. J. (2007). Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Of Systematic Reviews (Online)*, *(2)* (CD003120). doi: 10.1002/14651858.CD003120.pub2

Bokde, A. L., Pietrini, P., Ibanez, V., Furey, M. L., Alexander, G. E., Graff-Radford, N. R., Rapoport, S. I., Schapiro, M. B., & Horwitz, B. (2001). The effect of brain atrophy on cerebral hypometabolism in the visual variant of Alzheimer disease. *Archives of Neurology*, *58*, 480–486. doi:10.1001/archneur.58.3.480

Borruat, F. X. (2013). Posterior cortical atrophy: Review of the recent literature. *Current Neurology and Neuroscience Reports*, *13*, 406. doi:10.1007/s11910-013-0406-8

Buxbaum, L. J., Haaland, K. Y., Hallet, M., Wheaton, L., Heilman, K. M., Rodriguez, A., & Gonzalez Rothi, L. J. (2008). Treatment of limb apraxia: Moving forward to improved action. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists*, *87*, 149–161. doi:10.1097/PHM.0b013e31815e6727

Caroppo, P., Belin, C., Grabli, D., Maillet, D., De Septenville, A., Migliaccio, R., Clot, F., Lamari, F., Camuzat, A., Brice, A., Dubois, B., & Le Ber, I. (2015). Posterior cortical atrophy as an extreme phenotype of GRN mutations. *JAMA Neurology*, *72*, 224–228. doi:10.1001/jamaneurol.2014.3308

Carrasquillo, M. M., Barber, I., Lincoln, S. J., Murray, M. E., Camsari, G. B., Khan, Q. A., Nguyen, T., Ma, L., Bisceglio, G. D., Crook, J. E., Younkin, S. G., Dickson, D. W., Boeve, B. F., Graff-Radford, N. R., Morgan, K., & Ertekin-Taner, N. (2016). Evaluating pathogenic dementia variants in posterior cortical atrophy. *Neurobiology of Aging*, *37*, 38–44. doi:10.1016/j.neurobiolaging.2015.09.023

Carrasquillo, M. M., Khan, Q., Murray, M. E., Krishnan, S., Aakre, J., Pankratz, S., Nguyen, T., Ma, L., Bisceglio, G., Petersen, R. C., Younkin, S. G., Dickson, D. W., Boeve, B. F., Graff-Radford, N. R., & Ertekin-Taner, N. (2014). Late-onset Alzheimer disease genetic variants in posterior cortical atrophy and posterior AD. *Neurology*, *82*, 1455–1462. doi:10.1212/WNL.0000000000000335

Chan, D., Crutch, S. J., & Warrington, E. K. (2001). A disorder of colour perception associated with abnormal colour after-images: A defect of the primary visual cortex. *Journal of Neurology, Neurosurgery, and Psychiatry*, *71*, 515–517. doi:10.1136/jnnp.71.4.515

Chan, L. T., Lynch, W., De May, M., Horton, J. C., Miller, B. L., & Rabinovici, G. D. (2015). Prodromal posterior cortical atrophy: Clinical, neuropsychological, and radiological correlation. *Neurocase*, *21*, 44–55. doi:10.1080/13554794.2013.860176

Che, X., Zhao, Q., Huang, Y., Li, X., Ren, R., Chen, S., Wang, G., & Guo, Q. (2017). Genetic features of MAPT, GRN, C9orf72 and CHCHD10 gene mutations in chinese patients with frontotemporal dementia. *Current Alzheimer Research*, *14*. doi:10.2174/1567205014666170426105713

Chechlacz, M., & Humphreys, G. W. (2014). The enigma of Balint's syndrome: Neural substrates and cognitive deficits. *Frontiers in Human Neuroscience*, *8*, 123. doi:10.3389/fnhum.2014.00123

Crutch, S. J., Lehmann, M., Schott, J. M., Rabinovici, G. D., Rossor, M. N., & Fox, N. C. (2011). Abnormal visual phenomena in posterior cortical atrophy. *Neurocase*, *17*, 160–177. doi:10.1080/13554794.2010.504729

Crutch, S. J., Lehmann, M., Gorgoraptis, N., Kaski, D., Ryan, N., Husain, M., & Warrington, E. K. (2012). Posterior cortical atrophy. *Lancet Neurology*, *11*, 170–178. doi:10.1016/S1474-4422(11)70289-7

Crutch, S. J., Lehmann, M., Warren, J. D., & Rohrer, J. D. (2013). The language profile of posterior cortical atrophy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*, 460–466. doi:10.1136/jnnp-2012-303309

Crutch, S. J., Schott, J. M., Rabinovici, G. D., Murray, M., Snowden, J. S., van der Flier, W. M., Dickerson, B. C., Vandenberghe, R., Ahmed, S., Bak, T. H., Boeve, B. F., Butler, C., Cappa, S. F., Ceccaldi, M., de Souza, L. C., Dubois, B., Felician, O., Galasko, D., Graff-Radford, J., Graff-Radford, N. R., Hof, P. R., Krolak-Salmon, P., Lehman, M., Magnin, E., Mendez, M. F., Nestor, P. J., Onyike, C. U., Pelak, V. S., Pijnenburg, Y., Primativo, S. Rossor, M. N., Ryan, N. S., Scheltens, P., Shakespeare, T. J., Suárez González, A., Tang-Wai, D. F., Yong, K. X., Carrillo, M., & Fox, N. C. (2017). Consensus classification of posterior cortical atrophy. *Alzheimer's & Dementia : the Journal of the Alzheimer's Association*. doi:10.1016/j.jalz.2017.01.014

Crutch, S. J., & Warrington, E. K. (2007). Foveal crowding in posterior cortical atrophy: A specific early-visual-processing deficit affecting

word reading. *Cognitive Neuropsychology*, *24*, 843–866. doi:10.1080/02643290701754240

De Renzi, E. (1986). Slowly progressive visual agnosia or apraxia without dementia. *Cortex*, *22*, 171–180. doi:10.1016/S0010-9452(86)80041-7

DeKosky, S. T., Williamson, J. D., Fitzpatrick, A. L., Kronmal, R. A., Ives, D. G., Saxton, J. A., Lopez, O. L., Burke, G., Carlson, M. C., Fried, L. P., Kuller, L. H., Robbins, J. A., Tracy, R. P., Woolard, N. F., Dunn, L., Snitz, B. E., Nahin, R. L., & Furberg, C. D. (2008). Ginkgo biloba for prevention of dementia: A randomized controlled trial. *Jama*, *300*, 2253–2262. doi:10.1001/jama.2008.683

Denburg, N. L., Jones, R. D., & Tranel, D. (2009). Recognition without awareness in a patient with simultanagnosia. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, *72*, 5–12. doi:10.1016/j.ijpsycho.2008.02.012

Depaz, R., Haik, S., Peoc'h, K., Seilhean, D., Grabli, D., Vicart, S., Sarazin, M., DeToffol, B., Remy, C., Fallet-Bianco, C., Laplanche, J. L., Fontaine, B., & Brandel, J. P. (2012). Long-standing prion dementia manifesting as posterior cortical atrophy. *Alzheimer Disease and Associated Disorders*, *26*, 289–292. doi:10.1097/WAD.0b013e318231e449

Dovern, A., Fink, G. R., & Weiss, P. H. (2012). Diagnosis and treatment of upper limb apraxia. *Journal of Neurology*, *259*, 1269–1283. doi:10.1007/s00415-011-6336-y

Farah, M. (1990). *Visual agnosia: Disorders of object vision and what they tell us about normal vision*. Cambridge, MA: MIT.

Formaglio, M., Costes, N., Seguin, J., Tholance, Y., Le Bars, D., Roullet-Solignac, I., Mercier, B., Krolak-Salmon, P., & Vighetto, A. (2011). *In vivo* demonstration of amyloid burden in posterior cortical atrophy: A case series with PET and CSF findings. *Journal of Neurology*, *258*, 1841–1851. doi:10.1007/s00415-011-6030-0

Friedman, R. B., & Alexander, M. P. (1989). Written spelling agraphia. *Brain and Language*, *36*, 503–517. doi:10.1016/0093-934X(89)90081-3

Funayama, M., & Nakajima, A. (2015). Progressive transcortical sensory aphasia and progressive ideational apraxia owing to temporoparietal cortical atrophy. *BMC Neurology*, *15*, 231. doi:10.1186/s12883-015-0490-2

Galimberti, D., & Scarpini, E. (2012). Genetics of frontotemporal lobar degeneration. *Frontiers in Neurology*, *3*, 52. doi:10.3389/fneur.2012.00052

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*, *14*, 21–36. doi:10.1006/nimg.2001.0786

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*, *15*, 20–25. doi:10.1016/0166-2236(92)90344-8

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., Ogar, J. M., Roher, J. D., Black, S., Boeve, B. F., Manes, F., Dronkers, N. F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B. L., Knopman, D. S., Hodges, J. R., Mesulam, M. M., & Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, *76*, 1006–1014. doi:10.1212/WNL.0b013e31821103e6

Guerreiro, R., Bras, J., Wojtas, A., Rademakers, R., Hardy, J., & Graff-Radford, N. (2014). Nonsense mutation in PRNP associated with clinical Alzheimer's disease. *Neurobiology of Aging*, *35*, e2613–2656. doi:10.1016/j.neurobiolaging.2014.05.013

Guerreiro, R. J., Lohmann, E., Brás, J. M., Gibbs, J. R., Rohrer, J. D., Gurunlian, N., Dursun, B., Bilgic, B., Hanagasi, H., Gurvit, H., Emre, M., Singleton, A., & Hardy, J. (2013). Using exome sequencing to reveal mutations in TREM2 presenting as a frontotemporal dementia–Like syndrome without bone involvement. *JAMA Neurology*, *70*, 78–84. doi:10.1001/jamaneurol.2013.579

Hecaen, H., & De Ajuriaguerra, J. (1954). Balint's syndrome (psychic paralysis of visual fixation) and its minor forms. *Brain*, *77*, 373–400. doi:10.1093/brain/77.3.373

Hof, P. R., Archin, N., Osmand, A. P., Dougherty, J. H., Wells, C., Bouras, C., & Morrison, J. H. (1993). Posterior cortical atrophy in Alzheimer's disease: Analysis of a new case and re-evaluation of a historical report. *Acta Neuropathologica*, *86*, 215–223. doi:10.1007/BF00304135

Hof, P. R., Vogt, B. A., Bouras, C., & Morrison, J. H. (1997). Atypical form of Alzheimer's disease with prominent posterior cortical atrophy: A review of lesion distribution and circuit disconnection in cortical visual pathways. *Vision Research*, *37*, 3609–3625. doi:10.1016/S0042-6989(96)00240-4

Höglinger, G. U., Melhem, N. M, Dickson, D. W., Sleiman, P. M., Wang, L. S., Klei, L., Rademakers, R., de Silva, R., Litvan, I., Riley, D. E., van Swieten, J. C., Heutink, P., Wszolek, Z. K., Uitti, R. J., Vandrovcova, J., Hurtig, H. I., Gross, R.G., Maetzler, W., Goldwurm, S., Tolosa, E., Borroni, B., Pastor, P., Cantwell, L. B., Han, M. R., Dillman, A., van der Brug, M. P., Gibbs, J. R., Cookson, M. R., Hernandez, D. G., Singleton, A. B., Farrer, M. J., Yu, C. E., Golbe, L. I., Revesz, T., Hardy, J., Lees, A. J., Devlin, B., Hakonarson, H., Müller, U., & Schellenberg, G. D. (2011). Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. *Nature Genetics*, *43*, 699–705. doi:10.1038/ng.859

Holmes, G. (1918). Disturbances of visual orientation. *The British Journal of Ophthalmology*, *2*, 449. doi:10.1136/bjo.2.9.449

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, *17*, 825–841. doi:10.1006/nimg.2002.1132

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*, 143–156. doi:10.1016/S1361-8415(01)00036-6

Kas, A., De Souza, L. C., Samri, D., Bartolomeo, P., Lacomblez, L., Kalafat, M., Migliaccio, R., Thiebaut de Schotten, M., Cohen, L., Dubois, B., Habert, M. O., & Sarazin, M. (2011). Neural correlates of cognitive impairment in posterior cortical atrophy. *Brain*, *134*, 1464–1478. doi:10.1093/brain/awr055

Kennedy, J., Lehmann, M., Sokolska, M. J., Archer, H., Warrington, E. K., Fox, N. C., & Crutch, S. J (2012). Visualizing the emergence of posterior cortical atrophy. *Neurocase*, *18*, 248–257. doi:10.1080/13554794.2011.588180

Kim, S. (2015). Cognitive rehabilitation for elderly people with early-stage Alzheimer's disease. *Journal Physical Therapeutics Sciences*, *27*, 543–546. doi:10.1589/jpts.27.543

Kinsbourne, M., & Warrington, E. K. (1962). A disorder of simultaneous form perception. *Brain*, *85*, 461–486. doi:10.1093/brain/85.3.461

Lanoiselee, H. M., Nicolas, G., Wallon, D., Rovelet-Lecrux, A., Lacour, M., Rousseau, S., Richard, A. C., Pasquier, F., Rollin-Sillaire, A., Martinaud, O., Quillard-Muraine, M., de la Sayette, V., Boutoleau-Bretonniere, C., Etcharry-Bouyx, F., Chauvire, V., Sarazin, M., le Ber, I., Epelbaum, S., Jonveaux, T., Rouaud, O., Ceccaldi, M., Félician, O., Godefroy, O., Formaglio, M., Croisile, B., Auriacombe, S., Chamard, L., VIncent, J. L., Sauvée, M. Marelli-Tosi, C., Gabelle, A., Ozsancak, C., Pariente, J., Paquet, C., Hannequin, D., & Campion, D. (2017). APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. *PLoS Medicine*, *14*, e1002270. doi:10.1371/journal.pmed.1002270

Lehmann, M., Barnes, J., Ridgway, G. R., Wattam-Bell, J., Warrington, E. K., Fox, N. C., & Crutch, S. J. (2012). Global gray matter changes in posterior cortical atrophy: A serial imaging study. *Alzheimer's & Dementia : the Journal of the Alzheimer's Association*, *8*, 502–512. doi:10.1016/j.jalz.2011.09.225

Lehmann, M., Barnes, J., Ridgway, G. R., Ryan, N. S., Warrington, E. K., Crutch, S. J., & Fox, N. C. (2011). Basic visual function and cortical thickness patterns in posterior cortical atrophy. *Cerebral Cortex (New York, N.Y. : 1991)*, *21*, 2122–2132. doi:10.1093/cercor/bhq287

Levine, D. N., Lee, J. M., & Fisher, C. M. (1993). The visual variant of Alzheimer's disease: A clinicopathologic case study. *Neurology*, *43*, 305–313. doi:10.1212/WNL.43.2.305

Luria, A. R. (1959). Disorders of "simultaneous perception" in a case of bilateral occipito-parietal brain injury. *Brain*, *82*, 437–449. doi:10.1093/brain/82.3.437

Macfarlane, R. G., Wroe, S. J., Collinge, J., Yousry, T. A., & Jager, H. R. (2007). Neuroimaging findings in human prion disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *78*, 664–670. doi:10.1136/jnnp.2006.094821

Magnin, E., Sylvestre, G., Lenoir, F., Dariel, E., Bonnet, L., Chopard, G., Tio, G., Hidalgo, J., Ferreira, S., Mertz, C., Binetruy, M., Chamard, L., Haffen, S., Ryff, I., Laurent, E., Moulin, T., Vandel, P., & Rumbach, L. (2013). Logopenic syndrome in posterior cortical atrophy. *Journal of Neurology*, *260*, 528–533. doi:10.1007/s00415-012-6671-7

Maguire, E. A., Frith, C. D., Burgess, N., Donnett, J. G., & O'Keefe, J. (1998). Knowing where things are parahippocampal involvement in encoding object locations in virtual large-scale space. *Journal of Cognitive Neuroscience*, *10*, 61–76. doi:10.1162/089892998563789

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 4398–4403. doi:10.1073/pnas.070039597

McMonagle, P., Deering, F., Berliner, Y., & Kertesz, A. (2006). The cognitive profile of posterior cortical atrophy. *Neurology*, *66*, 331–338. doi:10.1212/01.wnl.0000196477.78548.db

Mendez, M. F. (2001). Visuospatial deficits with preserved reading ability in a patient with posterior cortical atrophy. *Cortex*, *37*, 535–543. doi:10.1016/S0010-9452(08)70592-6

Mendez, M. F., & Cherrier, M. M. (1998). The evolution of alexia and simultanagnosia in posterior cortical atrophy. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *11*, 76–82.

Mendez, M. F., Ghajarania, M., & Perryman, K. M. (2002). Posterior cortical atrophy: Clinical characteristics and differences compared to Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *14*, 33–40. doi:10.1159/000058331

Mevorach, C., Shalev, L., Green, R. J., Chechlacz, M., Riddoch, M. J., & Humphreys, G. W. (2014). Hierarchical processing in Balint's syndrome: A failure of flexible top-down attention. *Frontiers in Human Neuroscience*, *8*, 113. doi:10.3389/fnhum.2014.00113

Migliaccio, R., Agosta, F., Rascovsky, K., Karydas, A., Bonasera, S., Rabinovici, G. D., Miller, B. L., & Gorno-Tempini, M. L. (2009). Clinical syndromes associated with posterior atrophy: Early age at onset AD spectrum. *Neurology*, *73*, 1571–1578. doi:10.1212/WNL.0b013e3181c0d427

Migliaccio, R., Agosta, F., Scola, E., Magnani, G., Cappa, S. F., Pagani, E., Canu, E., Comi, G., Falini, A., Gorno-Tempini, M. L., Bartolomeo, P., & Filippi, M. (2012). Ventral and dorsal visual streams in posterior cortical atrophy: A DT MRI study. *Neurobiology of Aging*, *33*, 2572–2584. doi:10.1016/j.neurobiolaging.2011.12.025

Mizuno, M., Sartori, G., Liccione, D., Battelli, L., & Campo, R. (1996). Progressive visual agnosia with posterior cortical atrophy. *Clinical Neurology and Neurosurgery*, *98*, 176–178. doi:10.1016/0303-8467(95)00091-7

Moreaud, O. (2003). Balint syndrome. *Archives of Neurology*, *60*, 1329–1331. doi:10.1001/archneur.60.9.1329

Oken, B. S., Storzbach, D. M., & Kaye, J. A. (1998). The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Archives of Neurology*, *55*, 1409–1415. doi:10.1001/archneur.55.11.1409

Ortner, M., & Kurz, A. (2015). [Posterior cortical atrophy: Pathology, diagnosis and treatment of a rare form of dementia]. *Der Nervenarzt*, *86*, 833–839. doi:10.1007/s00115-015-4265-1

Paloneva, J., Manninen, T., Christman, G., Hovanes, K., Mandelin, J., Adolfsson, R., Bianchin, M., Bird, T., Miranda, R., Salmaggi, A., Tranebjærg, L., Konttinen, Y., & Peltonen, L. (2002). Mutations in two genes encoding different subunits of a receptor signaling complex result in an identical disease phenotype. *American Journal of Human Genetics*, *71*, 656–662. doi:10.1086/342259

Perez, F. M., Tunkel, R. S., Lachmann, E. A., & Nagler, W. (1996). Balint's syndrome arising from bilateral posterior cortical atrophy or infarction: Rehabilitation strategies and their limitation. *Disability and Rehabilitation*, *18*, 300–304. doi:10.3109/09638289609165884

Perry, D. C., Lehmann, M., Yokoyama, J. S., Karydas, A., Lee, J. J., Coppola, G., Grinberg, L. T., Geschwind, D., Seeley, W. W., Miller, B. L., Rosen, H., & Rabinovich, G. (2013). Progranulin mutations as risk factors for Alzheimer disease. *JAMA Neurology*, *70*, 774–778. doi:10.1001/2013.jamaneurol.393

Pievani, M., Filippini, N., van den Heuvel, M. P., Cappa, S. F., & Frisoni, G. B. (2014). Brain connectivity in neurodegenerative diseases–From phenotype to proteinopathy. *Nature Reviews Neurology*, *10*, 620–633. doi:10.1038/nrneurol.2014.178

Price, C. J., & Humphreys, G. W. (1995). Contrasting effects of letter-spacing in alexia: Further evidence that different strategies generate word length effects in reading. *The Quarterly Journal of Experimental Psychology. A, Human Experimental Psychology*, *48*, 573–597. doi:10.1080/14640749508401406

Roca, M., Gleichgerrcht, E., Torralva, T., & Manes, F. (2010). Cognitive rehabilitation in posterior cortical atrophy. *Neuropsychological Rehabilitation*, *20*, 528–540. doi:10.1080/09602011003597408

Rosenbloom, M. H., Alkalay, A., Agarwal, N., Baker, S. L., O'Neil, J. P., Janabi, M., Yen, I. V., Growdon, M., Jang, J., Madison, C., Mormino, E. C., Rosen, H. J., Gorno-Tempini, M. L., Weiner, M. W., Miller, B. L., Jagust, W. J., & Rabinovici, G. D. (2011). Distinct clinical and metabolic deficits in PCA and AD are not related to amyloid distribution. *Neurology*, *76*, 1789–1796. doi:10.1212/WNL.0b013e31821cccad

Ross, S. J., Graham, N., Stuart-Green, L., Prins, M., Xuereb, J., Patterson, K., & Hodges, J. R. (1996). Progressive biparietal atrophy: An atypical presentation of Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *61*, 388–395. doi:10.1136/jnnp.61.4.388

Ryan, N. S., Shakespeare, T. J., Lehmann, M., Keihaninejad, S., Nicholas, J. M., Leung, K. K., Fox, N. C., & Crutch, S. J. (2014). Motor features in posterior cortical atrophy and their imaging correlates. *Neurobiology of Aging*, *35*, 2845–2857. doi:10.1016/j.neurobiolaging.2014.05.028

Schmidtke, K., Hull, M., & Talazko, J. (2005). Posterior cortical atrophy: Variant of Alzheimer's disease? A case series with PET findings. *Journal of Neurology*, *252*, 27–35. doi:10.1007/s00415-005-0594-5

Schott, J. M., Crutch, S. J., Carrasquillo, M. M., Uphill, J., Shakespeare, T. J., Ryan, N. S., Yong, K. X., Lehmann, M., Ertekin-Taner, N., Graff-Radford, N. R., Boeve, B. F., Murray, M. E., Khan, Q. U., Petersen, R. C., Dickson, D. W., Knopman, D. S., Rabinovici, G. D., Miller, B. L., González, A. S., Gil-Néciga, E., Snowden, J. S., Harris, J, Pickering-Brown, S. M., Louwersheimer, E., van der Flier W. M., Scheltens, P., Pijnenburg, Y. A., Galasko, D., Sarazin, M., Dubois, B., Magnin, E., Galimberti, D., Scarpini, E., Cappa, S. F., Hodges, J. R., Halliday, G. M., Bartley, L., Carrillo, M. C., Bras, J. T., Hardy, J., Rossor, M. N., Collinge, J., Fox, N. C., & Mead, S. (2016). Genetic risk factors for the posterior cortical atrophy variant of Alzheimer's disease. *Alzheimer's & Dementia : the Journal of the Alzheimer's Association*, *12*, 862–871. doi:10.1016/j.jalz.2016.01.010

Schott, J. M., Ridha, B. H., Crutch, S. J., Healy, D. G., Uphill, J. B., Warrington, E. K., Rossor, M. N., & Fox, N. C. (2006). Apolipoprotein e genotype modifies the phenotype of Alzheimer disease. *Archives of Neurology*, *63*, 155–156. doi:10.1001/archneur.63.1.155

Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron*, *62*, 42–52. doi:10.1016/j.neuron.2009.03.024

Shakespeare, T. J., Yong, K. X., Frost, C., Kim, L. G., Warrington, E. K., & Crutch, S. J. (2013). *Scene perception in posterior cortical atrophy: Categorization, description and fixation patterns*.

Sitek, E. J., Narozanska, E., Peplonska, B., Filipek, S., Barczak, A., Styczyńska, M., Mlynarczyk, K, Brockhuis, B., Portelius, E., Religa, D., Barcikowska, M., Slawek, J., & Żekanowski, C. (2013). A patient with posterior cortical atrophy possesses a novel mutation in the presenilin 1 gene. *PLoS One*, *8*, e61074. doi:10.1371/journal.pone.0061074

Smith, S. M., De Stefano, N., Jenkinson, M., & Matthews, P. M. (2001). Normalized accurate measurement of longitudinal brain change. *Journal of Computer Assisted Tomography*, *25*, 466–475. doi:10.1097/00004728-200105000-00022

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23*, S208–219. doi:10.1016/j.neuroimage.2004.07.051

Snowden, J. S., Stopford, C. L., Julien, C. L., Thompson, J. C., Davidson, Y., Gibbons, L., Pritchard, A., Lendon, C. L., Richardson, A. M., Varma, A., Neary, D., & Mann, D. M. (2007). Cognitive phenotypes in Alzheimer's disease and genetic risk. *Cortex*, *43*, 835–845. doi:10.1016/S0010-9452(08)70683-X

Solomon, I. H., Schepker, J. A., & Harris, D. A. (2010). Prion neurotoxicity: Insights from prion protein mutants. *Current Issues in Molecular Biology*, *12*, 51–61.

Stark, M. E., Grafman, J., & Fertig, E. (1997). A restricted 'spotlight' of attention in visual object recognition. *Neuropsychologia*, *35*, 1233–1249. doi:10.1016/S0028-3932(97)00049-3

Suarez-Gonzalez, A., Henley, S. M., Walton, J., & Crutch, S. J. (2015). Posterior cortical atrophy: An atypical variant of Alzheimer disease. *The Psychiatric Clinics of North America*, *38*, 211–220. doi:10.1016/j.psc.2015.01.009

Tang-Wai, D., & Mapstone, M. (2006). What are we seeing? Is posterior cortical atrophy just Alzheimer disease? *Neurology*, *66*, 300–301. doi:10.1212/01.wnl.0000202093.81603.d8

Tang-Wai, D. F., Graff-Radford, N. R., Boeve, B. F., Dickson, D. W., Parisi, J. E., Crook, R., Caselli, R. J., Knopman, D. S., & Petersen, R. C. (2004). Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology*, *63*, 1168–1174. doi:10.1212/01.WNL.0000140289.18472.15

Tang-Wai, D. F., Josephs, K. A., Boeve, B. F., Dickson, D. W., Parisi, J. E., & Petersen, R. C. (2003). Pathologically confirmed corticobasal degeneration presenting with visuospatial dysfunction. *Neurology*, *61*, 1134–1135. doi:10.1212/01.WNL.0000086814.35352.B3

Tremolizzo, L., Susani, E., Mapelli, C., Isella, V., Bertola, F., Ferrarese, C., & Appollonio, I. (2015). First report of PSEN2 mutation presenting as posterior cortical atrophy. *Alzheimer Disease and Associated Disorders*, *29*, 249–251. doi:10.1097/WAD.0000000000000052

van der Flier, W. M., Schoonenboom, S. N., Pijnenburg, Y. A., Fox, N. C., & Scheltens, P. (2006). The effect of APOE genotype on clinical phenotype in Alzheimer disease. *Neurology*, *67*, 526–527. doi:10.1212/01.wnl.0000228222.17111.2a

Videaud, H., Torny, F., Cartz-Piver, L., Deschamps-Vergara, N., & Couratier, P. (2012). [Impact of drug-free care in posterior cortical atrophy: Preliminary experience with a psycho-educative program]. *Revue Neurologique*, *168*, 861–867. doi:10.1016/j.neurol.2011.10.013

Wadia, P. M., & Lang, A. E. (2007). The many faces of corticobasal degeneration. *Parkinsonism & Related Disorders*, *13*, S336–340. doi:10.1016/S1353-8020(08)70027-0

Whitwell, J. L., Graff-Radford, J., Singh, T. D., Drubach, D. A., Senjem, M. L., Spychalla, A. J., Tosakulwong, N., Lowe, V. J., & Josephs, K. A. (2017). 18F-FDG PET in posterior cortical atrophy and dementia with lewy bodies. *Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine*, *58*, 632–638. doi:10.2967/jnumed.116.179903

Whitwell, J. L., Jack, C. R. Jr., Kantarci, K., Weigand, S. D., Boeve, B. F., Knopman, D. S., Drubach, D. A., Tang-Wai, D. F., Petersen, R. C., & Josephs, K. A. (2007). Imaging correlates of posterior cortical atrophy. *Neurobiology of Aging*, *28*, 1051–1061. doi:10.1016/j.neurobiolaging.2006.05.026

Wojtas, A., Heggeli, K. A., Finch, N., Baker, M., Dejesus-Hernandez, M., Younkin, S. G., Dickson, D. W., Graff-Radford, N. R., & Rademakers, R. (2012). C9ORF72 repeat expansions and other FTD gene mutations in a clinical AD patient series from Mayo Clinic. *American Journal of Neurodegenerative Disease*, *1*, 107–118.

Yong, K. X., Rajdev, K., Shakespeare, T. J., Leff, A. P., & Crutch, S. J. (2015). Facilitating text reading in posterior cortical atrophy. *Neurology*, *85*, 339–348. doi:10.1212/WNL.0000000000001782

Yong, K. X., Shakespeare, T. J., Cash, D., Henley, S. M., Nicholas, J. M., Ridgway, G. R., Golden, H. L., Warrington, E. K., Carton, A. M., Kaski, D., Schott, J. M., Warren, J. D., & Crutch, S. J. (2014). Prominent effects and neural correlates of visual crowding in a neurodegenerative disease population. *Brain*, *137*, 3284–3299. doi:10.1093/brain/awu293

Zakzanis, K. K., & Boulos, M. I. (2001). Posterior cortical atrophy. *Neurologist*, *7*, 341–349. doi:10.1097/00127893-200111000-00003

Zhang, C. C., Xing, A., Tan, M. S., Tan, L., & Yu, J. T. (2016). The role of MAPT in neurodegenerative diseases: Genetics, mechanisms and therapy. *Molecular Neurobiology*, *53*, 4893–4904. doi:10.1007/s12035-015-9415-8