UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

DIPARTIMENTO DI CHIRURGIA E MEDICINA TRASLAZIONALE

Scuola unica di Dottorato di Ricerca
Dottorato di Ricerca in Neuroscienze – XXVII Ciclo

PHENOTYPIC AND METABOLIC IMAGING CHARACTERIZATION OF POSTERIOR COGNITIVE DYSFUNCTIONS

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Anno Accademico 2013-2014

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Abstract

In the last decade, the differential diagnosis of dementia has become very challenging. Different clinical syndromes can in fact be associated with the same underlying pathology and different pathologies can be associated with the same clinical phenotype, making it very difficult to distinguish them *in vivo.* In the present project we focused on the differential diagnosis of cognitive syndromes affecting, at onset, posterior cerebral networks with particular reference to PCA, CBD and LBD.

We enrolled 70 consecutive patients, referred to the Neuropsychology laboratory of the Neurology Department of S. Gerardo Hospital (Monza, IT), with a cognitive profile characterized primarily by impairment of posterior cognitive functions and a relative spare of language and memory functions. Each patient underwent, an extensive neuropsychological battery, a neurological examination and a [18F]FDG-PET.

Applying Principal Components Analysis to all the tasks of posterior cognitive functions and correlating the results with cerebral hypometabolism, we highlighted three syndromes: an Apperceptive syndrome associated with a prevailing right posterior hypometabolism; a Gerstman-Apraxia syndrome coupled with a left ventro-dorsal hypometabolism and an Associative syndrome correlated with a left ventral hypometabolism;

In our opinion, these syndromes express tasks and functions localization more than dorsal and ventral visual pathways neuro-anatomy, as previously reported. No clear association between one of the syndromes and the clinical diagnosis according to current diagnostic criteria was found; these syndrome can present isolated or in association.

Although this study confirms the difficulties in differential diagnosis between the cognitive syndromes with posterior onset, it improves knowledge about the nature of their cognitive impairment and it can be a first step to the identification of cognitive markers or patterns linked to neuropathology.

1. Introduction

In the last decade, the differential diagnosis of dementia has become very challenging. Advances in the clinical, neuropathological, imaging and genetic characterization of dementia syndromes have increased our appreciation of the complexities of neurodegeneration and the phenotypic variability of several disorders. Different clinical syndromes can in fact be associated with the same underlying pathology and different pathologies can be associated with the same clinical phenotype, making it very difficult to distinguish them *in vivo.*

In the present project we focused on the differential diagnosis of cognitive syndromes affecting, at onset, posterior cerebral networks with particular reference to PCA, CBD and LBD.

The expression "posterior cortical atrophy" (PCA) was first applied to five patients with progressive dementia initially presenting with higher order visuospatial dysfunction and relative preservation of memory, language and executive abilities (Benson et al., 1988). Pathological studies have shown that Alzheimer's disease (AD) is the most common underlying cause of PCA (Hof et al., 1989; Galton et al., 2000; Renner et al., 2004; Tang-Wai et al., 2004; Alladi et al., 2007); however, there are several cases of PCA that are attributable to other aetiologies such as corticobasal degeneration, dementia with Lewy bodies, prion disease and subcortical gliosis (Victoroff et al., 1994; Renner et al., 2004; Tang-Wai et al., 2003). For instance, in the largest series published to date, Renner at al. (2004) reported pathological data of 21 PCA patients, of whom 14 had AD (one with Parkinson's disease associated), two AD-Lewy bodies variant, one Lewy bodies disease with coexisting subcortical gliosis, two corticobasal degeneration (CBD) and two prion-associated diseases (Renner et al., 2004).

These findings show that there is an important cognitive and clinical overlap between these syndromes and it s not easy make differential diagnosis only on the basis of cognitive profile. In the study reported earlier (Renner et al., 2004) patients demonstrated various combinations of posterior cognitive symptoms despite their pathological diagnosis (ocular apraxia, optic ataxia, simultanagnosia, acalculia, agraphia, finger agnosia, and left-right disorientation) while constructional, dressing, and ideomotor apraxia were common. No post-hoc direct comparisons between pathologies were conducted.

In another study, McMonagle et al., (2006) described 19 clinically diagnosed PCA; although some patients presented characteristics (spontaneous parkinsonism) of Lewy bodies dementia (LBD) and of CBD (alien limb phenomena or prominently asymmetric limb apraxia) all individuals had identical cognitive deficits (McMonagle et al., 2006).

But even the presence of motor symptoms does not help diagnosis. In a recent study, Ryan and colleagues (2014) made a comparison between PCA with motor symptoms and PCA without motor symptoms (pure PCA) and they found out that the two groups overlapped in the neuropsychological tests (Ryan et al., 2014).

This clinical overlap is evident also in the current diagnostic criteria for PCA, CBD and LBD.

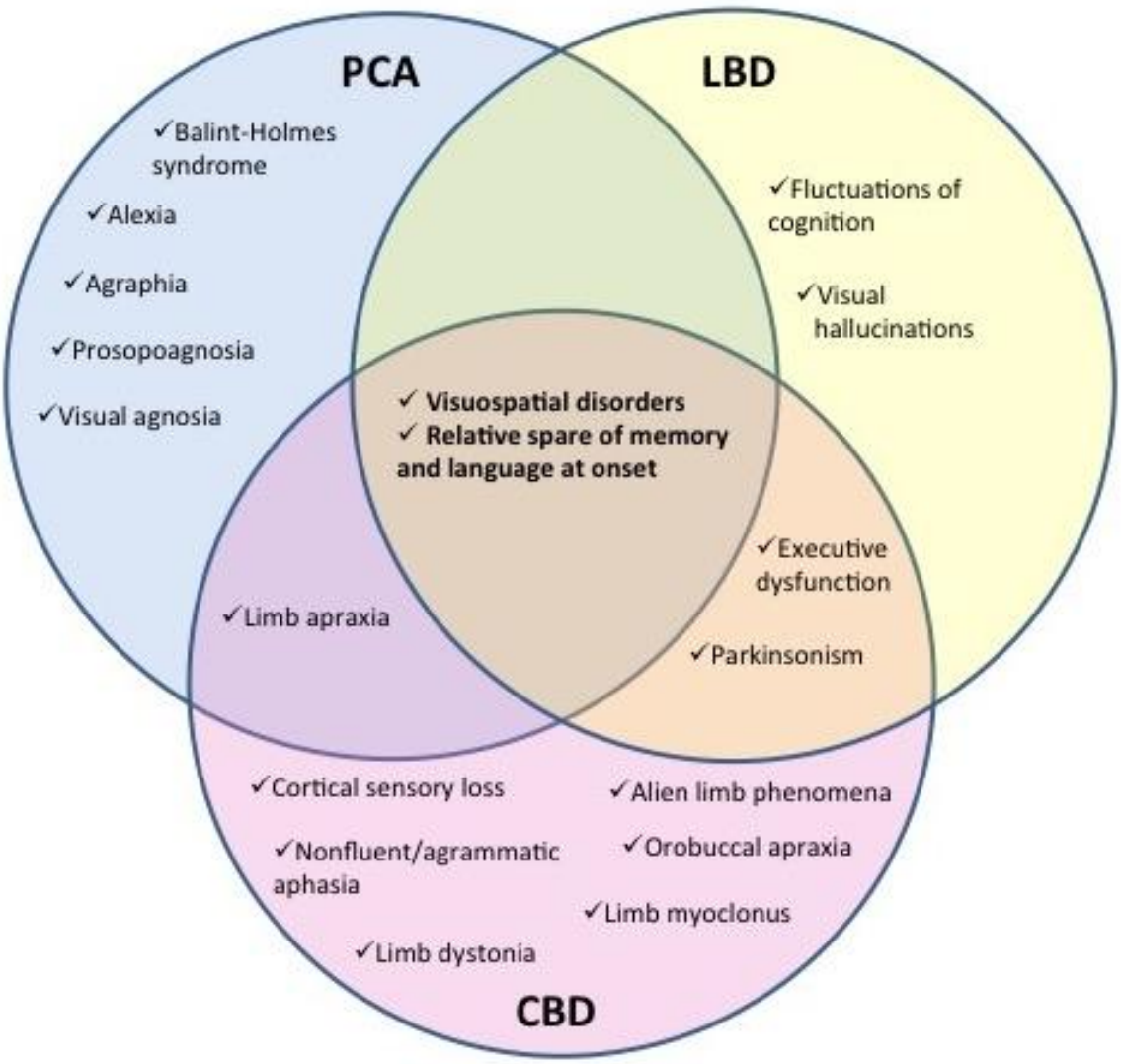

Figure 1. Overlap in diagnostic criteria of PCA, CBD and LBD.

Visuospatial disorders and posterior brain atrophy or hypometabolism can be present in all thethree syndromes at onset and other symptoms (e.g. limb apraxia) are shared by two of them.

These data show clearly the difficulties in distinguishing between these syndromes *in vivo*, especially in the first phases of illness and by considering only cognitive aspects, so the aim of the present project is to characterize these clinical syndromes with an exclusively data-driven approach.

1.1. Corticobasal degeneration

Corticobasal degeneration (CBD) is a sporadic neurodegenerative disease belonging to a group of disorders called tauopathies, characterized by asymmetrical onset of various types of motor dysfunction, including akinesia and rigidity, dystonia, myoclonus and postural instability; also, limb apraxia, cortical sensory impairment, alien limb syndrome and visuoconstructional deficits may constitute the presenting symptoms.

CBD was first clearly described in 1968 by Rebeiz and colleagues in three patients, who presented with progressive asymmetric limb rigidity and bradykinesia combined with higher cortical disorders, such as apraxia (Rebeiz et al., 1968).

As understanding of this complex disease has developed since Rebeiz's first description, it has become clear that the corticobasal spectrum involves a clinical syndrome and a pathological entity that only sometimes overlap. Because of this, the clinical diagnosis is now labeled as 'corticobasal syndrome' (CBS) while the term CBD is reserved for pathologically confirmed diagnoses (Doran et al., 2003). It is now in fact recognized that CBD (i.e. the pathological condition) may have several different clinical presentations aside from CBS that can change even in a single individual over time (Boeve et al., 2011).

1.1.1. Epidemiology

CBD is a rare neurodegenerative disease and the estimated incidence rate is 0.62 to 0.92 per 100000 per year (Togasaki and Tanner, 2000).

The onset of symptoms is typically in the sixth and seventh decades of life (Riley et al., 1990), with a range of ages at onset of 45-75 (Josephs et al., 2006), while mean disease duration in a pathology series considered by Wenning and colleagues was 7.9 years (Wenning et al., 1998). Also, men and women are equally affected by CBD (Josephs et al., 2006).

1.1.2. Pathology and genetics

CBD is characterized by the accumulation of insoluble hyper-phosphorylated 4R-tau protein in the form of paired helical filaments (PHFs) in the brain (Hernàndez and Avila, 2007). Although no tau mutations have been found in CBD, there is evidence of the involvement of the tau gene. An analysis of tau polymorphism in CBD, in fact, has pointed out that the

occurrence of H1 tau haplotypes and H1/H1 genotypes is significantly higher in patients with CBD compared to controls (Houlden et al., 2001).

The Office of Rare Diseases published neuropathological criteria for CBD in 2002 (Dickson et al., 2002). The criteria emphasize the presence of tau-immunoreactive lesions in addition to the presence of ballooned achromatic neurons, cortical atrophy and nigral degeneration.

Given the subtle nature of focal cortical atrophy that is typical of CBD, the gross findings give supportive information but are not crucial to the diagnosis, which is basically based on histopathologic findings (Dickson et al., 2002). However, the atrophy may be asymmetric and concentrates in the parietal regions and basal ganglia, insula and frontal lobes (Schofield et al., 2005; Boxer et al., 2006). Substantia nigra, striatum and to the lesser degree the amygdala are also involved (Dickson et al., 2002).

1.1.3. Clinical features

Initial reports of CBD described hallmark clinical features including asymmetric disease, parkinsonism, tremor, limb dystonia, myoclonus, alien limb phenomena, cortical sensory loss and apraxia.

But as previously declared, over the past 40 years it has become clear that the clinical syndrome of CBS does not correlate reliably with CBD (Armstrong and Lang, 2011). CBS can in fact be the clinical phenotype of other neuropathological disorders, including Parkinson's disease (PD) (Hughes et al., 2002), Progressive supranuclear palsy (PSP), Pick's disease (PiD), Alzheimer's disease (AD), frontotemporal dementia (FTD) and Creutzfeldt-Jakob disease (CJD) (Boeve et al., 1999; Josephs et al., 2006). On the other hand, CBD can present clinically as the CBS, dementia, a progressive aphasia syndrome, frontotemporal dementia, posterior cortical atrophy and progressive speech apraxia (Boeve et al., 2003).

Furthermore, while previous clinical criteria excluded 'early dementia' to increase diagnostic specificity, now dementia is recognized as a presenting and predominant feature in many cases of CBD (Armstrong et al., 2013).

In 2013 Armstrong and colleagues published a review of 103 articles including clinical features of post-mortem confirmed CBD cases, and 106 brain bank non-overlapping CBD cases (Armstrong et al., 2013). They distinguished between motor features (Table 1) and higher cortical features (Table 2), plus other symptoms (Table 3), and outlined which features were developed at presentation and which ones during the course of the disease.

Motor features

FEATURE	At onset, n (%)	Entire course, n (%)
Limb rigidity	65/114 (57)	153/180 (85)
Bradykinesia or clumsy limb	53/111 (48)	126/165 (76)
Postural instability	20/49 (41)	73/94 (78)
Falls	27/76 (36)	83/111 (75)
Abnormal gait	30/92 (33)	102/140 (73)
Axial rigidity	18/67 (27)	68/98 (69)
Tremor	17/38 (20)	50/127 (39)
Limb dystonia	18/91 (20)	47/123 (38)
Myoclonus	14/94 (15)	34/128 (27)

Table 1. Frequency of motor features in available brain banks and studies with ≥5 pathologically confirmed corticobasal degeneration (Armstrong et al., 2013).

The motor features manifest with asymmetric onset of levodopa-resistant parkinsonism, dystonia and myoclonus.

Higher cortical features

FEATURE	At onset, n (%)	Entire course, n (%)
Cognitive impairment (general)	59/114 (52)	123/175 (70)
Behavioral changes	52/113 (46)	82/150 (55)
Limb apraxia	46/102 (45)	81/142 (57)
Aphasia	40/101 (40)	80/155 (52)
Depression	21/80 (26)	42/82 (51)
Cortical sensory loss	20/81 (25)	29/107 (27)
Alien limb	20/90 (22)	24/81 (30)

Table 2. Frequency of higher cortical features in available brain banks and studies with ≥5 pathologically confirmed corticobasal degeneration (Armstrong et al., 2013)

Limb apraxia is core to all diagnostic criteria. Apraxia has been defined as the inability to carry out learned, skilled motor acts despite preserved motor and sensory systems, coordination, comprehension, and cooperation (Heilman et al., 2003). Damage to the conceptual system of the actions produces ideational apraxia, while damage to the production system results in ideomotor and limb-kinetic apraxia. Patients with CBD usually have asymmetric ideomotor and limb-kinetic apraxia mainly characterized by spatial, temporal and sequencing errors that reflect disruption of the production system (Peigneux et al., 2001).
Specifically, ideomotor apraxia is an impairment in timing, sequencing and spatially organizing gestures and is typically demonstrated when a patient is asked verbally to perform a gesture with a limb. Most authors also include the inability to imitate another person's gesture, to perform the appropriate action in response to a visually presented object, or to

carry out a movement using the actual object (Goldman Gross and Grossman, 2008). Apraxia's anatomical basis lies mostly in the damage to the left frontal and parietal cortex as well as to the white matter connections between these areas. Other regions involved in the praxis are the anterior part of the corpus callosum and basal ganglia via connections to the frontal and parietal cortex (Goldman Gross and Grossman, 2008). Frontal and ganglionic lesions determine the so-called limb-kinetic apraxia, which affects the limb contralateral to the lesion side and is characterized by loss of finger and hand dexterity. In limb-kinetic apraxia all movements are slow coarse and awkward, frequently with other movement intrusions (Belfor et al., 2006). In more advanced cases of CBD patients developed severe apraxia including ideomotor and ideational components, which correlated with global cognitive impairment and it likely results from progression of the disease in to the parietal lobes or diffuse cortical damage (Leiguarda et al., 1994).

Oral apraxia and 'apraxia of eyelid opening' were also included in some case reports. Frasson observed oral impairment in 2/3 of patients with left hemisphere damage (Frasson et al., 1998). Cortical sensory deficits may present as agraphesthesia, astereoagnosia, or extinction to double simultaneous stimulation (Belfor et al., 2006). Alien limb phenomena, as reported in table 2, were described in 30% of compiled CBD cases (Armstrong et al., 2013).

Language impairments are now recognized as a frequent and commonly presenting feature of CBD. Aphasia was reported in 52% of cases over the disease course (table 2) and tends to be mostly non-fluent (Graham et al., 2003). It's associated with left frontal and parietal cortical damage and subcortical white matter and corpus callosum abnormalities (Frattali et al., 2000). 70% of patients had cognitive impairment during the course of the disease. Neuropsychological testing in one study revealed that patients with CBD had difficulties with learning tasks, word fluency, verbal comprehension, perceptual organization and cognitive flexibility (Vanvoorst et al., 2008). Another study outlined impairments in executive, language and visuospatial and constructional domains with relatively preserved episodic memory (Murray et al., 2007). Deficits in visuospatial tasks are frequent, with involvement of frontoparietal regions (Frasson et al., 1998). Another cognitive feature of CBD is acalculia (Belfor et al., 2006).

Behavioral changes and executive dysfunction are frequent in CBD (Grimes et al., 1999). Symptoms include apathy, bizarre or antisocial behavior, personality changes, irritability, disinhibition, and hypersexuality. Clinical depression was also described in 51% of cases.

Other features

FEATURE	At onset, n (%)	Entire course, n (%)
Abnormal eye movements	29/88 (33)	90/150 (60)
Hyperreflexia	17/57 (30)	58/116 (50)
Speech changes	18/77 (23)	59/112 (53)

Table 3. Frequency of other features in available brain banks and studies with ≥5 pathologically confirmed corticobasal degeneration (Armstrong et al., 2013)

Speech abnormalities were described in 53% of cases (table 3). Problems with speech are likely due to dysarthria (Graham et al., 2003).

Eye movement abnormalities are often described, but details are rarely provided and terminology is often ambiguous. Initially, oculomotor impairment may present as an ocular gaze apraxia or full Balint's syndrome, and may evolve into a supranuclear gaze palsy. Studies of patients with CBS described an increase in the latency of saccade initiation with relatively preserved saccade velocity (Vidailhet and Rivaud-Péchoux, 2000; Rivaud-Pèchoux, et al., 2000).

1.1.4. Neuroimaging

Morphological imaging: magnetic resonance imaging (MRI)

The exact role of MRI in diagnosing CBD is at the moment still evolving, but some findings can be supportive of the diagnosis of CBS, such as asymmetrical cortical and cerebral peduncle atrophy, with the more prominent atrophy contralateral to the side most severely affected clinically. Atrophy in the posterior frontal and parietal lobes is much more severe than in the other lobes. Atrophy in the occipital lobe is rarely observed. Atrophy in the temporal and anterobasal frontal lobes is a frequent finding, but is commonly less severe than in the posterior frontal and parietal lobes. Basal ganglia changes reported to date have been variable (Koyama et al., 2007).

In pathologically proven CBD, MRI scans show diffuse bilateral atrophy with variable frontoparietal involvement, controlateral to the first and most affected side (Gibb et al., 1989). Yamauchi et al. (Yamauchi et al., 1998) also reported atrophy of the middle part of the corpus callosum. Later, MRI studies confirmed asymmetric cortical atrophy of frontoparietal regions. Basal ganglia atrophy has also been described (Josephs et al., 2008). When CBS patients with CBD pathology are compared to CBS patients with other neurodegenerative pathologies, no features are found to be specific for CBD at MRI (Josephs et al., 2004).

Morphological imaging: diffusion tension imaging (DTI)

By assessing the directional diffusion of water molecules, diffusion-weighted MRI permits the visualization of the degeneration of specific white matter tracts. The study of Whitwell and colleagues about the application of DTI in nine patients with a clinical diagnosis of CBS has shown a peculiar pattern of degeneration. The most striking regions of reduced signal (i.e. of major degeneration) have been observed in supratentorial regions, including the body of corpus callosum, white matter of the premotor, prefrontal and motor cortices and the middle cingulate bundle. These abnormalities were asymmetrical, with greater involvement in the most involved hemisphere. Other affected regions have been observed in the parietal lobes in the pons and cerebellum of both hemispheres (Whitwell et al., 2014).

Functional imaging: single positron emission computed tomography (Spect) and positron emission tomography (PET)

CBS SPECT with [99mTc]ethyl cysteinate dimer (ECD) shows asymmetric hypoperfusion in the frontotemporal areas, in the basal ganglia, and in the thalamus. The side of the hypoperfusion is commonly contralateral to the clinically most severely affected side (Figure 2) (Koyama et al., 2007).

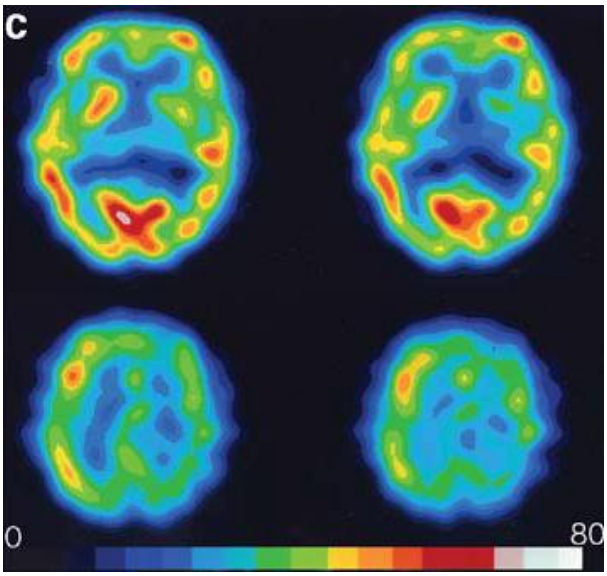

Figure 2. ECD-SPECT images show decreased perfusion in the left frontoparietal lobes and in the left basal ganglia (Koyama et al., 2007).

Koyama and colleagues also note that asymmetric hypoperfusion can be more easily detected than asymmetric atrophy or hyperintensity, sustaining the larger sensitivity of SPECT in detecting asymmetry. On the other hand, they couldn't find the reason of the moderate hypoperfusion in the basal ganglia and thalamus, whereas no signal or volume change could be detected on MR imaging in the same regions. Positron emission tomography imaging with [18 F]-fluorodeoxyglucose (FDG) shows asymmetrical patterns of glucose metabolism (Klaffke et al., 2006; Eckert et al., 2005). In a study of Juh and colleagues, the areas of greater hypometabolism in CBD patients were the parietal and the frontal cortex, the cingulate cortex, the precentral gyrus, and the thalamus (Juh et al., 2005) (Figure 3).

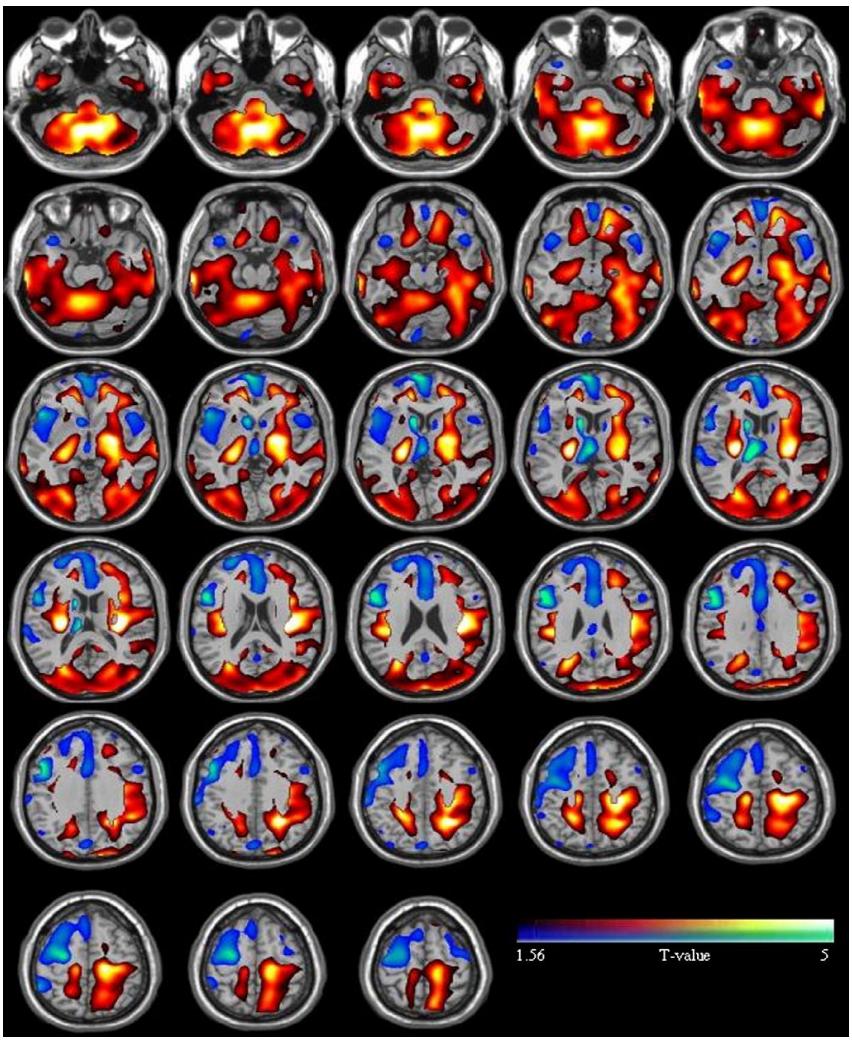

Figure 3. Detailed templates (whole brain) of abnormal asymmetric glucose metabolism in a patient with CBD (PET image) (Eckert et al., 2005).

1.1.5. Clinical diagnostic criteria

Various clinical diagnostic criteria have been proposed through the years (Kumar et al., 1998; Lang et al., 1994; Riley et al., 1990; Litvan et al.,1998), but despite the large number of studies, the pathology of CBD is predicted ante mortem in only 25 to 56% of cases (Boeve et al., 1999; Boeve, 2005; Grimes et al.,1999; Murray et al., 2007). An important limit is the fact that they reflect CBS alone and not the more recently recognized behavioral presentations of CBD (Armstrong et al., 2013). In 2013 Armstrong and colleagues, as previously described, proposed two new sets of criteria (Armstrong et al., 2013) (Table 4 and 5). A more specific one for probable CBD which attempts to maximize the chance of diagnosing classic CBD without contamination from other pathologies; and a broader set for possible CBD that has less specificity for CBD pathology while still representing probable tau-based pathology. This distinction has been necessary, as the great clinicopathologic heterogeneity and the varying phenotypes of CBD confound the development of specific criteria. Specialist consensus among behavioral neurology, neuropsychology, and movement disorders specialists, brain bank cases and a critical literature review have been used to develop these new diagnostic criteria (Armstrong et al., 2013).

In particular, Armstrong and colleagues in their sets of criteria, described four clinical phenotypes of CBD: 1) corticobasal syndrome (CBS), 2) frontal behavioral-spatial syndrome (FBS), 3) nonfluent/agrammatic variant of primary progressive aphasia (NAV), and 4) progressive supranuclear palsy syndrome (PSP) (Armstrong et al., 2013) (Table 4).

Both sets of criteria require insidious onset and gradual progression with symptom duration of at least 1 year. Age at onset ≥50 years is required for probable-CBD, given that this will identify 98% of patients with CBD and exclude pathologies with younger age at onset. No age minimum is set for possible-CBD. In addition, a family history (>1 relative) of a similar neurodegenerative disease is an exclusion criterion for probable-CBD but not for possible-CBD (Table 5).

Features suggestive of idiopathic PD are exclusion criteria for both diagnostic criteria, as are hallucinations, which are much more suggestive of PD than CBD.

Prominent dysautonomia and cerebellar signs are thought to be more suggestive of multiple system atrophy than CBD and are exclusion criteria based on consensus.

Mutations known to be associated with AD are also exclusion criteria. Similarly, imaging studies suggestive of other pathologies are exclusion criteria for CBD diagnoses, but CBD-supportive imaging is not included as a criterion, given the need for further validation.

SYNDROME	FEATURE
Probable corticobasal syndrome	Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) oral or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) oral or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena
Frontal behavioral-spatial syndrome	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia	Effortful, agrammatic speech plus at least one of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

Table 4. Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration (Armstrong et al., 2013).

	Probable CBD	Possible CBD
Presentation	Insidious onset and gradual progression	Insidious onset and gradual progression
Minimum duration of symptoms, years	1	1
Age at onset, y	≥50	No minimum
Family history (2 or more relatives)	Exclusion	Permitted
Permitted phenotypes (see table 5 for criteria)	1) Probable CBS or 2) FBS or NAV plus at least one CBS feature (a-f)	1) Possible CBS or 2) FBS or NAV plus at least one CBS feature (b-f)
Genetic mutation affecting tau (e.g., MAPT)	Exclusion	Permitted

Table 5. Diagnostic criteria for corticobasal degeneration (Armstrong et al., 2013).
Abbreviation: CBD = corticobasal degeneration; CBS = corticobasal syndrome; FBS = frontal behavioral-spatial syndrome; NAV = nonfluent/agrammatic variant of primary progressive aphasia

1.1.6. Management

Unfortunately, at present, the etiology and pathogenesis of CBD are unknown and no definitive disease-modifying interventions against CBD have been identified. In the future, treatments designed to interfere with the various processes underlying the pathological aggregation of phosphorylated 4R-tau may effectively slow down the inexorable progression of the disease. Until then, treatment of CBD is limited to symptomatic interventions and attempts to improve function, concluding with palliative care (Armstrong and Lang, 2011).

A number of therapeutical approaches, other than pharmacological, are also important in CBD: physical therapy was reported to provide benefit (Boeve et al., 2008), while the potential of speech and language therapy for CBD-related aphasia and speech apraxia remains unclear.

1.2. Posterior cortical atrophy

Posterior cortical atrophy (PCA) is a neurodegenerative condition characterised by a progressive, often dramatic and relatively selective decline in visual-processing skills and other functions subserved by parietal, occipital, and occipito-temporal regions (Crutch et al., 2012).

The term posterior cortical atrophy was firstly used by Benson et al. in 1988 to describe five patients with progressive visuospatial impairment, but relatively preserved memory, insight and judgment (Benson et al., 1988). Many additional cases have since been described and the most common features are alexia out of proportion to other language impairments, Balint-Holmes syndrome (simultanagnosia, optic ataxia and ocular apraxia), visual agnosia, which is primarily apperceptive, transcortical sensory aphasia, apraxia, and some or all of the elements of Gerstmann syndrome (agraphia, acalculia, finger agnosia, right-left disorientation) (Mendez, 2004; Renner et al., 2004; Tang-Wai et al., 2004).

Classically, PCA has also been classified into two subtypes based on anatomical location of the lesion: dorsal, which presents with Balint's syndrome and apraxia, and ventral, which presents with alexia and visual agnosia. Both have preserved memory and insight until late in the illness progression (Aharon-Peretz et al., 1999; Benson et al., 1988; Goethals and Santens, 2001; Mendez et al., 2002; McMonagle et al., 2006).

1.2.1. Epidemiology

The prevalence and incidence of PCA are presently unknown. Furthermore, every value is easily underestimated because of lack of validated criteria of diagnosis. However, Snowden and colleagues (2007) noted that, of 523 patients with Alzheimer's disease, 5% had a predominant visual symptomatology, compatible with PCA (Snowden et al., 2007).

The onset is insidious and patients with PCA usually report symptoms that started years before diagnosis. Most studies recording age of symptom onset from mid-50s to early 60s (Mendez et al., 2002; McMonagle et al., 2006), although some researchers have reported a wider age spread ranging from 40-45 years of age to 75-85 years, according to the study (Kas, et al., 2011; Tang-Wai, et al., 2004). However, PCA occurs at an earlier age than classical AD.

In terms of sex distribution, no difference in prevalence has been observed (Renner et al., 2004; Mendez et al., 2002) whereas some researchers have reported a higher representation in women (Kas et al., 2011; Lehmann, et al., 2011).

1.2.2. Pathology and genetics

Genetics of PCA is still unclear. In some studies, important differences between apolipoprotein E (APOE) genotypes have been noticed in patients with PCA versus amnestic AD by Snowden et al. (2007), while, in other studies, no significant difference in APOE was recorded (Mendez et al., 2002; Tang-Wai and Mapstone, 2006; Migliaccio et al., 2009; Baumann et al., 2010).

Findings of pathology studies show that AD is the most common underlying cause of PCA (Renner et al., 2004; Tang-Wai et al., 2004; Hof et al., 1990; Alladi et al., 2007). However, some cases are associated with other histological patterns, such as corticobasal degeneration, dementia with Lewy bodies, prion disease and subcortical gliosis (Victoroff et al., 1994; Tang-Wai, et al., 2003; Renner et al., 2004; Jellinger et al., 2011).

1.2.3. Clinical features

The clinical presentation of PCA is influenced by several factors, including time taken before an individual presents to medical services, the individual's specific pattern of deficits and patient's psychological response to symptoms. PCA, due to the relatively young age at onset and the unusual nature of its symptom leads to misdiagnosis of many patients as depressed, anxious or even malingering in the early stage of the disease; depression and anxiety is likely to be caused by patients awareness of their deficits. Patients are frequently first referred to, opticians and ophthalmologists believing that an ocular abnormality is responsible for their visual symptoms In case of visuospatial deficit, the complaints are often aspecific, such as blurred vision or lack of sharpness. The complaint can also concern visuoperceptual aspects, such as recognizing faces, topographical landmarks or objects of daily life. Complaints of impaired reading abilities may be due to visuoperceptual difficulties (agnosic alexia), but more often to a visuospatial deficit (alexia due to simultanagnosia or unilateral spatial neglect). Furthermore, some patients present with praxic difficulties (Crutch et al., 2012). Although memory loss is a frequent complaint of PCA, reported in 53.3% of patients, it is significantly less frequent than in typical AD (tAD) cases (Charles and Hillis, 2005).

However, longitudinal studies have shown that anterograde memory and executive functions gradually deteriorate in some patients leading to a more global dementia state (McMonagle et al., 2006).

It has been suggested that separated biparietal (dorsal), occipitotemporal (ventral) and primary visual (striate cortex; caudal) forms of PCA exist (Ross et al., 1996; Galton et al., 2000). However these claims are based on findings from single case reports; subsequent studies have revealed considerable overlap in the neuropsychological profiles and patterns of cortical thinning (McMonagle et al., 2006; Lehmann et al., 2011).

The biparietal syndrome, although often asymmetric, would be characterized by initially visuospatial symptoms, agraphia and dyspraxia; with the progression of the pathology patients may manifest with a full Balint syndrome but show preservation of visual field, basic perceptual abilities and object recognition and reading. These deficits reflect the interruption of the dorsal stream of visuomotor processing which is critical for objects location and visually guided movements and damage to the areas of the parietal lobe involved in general motor programming and writing (Ross et al., 1996).

Indeed, patients with PCA have difficulty in drawing or copying objects and often primary progressive limb apraxia emerges in case reports (De Renzi, 1986; Aharon-Peretz et al., 1999; Goethals and Santens, 2001).

Unilateral spatial neglect contralateral to the hemisphere in which the lesion predominates was also described; Andrade et al. (2010) observed visual hemineglect to be a frequent finding in PCA, consistent with asymmetric atrophy and hypoperfusion of the parieto-temporal and prefrontal regions (Andrade et al., 2012).

The occipitotemporal syndrome would present with complaints of visual distortion, difficulty in object recognition (apperceptive deficit), topographical agnosia, prosopagnosia and alexia; examinations show restrictive visual fields or unilateral extinction on bilateral stimulation, impaired colour vision and stereopsis. These deficits manifest the disruption of the ventral stream of higher order visual processing, which is vital for object, face and written word identification (Ross et al., 1996).

Lastly, owing to the posterior localization of cerebral atrophy in PCA, retrochiasmal visual pathways dysfunction can occur. Recent reports tend to demonstrate that the incidence of homonymous visual field defects in PCA is higher than previously thought, ranging from 50% to 100% (Reñé et al., 2012). However, because of the dementing nature of PCA, visual

field examination can sometimes be problematic, and neither computerized static nor kinetic manual perimetry can be performed properly in some patients. At a more advanced stage, some patients show cortical blindness. The presence of homonymous hemianopia (HH) indicates that the visual cortex may be damaged, as well as the occipitoparietal and occipitotemporal associative cortex (Borruat, 2013).

These various visual syndromes are often associated with apraxia (limb or dressing apraxia) and with a full or partial Gerstmann's syndrome (agraphia, acalculia, left-right confusion, finger agnosia) (McMonagle et a., 2006).

Although most investigations of PCA focus on the prominent visual syndrome, even the earliest reports of PCA described some early impairment of language skills. In a recent study, Crutch described a group of PCA was markedly anomic and had reduced phonemic fluency; if compared with logopenic aphasia patients they were similar in in repetition and digit span while they were spared in comprehension and spontaneous speech; this suggests that PCA patients seems to have particular difficulties in retrieval and manipulation of phonological information (Crutch et al., 2013).

Finally, other symptoms was described such as extrapyramidal signs, myoclonus and grasp reflex (Snowden et al., 2007); nonetheless, the presence of features of clear symmetrical motor parkinsonism (suggestive of Lewy bodies pathology), or prominent asymmetric myoclonus and dystonia (suggestive of corticobasal degeneration) may give important clues to the underlying pathology, although there are currently relatively sparse pathological data on which these clinical observation can be confirmed (Crutch et al., 2012).

1.2.4. Neuroimaging

Morphological imaging: MRI

Traditionally, anatomical neuroimaging (mostly MRI) has been used to help in identifying PCA (Benson et al., 1988). Occipito-parietal atrophy without mesio-temporal atrophy (characteristic of AD) is classically described as the initial MRI pattern of PCA. However, some cases show general cortical atrophy. Kennedy et al provided the natural history of PCA on MRI. They described one healthy control: initial neuropsychological examination and MRI were normal. However, after 5 years both revealed anomalies that progressively worsened. Cortical atrophy involved first the superior parietal and inferior temporal cortices and, one year later, also the inferior parietal and occipital areas. Another year later, the medial

temporal lobe was damaged, and, in the end, global posterior cerebral atrophy was observed (Kennedy et al., 2012) (Figure 4).

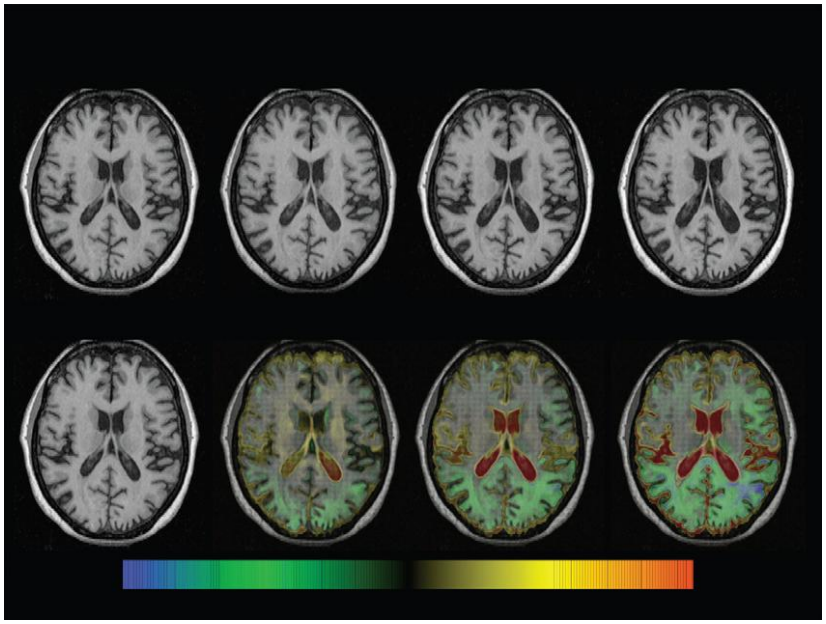

Figure 4. Evolution of neurodegeneration in posterior cortical atrophy. Registered serial MRIs showing axial views of a woman with posterior cortical atrophy at four time points (age 59–63 years old). Repeat scans were fluid-registered to the baseline image and colour-coded voxel-compression maps were produced. The scale shows the percentage volume change per voxel (–20 to 20%), with green and blue representing contraction and yellow and red representing expansion. (Crutch et al., 2012).

It is noteworthy that in several studies, researchers report asymmetric atrophy patterns in PCA (right greater than left), but these differences could be due to selection biases in the diagnosis and recruitment of patients with prominent visual dysfunction (Crutch et al., 2012).

Morphological imaging: DTI

Other researchers have hypothesized that cognitive functions might not depend only on grey matter dysfunction, but also on the integrity of brain networks. Cognitive dysfunctions might then result from interruption of information flow between different cortical areas. Using tractography, Migliaccio et al. (2012a) reported important white matter damage in the right hemisphere in addition to typical grey matter atrophy in one patient with PCA. White matter atrophy of the ventral and dorsal streams have also been demonstrated by diffusion-tensor MRI (DT-MRI) in a series of seven PCA patients (Migliaccio et al., 2012b). White matter atrophy can contribute to the clinical symptomathology of patients with PCA versus typical

AD. White matter atrophy in PCA was more pronounced in the occipital lobe, whereas typical AD patients showed more damage in the medial temporal regions (Migliaccio et al., 2012c).

Functional imaging: SPECT and PET

In Kas et al. (2011), posterior hypoperfusion was found in all 39 PCA patients, and the extent of the hypoperfused areas progressively increased. Initially, hypoperfusion was observed in the dorsal parietal cortices, and later in the occipito-temporal cortices. When compared with typical AD patients, PCA cases were characterized by more severe posterior hypoperfusion (occipital, parietal and posterior temporal cortices). Furthermore, they demonstrated also hypoperfusion of a small area corresponding to the frontal eye fields (FEF) Involvement of FEF could play a role in the oculomotor apraxia present in some PCA patients (Kas et al., 2011; Nestor et al., 2003).

Another SPECT study in a series of 27 PCA patients revealed that visuospatial deficits, included hemineglect, were associated with contralateral parietal cortex hypoperfusion and interhemispheric perfusion asymmetries (Andrade et al., 2013).

In PCA, posterior hypometabolism can be demonstrated by FDG-PET, and FDG-PET can be used to support a clinical suspicion of PCA. Data from FDG-PET accord largely with structural changes in parieto-occipital areas (Figure 5).

In addition to posterior regions, FDG-PET show specific areas of hypometabolism in the FEF bilaterally, which can occur secondary to loss of input from occipito-parietal regions and be the cause of oculomotor apraxia in PCA. (Kas et al., 2011).

Neuropathological studies demonstrated that the primary cause of PCA is Alzheimer's disease (Renner et al., 2004; Tang-Wai et al., 2004). Indeed, prominent deposits of amyloid were found in the posterior association areas, and maximal deposition was in the frontal cortex (La Joie et al., 2012).

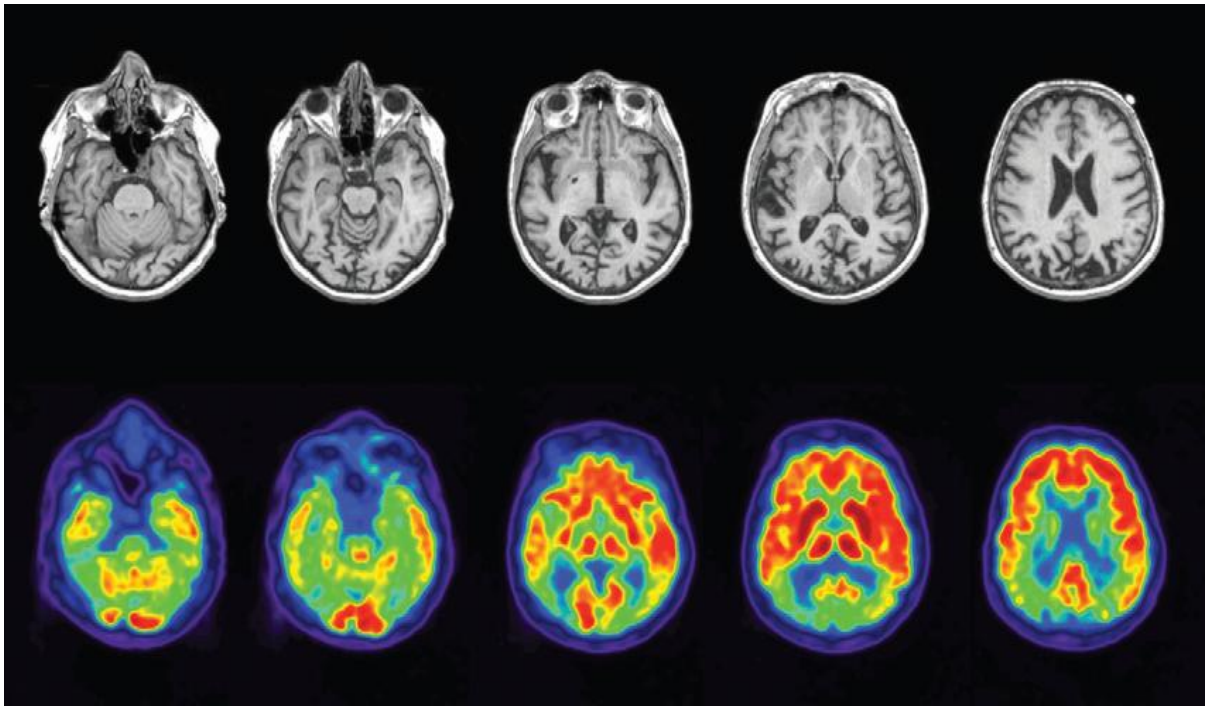

Figure 5. Brain imaging of a 62-year-old woman with visuospatial dysfunction. Images are in R-L neurological orientation. Brain MRI showed striking atrophy in bilateral parietal, posterior temporal, and lateral occipital cortex (upper row), and FDG-PET (lower row) showed hypometabolism in the same regions, left worse than right. Frontal cortex, medial temporal cortex, and hippocampus were spared (Crutch et al., 2012).

1.2.5. Clinical diagnostic criteria

Up to now, there are no validated diagnostic criteria for PCA. Published studies have considered more or less restrictive criteria regarding the degree of purity of visual disorders versus other cognitive and particularly memory and dysexecutive disorders, with the acceptance or not of the presence of a HH or of motor problem (parkinsonism, dystonia) and the requirement or not of the presence of cortical atrophy on imaging techniques (Mendez et al., 2002; Renner et al., 2004; Tang-Wai et al., 2004; McMonagle et al., 2006; Crutch et al., 2012). Basically all sets of criteria agree on the need of presence of the following elements: insidious onset and gradual progression, visual deficits in the absence of ocular diseases, relatively preserved episodic memory, verbal fluency and personal insight, symptoms including visual agnosia, simultanagnosia, optic ataxia, ocular apraxia, ideomotor apraxia, environmental disorientation, agraphia and acalculia (Table 6).

PCA diagnostic criteria	
(1) Presentation with progressive visual or visuospatial impairment in the absence of ophthalmologic impairment	
(2) Evidence of complex visual disorder on examination: element's of Balint syndrome, visual agnosia, dressing apraxia or environmental disorientation	
(3) Proportionately less memory loss or reduced verbal fluency.	
PCA patients were further divided into three sub-groups	
(1) Biparietal syndrome	Apraxia, visuospatial problems, agraphia, Balint syndrome with preserved basic perceptual abilities, object recognition and reading
(2) Occipitotemporal syndrome	Alexia, apperceptive agnosia and/or prosopoagnosia
(3) Visual variant	Primary visual failure and impairment of basic perceptual abilities

Table 6. Diagnostic criteria of PCA (reported in Alladi et al., 2007; McMonagle et al., 2006).

1.2.6. Management

Studies on therapeutic options in PCA are very scant. Patients with PCA are usually treated with cholinesterase inhibitors, by analogy with treatment of typical AD patients. No reports have been published that confirm the effectiveness of acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) in PCA. Antidepressant drugs might also be useful in patients with low mood, and trials of levodopa could be appropriate in individuals with parkinsonism (Crutch et al., 2012).

Non-pharmacologic therapies have been proposed for a few PCA patients. The aim of behavioral rehabilitation is to increase self-confidence and self-esteem, in order to help patients to cope with their visual symptoms. The approach involves the transfer of learning from therapy into daily life. Perez and coworkers (Perez et al., 1996) described the improvement in areas of visual discrimination, reading, writing and daily tasks in a patient with PCA after 12 month of occupational therapy including compensatory strategies.

Though these types of intervention show some positive results, they are insufficient against the course of PCA: as symptoms worsen and mental status deteriorates, such rehabilitation efforts become less effective and more difficult to implement. Therefore, PCA carries prognostic and therapeutical implications similar to those of AD (Zakzani and Boulos, 2001).

1.3. Dementia with Lewy bodies

Dementia with Lewy bodies (LBD) is the second most common type of degenerative dementia following Alzheimer's disease. The characteristic features of LBD are spontaneous parkinsonism, recurrent visual hallucinations, fluctuating cognition, R.E.M. sleep behaviour disorder (RBD), severe sensitivity to antipsychotic medications and reduction in striatal dopamine transporters on single photon emission computed tomography (SPECT) or positron emission tomography (PET) (McKeith et al., 2005). The term "Lewy Bodies" was first used in 1919 to indicate the eosinophilic intracytoplasmic inclusions in the dorsal vagal nuclei and substantia innominata of PD brains described by Fritz Heinrich Lewy in 1912 (Kosaka et al., 2014).

The first autopsied case of progressive dementia and parkinsonism was reported in 1976 by Kosaka et al.; the patient was clinically diagnosed as presenile Alzheimer's disease with parkinsonism and the autopsy revealed numerous intracytoplasmic eosinophilic inclusions in small neurons at the deeper cortical layers and typical Lewy bodies in the brain stem nuclei, in addition to the Alzheimer pathology (Kosaka et al., 1976).

The same group proposed in 1984 the term "Diffuse Lewy Body disease" (DLBD) to describe "…progressive dementia and Parkinson symptoms of presenile or senile, or sometimes of younger onset, and neuropathologically by numerous Lewy bodies and neuronal cell loss in the central and autonomic nervous systems, frequently followed by various degrees of Alzheimer pathology" (Kosaka et al. 1984).

1.3.1. Epidemiology

LBD accounts for around 4.2% of all dementia diagnosed in the community; the mean prevalence in the whole population is 0.36%. Annual incidence rates were found to be 3.8% (range 3.2–4.5%) of new dementia diagnoses and 0.87 (range 0.57–1.4) cases/1000 person-years. At present there are no consistent data about gender differences (meta analysis of Vann Jones et al., 2014).

1.3.2. Pathology and genetics

LBD is considered a synucleinopathy, along with PD and multiple system atrophy (MSA). It is distinguished pathologically by the presence of Lewy bodies, which are intracellular

inclusions with an eosinphilic core and marked by a peripheral halo. Structurally, Lewy bodies and Lewy neuritis are aggregations of alpha-synuclein; they are also associated with intermediate filaments, chaperone proteins, and elements of the ubiquitine-proteasome system, but these features are not specific for Lewy bodies and are found in other neuronal inclusions (McNaught et al., 2002) In LBD, Lewy bodies are found not only in the substantia nigra and brainstem nuclei, as in PD, but also in the limbic system, parahippocampal cortices, amygdala and cortex as well. (Kosaka et al., 1990). LBD can also demonstrate some pathologic features of AD including β-amyloid deposits and tau neurofibrillary tangles, though in lower density than AD (McKeith et al, 2006).

Lewy Body disorders have been associated with alpha-synuclein gene mutations and multiplications resulting in high concentrations and accumulation of alpha-synuclein. In particular it seems that triplication of alpha-synuclein gene can cause LBD, PD and Parkinson Disease Dementia (PDD) whereas gene duplication is associated only with motor PD. (McKeith et al., 2005; Singleton et al., 1996; Zarranz et al., 2004)

1.3.3. Clinical features

Core features of LBD are dementia with fluctuating cognition, visual hallucinations and parkinsonism. Dementia can derive not only from cognitive impairment but also from neuropsychiatric, motor, sleep and autonomic dysfunction (McKeith et al., 2005).

Fluctuations are defined as spontaneous alteration in cognition, attention and arousal. Features of disturbed arousal may include episodes of excessive daytime somnolence, staring spells, diminished awareness of surroundings, and incoherent or illogical thoughts. Fluctuating cognition and abilities have also been described as periods of behavioral confusion, inattention, and incoherent speech alternating with episodes of lucidity and capable task performance. (Ferman et al., 2004; Walker et al., 2000; Ballard et al., 2001). Byrne et al. (Byrne et al., 1989) described fluctuations in the level of arousal and cognitive performance in 12 patients with LBD. One patient had day-to-day changes of more than 50% on the Mini-Mental State Examination; another patient experienced confusional episodes that were so catastrophic that she varied from being mute, confused, and unable to stand without assistance to being capable of carrying on a conversation (Byrne et al., 1989).

The cognitive profile of LBD is characterized by attentional deficits and prominent executive and visuospatial dysfunction (Calderon et al., 2001; Collerton et al., 2003); A meta-analyses

of 21 studies revealed that, if compared with AD patients, LBD patients are more impaired in visual-perceptual, semantic, attentional, executive and speeded tasks (Collerton et al., 2003). Another comparison with AD patients showed that a group of LBD patients was significantly worse on sustained and divided attention, verbal short term memory, some sub-tests of VOSP (cube analysis, object decision and fragmented letters), visual search, Wisconsin Card Sorting Test and FAS verbal fluency; on the opposite LBD were better in immediate and delayed stories recall; no differences was seen in words recall (Calderon et al., 2001). A more recent study with autopsy-proven diagnoses confirmed differences in visuospatial and memory tasks but not in attention and fluency tasks (Yoshizawa et al., 2013).

Visual hallucinations are one of the most useful symptom to a clinical diagnosis of LBD and they are generally present early in the course of illness. (McKeith et al., 2005). Hallucinations in other modalities, particularly auditory, may also occur in LBD but do so less frequently. Typical themes are of people and animals intruding into the patient's home, but inanimate objects are also seen and abstract perceptions such as writing on walls and ceiling are not unusual. The images are characteristically seen (and described) in considerable detail (McKeith et al., 1996). There is considerable overlap between true visual hallucinatory symptoms and other perceptual disorders, including misidentification syndromes and visual agnosias (McKeith et al., 1996).

Bilateral symmetric parkinsonism, especially limb rigidity and bradikinesia are common in LBD. The severity of extrapyramidal motor features in LBD is generally similar to that of age-matched patients with idiopathic Parkinson's Disease (PD) (McKeith et al., 2005). Tremors occurs less frequently than PD, and when present is tipically a symmetric postural tremor, rather than an asymmetric tremor. Gait disturbance mimics that of PD with shuffling, slow turns and reduced arm swing. There are more falls in LBD patients than AD patients; falls may be related to dysautonomia, cognitive impairment, motor symptoms or a combination of these factors. (Allan et al., 2009). Levodopa responsiveness in LBD is almost certainly less than in uncomplicated PD (Molloy et al., 2005).

In addition to core features there are other features that are suggestive for LBD. RBD is also common and is manifested by vivid and often frightening dreams during R.E.M. sleep, but without muscle atonia; patients therefore appear to "act out their dreams" vocalizing, flailing limbs and moving around the bed sometimes violently. Vivid visual images are often reported, although the patient may have little recall of these episodes. RBD is thought to

precede cognitive and motor features of LBD sometimes by several years; RBD is frequently associated with an underlying synucleinopathy. (McKeith et al., 2005).

Another suggestive feature is a severe neuroleptic sensitivity characterized by the acute onset or exacerbation of parkinsonism and impaired consciousness. (McKeith et al., 2005).

Finally severe autonomic dysfunction may occur early in disease producing orthostatic hypotension, neurocardiovascular instability, urinary incontinence, constipation and impotence as well as eating and swallowing difficulties (Horimoto et al., 2003).

1.3.4. Neuroimaging

Morphological imaging: MRI

Structural neuroimaging with MRI has been widely used to compare regional structural changes in patients with LBD against AD, PDD and their healthy controls. Comparisons with healthy subjects using voxel-based morphometry (VBM) showed a grey matter loss in the dorsal midbrain and a region of the substantia innominata (SI). Small regions of loss were also identified in the posterior hippocampus, insula, in the frontal and parietal lobes and in a region surrounding the third ventricle (Whitwell et al., 2007; Burton et al., 2002). Cousins and colleagues have also observed reduced putamen volume in LBD patients (Cousins et al., 2003). In a recent VBM study, LBD group showed by a predominant parietal, occipital and subcortical atrophy if compared with control subjects (Borroni et al., 2015).

Both cross-sectional and longitudinal studies have shown that LBD is associated with less pronounced global atrophy than AD. The most consistent finding is the relative preservation of the medial temporal lobe (MTL) in LBD compared to AD (Watson et al., 2012); however the MTL atrophy seems to have less discriminative power in the oldest (> 85 years) (Barkhof et al., 2007).

Conversely, the midbrain appears to be more affected in LBD than AD, with the SI showing greater atrophy (Whitwell et al., 2007; Hanyu et al., 2005). The SI contains the nucleus basalis of Meynert, which is highly involved in the cholinergic neurotransmitter system. In addition, Whitwell and colleagues (Whitwell et al., 2007) demonstrated that increased dorsal mesopontine grey matter atrophy distinguished patients with clinically diagnosed LBD and AD.

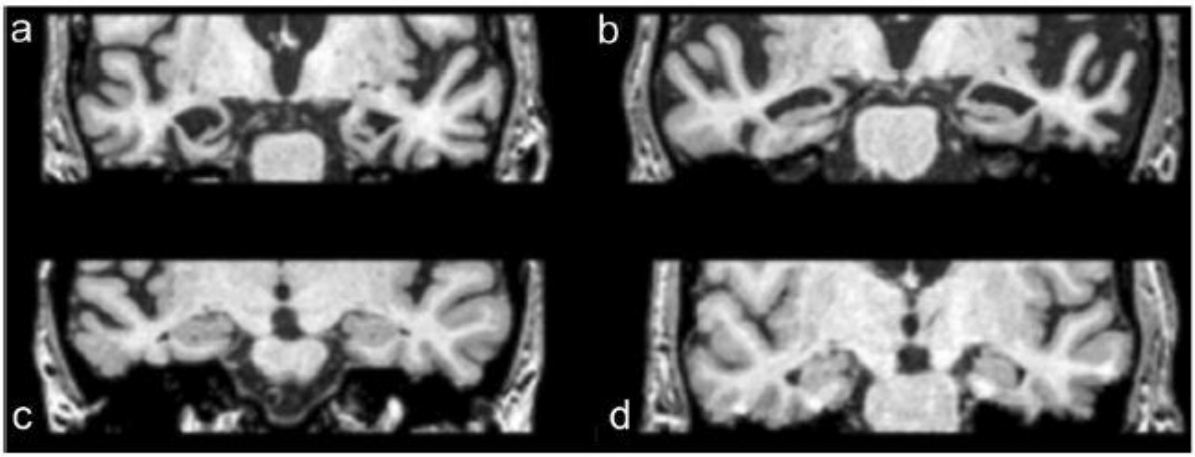

Figure 6. Preservation of medial temporal lobe in dementia with Lewy bodies compared to Alzheimer's disease. (a) A 76-year-old female with Alzheimer's disease (AD). (b) A 72-year-old male with AD. (c) A 75-year-old female with AD. (d) A 73 year old male with dementia with Lewy bodies. (Watson et al., 2012).

Finally, comparisons between LBD and PDD have converged to reveal a pattern of more pronounced grey matter loss in LBD; localizations of grey matter reductions appear to be variable among studies (Beyer et al., 2007; Lee et al., 2010; Sanchez-Castaneda et al., 2010).

Morphological imaging: DTI

Some studies have reported diffusion abnormalities in LBD of the corpus callosum and the frontal, parietal, occipital, and, to a lesser extent, temporal white matter when compared to controls, while other studies have found very little change in DTI parameters compared to controls and AD patients. The modest involvement of the temporal lobe is consistent with the relative preservation of global neuropsychological meausures and memory domain in LBD compared to AD (Firbank et al., 2011; Kantarci et al., 2010). Two DTI studies have also identified white matter alterations in the longitudinal fasciculus (Kantarci et al., 2010; Ota et al., 2009); those abnormalities could be associated with visuo-spatial impairment and visual hallucinations in LBD patients. A recent study demonstrated distinct patterns of white matter alterations between LBD and AD, with a more parieto-occipital predominance of alterations in LBD as opposed to more diffuse pattern of change in AD (Watson et al., 2012).

Functional imaging: functional MRI (fMRI), SPECT and PET

There are still relatively few fMRI studies in LBD. One of this study involving visual presentation of color, face and motion paradigms found greater activation in the superior temporal sulcus in LBD compared to AD group during the motor part of the tasks (Sauer et

al., 2006) Another fMRI study did not show significant differences in functional response between LBD and healthy subjects to checkerboard, objects or motion stimuli in V1, V2 and V3, suggesting a relative sparing of primary visual functions, but showed a decreased activation in response to motion stimuli in V5 in LBD group this finding seems to indicate that visuospatial and perceptual difficulties in LBD can derive from abnormalities in associative areas and not in the primary visual cortex (Taylor et al., 2012).

PET and SPECT are well-established, reliable imaging methods to assess molecular changes in LBD. The focus on SPECT has been on the demonstration of alterations in the dopamine transporter (DAT) reflecting changes in the nigrostriatal pathway. DAT loss is related to the clinical feature of motor parkinsonism but it can be also be present without motor features (Roselli et al., 2009). Imaging ligands, such as ^{123}FP-CIT, have been developed for SPECT to visualize DAT loss *in vivo*. In healthy volunteers and AD patients the ligand is taken up in the caudate and putamen where neurons expressing the DAT are concentrated; in LBD, however, ligand uptake is almost absent in the putamen, and is reduced in the caudate (Mak et al., 2014). The effectiveness of ^{123}FP-CIT-SPECT in the distinction between LBD and AD is further confirmed in a autopsy study (88% sensitivity and 100% specificity) (Walker et al., 2007).

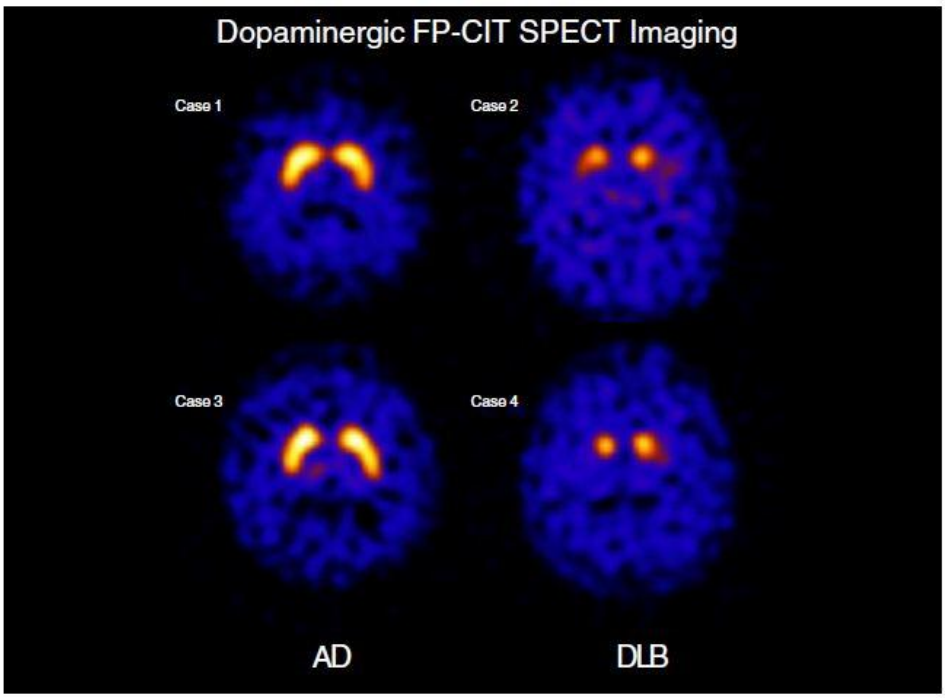

Figure 7. Comparison of FP-CIT scans between AD and LBD. In the LBD group, reduced uptake is evident in the caudate while more extensive loss is found in the putamen (Mak et al., 2014).

Perfusion studies have consistently highlighted a distinctive pattern of occipital hypoperfusion in LBD when compared to AD, affecting both primary visual cortex and visual association areas, and including the precuneus (Lobotesis et al., 2001; Minoshima et al., 2002; Hanyu et al., 2006). Another SPECT study demonstrated relatively preserved medial temporal lobe perfusion in LBD in addition to occipital hypoperfusion in LBD when compared to AD (Ishii et al., 1999).

Consistent with SPECT findings, FDG-PET studies have shown a distinctive pattern of hypometabolism in the occipital cortex and visual associations cortices, with relative preservation of the posterior cingulate, which is normally markedly affected in AD (Klein et al., 2010; Perneczky et al., 2008).

1.3.5. Clinical diagnostic criteria

Central characteristics	Dementia with impairments in daily functioning; may have intact memory function at onset; deficits on tests of attention, executive functions, and visuospatial ability may be prominent.
Core characteristics	- Fluctuations cognition/attention and alertness - Visual Hallucinations - Parkinsonism
Suggestive characteristics	- R.E.M. sleep behavior disorder - Neuroleptic sensitivity - Reduced dopaminergic activity in the basal ganglia demonstrated by SPECT or PET imaging
Possible LBD	Central characteristic and At least 2 core characteristics or 1 core and 1 suggestive characteristic
Probable LBD	Central characteristic and 1 core characteristics or 1 or more suggestive characteristic
Supporting characteristics	Repeated falls or syncope, transient impairments in consciousness, autonomic dysfunction (i.e. in the form of orthostatic hypotension or urinary incontinence), hallucinations in nonvisual modalities, systematic delusions, depression, intact medial temporal lobe on anatomic imaging, reduced (particularly occipital lobe) metabolism on metabolic imaging (SPECT or PET), pathologic MIBG-SPECT scan of myocardium, EEG showing slow activity with intermittent temporal sharp waves.

Table 7. Diagnostic criteria of LBD (Mayo et al., 2014, adapted from McKeith et al, 2005).

Criteria for diagnosis of LBD are based upon the triad of fluctuating cognitive impairment, recurrent visual hallucinations and motor features of parkinsonism. The first set of criteria was released in 1996 (McKeith et al., 1996) by consortium on LBD and revised in 2005 in order to increase diagnostic sensitivity (McKeith et al., 2005). In the last release, distinction is

made between clinical features that are *suggestive* of LBD, i.e. have been demonstrated to be significantly more frequent than in other dementias, and *supportive* features, which commonly occur but with lower specificity. In table 7 diagnostic criteria are summarized (McKeith et al., 2005).

1.3.6. Management

Patient management in LBD is complex due to cognitive, neuropsychiatric, movement and sleep disorders. Nonpharmacologic interventions, such as strategies to help social interaction and increase level of arousal and attention, have the potential to improve many of the symptoms and functional impairments but none has yet been systematically evaluated (McKeith et al., 2005).

With respect to pharmacological treatments, to date there are no disease-modifying agents and several symptoms-based treatments are commonly employed (Mayo and Bordelon, 2014). Cholinesterase inhibitors, as in AD, can be beneficial for cognitive and behavioral impairments as well as hallucinations in some cases (Samuel et al., 2000; Mori et al., 2012). Memantine has also been suggested to improve attention and episodic memory in LBD patients, though sedation is a possible adverse effect (Wesnes et al., 2015). In terms of antipsychotic use for behavior and hallucinations, quetiapine can sometimes be useful and better tolerated than other typical and atypical neuroleptics (Fernandez et al., 2002). Depression is common in LBD but there are no systematic studies of its management; use of selective serotonin reuptake inhibitors (SSRIs) has demonstrated benefit for depression and also for anxiety and emotional lability. Tryciclic antidepressant should be avoided for the potential anticholinergic exacerbations (McKeith et al., 2005). Finally, parkinsonism can be treated with dopaminergic agents; levodopa is preferred to dopamine agonists because of the greater potential of worsening hallucinations and because they seem to have less benefit in motor symptom control (McKeith et al., 1992).

2. Aim of the study

The aim of the present study was to analytically characterize a group of neurodegenerative patients with early visuospatial and/or praxic deficits by a detailed neuropsychological evaluation and by functional neuroimaging and then to apply a Principal Components Analysis to their posterior cognitive profile in order to see if this analysis allowed us to highlight possible subsyndromes.

Secondly we aimed to compare the diagnosis based on current diagnostic criteria and the classification of patients made with Principal Components Analysis to verify if this approach, driven exclusively by empirical data, would yield converging results.

3. Materials and methods

3.1. Participants

3.1.1. Patients

Seventy patients, referred to the Neuropsychology laboratory of the Neurology Department of S. Gerardo Hospital (Monza, IT), with a cognitive profile characterized primarily by impairment of posterior cognitive functions and a relative spare of language and memory functions, were selected. Each patient underwent, in a first session, to a neuropsychological battery assessing all the principal cognitive domains and, in a second session, to a neurological examination and an experimental neuropsychological battery testing all the posterior cognitive functions not evaluated in the first session.

47 out of 70 patients also underwent a [18F]FDG-PET in close proximity (max 6 months) to the neuropsychological assessment.

Clinical diagnosis was made according to the current diagnostic criteria reported in the introduction; for AD we used the diagnostic criteria of the association workgroups on diagnostic guidelines for Alzheimer's disease (McKhann et al., 2011).

3.1.2. Healthy controls

For the neuropsychological battery, control subjects were necessary for the task not standardized for the Italian population. 56 healthy subjects were recruited (26 men and 30 women; mean age 70.3 ± 9.2; range: 51-85. Mean education 9.2 ± 3.5).

On the other hand, in relation to the functional neuroimaging 33 healthy controls (mean age 67.7 ± 9.8; range 50-86). have been recruited, between October 2012 and May 2014, in the department of Nuclear Medicine of the San Gerardo Hospital. All controls were selected among oncological patients with a negative neurological history, and they all gave written informed consent to the cerebral [18F]FDG-PET contextually to the total-body [18F]FDG-PET already planned in their oncological follow-up.

Inclusion criteria for these subjects were:

- age greater than 50 years;
- oncological patients in M0 stage, who underwent no chemotherapy;

- patients able to give a valid informed consent;
- MMSE ≥ 28/30.

Exclusion criteria were:

- positive history for diabetes mellitus;
- positive history for HIV;
- positive history for substances abuse;
- positive history for great head injury, stroke or other neurological cerebral diseases;
- pharmacological therapy of long duration with benzodiazepines or analgesics (e.g. NSAIDs).

3.2. Behavioral protocol

3.2.1. Standard neuropsychological battery

Each patient underwent the following standard neuropsychological assessment battery.

Global cognitive evaluation:

- MMSE (Measso et al., 1993)

Attention:

- Attentional matrices (Spinnler et al., 1987)

Memory:

- Digit span (Orsini et al., 1987)
- Semantically related words list (Mauri et al., 1997):
    - immediate recall
    - delayed recall
    - identification

Language, executive functions and logical skills:

- Token test (Spinnler et al., 1987)
- Phonemic fluency (Novelli et al., 1986)

- Semantic fluency (Novelli et al., 1986)
- FAB – Frontal Assessment Battery (Dubois et al., 2000; italian version of Appollonio et al., 2005)
- Raven's colored matrices (Basso et al., 1987)

Visuoconstructional and visuoperceptual skills:

- Rey-Osterrieth complex figure (Caffara et al., 2002)
- Poppelreuter-Ghent Test (PGT) (De Renzi et al., 1969)

Praxis

- Ideomotor apraxia test (De Renzi et al., 1980)

Neuropsychiatric and functional evaluation:

- Geriatric Depression Scale (GDS) (Yesavage et al., 1983)
- Neuropsychiatric Inventory (NPI) (Cummings et al., 1994)
- Functional activities questionnaire (FAQ) (Pfeffer et al., 1982)
- Activities of daily living (ADL) (Katz et al., 1963)

3.2.2. Experimental neuropsychological battery

Each recruited patient underwent also the following experimental battery. For the functions of which a standardized task was not available, we developed a new task; description and administration of each new task is reported below.

Semantic

- Semantic association

  - patients have to choose which of two stimuli, belongs to the same semantic class of the *probe* stimulus. The distractor is similar in terms of visual features to the *probe* but without semantic relation with it. The aim of this task is to distinguish between a semantic deficit from an agnosic one.

Visuospatial and visuoperceptual skills:

- Benton judgement of line orientation (Benton, 1992; italian version of Ferracuti et al.)
- Benton test of facial recognition (Benton et al., 1992; Italian version of Ferracuti et al.)
- Colors categorization

  - patients is asked to divide 24 colored cards into 6 categories on the basis of the different nuances of colours.
- Lines bisection test (Diller et al., 1974)

Praxis:

- Orobuccal apraxia test (Spinnler et al., 1987)

Balint-Holmes' syndrome assessment:

- Simultanagnosia - Recognition of Navon letters (Navon, 1977)

- we created 15 stimuli in which small letters are arranged to form larger letters (see .Figure 8). Patients are asked to identify the large letters and not the small ones. Maximum score is 15.

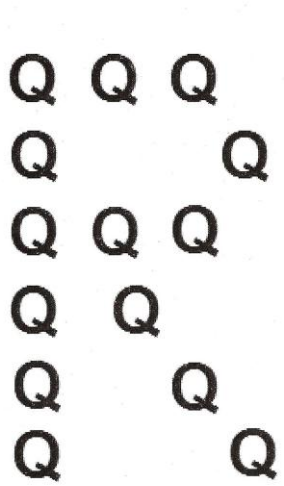

Figure 8. Example of a Navon letter. Patients with simultanagnosia often read the local level (Q), whereas are absolutely unable to see the global level (R)

- Gaze apraxia test

  - the patient is asked to direct gaze randomly, without moving the head, to the right, to the left, up and down. Every direction is evaluated twice. Two points are given if the movement is rapid and precise, one point is given if the movement is not precise and

slowed and no points are given if the patient doesn't perform any movement. Maximum score is 16.

- Optic Ataxia test

  - In this test the ability to perform reaching movements in the peripheral visual field is assessed. The patient is asked to stare at the examiner's nose for the whole duration of the examination and to grasp an object, placed in four different positions of peripheral visual field. The task has to be performed with both hands. Three points are given if the patient reaches the object at the first attempt, 2 points are given if the object is reached at the second attempt and one point is given if patient reaches the object at the third attempt. Maximum score is 24 for each hand.

Gerstmann's syndrome assessment:

- Acalculia test

  - patients have to perform mentally 12 simple operations (3 additions, 3 subtractions, 3 multiplications and 3 division). The maximum score is 12, one point for each operation.
- Agraphia – Dictation subtest of Aachen Aphasia Test (AAT) (Huber et al., 1983; italian version by Luzzatti et al., 1996)
- Fingers Agnosia test (Spinnler et al., 1987)
- Right-left orientation test (Benton et al., 1994)

Graphesthesia:

- Graphesthesia test

  - patients have to identify single numbers and simple letters written with a pen cap on the inner face of both forearms. Each stimulus is presented twice; two points are given if the patients identify stimulus at the first presentation, one point is given if the stimulus are identified at the second presentation. The task consists of 6 numbers and 6 letters for a total score of 48.

Functional evaluation:

- Functional Inventory

  - we developed a 10 multiple choice questions inventory with the aim to assess functional status not depending on praxis abilities. It evaluates orientation, memory, interests in

personal care, problem solving and language abilities. The inventory was filled by caregivers.

R.E.M. behavior disorders (RBD):

- R.E.M. behavior disorders inventory

  - we developed a 6 multiple choice questions inventory investigating possible sleep behavior disorders such as motor events during sleep that were associated with dreaming and self-injuries or injuries to the patient's bed partner. The questionnaire was administered to the *caregivers*.

3.2.3. Neurological evaluation

Each patient also underwent a neurological exam, performed by an expert neurologist, evaluating the possible presence of extrapiramidal symptoms, motor disorder, myoclonus, dystonia and alien limb phenomenon. Each scale is described below.

Extrapiramidal symptoms

- The Unified Parkinson's Disease Rating Scale (UPDRS) part III (MDS, 2003)

  - Different aspects are observed and evaluated: speech, facial expression, tremors, rigidity, gait, bradykinesia or hypokinesia, posture and posture stability.

Myoclonus

- The Unified Myoclonus Rating Scale (UMRS) (derived from Frucht et al., 2002)

  - Item evaluating myoclonus in upper limbs was used.

Dystonia

- The Fahn-Marsden dystonia scale (derived from Burke et al., 1985)

  - Item evaluating dystonia in upper limbs was used.

Alien limb phenomenon

- We formally test levitation by asking patients to maintain both arms in an outstretched horizontal position with hands looking up and down for 20 secs; any involuntary deviation of the arms is noted.

3.2.4. Statistical analysis

All analyses were conducted using SPSS 21.0 (SPSS Inc, Chicago, Illinois).

Firstly, comparisons between groups for demographic and clinical characteristics were performed with Kruskal-Wallis analyses; for the significant comparisons we performed post tests with Mann-Whitney choosing a significant level of $p < 0.01$.

Then, we conducted a "*principal components analysis*" (PCAnalysis) on neuropsychological tests of posterior cognitive functions to highlight possible posterior subsyndromes in the whole sample; PCAnalysis is a multivariate technique that analyzes a data table representing observations described by several dependent variables, which are, in general, inter-correlated. Its goals are extract the most important information from the data table, compress the size of the data set by keeping only this important information, simplify the description of the data set and analyze the structure of the observations and the variables. In order to achieve this goals PCAnalysis computes new variables called *principal components* which are obtained as a linear combination of the original variables; the first principal components is required to explain the larger possible variance of the data table; the second component is computed under the constraints to be orthogonal to the first one and to have the larger possible variance and so on for the other components. The values of the new variables - *factor scores* - are standardized and can be used for further analyses (Abdi and Williams, 2010).

We decided to perform PCA using standardized residuals of a linear regression conducted using the scores of each posterior test as the dependent variable and age, education and disease's duration as independent variables; this step allowed us to have a data set in which the influence of age, education and duration of disease on task scores was eliminated. For the tests in which no effects of the independent variables on the scores was observed, we used z scores. In a second step we also conducted regression analysis including raw MMSE score in the independent variables to evaluate the effect of disease stage on PCAnalysis (see Appendix).

Because in PCAnalysis, variables with a correlation higher than 0.8 and variables that correlate with few other variables should be eliminated, we firstly conducted a Spearman correlation analysis on posterior tests standardized residuals scores or z scores to select variables. We decided to not include gaze apraxia because patient's performances could be biased by gaze palsy. Right and left arm apraxia were too inter-correlated (Spearman rho of 0.841; $p < 0.0001$), therefore we sum the two scores and we use a global score for limb apraxia. In order to reduce the numbers of variables and increase the validity of the analysis, we also decided to use a global score of Gerstmann syndrome (by calculating the mean of the scores of acalculia, right-left orientation, agraphia and fingers agnosia for each patient) and of Balint-Holmes syndrome (mean of Navon test scores and optic ataxia scores).

PCAnalysis was hence conducted on the following tasks: Balint-Holmes and Gerstmann composite scores, Benton JLO, semantic association, face recognition test, Poppelreuter-Ghent test, ROCF copy, limb apraxia, colors categorization and line bisection. (see table 8 for correlation coefficient).

Varimax rotation was applied to simplify the interpretation because, after a *varimax* rotation, each original variable tends to be associated with one (or a small number) of components, and each component represents only a small number of variables (Abdi and Williams, 2010).

Finally, only variable loadings higher than 0.4 for each component was considered.

After running PCAnalysis, we saved *factor scores* for each component and used them to classify patients within subsyndromes. Patients with a *factor score* $\leq$ -1 were considered *proportionally more impaired* in that component, while patients with a score $\geq$ 1 were considered as *proportionally spared*.

The individual profiles of *factor scores* were confronted with patients' diagnosis based on standardized clinical criteria. Note that, regardless the absolute severity of deficits in each component, patients were defined as pseudofocal if the relative degree of impairment across the components was significantly different. For instance, a patient with a factor score= -1.5 in Component 1 and = 0.5 in Component 2 would be classified like a patient with a factor score= 0.5 in Component 1 and = +1.5 in Component 2, given that both patients were relatively more impaired in Component 1 than in Component 2, even if with a different degree of severity.

3.3. Imaging protocol

3.3.1. [18F]FDG-PET data acquisition

The patients and the selected controls underwent a [18F]FDG-PET. All of them had fasted beforehand for at least 8 hours. Procedural protocol includes at first the measurement of glycaemia that must remain under 160 mg/dl, in order that the radiotracer uptake is not altered by the presence of high glycaemia plasmatic levels. These would in fact undermine the significance of the methodic by competing with the radiomarked glucose.

The injection of the radiotracer includes the locating of a peripheral venous access and the subsequent cannulation; an amount of 250 mBq of radiopharmaceutical is then injected as slow infusion (ca. 20 sec) followed by a flush of physiological solution. After the injection the subjects were moved for 45 minutes in a dark room, where patients could lie down with eyes closed. This was necessary in order to reduce the visual and auditive sensations that could determine a radiotracer accumulation of artifactual nature, in particular in the calcarine fissure.

The subsequent PET acquisition started with the correct positioning of the patient on the table, with the skull oriented along the orbitomeatal line. Essential was the maintenance of the immobility of the skull during the images acquisition; for this aim a headrest specific for the machinery was used. The [18F]FDG-PET scans was performed using a Discovery-600© (CT integrated). At first a CT scan was performed for the correction of attenuation. The effective acquisition lasted 15', time necessary to the acquisition of sections with a thickness of 3.27 mm and a matrix of 128 x 128 pixel. Data was then reconstructed by an iteration reconstruction algorithm type OSEM (ordered subset expectation maximization).

3.3.2. [18F]FDG-PET data analysis: pre-processing

Spatial pre-processing and voxel-based statistical analysis were performed using SPM8 (Wellcome Department Imaging Neuroscience, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in Matrix laboratory (MatLab 7.11.2 R2012a Service Pack. The Math-Works, Inc., Natick, MA).

Patients' images were exported with the format Digital Imaging and Communication in Medicine – DICOM (.dcm) from the station Xeleris (GE) and subsequently transformed into the format ANALYZE with SPM, obtaining a file header (.hdr), that gives information about

the image and its acquisition process, and a file image (.img), containing information about the voxels' distribution and dimension.

All images were then pre-processed, setting the origin and orienting them along transaxial planes parallel to the AC-PC line (a virtual line connecting the anterior and the posterior commissure). Each image was spatially normalized into Montreal Neurological Institute (MNI, McGill University, Montreal, Que., Canada) standard templates. The image sets were then smoothed with an isotropic Gaussian filter of 16 mm FWHM (full-width at 52 half maximum). All images were so composed by corresponding voxels localized in the same regions, and thus comparable.

3.3.3. [18F]FDG-PET data analysis: quantitative analysis

Firstly we performed a t-test between cerebral metabolism of healthy subjects and patients; we used a significance levels of $p < 0.001$ and a voxel threshold of 500.

Then we performed a multiple regression using cerebral metabolism and *factor scores* of the whole patients sample for each obtained component; we used sex as covariate. For this analyses we decided to use a significance level of $p < 0.01$ and a voxel threshold of 100.

For t-test, the clusters obtained corresponded to the regions composed by the voxels that according to the statistical test didn't verify the null hypothesis in the patients, and thus diverged significantly from the healthy controls, while for regression analyses clusters obtained represented regions of which activities correlated with *factor scores*. At the end of analysis an anatomical labeling of hypometabolism clusters was performed using MRIcro (http://www.mccauslandcenter.sc.edu/mricro).

	Benton JLO	Balint-Holmes syndrome	Gerstmann syndrome	Semantic association	Colors categor.	Line bisection	ROCF copy	Limb apraxia	Face recogn. test	PGT
Benton JLO	1	0.480**	0.305*	0.184	-0.085	0.263*	0.288*	0.374**	0.241*	0.349**
p value <	--	0.0001	0.011	0.128	0.482	0.028	0.016	0.002	0.048	0.005
Balint-Holmes s.		1	0.192	0.171	0.013	0.240	0.440**	0.304*	0.197	0.287*
p value <		--	0.134	0.179	0.922	0.059	0.0001	0.016	0.126	0.028
Gerstmann s.			1	0.140	0.056	0.158	0.120	0.435**	0.149	0.161
p value <			--	0.256	0.651	0.199	0.329	0.0001	0.230	0.209
Semantic association				1	0.187	-0.002	0.177	0.193	0.129	0.294*
				--	0.121	0.986	0.143	0.112	0.294	0.018
Colors categorization					1	0.004	-0.059	0.022	0.131	0.126
p value <					--	0.977	0.627	0.860	0.287	0.322
Line bisection						1	0.196	0.213	0.028	0.346**
p value <						--	0.103	0.079	0.819	0.005
ROCF copy							1	0.139	0.312**	0.529**
p value <							--	0.255	0.01	0.0001
Limb apraxia								1	0.258*	0.293*
p value <								--	0.035	0.02
Face recognition test									1	0.274*
p value <									--	0.03
PGT										1
p value <										--

Table 8. Spearman correlation between variables of PCAnalysis. * p< 0.05; ** p< 0.01. Benton JLO Benton judgement of line orientation, ROCF Rey-Osterrieth complex figure, PGT Poppelreuter-Ghent test.

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4. Results

4.1. Socio-demographic and clinical features of the study population

We enrolled 70 patients (26 men and 44 women; mean age 73.9 ± 6.8), 53 met diagnostic criteria for one syndrome, 9 met diagnostic criteria for more than one set of criteria and 8 did not meet any diagnostic criteria (NAS). 21 were diagnosed with PCA, 19 with CBD, 10 with AD and 3 with LBD; 4 met criteria of PCA and CBD, 2 PCA and AD, 2 AD and LBD, 1 LBD and CBD. See tables 9, 10, 11 and 12 for demographic, clinic and neuropsychological features. We reported mean scores for groups of patients with more than 8 members and individual scores and data for the other patients.

4.1.2. Group comparisons results

No differences between groups were found in age, education, disease duration and adjusted MMSE. Kruskal-Wallis analysis showed significant differences for the following tasks: Poppelreuter-Ghent test, fingers agnosia, delayed recall of word list, recognition of word list, phonemic fluency, semantic fluency, orobuccal apraxia, right-left orientation test, acalculia, total score of UPDRS, graphestesia test and line bisection. Post tests results are reported in superscript in table 9 and 10.

AD patients were significantly worse than the other groups in delayed recall and recognition of word list; AD were also more impaired than NAS in semantic fluency and right-left orientation. CBD patients were significantly more impaired than the other groups in phonemic fluency; they were also worst in UPDRS than AD and PCA and in orobuccal apraxia than NAS. PCA were more impaired than CBD and NAS in fingers agnosia, in Poppelreuter-Ghent than CBD, in graphestesia and line bisection than NAS. Acalculia did not show a significant difference between groups in post tests for $p < 0.01$.

	Cut-off scores	PCA n= 21	CBD n=19	AD n = 10	NAS n= 8
Age	--	71.6 ± 8.1	75.5 ± 5.1	75.1 ± 6.7	75.5 ± 6.8
Education (years)	--	6.4 ± 2.5	6.2 ± 3.0	5.7 ± 2.9	7.5 ± 3.8
Sex (no of men/women)	--	5/16	10/9	2/8	4/4
Disease duration (months)	--	34.1 ± 21.2	21.6 ± 15.9	28.1 ± 10.1	23.3 ± 13.8
Adjusted MMSE	≥ 24.0	24.0 ± 2.8	25.3 ± 3.3	22.7 ± 1.5	25.4 ± 2.3
Attentional matrices	≥ 31.0	29.6 ± 11.9	29.2 ± 8.2	32.3 ± 8.1	36.9 ± 7.4
Digit span	≥ 3.8	4.6 ± 0.9	4.1 ± 0.9	4.3 ± 0.8	4.9 ± 0.8
Word list recall					
- Immediate	≥ 28.0	28.3 ± 8.3	23.7 ± 6.8	20.5 ± 6.0	27.1 ± 10.0
- Delayed	≥ 4.8	5.7 ± 2.9	5.0 ± 3.1	1.7[a,b,d] ± 1.7	5.4 ± 1.8
- Identification	≥ 22.6	23.9 ± 4.0	25.1 ± 3.4	19.9 [a,b,d] ± 1.8	25.5 ± 3.7
Token test	≥ 26.5	27.5 ± 4.3	27.6 ± 4.0	28.7 ± 1.8	29.7 ± 4.7
Phonemic fluency	≥ 17.0	19.1 ± 7.0	13.0 [a,c,d] ± 5.4	19.9 ± 5.3	22.1 ± 6.7
Semantic fluency	≥ 25.0	20.8 ± 6.2	19.7 ± 6.0	15.1[d] ± 4.4	22.6 ± 5.0
FAB	≥ 13.5	10.8 ± 2.6	10.1 ± 3.3	9.5 ± 2.7	12.6 ± 2.1
RCPM	≥ 19.0	14.3 ± 3.5	16.1 ± 4.7	17.2 ± 2.8	17.6 ± 3.9
Copy of ROCF	≥ 28.9	10.7 ± 6.2	12.9 ± 6.5	11.8 ± 3.6	12.3 ± 5.4
Poppelreuter-Ghent test	≥ 51.3	42.7[b] ± 9.9	53.0 ± 5.8	48.2 ± 6.8	49.8 ± 7.0
Limb apraxia					
- Right arm	≥ 53.0	53.1 ± 9.3	57.7 ± 8.6	59.2 ± 6.0	62.1 ± 6.8
- Left arm	≥ 53.0	52.6 ± 10.8	56.4 ± 10.7	61.1 ± 6.8	61.6 ± 4.6

Table 9. Socio-demographic, clinical and neuropsychological features of groups with more than 8 patients. Cognitive test scores are raw. MMSE Mini Mental State Examination, ROCF Rey-Osterrieth complex figure, RCPM Raven's color progressive matrices, FAB frontal assessment battery ; $p < 0.01$ versus [a]PCA, [b]CBD, [c]AD, [d]NAS

	Cut-off scores	PCA n= 21	CBD n=19	AD n = 10	NAS n= 8
UPDRS motor score	--	8.3 ± 6.9	17.6[a,c] ± 12.1	7.2 ± 2.6	9.0 ± 9.0
Upper limb myoclonus	--	0 ± 0	0.3 ± 0.6	0 ± 0	0.8 ± 2.0
Upper limbs dystonia	--	0.2 ± 0.4	0.2 ± 0.6	0 ± 0	0 ± 0
RBD inventory	--	0.4 ± 0.8	0.7 ±1.0	0 ± 0	1.6 ± 2.4
Functional inventory	--	14.8 ± 4.2	15.7 ± 4.0	14.7 ± 3.0	13.3 ± 4.9
Graphestesia test	≥ 32.0	13.9[d] ± 8.8	20.8 ± 10.3	22.1 ± 7.9	26.8 ± 7.9
Benton JLO	≥ 19.0	9.0 ± 6.1	11.8 ± 6.0	8.7 ± 4.7	13.8 ± 7.3
Benton faces	≥ 41.0	35.8 ± 5.7	39.5 ± 4.4	36.1 ± 4.4	38.5 ± 5.8
Orobuccal apraxia	≥ 17.0	18.3 ± 1.7	16.6[d] ± 2.3	19.0± 1.3	19.3 ± 1.0
Optic ataxia	≥ 45.6	43.3 ± 6.3	43.4 ± 4.1	42.6 ± 8.9	45.4 ± 5.5
Gaze apraxia	≥ 13.7	13.6 ± 3.4	11.5 ± 3.9	14.6 ± 1.8	13.4 ± 2.4
Navon test	≥ 14.5	12.2 ± 1.6	13.0 ± 2.4	12.1 ± 2.8	13.0 ± 2.4
Acalculia	≥ 8.5	4.8 ± 3.0	6.8 ± 2.6	5.8 ± 1.9	7.9 ± 2.9
Fingers agnosia	≥ 14.0	16.2[b,d] ± 3.0	18.7 ± 1.9	18.4 ± 1.4	19.5 ± 2.1
Agraphia	≥ 28.2	26.2 ± 4.0	25.2 ± 4.9	26.3 ± 2.8	28.3 ± 1.5
Right-Left orientation	≥ 17.0	15.1 ± 4.3	17.1 ± 2.1	15.8[d] ± 2.1	18.8 ± 1.3
Semantic association	≥ 14.0	13.6 ± 1.7	14.1 ± 1.1	14.1 ± 1.0	13.6 ± 1.8
Colors categorization	≥ 21.5	21.0 ± 1.7	20.8 ± 2.1	21.6 ± 1.4	21.6 ± 0.7
Line bisection	≥ 8	7.4[d] ± 1.4	8.3 ± 1.1	8.3 ± 1.3	8.9 ± 0.4
GDS	< 6	3.8 ± 3.0	4.2 ± 4.0	3.1 ± 2.2	5.6 ± 4.3
NPI total score	= 0	7.5 ± 7.2	13.1 ± 13.8	9.3 ± 8.6	9.7 ± 6.9

Table 10. Clinical and neuropsychological features of patients. Cognitive test scores are raw. Benton JLO Benton judgement of line orientation, GDS geriatric depression scale, NPI neuropsychiatric inventory; $p < 0.01$ versus [a]PCA, [b]CBD, [c]AD, [d]NAS.

		LBD			PCA and CBD				PCA and AD		AD and LBD		CBD LBD
	Cut-off scores	B.A.	M.M	S.P.G.	N.G.	A.M.	C.L.	S.A.	I.A.	P.L.	A.M.	V.C.	S.B.
Age	--	82	70	70	77	73	78	78	77	75	61	77	76
Education (years)	--	8	8	5	5	5	0	5	13	5	17	5	5
Sex	--	w	m	w	w	w	w	m	m	w	m	w	m
Disease duration (months)	--	13	11	28	19	28	6	36	45	25	25	73	6
Adjusted MMSE	≥ 24.0	26.2	26.2	24.9	25.03	21.03	24.24	20.03	19.86	25.05	22.46	21.03	27.03
Attentional matrices	≥ 31.0	36	40	34	40	26	27	27	19	38	28	39	39
Digit span	≥ 3.8	4	3	5	4	5	3	5	4	5	5	6	5
Word list recall													
- Immediate	≥ 28.0	17	26	28	35	33	32	14	11	23	19	25	35
- Delayed	≥ 4.8	3	5	8	7	3	6	1	2	3	2	1	6
- Identification	≥ 22.6	26	24	32	28	17	26	15	19	23	26	--	24
Token test	≥ 26.5	31.5	31.5	27.5	27.5	24	22	27	24	30.5	26.5	30	31.5
Phonemic fluency	≥ 17.0	29	26	21	23	14	11	12	18	15	19	24	31
Semantic fluency	≥ 25.0	15	32	17	26	18	18	14	15	20	17	16	35
FAB	≥ 13.5	13	12	13	12	9	6	11	8	12	12	13	11
RCPM	≥ 19.0	24	20	12	13	18	7	8	13	12	19	19	23
Copy of ROCF	≥ 28.9	20	17	6.5	18	13.5	10.5	3.5	5.5	8	17	10.5	13.5
Poppelreuter-Ghent test	≥ 51.3	50	56	50	51	47	46	--	31	39	42	65	49
Limb apraxia													
- Right arm	≥ 53.0	66	61	69	47	56	52	55	43	52	61	65	60
- Left arm	≥ 53.0	69	67	67	58	50	50	49	51	51	63	64	57

Table 11. Socio-demographic, clinical and neuropsychological features of patients. Cognitive test scores are raw. MMSE Mini Mental State Examination, ROCF Rey-Osterrieth complex figure, RCPM Raven's color progressive matrices, FAB frontal assessment battery.

		LBD			PCA e CBD				PCA e AD		AD e LBD		CBD LBD
	Cut-off scores	B.A.	M.M	S.P.G.	N.G.	A.M.	C.L.	S.A.	I.A.	P.L.	A.M.	V.C.	S.B.
UPDRS motor score	--	19	10	4	18	2	11	8	--	--	2.5	5	13
Upper limbs myoclonus	--	0	0	0	0	0	0	0	0	0	0	--	0
Upper limbs dystonia	--	1	--	0	0	0	0	0	0	1	0	0	0
RBD inventory	--	0	5	--	0	--	1	1	1	0	7	0	3
Functional inventory	--	18	15	6	20	19	--	8	16	17	17	13	19
Graphestesia test	≥ 32.0	33	9	34	19	15	13	21	18	17	24	23	18
Benton JLO	≥ 19.0	18	19	9	7	10	3	--	14	10	16	9	16
Benton faces	≥ 41.0	34	41	39	43	39	28	34	39	41	45	39	41
Orobuccal apraxia	≥ 17.0	--	--	20	--	19	--	18	14	15	20	--	--
Optic ataxia	≥ 45.6	46	47	42	40	44	28	45	48	46	47	--	45
Gaze apraxia	≥ 13.7	16	16	15	14	16	13	12	13	15	16	15	--
Navon test	≥ 14.5	15	14	12	11	7	12	12	13	4	15	13	14
Acalculia	≥ 8.5	9	4	5	3	5	--	6	5	9	8	5	7
Fingers agnosia	≥ 14.0	20	21	20	19	19	11	12	17	16	17	17	16
Agraphia	≥ 28.2	30	21	26	28	24	--	29	30	28	30	28	22
Right-Left orientation	≥ 17.0	17	18	18	15	16	11	19	17	17	15	12	19
Semantic association	≥ 14.0	15	15	14	15	13	14	15	11	15	15	15	15
Colors categorization	≥ 21.5	20	21	22	22	24	24	24	21	22	20	24	24
Line bisection	≥ 8	9	9	9	7	9	7	7	9	8	8	4	7
GDS	< 6	9	8	9	3	0	4	2	4	0	8	11	5
NPI total score	$= 0$	24	16	--	1	8	12	57	19	2	6	14	6

Table 12. Socio-demographic, clinical and neuropsychological features of patients. Cognitive test scores are raw. Benton JLO Benton judgement of line orientation, GDS geriatric depression scale, NPI neuropsychiatric inventory, FM scale modified Fahn-Marsden dystonia scale modified.

4.2. Principal Component Analysis

4.2.2. Components extraction

PCAnalysis extracted four components (with eigenvalues of 3.18, 1.3, 1.1 e 1.0 respectively) accounting for 66% of the variance. In table 13, components and loadings are reported. Kaiser-Meyer-Olkin measure of sampling adequacy was 0.739 and the determinant was 0.129.

	Component			
	1	**2**	**3**	**4**
ROCF copy	0.824			
Poppelreuter-Ghent test	0.685			
Balint Holmes syndrome	0.651			
Face recognition test	0.555			-0.515
Gerstmann syndrome		0.836		
Limb apraxia		0.784		
Benton JLO	0.502	0.515		
Colors categorization			0.817	
Semantic association			0.636	
Line bisection				0.769

Table 13. Extracted components and variable loadings.

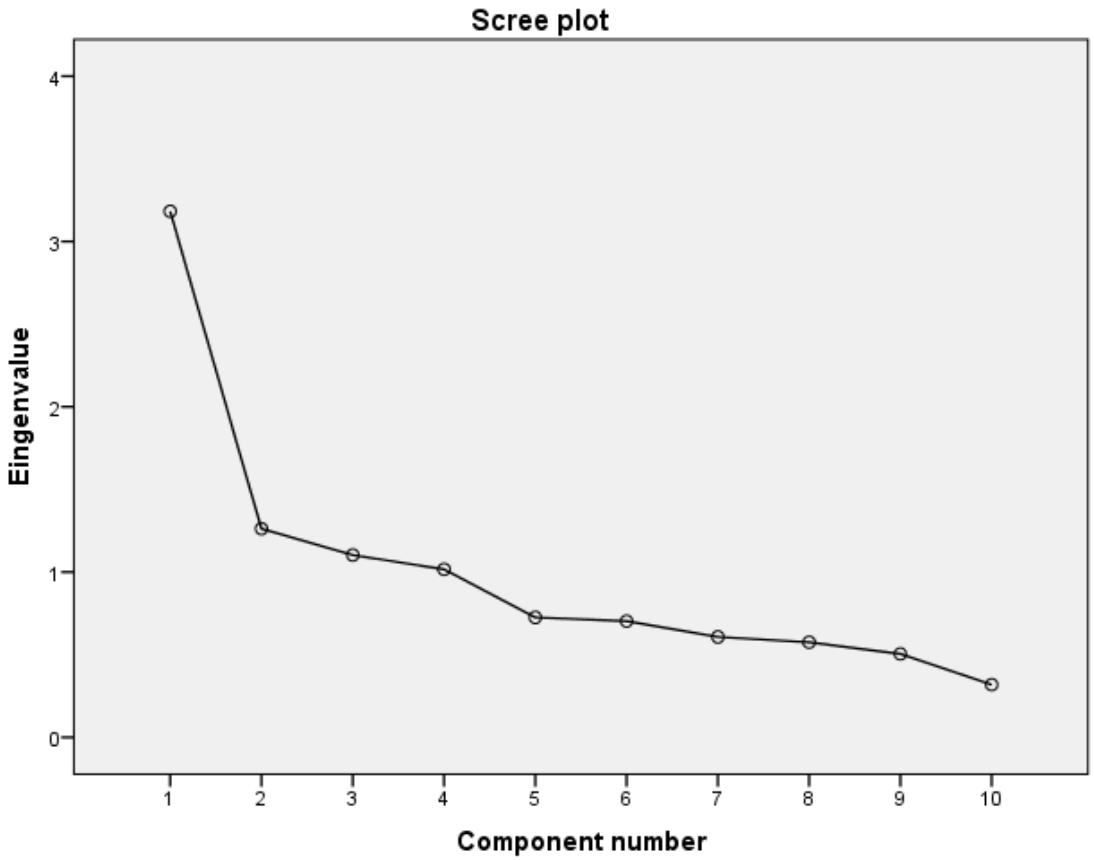


Figure 9. Scree plot of components extraction.

As can be seen from Table 13, ROCF copy, Poppelreuter-Ghent test, Balint-Holmes syndrome composite score, face recognition test and Benton JLO loaded on the first component that accounts for 23% of the variance; we labeled this component as Apperceptive Cluster (ApC).

The second component accounts for the 20% of the total variance and is loaded by Gerstmann syndrome composite score, limb apraxia and Benton JLO; we labeled it as Gerstmann-Apraxia Cluster (GAC).

Color categorization and semantic association loaded on the third component, accounting for the 12% of the variance; this component was labeled as Associative Cluster (AsC).

Finally, PCAnalysis extracted a fourth component accounting for the 11% of the variance on which line bisection had a positive load and face recognition test had a negative load. This factor had an eigenvalue only just above the criterion of 1 (1.02) and was therefore disregarded as additional subsyndrome.

4.2.3. Patients classification

We considered *factor scores* to classify patients within the three subsyndromes emerged from PCAnalysis. Seven out of 70 patients resulted impaired only in the fourth component, which we did not consider as a subsyndrome. Therefore these seven cases were reclassified according to their factor scores in the other three components.

Thirty-nine percent of patients (n= 27) had a homogeneous impairment of the three posterior cognitive domains (*generalized impairment* – GI), while 61% (n = 43) showed a differential impairment in one or two components (Figure 10). More precisely, considering the 61%, 28 (65%) had one or two factor scores $\leq$ -1, while the remaining 15 (34%) had one or two factor scores > 1. As reported in the Methods, these latter cases were considered as proportionally more impaired in the component or components with the lower factor scores. In order to be sure that they could not represent GI patients in an earlier disease stage than the other GI cases, we compared their disease duration with disease duration of GI patients. Given that no significant difference was observed ($t = -1.465$; $p = 0.157$), those 15 patients were considered pseudofocal (like the other 28 cases with a differential impairment across the various posterior components).

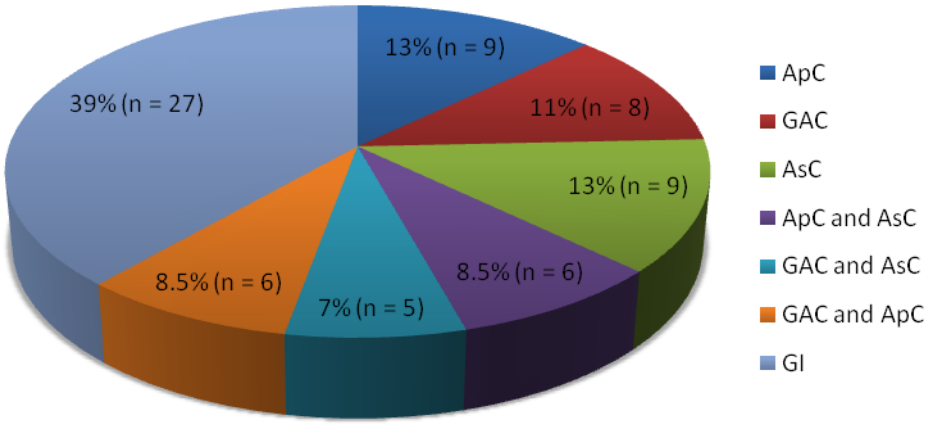


Figure 10. Patients classification within subsyndromes.

Of the 21 PCA, 47.5% (n = 10) showed one subsyndrome while the 24% (n = 5) showed a combination of two subsyndrome; the remaining 28.5% (n = 6) of patients had a GI (Figure 11).

Of the 19 CBD, 47.5% (n = 9) showed one subsyndrome, one patient (5%) showed a combination of two subsyndrome, while the 47.5% (n = 9) had a GI (Figure 11).

Of the 10 AD, 30% (n = 3) showed one subsyndrome, 20% (n = 2) showed two subsyndromes and the 50% (n = 5) had a GI (Figure 11).

Twenty-five percent (n = 2) of NAS patients were AsC, 25% (n = 2) Apc + AsC and 50% (n = 4) had a GI (Figure 11).

Considering the patients meeting diagnostic criteria for more than one dementia, 80% (n = 6) showed a combination of two subsyndromes and the remaining 20% (n = 2) had a GI (Figure 12).

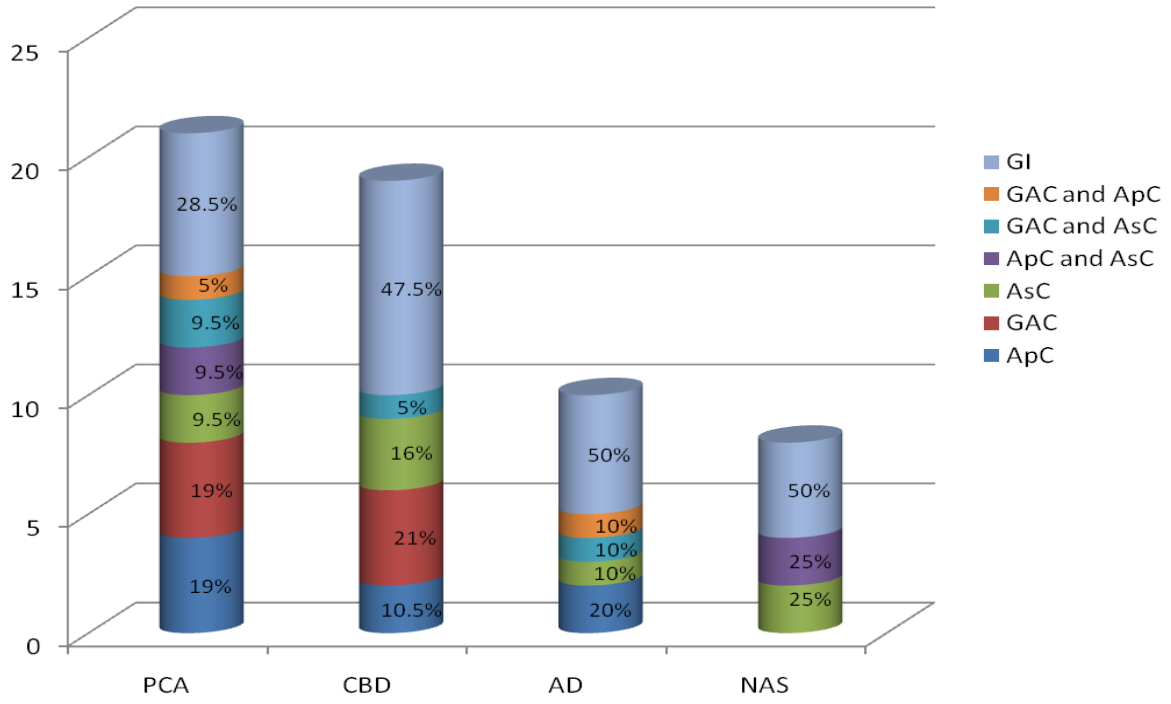


Figure 11. Patients classification within subsyndromes.

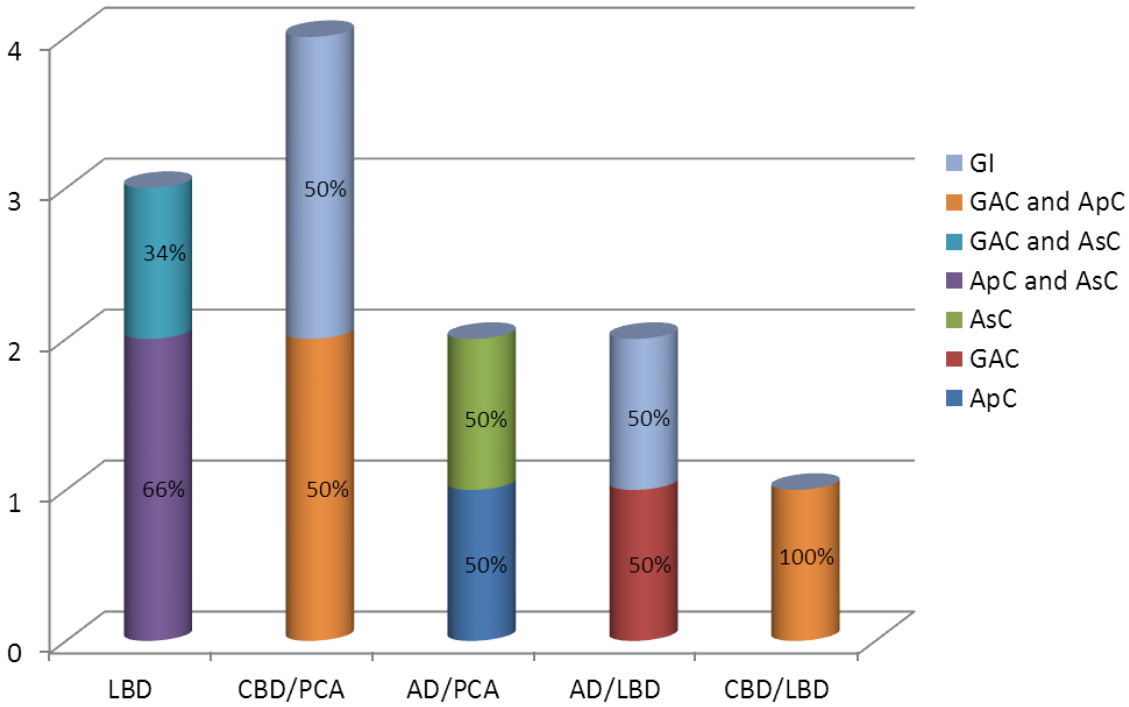


Figure 12. Patients classification within subsyndromes.

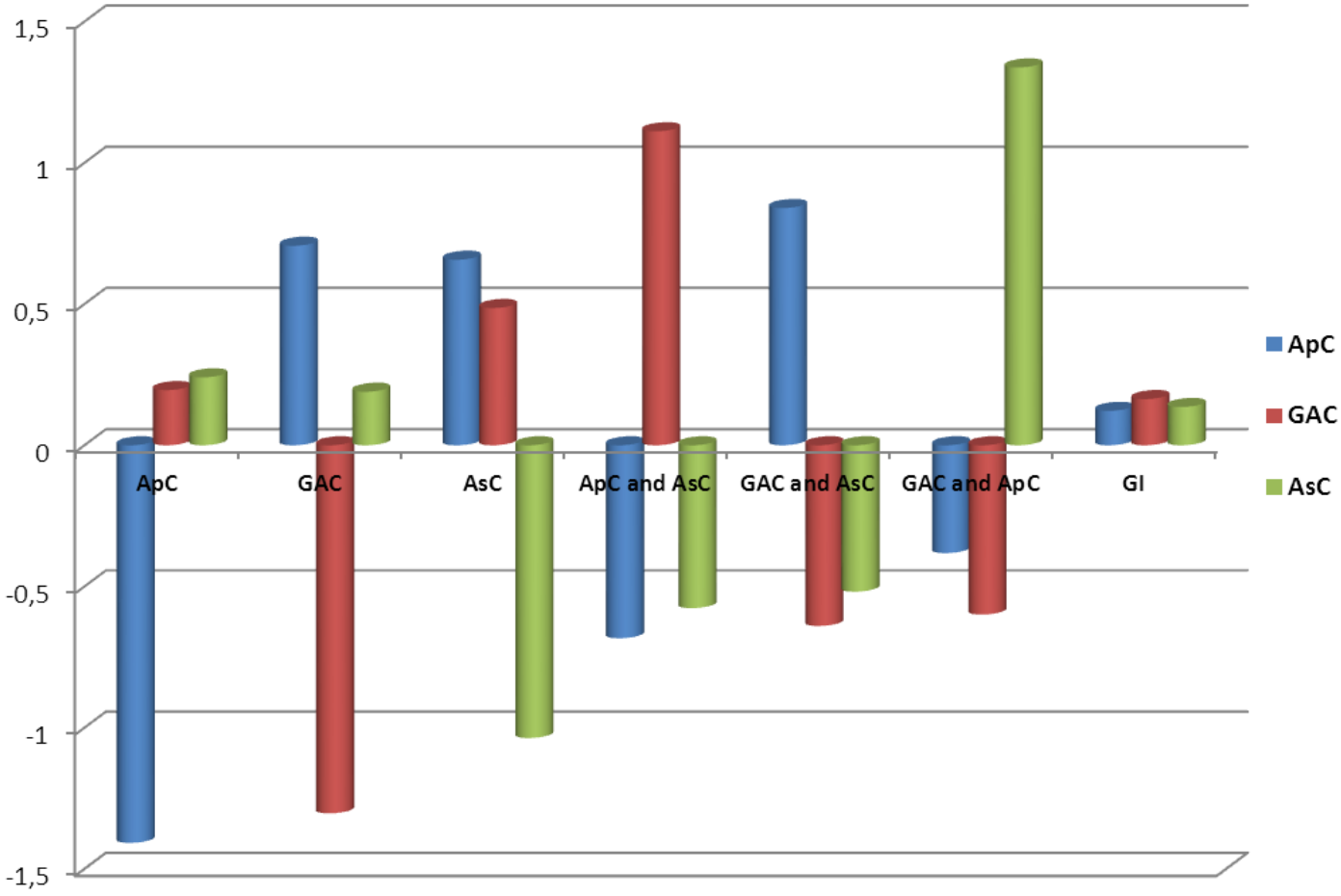


Figure 13. *Factor scores* means of the different profiles observed.

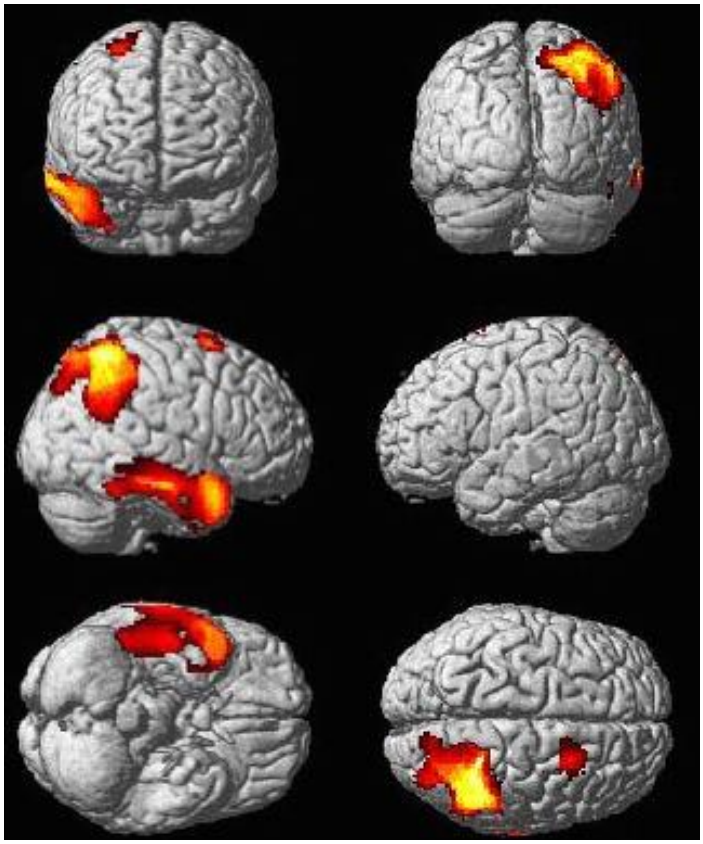
4.3. [18F]FDG-PET data analysis: results

4.3.1. Cerebral metabolism differences between patients and healthy controls

Comparison between the whole sample of patients and healthy controls showed three clusters of hypometabolism with p<0.001 and a voxel extent of 500. The first cluster has an extent of 5263 voxels and has its peak of significance in the right supramarginal gyrus (BA 40; x= 26, y= - 42, z =46 zscore =5.1). The second cluster has an extent of 514 voxels and its peak is in the right superior frontal gyrus (BA 6; x= 28, y= 10, z = 70; zscore= 4.4). The third cluster has an extent of 2672 voxels and the peak is in the middle temporal pole (BA 38; BA 6; x= 48, y= 16, z = -26; zscore= 4.4). In Table 14 brain regions showing the greatest significant effects are reported.

	Talairach Coordinates							
	x	*y*	*z*	*Z score*	*x*	*y*	*z*	*Z score*
Brain regions (BA)	**Left hemisphere**				**Right hemisphere**			
Frontal Cortex								
Sup. frontal gyrus (6)					28	10	70	4.4
Parietal Cortex								
Sup. parietal gyrus (7)					16	-78	60	3.5
Angular gyrus (39)					42	-50	30	5.0
Supramarginal gyrus (40)					26	-42	46	5.1
Temporal cortex								
Sup. temporal gyrus (22)					74	-22	-10	3.9
Mid. temporal gyrus (21)					70	-14	-16	3.7
Mid. temporal pole (38)					48	16	-26	4.1
Inf. temporal gyrus (20)					46	-44	-22	3.7
Fusiform gyrus (20)					32	0	-46	3.2
Occipital cortex								
Mid. occipital gyrus(19)					36	-82	42	3.5

Table 14. Group main effect.



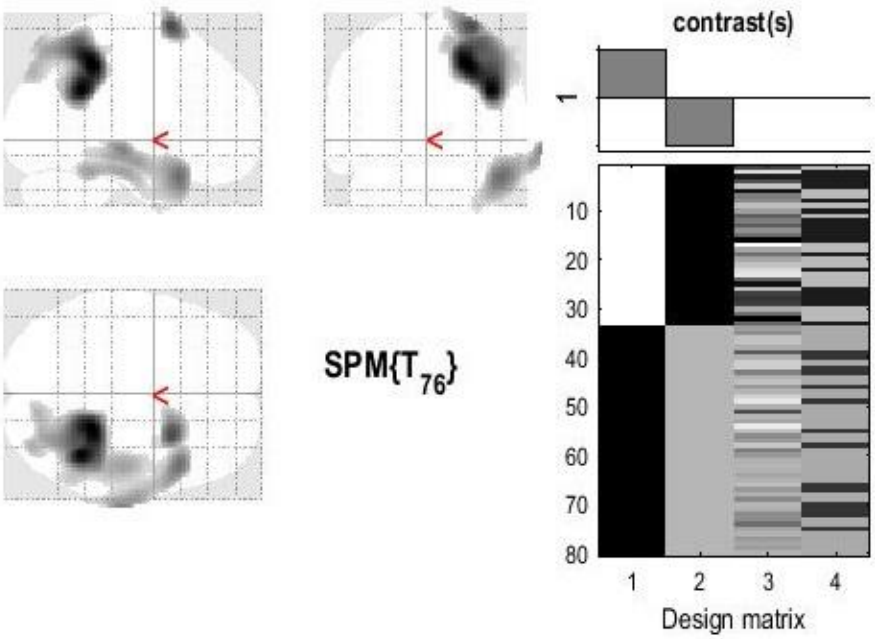


Figure 14. Significant differences between patients and healthy controls.

4.3.2. Multiple regression between cerebral hypometabolism and *factor scores*

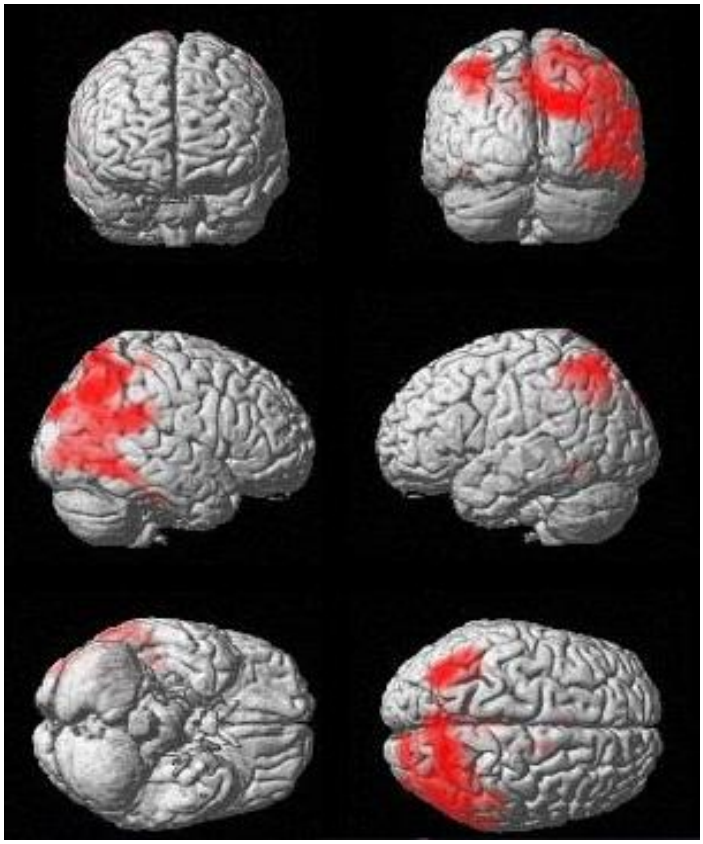
For this analyses a significance level of $p < 0.01$ and a voxel threshold of 100 was considered.

Apperceptive Cluster

The regression analyses showed a large posterior cluster of areas that correlated with *factor scores* of the ApC component. The peaks of correlation are found in the right superior occipital gyrus, in the left superior parietal gyrus, in the right cuneus, precuneus, posterior cingulum, in the superior temporal gyrus and in the fusiform gyrus. Another cluster was observed in the frontal lobe and in particular in the right superior frontal gyrus and prencentral gyrus and in the left SMA. See Table 15 and Figure 15.

	Talairach Coordinates							
	x	*y*	*z*	*Z score*	*x*	*y*	*z*	*Z score*
Brain regions (BA)	**Left hemisphere**				**Right hemisphere**			
Frontal cortex								
Superior frontal gyrus (6)					14	-6	80	2.6
Precentral gyrus (4)					16	-22	86	2.7
SMA (6)	-4	8	78	2.7				
Parietal cortex								
Postcentral (2)					52	-38	64	3.2
Sup. parietal gyrus (2)					52	-42	62	3.0
Sup. parietal gyrus (7)	-38	-70	60	3.8	20	-66	66	3.1
Precuneus (23)					8	-50	22	3.6
Posterior cingulum (26)					4	-42	28	3.6
Temporal cortex								
Sup. temporal gyrus (41)					46	-42	22	3.5
Sup. temporal gyrus (22)					68	-48	20	2.9
Fusiform gyrus (37)					36	-62	10	3.4
Occipital cortex								
Sup. occipital gyrus (18)					20	-96	34	4.0
Mid. occipital gyrus (7)	-34	-66	40	3.1				
Mid. occipital gyrus (19)					34	-68	36	3.2
Inf. occipital gyrus (19)					44	-92	-2	3.3
Cuneus (18)					18	-66	30	3.7

Table 15. Results of regression between cerebral metabolism and *factor scores* of ApC.



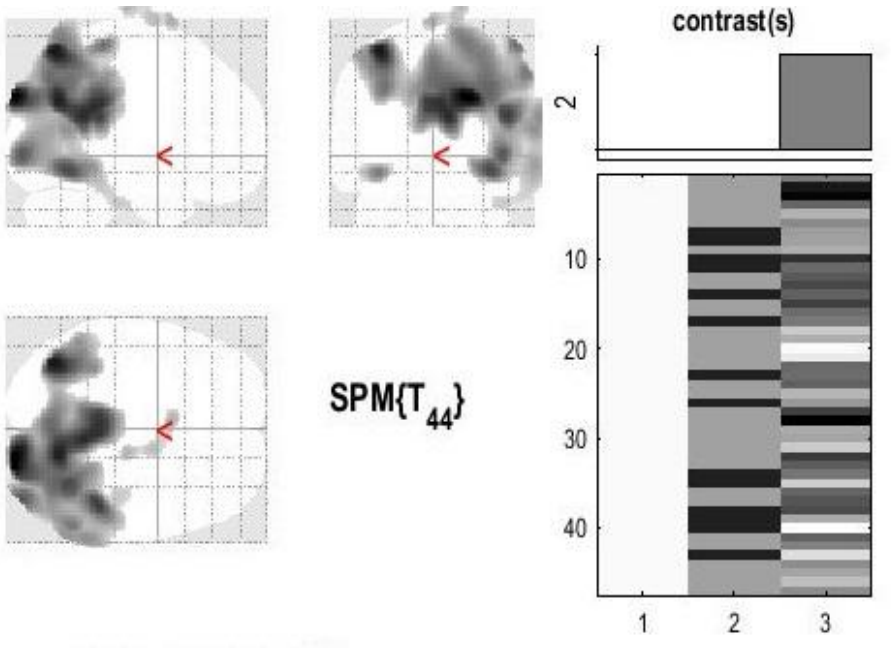


Figure 15. Results of regression between cerebral metabolism and *factor scores* of ApC.

Gerstmann-Apraxia Cluster

For this component, the analyses showed correlation in left middle occipital gyrus, superior temporal gyrus and angular gyrus. In the right hemisphere, this component showed a significant correlation with cerebellum. See Table 16 and Figure 16.

	Talairach Coordinates							
	x	*y*	*z*	*Z score*	*x*	*y*	*z*	*Z score*
Brain regions (BA)	**Left hemisphere**				**Right hemisphere**			
Parietal Cortex								
Angular gyrus (22)	-68	-58	24	2.5				
Temporal cortex								
Sup. temporal gyrus (22)	-60	-48	22	2.6				
Occipital cortex								
Mid occipital gyrus (39)	-40	-76	16	2.7				
Cerebellum					44	-66	-24	2.7

Table 16. Results of regression between cerebral metabolism and *factor scores* of GAC.

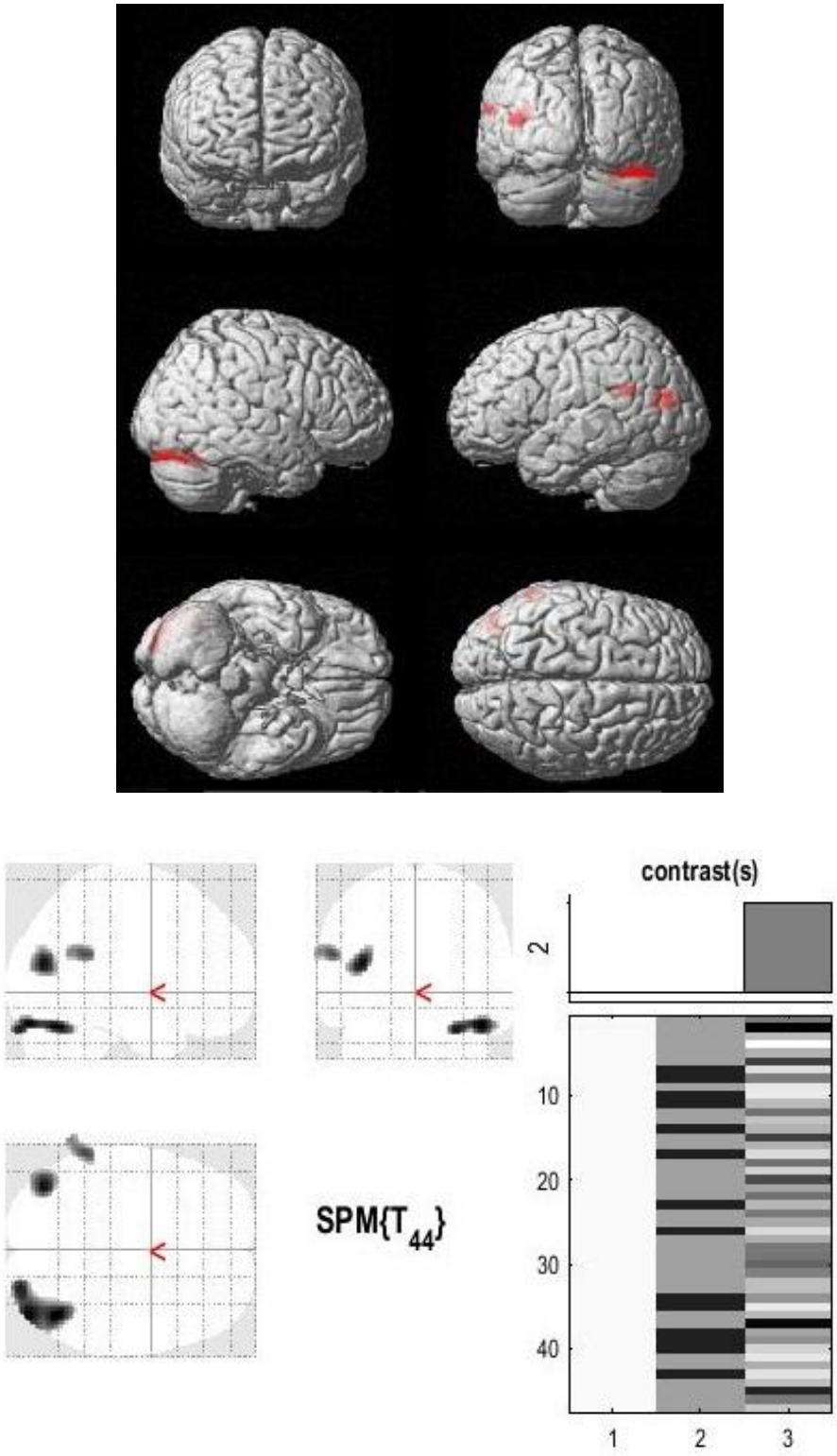


Figure 16. Results of regression between cerebral metabolism and *factor scores* of GAC.

Associative Cluster

The third component showed a left temporal cluster including middle occipital gyrus, superior and middle temporal gyrus and angular gyrus. See Table 17 and Figure 17.

	Talairach Coordinates							
	x	*y*	*z*	*Z score*	*x*	*y*	*z*	*Z score*
Brain regions (BA)	**Left hemisphere**				**Right hemisphere**			
Parietal cortex								
Angular gyrus (39)	-50	-62	8	2.9				
Temporal cortex								
Sup. temporal gyrus (42)	-62	-46	24	2.9				
Mid. temporal gyrus (21)	-54	-34	-6	2.8				
Occipital cortex								
Mid occipital gyrus (39)	-38	-70	18	2.9				

Table 17. Results of regression between cerebral metabolism and *factor scores* of AsC.

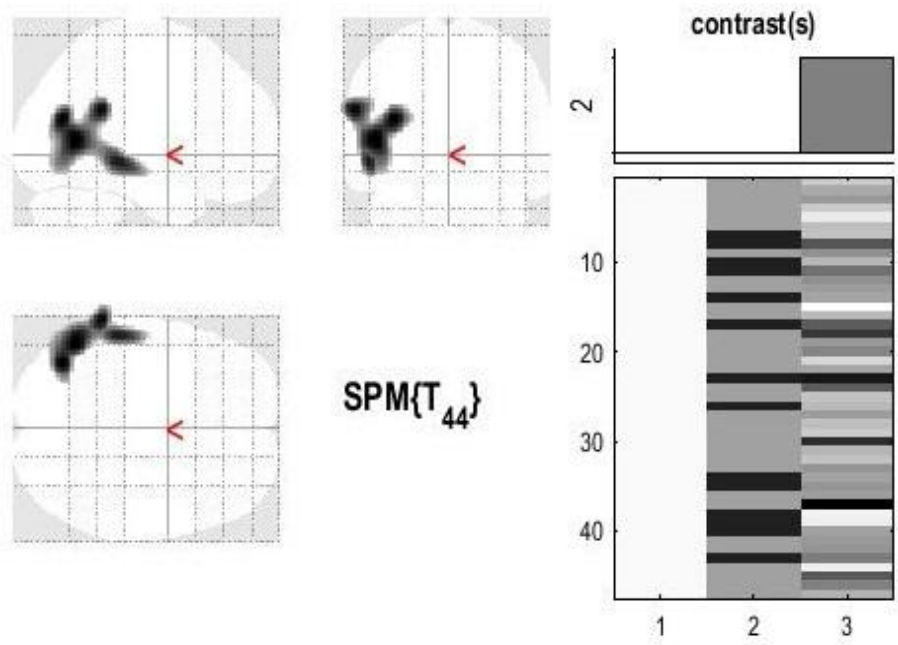


Figure 17. Results of regression between cerebral metabolism and *factor scores* of AsC.

Component four

For the sake of completeness we conducted multiple regression also with factor scores of the fourth component extracted. A large right hemisphere cluster was observed. The peaks of correlation was located in right supramarginal gyrus, superior parietal gyrus, precuneus and in superior frontal gyrus. Correlation was also observed in left supramarginal gyrus, superior parietal gyrus and cuneus although with a lower significance and extension. See Table 18 and Figure 18.

	Talairach Coordinates							
	x	*y*	*z*	*Z score*	*x*	*y*	*z*	*Z score*
Brain regions (BA)	**Left hemisphere**				**Right hemisphere**			
Frontal cortex								
Sup. frontal gyrus (6)					28	-8	74	3.8
Mid. frontal gyrus (9)					40	30	52	3.2
Precentral gyrus (4)					52	-14	64	3.2
Precentral gyrus (44)					44	6	32	2.6
Inf. frontal gyrus tri. (48)					36	18	24	3.0
Inf. frontal gyrus op. (48)					50	10	4	2.6
Parietal cortex								
Sup. parietal gyrus (7)	-34	-82	50	3.3				
Sup. parietal gyrus (40)					40	-58	64	3.6
Precuneus (7)					6	-66	72	3.7
Mid. Cingulum (23)					12	-36	46	2.8
Supramarginal gyrus (22)					68	-44	28	4.1
Supramarginal gyrus (40)					44	-34	38	4.0
Supramarginal gyrus (48)	-56	-44	32	2.7				
Temporal cortex								
Mid. temporal gyrus (39)					42	-60	22	2.7
Occipital cortex								
Sup. occipital gyrus (19)					32	-84	46	3.5
Mid. occipital gyrus (19)					-28	-92	40	2.9
Mid. occipital gyrus (39)					44	-78	34	3.1
Cuneus (18)	-10	-92	30	3.3				
Cuneus (19)					18	-90	46	3.2

Table 18. Results of regression between cerebral metabolism and *factor scores* of component four.

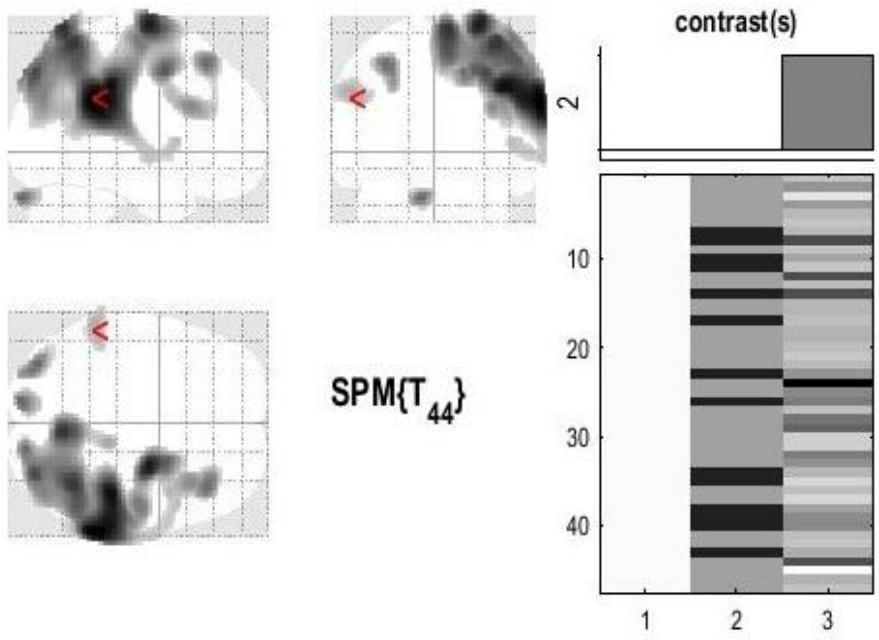


Figure 18. Results of regression between cerebral metabolism and *factor scores* of component four.

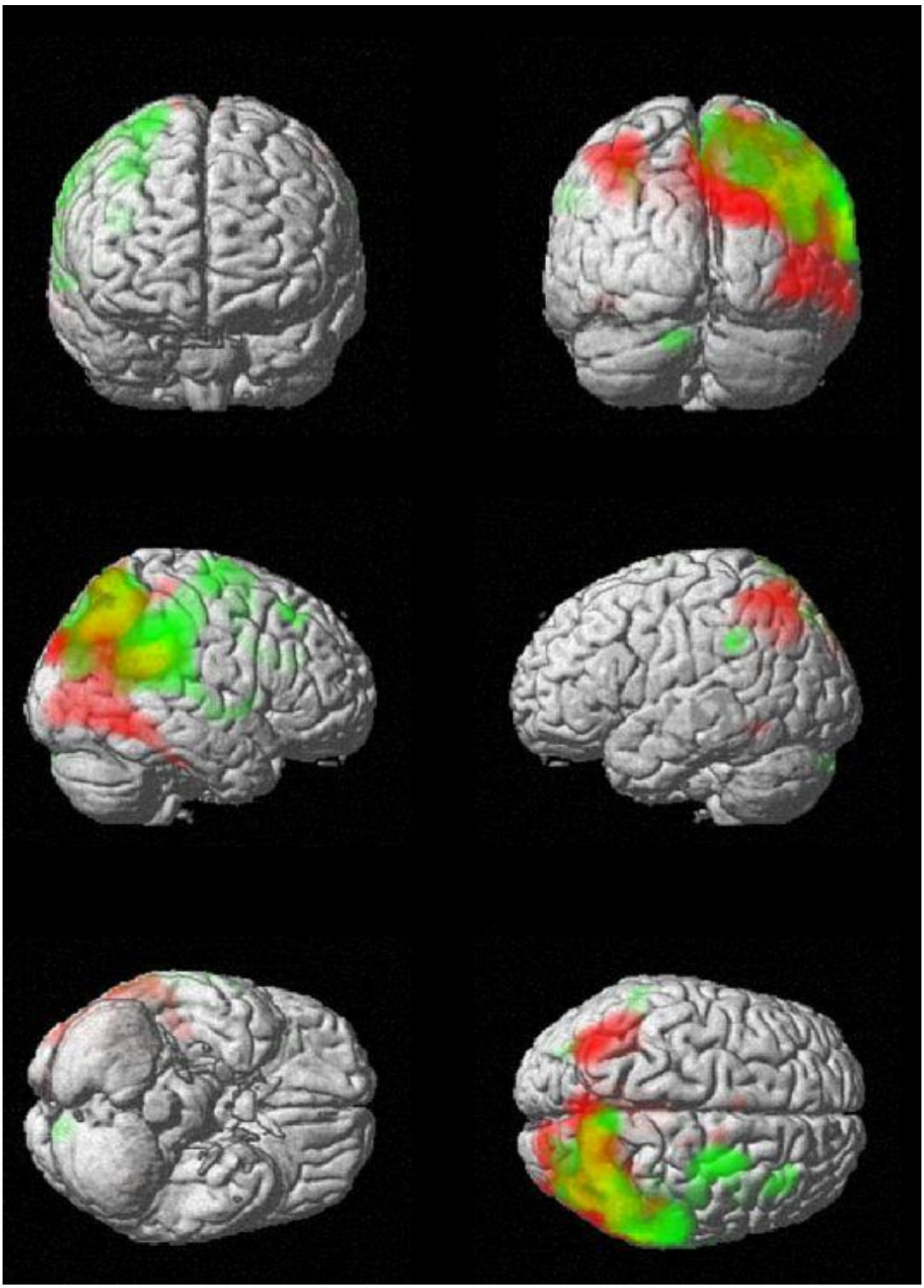


Figure 19. Representation of the results of the multiple regressions for ApC and component four.

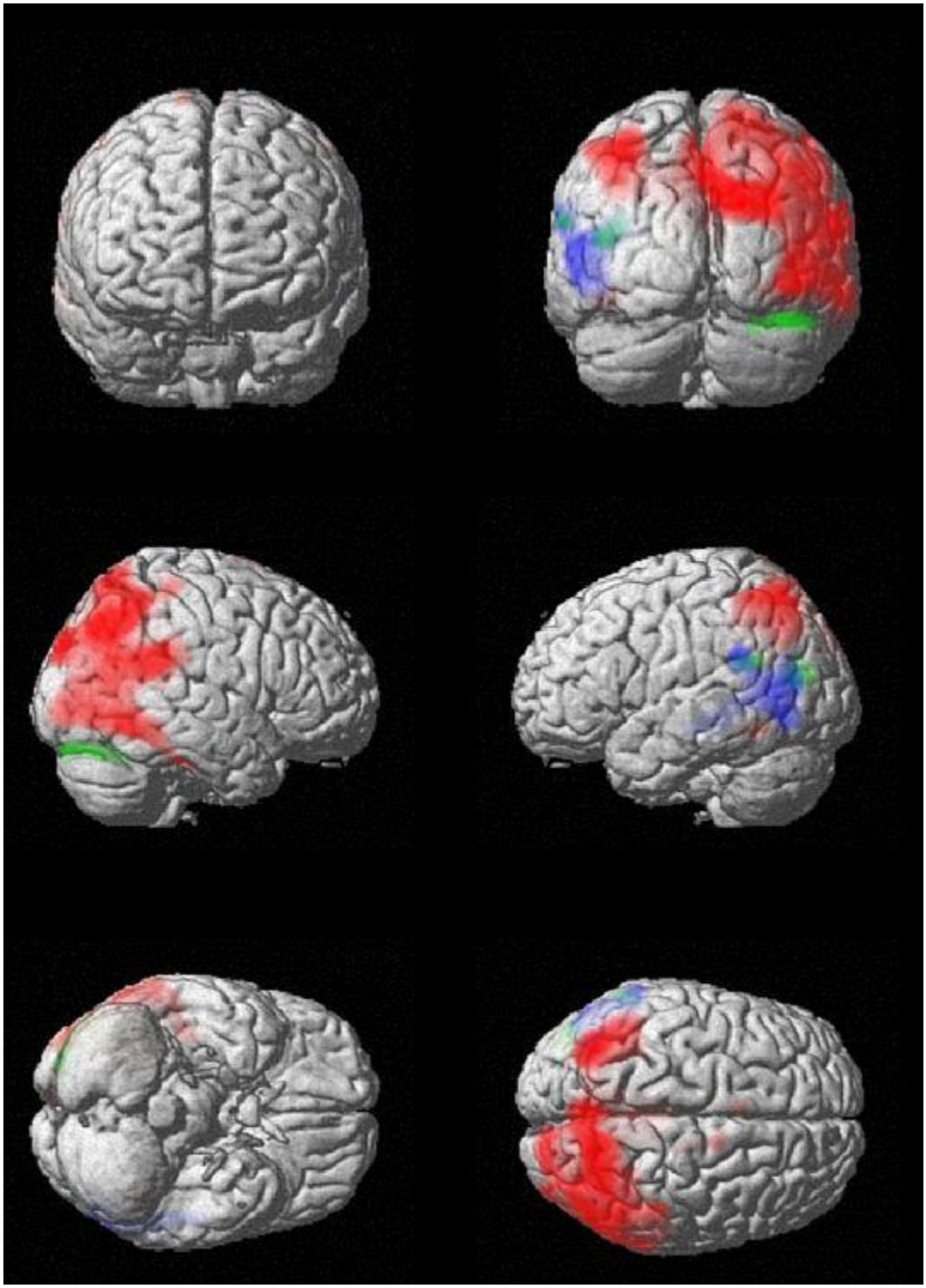


Figure 20. Representation of the results of the multiple regressions for the three subsyndromes extracted. In red, green and blue are represented areas of which activity was correlated with *factor scores* of ApC, GAC and AsC, respectively.

5. Discussion

In the present project we focused on the differential diagnosis of cognitive syndromes affecting, at onset, posterior cerebral networks.

The aim of this study was to characterize a group of patients, with early visuo-spatial or praxic deficits and a relative spare of memory and language functions, on the basis of the posterior cognitive profile, using PCAnalysis; secondly we aimed to compare the diagnosis based on current diagnostic criteria and the classification of patients made with PCAnalysis to verify if this approach, driven exclusively by empirical data, would yield converging results. In the last part of the project, in a subgroup of patients, we also correlated the results of PCAnalysis with cerebral hypometabolism measured with 18F]FDG-PET.

Our sample was composed of 70 patients: 21 PCA, 19 CBD, 10 AD, 8 NAS and 12 patients that met more than one set of diagnostic criteria. As reported in literature (Renner et al., 2004; McMonagle et al., 2006; Ryan et al., 2014) we observed a general overlapping of the posterior cognitive profile; few differences were observed: PCA resulted more impaired than CBD in apperceptive agnosia and fingers agnosia; they resulted also worst than NAS group in fingers agnosia and line bisection. Considering the whole cognitive profile AD resulted more impaired in memory than the other groups; CBD presented significantly more signs of parkinsonism than PCA and AD, and they were worst in orobuccal apraxia than NAS patients, as expected from diagnostic criteria (Armstrong et al., 2013).

SPM comparison of cerebral metabolism between healthy subjects and our sub-group of 47 patients showed significant hypometabolism primarily in the posterior right hemisphere and in particular in the angular gyrus, in the supramarginal gyrus and in the temporal lobe, including the pole. These findings reflect previous studies that showed prevalent posterior cortical alterations in these patients, with a major involvement of the right hemisphere (Nestor et al., 2003; Lehmann et al., 2011; Whitwell et al., 2007). We also found a smaller area of hypometabolism in the frontal cortex corresponding to the superior frontal gyrus (BA 6); our hypothesis is that this dysfunction can be related to oculomotor apraxia even if the hypometabolic area is not exactly correspondent to FEF, as reported in previous works (Nestor et a., 2003; Kas et al., 2011). Considering the heterogeneity of our sample, another possible explanation could be the presence of CBD patients in which a frontal hypometabolism has been described (Juh et al., 2005).

PCAnalysis extracted from our data set four components. The first component, that we labeled "Apperceptive Cluster" (ApC), was loaded by ROCF copy, Poppelreuter-Ghent test, Balint-Holmes syndrome, face recognition test and Benton JLO. *Factor scores* derived from this component correlated with a large cluster of hypometabolism in right hemisphere including superior parietal gyrus, superior temporal gyrus and fusiform gyrus, occipital cortex and a frontal cluster (BA 4 and 6); hypometabolism of superior parietal gyrus and middle occipital gyrus was evident also in the left hemisphere. These metabolic correlates are consistent with the previous findings; different lesional and functional imaging studies showed the role of this posterior brain areas in the execution of this tasks. Right occipito-parietal, superior parietal and occipital cortices seems to be crucial for ROCF, Benton JLO, Poppelreuter-Ghent test (Ishioka et al., 2011; Tranel et al., 2009; Biesbroek et al., 2014) while Balint-Holmes syndrome is caused by bilateral occipito-parietal lesions (Valenza et al., 2004; Walsh et al., 2012); right fusiform gyrus is involved in face processing (Tranel et al., 2009). Visuoperceptive functions seem also to be related to the activity of right temporal lobe (Biesbroek et al., 2014; Fujimory et al., 2000) and frontal lobe (Biesbroek et al., 2014). Another finding, consistent with our results, is the activation of precuneus in a fMRI task similar to Benton JLO (Walsh et al., 2012). In discrepancy with literature (Biesbroek et al., 2014; Tranel et al., 2009), in our anatomical correlation, we did not observe right supramarginal and angular gyrus, even if these were areas strongly hypometabolic in our sample, maybe because of these areas are not crucial in all the tasks that loaded on ApC and that not all the tasks contributed with the same loading on the component; another explanation could be the fact that correlation has been performed in a sub-group of patient, while *factor scores* were calculated in the whole sample.

The second component, labeled "Gerstmann-Apraxia Cluster" (GAC) was loaded by Gerstmann syndrome, limb apraxia and Benton JLO and had as hypometabolism correlates the left parieto-temporal-occipital junction (including angular gyrus) and a cluster in the right cerebellum. Even if there's no agreement on considering Gerstmann syndrome a real syndrome, the importance of left angular gyrus or left subangular regions has been showed in several studies (Mazzoni et al. 1990; Mayer et al., 1999; Carota et al., 2004). Also for limb apraxia there's agreement on the role of left parietal lobe (Karenken et al., 1998; Buxbaum et al., 2007; Goldmann Gross and Grossman, 2008). Correlation with right cerebellum could be caused by crossed cerebrocerebellar diaschisis or by the implication of cerebrocerebellar network in the pathophysiology of different forms of apraxia as reported in Mariën et al. (2015).

The third compenent labeled “Associative Cluster” (AsC) was loaded by semantic association and color categorization; hypometabolism correlation was observed in the posterior part of left hemisphere and in particular in the angular gyrus, in the superior and middle temporal gyri and in the middle occipital gyrus. Color perception is usually associated with activations of left fusiform gyrus (Chao and Martin, 1999; Simmons et al., 2007), but in our task also some other aspects of color processing could have been elicited, in particular semantic information retrieval about colors; this seems to be in agreement with a study of Roux et colleagues (2003) in which a direct intracranial stimulation of left angular gyrus interfered with colors naming. There are also several evidences that show the importance of lateral temporal cortex in semantic knowledge in particular in naming and recognition of objects (Tranel et al., 1997). Our hypotheses is that this component reflects the retrieving of semantic visual characteristics of our stimuli, given that semantic association task is a visual matching of pictures.

The last component was loaded positively by line bisection and negatively with face recognition test; as reported in the Results, this factor had an eigenvalue only just above the criterion of 1 and it was actually composed of one test, therefore it was disregarded as additional subsyndrome. For the sake of completeness we conducted multiple regression with cerebral metabolism and it showed a large cluster in the right hemisphere and some areas in the left hemisphere; peak of hypometabolism was found in right supramarginal gyrus, right superior frontal gyrus, right precuneus and superior occipital gyrus. These findings are, again, in agreement with literature; lesions of temporo-parietal junction (Vallar and Perani, 1986), posterior parietal cortex (Azouvi et al., 2002), supramarginal gyrus (Doricchi and Tomaiuolo, 2003), as well as dorsolateral and inferior fontal cortices (Ringman et al., 2004) have been described to be crucial in causing neglect.

This pattern of correlation shares some areas with the correlation pattern of ApC, even if it included more dorsal and anterior areas. The common areas are the superior parietal gyrus bilaterally, the right precuneus, the right superior frontal gyrus, the right superior temporal gyrus and the right superior occipital gyrus; as discussed above for the first component, correlation with these areas seems to account for visuoperceptive components of line bisection task. Differences of correlation pattern were observed in the inferior part of right occipital lobe and in the right fusiform gyrus. This difference in the correlation pattern in right fusiform gyrus could be explained by the fact that face recognition task has a negative load on the fourth component and this indicates a relative spared face processing. This hypothesis seems to be confirmed by data from those seven patients that resulted impaired in this fourth

component; their performance in face recognition test is significantly better than patients resulted impaired in ApC ($U = 2.5$; $p = 0.005$).

Taken together, with PCAnalysis we have highlighted three subsyndromes: the first one (ApC) is prevalently right-sided and it seems to reflects apperceptive and visuospatial deficit, the second (GAC) and the third one (AsC) are left-sided and they reflect praxics and associative disorders, respectively.

Previous works have described different subtypes of PCA hypothesizing the presence of a biparietal variant, an occipito-temporal variant and a visual failure variant (Galton et al., 2000; Ross et al., 1996; patients with biparietal (although often asymmetric) variant were characterized by visuospatial deficits, apraxia, dysgraphia and Balint-Holmes syndrome patients presenting with the occipito-temporal variant had deficits in objects recognition, topographic agnosia, alexia, prosopoagnosia, impaired colors vision and Gerstmann syndrome. Visual failure variant is very rare, seems to be caused by dysfunction of visual cortex and it is characterized by reading difficulties, locating and identifying objects deficits (Galton et al., 2000). Also McMonagle and colleagues in 2006 described a group of 19 PCA testing dysfunctions in both dorsal and ventral visual stream; dorsal stream signs were most prevalent among the patients while no patients showed a pure ventral stream syndrome (McMonagle et al., 2006). More recently, Lehmann and colleagues found trends toward a lower cortical thickness in ventral and dorsal regions in patients with objects decision deficits and spatial deficits, respectively (Lehmann et al., 2011).

Our findings are not totally in agreement with the literature; in our sample of patients, we found a large cluster of anatomical correlation in the right hemisphere including both ventral and dorsal visual streams for the ApC component while the other two clusters (GAC and AsC) are left-sided and they are located on the boundaries between the two visual streams. Our hypothesis is that there are clinical syndromes more related to tasks and functions localization instead of syndromes related to visual pathways neuro-anatomy. We highlighted a posterior right hemisphere syndrome that seems to account for the visuopercetive and visuospatial deficits and that reflects previous findings on lateralization of posterior clinical syndromes (Nestor et al., 2003; Lehmann et al., 2011; Whitwell et al., 2007). Secondly, we described two left syndromes; GAC component seems to rely on the so called “ventro-dorsal” visual stream proposed by Rizzolatti and Matelli in 2003, a system devoted to object use representations that causes limb apraxia if lesioned (Binkofski and Bubxbaum, 2013). Finally, the third syndrome is located in the left posterior part of the ventral stream and it accounts for deficits in visual semantics processing.

These differences with previous findings could have been influenced by different aspects; our sample is larger than the previous reports: we described 70 patients while Lehmann (2001) described 21 patients and McMonagle (2006) had a group of 19 PCA; another reason could be the difference in neuropsychological battery that could emphasize different aspects of the different groups of patients. Finally, our population was likely not homogeneous in term of neuropathology while Galton et colleagues (2000) described the posterior cortical atrophy variants in a group of 13 autopsy-proven AD; we can not be sure that different pathologies affects brain structure and neural pathways in the same way.

According to literature, we confirmed the cognitive overlap of these clinical syndromes and the difficulty in finding some cognitive aspects that can help *in vivo* differential diagnoses. Considering the whole sample, the 39% percent of patients resulted GI and this means that they are not prominently impaired in one component than in the others; the other 61% presented a prominent impairment in one (37% of the whole sample) or two components (23%). No patients showed impairment in all three components. Considering clinical diagnoses according to current diagnostic criteria no significant association was found between a clinical diagnosis and the impairment in a certain component; if we consider together the ApC and AsC components, that from diagnostic criteria could be more impaired in PCA, we can observe a slight trend (38% of PCA, 30% of AD, 26% of CBD and 100% of AD/PCA); in the NAS group we observed the 50% (4 out of 8) of patients that are AsC, ApC or both; this finding could maybe orientate to a different diagnosis for this patients.

Taken together, we observed several cognitive profiles, confirming again the heterogeneity of these patients; a group of patients presented with pseudofocal impairment involving prominently on of two subsyndromes while the other group of patients is characterized by a profile in which none of the components is impaired significantly more than the others. These differences do not seem to be caused by disease duration or severity but to different onset of cognitive impairment.

In conclusion, in our group of patients, we highlighted three syndromes that express tasks and functions localization more than dorsal and ventral visual pathways neuro-anatomy, as previously reported; we identify a right posterior syndrome, a left ventro-dorsal syndrome and a left ventral syndrome. These syndromes can present isolated or in association and to date they do not seem to overcome the issue of *in vivo* differential diagnosis.

Although this study confirms the difficulties in differential diagnosis between the cognitive syndromes with posterior onset, it improves knowledge about the nature of their cognitive impairment and it can be a first step to the identification of cognitive markers - or patterns -

linked to neuropathology. For these reasons further investigations will be directed in increasing sample size, that will allow us to make direct comparisons between sub-group of patients and to associate to neuropsychological assessment, some neuropathology biomarkers.

6. Appendix

Below is reported a PCAnalysis in which standardized residuals of the variables derived from a linear regression including raw MMSE score besides age, education and disease duration.

6.1. Components extraction

PCAnalysis extracted four components (with eigenvalues of 2.56, 1.3, 1.2 e 1.1 respectively) accounting for 62% of the variance. In table 19, components and loadings are reported. Kaiser-Meyer-Olkin measure of sampling adequacy was 0.653 and the determinant was 0.245.

	Component			
	1	**2**	**3**	**4**
ROCF copy	0.769			
Balint Holmes syndrome	0.677			
Poppelreuter-Ghent test	0.670			
Benton JLO	0.517	0.457		
Gerstmann syndrome		0.807		
Limb apraxia		0.772		
Colors categorization			0.803	
Semantic association			0.676	
Line bisection				0.740
Face recognition test	0.461			-0.570

Table 19. Extracted components and variable loadings.

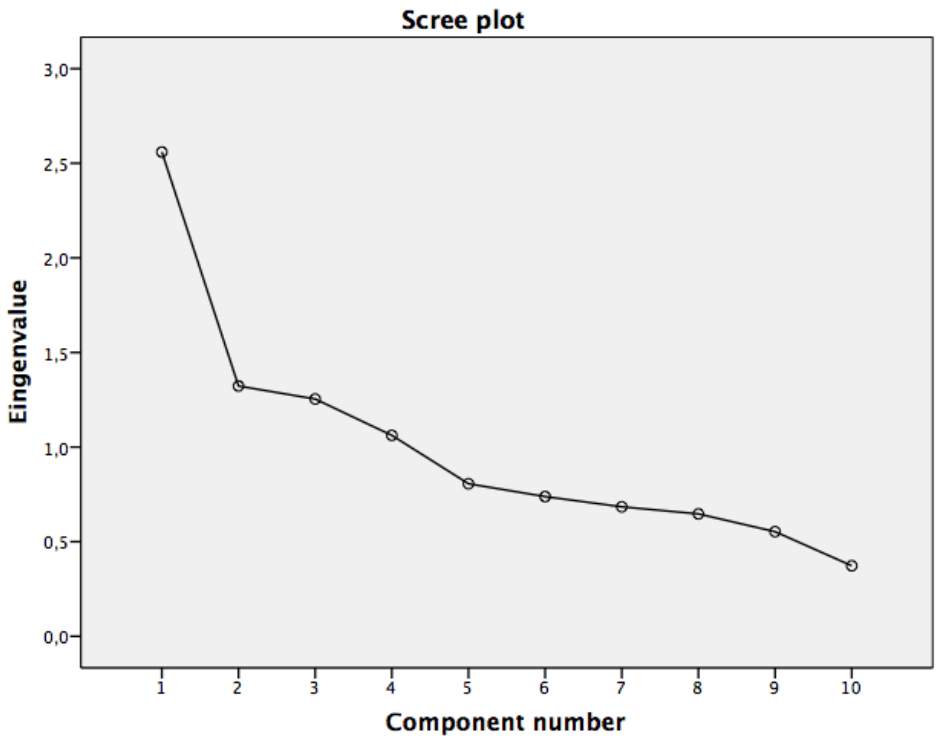


Figure 21. Scree plot of components extraction.

As can be seen from Table 19, ROCF copy, Balint-Holmes syndrome composite score, Poppelreuter-Ghent, Benton JLO test and face recognition test loaded on the first component that accounts for 21% of the variance;

The second component accounts for the 16% of the total variance and is loaded by Gerstmann syndrome composite score, limb apraxia and Benton JLO;

Color categorization and semantic association loaded on the third component, accounting for the 13% of the variance;

Finally, PCAnalysis extracted a fourth component account for the 11% of the variance on which line bisection had a positive load and face recognition test had a negative load.

7. References

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Ringraziamenti

Vorrei ringraziare il professor Appollonio, che mi ha dato la possibilità di raggiungere questo traguardo, dandomi fiducia e investendo su di me.

Grazie di cuore a Valeria, senza la quale questo lavoro non esisterebbe, perchè mi è sempre stata vicino in tutto il percorso, aiutandomi, guidandomi passo dopo passo e sopratutto stimolandomi e spingendomi a fidarmi della mia testa e delle mie capacità;

Non di meno, posso, e voglio, dire Grazie a Cristina che è sempre stata al mio fianco ogni giorno in questi anni sia sul lavoro che nella vita; come le ho già detto altre volte, la sua saggezza affettuosa, mi aiuta sempre a vedere le cose in maniera diversa e a modificare alcune mie rigidità.

Grazie a Manuela che è sempre stata disponibile e prodiga di consigli, oltre che amica.

Grazie a Laura per i suggerimenti delle sette di mattina.

Grazie a Debora, Valentina, Marilina, Priscilla, Giordano, Federica I, Federica M, Laura, Elisa, Ilaria, Giorgio, Fulvio, Emanuela e a tutte le altre persone che mi hanno aiutato nell'arruolamento dei pazienti e dei controlli, nelle valutazioni neurologiche e sostituendomi in altri compiti per permettermi di finire questo lavoro.

Grazie ai miei genitori che mi hanno aiutato in maniera considerevole nell'ultimo anno, e anche prima, permettendomi di lavorare tranquilla sapendo che Alessandro era a casa sereno e felice; lo stesso vale per Paola e Franco.

Grazie ad Andrea perchè c'è, perchè è la persona che crede in me più di tutte e non smette mai di ripetermelo.

Grazie ad Alessandro perchè la sua nascita mi ha fatto capire quali sono le cose che contano davvero permettendomi di vivere con meno ansia altre situazioni.

Infine…Grazie a me stessa…