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COGNITIVE IMPAIRMENT AND DEMENTIA – AN UPDATE

Hosted by
João Massano

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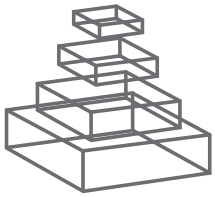

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COGNITIVE IMPAIRMENT AND DEMENTIA – AN UPDATE

Hosted By:
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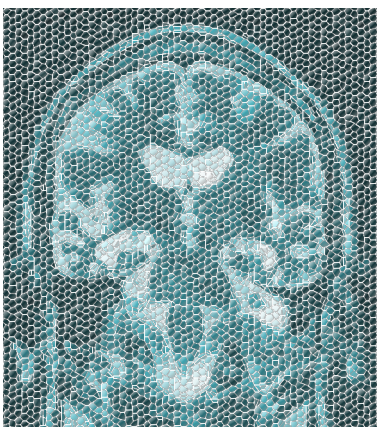

Cognitive impairment and dementia afflict a large number of people worldwide, being a major source of disability and loss of income. The amount of research on this subject is extensive, covering from basic to translational and clinical aspects. Therefore, it is hard to keep up with the amount of publications and novelties in this field, especially for the busy clinician. On the other hand, basic scientists often find it difficult to explore the vast clinical literature on this matter, as well as understand the clinical features of these disorders and to define the current research needs and directions. The main aim of this Frontiers Research Topic is to provide a solid and valuable platform of scientific synthesis regarding the current knowledge and literature on this theme, including clinical features, current and emergent diagnostic strategies, management (both present and future), and other important issues pertaining to cognitive impairment and dementia. The submission of research studies is also encouraged, in order to provide the readership with the most recent findings in the field.

Topics to be considered include:
-Mild cognitive impairment
-Alzheimer's disease
-Dementia with Lewy Bodies
-Frontotemporal Lobar Degeneration/Frontotemporal Dementia Syndromes
-Prion diseases
-Vascular cognitive impairment
-Other disorders: multiple sclerosis, normal pressure hydrocephalus, other secondary causes of cognitive impairment
-Early diagnosis in dementing disorders

-Clinical assessment
-Neuroimaging
-CSF and serum biomarkers
-Neuropathology
-Genetics
-Management, including current and emergent therapies, cognitive rehabilitation and other non-pharmacological treatments, ethical issues and end of life care

Table of Contents

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EDITORIAL
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Cognitive impairment and dementia—an update

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Cognitive disorders have become a major theme in modern neuroscience. Analyzing the impact of these conditions at various levels, from personal to social and economic, it is not surprising that the amount of research on this subject has grown to vast figures in the past years, thus making it hard to keep up with the sum of publications and novelties in this field, especially for the busy clinician. On the other hand, basic and translational scientists frequently find it difficult to explore the vast and often complex clinical literature on this matter, as well as understand the clinical features of these disorders, in order to define the current research needs and optimal future directions in innovation. The main aim of the Frontiers Research Topic "Cognitive impairment and dementia—an update" is to deliver an updated synthesis regarding the current knowledge and literature in this field, which will hopefully benefit clinicians and scientists from various fields. In this regard, open access publication brings clear advantages. We have been very fortunate, as outstanding contributions from several authors and working groups have been submitted, covering a wide range of subjects.

Galimberti and Scarpini (2012) have approached the ever more complex subject of frontotemporal dementia genetics. This mini-review deals with the major issues regarding this topic, including genes involved, phenotypic aspects, and even the fresh scientific breakthrough in this field—the association between FTD and the pathologic hexanucleotide repeat expansion in the *C9ORF72* gene. This scientific novelty brought a long looked-for molecular explanation for a significant number of cases seen in clinic, especially those associated with amyotrophic lateral sclerosis and a positive family history.

Alves et al. (2012) have produced a comprehensive review concerning the most important aspects of Alzheimer's disease (AD), including clinical features, genetics, pathophysiology, clinical genetic testing, diagnostic strategies, and management. This article is very well complemented by the manuscript from de Mendonça (2012), who provides important reflections concerning the recent changing paradigms of clinical and scientific thinking in AD. Contributing also to the topic of AD, Sá et al. (2012) share their research on the neuropsychological aspects of early and late onset AD. This is a large series from one single group detaining extensive experience in this field.

Mild cognitive impairment and dementia have been recognized as important features of Parkinson's disease (PD) in the last few years, despite the traditional emphasis on motor symptoms of the disease (Massano, 2011; Massano and Bhatia, 2012). In this regard, Meireles and Massano (2012) have written a broad review concerning the issue of cognitive decline in PD, covering the stages of mild cognitive impairment and dementia. Phenotypic aspects have been approached, as well as diagnostic issues, genetic factors, and practical management strategies. The paper by Almeida (2012) delves further on the role of glucocerebrosidase in PD and other neurodegenerative conditions, a topic receiving currently much attention from basic and translational researchers, as well as clinicians. Other genes related to lysosomal functioning have also been dealt with in the text. The manuscript by Massano and Garrett (2012) complements the theme of cognitive impairment in PD by in-depth reviewing the literature regarding the cognitive effects of deep brain stimulation in these patients, and the importance of accurate preoperative cognitive assessment, as well as some ethical issues in this setting.

Neuropathology has traditionally been an important diagnostic instrument in cognitive disorders, and pathological findings have provided the basis for important genetic and pathophysiological lines of research along the years. However, this is a complex subject, especially in the context of neurodegenerative disorders, and non-pathologists find it difficult to keep up with the terminology. The article by Taipa et al. (2012) will be a precious aid to all of those interested in learning more about this subject or simply optimize their current level of knowledge, as it summarizes important neuropathological findings in the most common neurodegenerative dementias, establishing also a relationship with relevant clinical features.

Behavioral and psychological symptoms of dementia are a major source of disability and decrement in quality of life, as well as caregiver burden. Moreover, they are commonly difficult to tackle in practice, even for experienced clinicians. Cerejeira et al. (2012) have produced a very useful and comprehensive text on this subject, ranging from diagnosis to management, which will greatly benefit the readership.

Cognitive dysfunction in multiple sclerosis (MS) is a particularly sensitive issue, as this disease afflicts preferentially young adults, being one of the most important causes of neurologically induced disability in this age range. A few important ideas can be extracted from the paper by Guimarães and Sá (2012), such as the fact that, beyond every other symptoms of the disease, cognitive dysfunction in MS is a matter to keep in mind. Patients deserve proper assessment and management, as groundbreaking disease modifying therapies became available along the years.

Elderly people are naturally at higher risk of sustaining confusional states, especially those who suffer from previous brain disease leading to cognitive impairment. Unfortunately, delirium is still too often overlooked by clinicians, which brings onerous consequences to patients, since management opportunities are lost and outcome will be less favorable, as Martins and Fernandes point out in their manuscript (Martins and Fernandes, 2012). This is a very common disorder, which only stresses the importance of professional education and awareness on these matters. Broadly speaking, this is obviously another important aim of this Frontiers Research Topic.

Finally, an inclusive acknowledgment is due to the authors who, with their hard work, have contributed to this Frontiers Research Topic. In addition, reviewers should also here be appraised, as the manuscripts have clearly been improved after the successive comments posted on the review forums. Their honest efforts and purely altruistic commitment with this challenge have been truly admirable.

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Genetics of frontotemporal lobar degeneration

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Frontotemporal lobar degeneration (FTLD), the most frequent neurodegenerative disorder with a presenile onset, presents with a spectrum of clinical manifestations, ranging from behavioral and executive impairment to language disorders and motor dysfunction. Familial aggregation is frequently reported, and about 10% of cases have an autosomal dominant transmission. Microtubule associated protein tau (*MAPT*) gene mutations have been the first ones identified and are associated with early onset behavioral variant frontotemporal dementia phenotype. More recently, progranulin gene (*GRN*) mutations were recognized in association with familial form of FTLD. In addition, other genes are linked to rare cases of familial FTLD. Lastly, a number of genetic risk factors for sporadic forms have also been identified. In this review, current knowledge about mutations at the basis of familial FTLD will be described, together with genetic risk factors influencing the susceptibility to FTLD.

Keywords: genetics, frontotemporal lobar degeneration, autosomal dominant, mutation, risk factor

NEW DIAGNOSTIC CRITERIA OF FRONTOTEMPORAL LOBAR DEGENERATION

Frontotemporal lobar degeneration (FTLD) represents a common cause of dementia in subjects under 65 years. The age at onset is typically 45–65 years, with a mean average in the 50s, and the prevalence is equal among men and women. It is associated with frontal and temporal lobe atrophy, involving the right and left hemispheres, in some cases asymmetrically (Rosen et al., 2006). It can be classified into two main cognitive syndromes (Neary et al., 1998): behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA), whose diagnostic criteria have been recently revised including neuroimaging and genetics (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

Behavioral variant frontotemporal dementia is the most frequent FTLD phenotype, characterized by behavioral alterations, such as disinhibition, overeating, and impulsiveness, and impairment of cognitive functions, with relative sparing of memory (Hou et al., 2004). Changes in social behavior, loss of empathy, and impairment of social insight are early and consistent symptoms of bvFTD, whose importance and role for the early diagnosis has been emphasized in the new consensus criteria (Rascovsky et al., 2011). According to these criteria, bvFTD main feature is the progressive deterioration of behavior and/or cognition by observation or history. If this criterion is satisfied, there are three further levels of certainty for bvFTD: possible, probable, or definite. "Possible" bvFTD requires three out of six clinically discriminating features (disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, and dysexecutive neuropsychological profile). "Probable" bvFTD meets the criteria of "possible" bvFTD plus (1) a significant functional decline (by caregiver report or evidenced at neuropsychological testing) (2) frontal and/or anterior temporal atrophy on MRI or CT, or frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT. "Definite" bvFTD imply the histopathological evidence of FTLD on biopsy or post mortem or the presence of a known pathogenic mutation. These new criteria have a flexible structure to account for the high heterogeneity at initial presentation.

Early and progressive changes in language functions represent the alternative presentation of FTLD. Progressive loss of speech, with hesitant, non-fluent speech output with phonetic/phonological errors, and distortions and/or agrammatism is typical of primary non-fluent aphasia (PNFA) subtype (Scarpini et al., 2006), whereas loss of knowledge about words and objects, anomia and single-word comprehension deficits are core features of the semantic variant of PPA, named semantic dementia (SD; Gorno-Tempini et al., 2011). A third subtype of PPA has been recently described as logopenic or phonological variant (LPA). It is characterized by phonological disorders, defective word retrieval, and sentence repetition deficits. This PPA subtype seems to be associated with underlying Alzheimer's disease (AD) pathology (Rabinovici et al., 2008).

GENETICS: AUTOSOMAL DOMINANT MUTATIONS

The presence of familial aggregation and the autosomal dominant transmission of the disease suggested so far a genetic cause (Snowden et al., 2002; Bird et al., 2003; Goldman et al., 2005). Up to 40% of patients have a family history suggesting FTLD in at least one extra family member (Goldman et al., 2005; Pickering-Brown, 2007), with a percentage of autosomal dominant cases accounting for 13.4% of the total (Goldman et al., 2005).

New criteria for bvFTD diagnosis (Rascovsky et al., 2011) include the presence of a known mutation as a biomarker. The demonstration of an autosomal dominant mutation is

requested for the diagnosis of "definite" bvFTD, and is the only criterion existing so far to make a definite diagnosis during life. Genes demonstrated to be responsible for familial FTLD include: microtubule associated protein tau (*MAPT*) gene, progranulin (*GRN*), valosin-containing protein (*VCP)-1*, chromatin-modifying 2B (*CHMP2B*), TAR-DNA binding protein 43 encoding gene (*TARBDP*), and, very recently, a novel hexanucleotide expansion in chromosome 9 (Dejesus-Hernandez et al., 2011; Renton et al., 2011).

MICROTUBULE ASSOCIATED PROTEIN TAU GENE

The first evidence of a genetic cause for familial FTLD came from the demonstration of a linkage with chromosome 17q21.2 in autosomal dominantly inherited form of FTD with parkinsonism (Lynch et al., 1994) resulting in the label of "frontotemporal dementia and parkinsonism linked to chromosome 17" (FTDP-17). The gene responsible for such association, named *MAPT* gene, was discovered few years later (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998). *MAPT* encodes the microtubule associated protein Tau, which is involved in microtubule stabilization and assembly. To date, more than 40 pathogenic *MAPT* mutations have been described in 134 families (http://www.molgen.ua.ac.be/). *MAPT* mutations can be non-synonymous, deletions, or intronic mutations located close to the splice-donor site of the intron after the alternatively spliced exon 10 (Rademakers et al., 2004). They are mainly clustered in exons 9–13, which contain the microtubule binding regions (Rademakers et al., 2002) and affect the normal function of tau, i.e., the stabilization of microtubules promoting their assembly by binding tubulin. Some mutations increase the free cytoplasmic portion of the protein promoting tau aggregation, whereas others lead to an aberrant phosphorylation of tau protein, which damages microtubule stabilization (Buée and Delacourte, 1999; Goedert and Jakes, 2005). Otherwise, many other mutations affect the alternative splicing, thus producing altered ratios of the different isoforms (3R/4R tau; Goedert et al., 1989). At autopsy, patients with *MAPT* mutations show tau-positive inclusions (Rademakers et al., 2004).

The clinical presentation in *MAPT* mutation carriers in mainly consistent with bvFTD, with a mean onset in the 50s (Yancopoulou and Spillantini, 2003; Villa et al., 2011). Nevertheless, cases of PNFA have been reported as well, with an onset even in the sixth decade of life (Villa et al., 2011).

PROGRANULIN GENE

After the discovery of *MAPT* as causal gene for FTDP-17, there were still numerous autosomal dominant FTLD cases genetically linked to the same chromosomal region of *MAPT* (chr17q21), in which no pathogenic mutations had been identified. A small region rich of genes, localized approximately 6.2 Mb in physical distance to *MAPT* locus, had been recognized as that one containing the gene responsible for the disease in these families. Systematic sequencing of candidate genes within this minimal region was performed and the first mutation in progranulin gene (*GRN*) was identified. It consists of a 4-bp insertion of *CTGC* between coding nucleotides 90 and 91, causing a frameshift and premature termination in progranulin (C31LfsX34; Baker et al., 2006). Cruts et al. (2006), analyzing other families with a FTLD pathology without *MAPT* mutation, found at the same time another mutation of five base pairs into the intron following the first non-coding exon of the *g*ene (IVS0 + 5G–C). This mutation causes the splicing out of the intron 0, leading the retention of mRNA within the nucleus and its degradation.

GRN gene encodes for the growth regulation factor progranulin, belonging to a family of proteins involved in many biological functions including development, wound repair, and inflammation by activating signaling cascades that control cell cycle progression (He and Bateman, 2003). Progranulin is a 593 amino acid protein, rich of cysteine with a molecular weight of 68.5 kDa, subjected to proteolysis by elastase in a process regulated by a secretory leukocyte protease inhibitor (SLPI; Zhu et al., 2002). It is expressed not only in neurons but also is the activated microglia (Baker et al., 2006).

Since the original identification of null-mutations in FTLD in 2006, 69 different mutations have been described so far (http://www.molgen.ua.ac.be/) in 231 families. Most of the known pathogenic *GRN* mutations, including frameshift, splice-site, and nonsense mutations, are predicted to result in a premature stop codon. The resulting aberrant mRNA is degraded through the process of nonsense mediated decay, leading to haploinsufficiency (Gass et al., 2006).

Clinically, mutations in *GRN* are associated with extremely heterogeneous phenotypes, including, besides the classical FTLD presentations, AD (Carecchio et al., 2009), corticobasal syndrome (CBS; Carecchio et al., 2011), or Mild Cognitive Impairment (Pietroboni et al., 2011). Age at disease onset is extremely wide, even in the same family (Pietroboni et al., 2011). In addition, the demonstration of the clinical overlap between psychiatric disorders and genetically determined FTLD comes from the recent description of a patient with heterosexual pedophilia (Rainero et al., 2011), who was a carrier of a *GRN* mutation and developed bvFTD over time, and from a second description reporting two clinically different, apparently sporadic FTLD cases sharing the previously described Thr272fs *GRN* mutation, who had had a premorbid bipolar disorder history (Cerami et al., 2011).

A major contribution to achieve a correct diagnosis independent of the phenotypic presentation is the demonstration that progranulin plasma levels are extremely low in *GRN* mutation carriers, even in asymptomatic subjects (Ghidoni et al., 2008; Finch et al., 2009; Carecchio et al., 2011; Pietroboni et al., 2011).

Notwithstanding the striking proximity of *MAPT* and *GRN* on chromosome 17, at this time, there is no clear link between these two genes, suggesting that their closeness is just a coincidence.

GRN-mutated FTLD cases at the neuropathological examination presented ubiquitin immunoreactive cytoplasmic and intranuclear neuronal inclusions similar to the microvacuolar-type still observed in a large proportion of apparently sporadic FTLD, and differing from the tau-positive inclusions typical of *MAPT* mutated cases. Soon after the identification of *GRN* mutation, truncated, and hyperphosphorylated isoforms of the TAR–DNA binding protein (TDP)-43 were recognized as main components of the ubiquitin-positive inclusions typical of the *GRN*-mutated families, as well as of idiopathic FTLD and of a proportion of amyotrophic lateral sclerosis (ALS) cases (Neumann et al., 2006).

GRN mutations account for about 5–10% of all FTD cases, markedly varying depending on the population considered (Cruts et al., 2006; Gass et al., 2006; Snowden et al., 2006). A collaborative study (Yu et al., 2010) analyzing *GRN* mutations in 434 FTLD patients, clinically ranging from bvFTD to PNFA, FTLD associated with parkinsonism or MND, estimates a frequency of 6.9% of all included FTLD-spectrum cases. In these cases, the 56.2% was represented by FTLD-U-diagnosed subjects with a known familial history of FTD, pathologically confirmed. Clinical information were available for 31 *GRN* mutation-positive patients: the most common phenotype was bvFTD ($n = 24$), while 3 patients were diagnosed with PNFA, 3 with AD, and 1 with CBS (Yu et al., 2010).

CHROMATIN-MODIFYING 2B

Few FTLD families display mutations in the *CHMP2B* gene, which encodes a component of the heteromeric endosomal sorting complex required for transport (ESCRT III complex) involved in the endosomal trafficking and degradation (Skibinski et al., 2005). To date, only four different mutations between or in the exons 5 and 6 have been so far described in five families (http://www.molgen.ua.ac.be/), making *CHMP2B* an extremely rare genetic cause of FTLD pathology. Neuropathologically, patients with *CHMP2B* mutations present FTLD-U with ubiquitin-positive but TDP-43-negative cytoplasmic inclusions (Holm et al., 2007). Behavioral and cognitive impairment associated with extrapyramidal and pyramidal signs are the main clinical manifestations in *CHMP2B* mutation carriers. Myoclonus can occur late in the course of the disease (Gydesen et al., 2002) and motor neuron disorders have been described in only two cases (Parkinson et al., 2006).

VALOSIN-CONTAINING PROTEIN-1

Some familial cases having mutations in the *VCP*-1 gene were reported (Watts et al., 2004). However, the phenotype associated with such mutations is inclusion body myopathy, Paget's disease of bone and less frequently FTD (IBMPFD; Kimonis et al., 2008). Myopathy is the more frequent clinical symptom, present in about 90% of affected subjects, whereas FTD is seen in about 30%, usually many years after the onset of muscle symptoms.

TARDBP

The most common clinical phenotype associated with *TARDBP* mutations is ALS, and aggregates made of TDP-43 have been described in brain and spinal cord of such patients. Nevertheless, *TARDBP* mutated subjects can present also parkinsonism in association with motor neuron dysfunction (see Pesiridis et al., 2009 for review). At present, *TARDBP* mutations have been found in 5% of familiar ALS and only rarely in FTD and FTD–MND subjects (Benajiba et al., 2009; Borroni et al., 2009).

Chr 9 HEXANUCLEOTIDE REPETITION

Lastly, one of the most intriguing discovery in the genetics of FTLD has been the investigation of FTD/MND families linked to a locus on chromosome 9q21-22. The first evidence of linkage with this locus comes from a study carried out in families with FTD–MND (Hosler et al., 2000). After some others reports confirming the linkage to chr9q21-22 in additional FTD–MND families (Morita et al., 2006; Rollinson et al., 2011), and a search lasting more than a decade, in 2011, two groups of researchers identified the gene responsible for the disease, the chromosome 9 open reading frame 72 (*C9ORF72*). Both these studies (Dejesus-Hernandez et al., 2011; Renton et al., 2011) reported a large hexanucleotide (*GGGGCC*) repeat expansion in the first intron of *C9ORF72* as responsible for a high number of familiar ALS or combined FTD–MND phenotype and TDP-43 based pathology. This mutation causes the loss of one alternatively spliced transcript, whose function is still unknown, and the formation of nuclear RNA foci. Wild-type alleles contain no more than 23–30 repeats, whereas mutated alleles have more than 100 repeats. These studies thus demonstrated that *C9ORF72* mutation is at present a major cause of both familiar FTD (12%) and ALS (22.5%) cases (Dejesus-Hernandez et al., 2011), with a higher prevalence in the northern population, reaching a prevalence of 46% of all familiar ALS, 21.1% of sporadic ALS, and 29.3% of FTD in the Finnish population (Renton et al., 2011). Clinically, the large clinical series reported in these studies show that the predominant phenotypes are consistent with bvFTD and ALS, with different phenotypic presentation even in the same family (i.e., FTD, ALS, or a combination of both). From the FTD series reported in Dejesus-Hernandez et al. (2011) study, 26.9% FTLD cases had concomitant ALS and more than 30% had relatives affected with ALS.

CONCLUSIVE REMARKS

In the last few years, it has become clear that there are multiple genetic autosomal dominant mutations leading to the development of FTLD. The most frequent are so far *MAPT* and *GRN* mutations that are associated with high phenotypic variability. Whereas the majority of *MAPT* mutations is characterized by an early onset of symptoms and is associated with a clear segregation across generations, age at disease onset is very wide in *GRN* mutation carriers. According to the most recent discoveries, the large hexanucleotide (*GGGGCC*) repeat expansion in the first intron of *C9ORF72* is not only one of the most frequent mutation associated with ALS and FTD–MND, but is also the second most frequent in FTLD, after *GRN* mutations (Gijselinck et al., 2012). Given the incomplete penetrance of such mutations, a number of cases are apparently sporadic, making more difficult to suspect the presence of a causal mutation. Regarding genetic counseling, at present no international shared guidelines are available.

GENETICS: RISK FACTORS

The first candidate-gene studied in FTLD was the well-known risk factor for late onset sporadic AD, *APOE*. A number of studies suggested an association between FTLD and *APOE∗4* allele (Farrer et al., 1995; Helisalmi et al., 1996; Gustafson et al., 1997; Stevens et al., 1997; Fabre et al., 2001; Bernardi et al., 2006). Nevertheless, other authors did not replicate these data (Geschwind et al., 1998; Riemenschneider et al., 2002; Short et al., 2002). Additional findings demonstrated an association between the *APOE∗4* allele and FTLD in males, but not females (Srinivasan et al., 2006). An increased frequency of the *APOE∗4* allele has been described in patients with SD compared to those with FTD and PNFA (Short et al., 2002).

Concerning the *APOE*2* allele, Bernardi et al. (2006) showed a protective effect of this allele toward FTLD, whereas other authors failed to do so (Riemenschneider et al., 2002; Short et al., 2002; Engelborghs et al., 2003; Srinivasan et al., 2006). A meta-analysis comprising a total of 364 FTD patients and 2671 controls demonstrated an increased susceptibility to FTD in *APOE*2* carriers (Verpillat et al., 2002).

Besides pathogenic mutations, several polymorphisms have been described both in *MAPT* and *GRN*. In Baker et al. (1999), two common *MAPT* haplotypes, named H1 and H2, were identified. They differ in nucleotide sequence and intron size, but are identical at the amino acid level. Homozygosis of the more common allele H1 predisposes to Progressive Supranuclear Palsy and CBS, but not to AD or Pick Disease (Baker et al., 1999; Di Maria et al., 2000).

A contribution of *GRN* genetic variability in sporadic FTLD has previously been shown (Rademakers et al., 2008), even though another study did not confirm these data (Rollinson et al., 2011). A further association analysis demonstrated that a single nucleotide polymorphism (SNP) in the *GRN* promoter influences the risk for FTLD (Galimberti et al., 2010).

A known polymorphism (*A-2518G*) in monocyte chemoattractant-1 (*MCP-1*) gene has been shown to exert a protective effects toward the development of FTLD (Galimberti et al., 2009), whereas Nitric Oxide Synthase (*NOS*)*3 G894T* (Glu298Asp) and *NOS1 C276T* SNPs likely increase the risk to develop FTLD (Venturelli et al., 2008, 2009). Further genetic risk factors, discovered on a candidate-gene basis, include BCL2-associated athanogene 1 (*BAG1*), an anti-apoptotic factor that interacts with tau and regulates its proteasomal degradation (Venturelli et al., 2011), *KIF24* (Venturelli et al., 2010), and defective in cullin neddylation 1 (DCN-1)-domain containing 1 (*DCUN1D1*; Villa et al., 2009).

Van Deerlin et al. (2010) reported the results of the first genome-wide association study (GWAS) on 515 individuals affected by FTLD with autopsy-proven TDP-43 inclusions pathology (FTLD–TDP) compared with 2509 healthy controls, showing an association with three SNPs mapping to a single linkage disequilibrium block on 7p21. This region contains the gene *TMEM106B*, whose variants may increase the risk to develop the disease by increasing *GRN* gene expression.

This association was confirmed in an independent Flanders–Belgian cohort of FTLD patients ($n = 288$; van der Zee et al., 2011). However, these findings were not confirmed by replication study performed in two clinical FTLD cohorts of British origin (Rollinson et al., 2011). Though these authors failed to detect any association of *TMEM106B*, the analysis of chromosome 9 locus revealed strong association in the London FTLD cohort and in the FTLD/ALS cases of the Manchester cohort, later confirmed with the discovery of the *C9ORF72* gene (Dejesus-Hernandez et al., 2011; Renton et al., 2011).

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Alzheimer's disease: a clinical practice-oriented review

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Investigation in the field of Alzheimer's disease (AD), the commonest cause of dementia, has been very active in recent years and it may be difficult for the clinician to keep up with all the innovations and to be aware of the implications they have in clinical practice. The authors, thus, reviewed recent literature on the theme in order to provide the clinician with an updated overview, intended to support decision-making on aspects of diagnosis and management. This article begins to focus on the concept of AD and on its pathogenesis. Afterward, epidemiology and non-genetic risk factors are approached. Genetics, including genetic risk factors and guidelines for genetic testing, are mentioned next. Recommendations for diagnosis of AD, including recently proposed criteria, are then reviewed. Data on the variants of AD is presented. First approach to the patient is dealt with next, followed by neuropsychological evaluation. Biomarkers, namely magnetic resonance imaging, single photon emission tomography, FDG PET, PiB PET, CSF tau, and Aβ analysis, as well as available data on their diagnostic accuracy, are also discussed. Factors predicting rate of disease progression are briefly mentioned. Finally, non-pharmacological and pharmacological treatments, including established and emerging drugs, are addressed.

Keywords: Alzheimer, AD pathogenesis, AD genetics, AD diagnosis, AD variants, AD neuropsychological evaluation, AD biomarkers, AD treatment

CONCEPT OF ALZHEIMER'S DISEASE

The present conceptualization of Alzheimer's disease (AD) is based on autopsy findings of widespread neuritic plaques and neurofibrillary tangles (NFT), described for the first time in 1906 by Alois Alzheimer in a case with early symptom onset (Alzheimer et al., 1995). The concept was subsequently generalized to late-onset cases when Blessed et al. observed identical pathology in elderly patients (Blessed et al., 1968; Seshadri et al., 2011).

The term "AD" may have distinct meanings in different contexts. AD has, in some settings, referred to the neuropathological criteria for AD, and, in other, to the clinical syndrome of progressive cognitive decline, typically at the stage of AD dementia (Sperling et al., 2011). The National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup on diagnostic guidelines for AD decided to define AD as encompassing the underlying pathophysiological disease process (Sperling et al., 2011) as opposed to having AD connote only the clinical stages of disease as proposed by the International Working Group for New Research Criteria for the Diagnosis of AD (Dubois et al., 2010). The NIA-AA workgroup thus considers that AD can be used to refer to dementia stages, as well as to MCI and pre-MCI phases.

Evidence from genetic at-risk and aging cohorts suggests that there may be a time lag of at least a decade between the beginning of the pathological cascade of AD and the onset of clinical impairment. The NIA-AA workgroup postulates that individuals with biomarker evidence of early AD pathology (AD-P) are at increased risk of progression to AD dementia (AD-D). However, the ability of the biomarkers of AD-P to predict the ulterior clinical course of cognitively normal persons remains to be established, and it is acknowledged that some of these individuals will never exhibit clinical symptoms in their lifetime (Sperling et al., 2011).

PATHOGENESIS

AD is the most frequent cerebral proteopathy (Jucker and Walker, 2011). Macroscopically, the AD brain is characterized by atrophy of the hippocampal formation and of the cerebral cortex, primarily involving the fronto-temporal association cortex, combined with ventricular enlargement, especially of the temporal horn, all of these findings being greater than expected for age (Walsh and Selkoe, 2004; Perl, 2010). Microscopically, its neuropathological hallmarks are the combined presence of extracellular β–amyloid-containing plaques and intraneuronal NFTs, the latter being formed by abnormally hyperphosphorylated tau protein (Terry, 1963; Alzheimer et al., 1995). The β-amyloid (Aβ) peptide and tau protein are thought to play a critical role in AD development, but several other mechanisms of neurodegeneration have been proposed, including pro-inflammatory responses (Wyss-Coray, 2007), mitochondrial dysfunction (Reddy, 2011), oxidative stress (Cai et al., 2011), genetic and environmental factors (Nelson et al., 2011), and apoptosis (Cai et al., 2011). The deleterious effects of these pathological changes provide the substrate for the etiopathogenesis of AD, and converge, ultimately, to synaptic dysfunction and neuronal cell loss (Götz et al., 2004; Walsh and Selkoe, 2004; LaFerla and Oddo, 2005; Arendt, 2009; Takahashi et al., 2010). This process occurs in particularly vulnerable brain

areas, such as those responsible for memory and cognition, namely the limbic and association cortices and some subcortical nuclei with large cortical projections (Walsh and Selkoe, 2004; LaFerla, 2010; Perl, 2010).

The pathological interaction between $A\beta_{42}$ and tau proteins and their relative contribution to neurodegeneration, synaptic and neuronal loss have been extensively investigated, but still remain to be completely elucidated.

The β-amyloid protein, a physiological peptide with a characteristic β-pleated sheet configuration, derives from sequential cleavage of the amyloid precursor protein (APP) by β secretase, followed by γ secretase (Glenner and Wong, 1984). Aβ can vary in length at the c-terminus, according to the pattern of cleavage of APP. The $A\beta_{1–40}$ isoform (with a total of 40 amino acid residues) is the most prevalent, followed by the $A\beta_{1–42}$ isoform (with 42 amino acid residues). The latter has hydrophobic properties and aggregates more readily than the $A\beta_{1–40}$ isoform, which turns it more amyloidogenic and prone to polymerize (Perl, 2010). Aβ that escapes from proteolytic degradation aggregates and polymerizes in various structurally distinct forms, including oligomeric, protofibrillar, amylospheroid, and fibrillar forms.

In the AD brain, neuritic plaques are composed of a central core containing β-amyloid protein, surrounded by clusters of dystrophic axons and dendrites (or neurites) and by glial recruitment (LaFerla and Oddo, 2005; Perl, 2010). Aβ deposits also tend to accumulate in the walls of the leptomeningeal, cerebral cortical and cerebellar blood vessels. Cerebral amyloid angiopathy is correlated with AD pathogenesis and may lead to vascular rupture and multiple lobar hemorrhages (Nicoll et al., 2004). The Aβ deposition on parenchyma or vascular walls in the brain appears to result from an increased anabolic activity or a decreased catabolic activity of Aβ.

Several mutations involving the APP gene, or genes encoding secretase complex components, can promote the amyloidogenic pathway and increase the $A\beta_{42}/A\beta_{40}$ ratio, promoting its aggregation. The study of the early onset familiar forms of AD, histopathologically indistinguishable from the sporadic form, provides compelling evidence for the Aβ protein role in the initiation of the neurotoxic cascade, corroborated by experiments involving animal and tissue-culture models (Götz et al., 2004). However, for the AD sporadic form, which is the more prevalent, totaling more than 95% of cases, the pathogenic trigger remains unidentified (Götz et al., 2004).

The "amyloid cascade hypothesis" postulates that the excessive formation and deposition of insoluble fibrillar Aβ, with consequent aggregation in plaques, is the initiating event in AD pathogenesis. This first insult triggers, secondarily, a neurotoxic cascade, including NFT formation, which ultimately leads to synaptic and neuronal loss in critical areas related with cognitive functions like memory (Herrup, 2010). However, neuropathological investigations have found a weak correlation between cerebral amyloid plaque burden and the severity of dementia (Terry et al., 1991; Nagy et al., 1996; Ingelsson, 2004). Moreover, evidence from earlier studies has suggested that the formation of soluble non-fibrillar $A\beta_{42}$ assemblies, termed oligomers and composed of small aggregates of 2–12 Aβ peptides, rather than insoluble amyloid plaques, may play a pivotal role in the AD neurodegenerative cascade. Some *in vitro* studies suggest that, in the early stages of AD, Aβ oligomers, through a potent pro-inflammatory response induction, attenuate microglial phagocytic function and, consequently, impair the clearance of fibrillar Aβ, promoting its deposition in the brain (Pan, 2011). In animal models, Aβ oligomers can be found in the hipoccampal CA1 region and in the entorhinal cortex, prior to the development of amyloid plaques and NFT (Wirths et al., 2001). There is also robust evidence, from studies involving transgenic mice and/or human AD patients, demonstrating that the early accumulation of intraneuronal Aβ oligomers can induce downstream effects, such as mitochondrial dysfunction (LaFerla et al., 2007; Amadoro et al., 2012), microgliosis and astrocytosis (Walsh and Selkoe, 2004), free radicals formation, oxidative stress and hyperphosphorylation of tau protein (Walsh and Selkoe, 2004; LaFerla and Oddo, 2005), synaptic dysfunction and neurotransmitter deficits (Walsh and Selkoe, 2004; Bao et al., 2012), leading to synaptic dysruption and cognitive decline (Walsh and Selkoe, 2004; LaFerla and Oddo, 2005; Arendt, 2009).

Besides amyloid plaques, the other major histopathological hallmark of AD consists of intraneuronal neurofibrillary lesions, which appear as NFT in soma or apical dendrites, as neuropil threads in distal dendrites and associated with Aβ plaques in dystrophic neurites. These proteinaceous aggregates consist of paired helical filaments, formed by hyperphosphorylated tau protein. Tau is a microtubule-associated protein, responsible for the assembly and stability of microtubules in the neuronal cell and for axoplasmatic transport. The microtubule connection is regulated by a complex interplay of isoform tau expression and tau phosphorylation (Perl, 2010). In the AD brain, tau protein becomes abnormally hyperphosphorylated at several Ser/Thr residues, detaches from axonal microtubules and aggregates into insoluble NFT. These changes result in disruption of axonal transport and intracellular organelles, including mitochondria (Reddy, 2011). Several phosphokinases have been implicated in tau hyperphosphorylation, namely glycogen synthase kinase 3β (GSK3β), cyclin dependent kinase 5 (CDK5) and extracellular signal-related kinase 2 (ERK2; Ballard et al., 2011a). Tau protein is the main constituent of NFT, but other proteins have been identified, such as ubiquitin (Perry et al., 1987), cholinesterases (Mesulam and Moran, 1987) and A4 amyloid protein (Hyman et al., 1989). There is evidence, based on an animal and tissue-culture study, that neurofibrillar degeneration may trigger or facilitate multiple pathological changes, including intraneuronal Aβ deposition, oxidative damage and glial activation, all of which can participate in mitochondrial dysfunction and neuronal damage (Götz et al., 2004).

Contrarily to what was observed for amyloid plaques, severity of dementia has been strongly correlated with NFT density (in studies involving human AD patients; Nagy et al., 1996), as well as with soluble oligomeric Aβ (Arendt, 2009).

Tau deposition and neurodegeneration occur in stereotyped fashion, progressing over six stages: stages I–II represent the clinically silent involvement of transentorhinal cortex; stages III–IV are characterized by lesions in entorhinal/transentorhinal regions and correspond to the phase of mild cognitive decline; in stages V–VI, there is severe neocortical destruction and fully developed dementia (Braak and Braak, 1995; Perl, 2010). Recent investigation

involving human brains indicates that pre-tangle material, able to induce NFT pathology, develops early in noradrenergic projection neurons of the locus coeruleus, before involvement of the transentorhinal region (Braak and Del Tredici, 2011). Tau pathology may then progress in a prodromical phase, during five or more decades, until it reaches a clinical threshold (Hyman and Goméz-Isla, 1994; Braak and Del Tredici, 2011; Nelson et al., 2011). These findings indicate that AD is not a mere extension of normal aging and challenge the traditional view suggesting that Aβ deposition precedes and triggers tau pathology (Gómez-Ramos and Asunción Morán, 2007; Braak and Del Tredici, 2011).

Synaptic loss in the hippocampus and neocortex is widely considered the major correlate of cognitive decline (Terry et al., 1991; Coleman and Yao, 2003; Walsh and Selkoe, 2004). Defects in synaptic transmission occur early in the disease, before the deposition of amyloid plaques or NFTs, and progress slowly (Walsh and Selkoe, 2004; Arendt, 2009). Several studies using AD human samples have found reduced expression of a group of genes encoding proteins involved in synaptic vesicle traffic, with consequent depletion of neurotransmitter systems and synaptic/neuronal loss (Coleman and Yao, 2003; Yao et al., 2003). Synaptic failure may lead to disruption of neuronal circuits and subsequently result in cognitive decline, even before structural cellular lesions (Yao et al., 2003; Arendt, 2009).

Studies on AD human samples indicate a strong anatomical correlation between synaptic loss markers and tangle formation (Honer et al., 1992; Callahan et al., 1999, 2002; Coleman and Yao, 2003). Furthermore, investigation using animal models has demonstrated the combined occurrence of $A\beta_{42}$ and hyperphosphorylated tau in hippocampal CA1 region, within neurites and postsynaptically, during the early stages of AD pathogenesis (Takahashi et al., 2010).

Despite major advances in our understanding of the AD neuropathology, it is still a matter of great debate and much remains to be explained.

GENETICS

GENETIC RISK FACTORS

AD can be divided into early (<60–65 years) and late (>60–65 years) onset forms. According to family history, AD cases may be classified as autosomal dominant, familial or sporadic (Goldman et al., 2011; **Table 1**).

Late-onset AD has a substantial genetic component, with an estimated heritability of 58–79% (Gatz et al., 2006; Wingo et al., 2012). It is probably governed by an array of low penetrance common risk alleles across a number of different loci (Avramopoulos, 2009). In the early 1990s, the association between the *APOE* gene and late-onset AD was described (Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993a,b). The *APOE* gene has been repeatedly implicated in the pathogenesis of AD and a Genome-Wide Association Study (GWAS) confirmed that this is the major susceptibility gene for late-onset forms (Coon et al., 2007). There are three common alleles of *APOE* (ε2, ε3, ε4), corresponding to six phenotypes. AD is associated with the ε4 allele, the presence of which increases the risk and reduces the average age at onset of AD in a dose-dependent manner (carriers of two *APOE* ε4 alleles have a higher risk and an earlier onset of AD than heterozygous subjects). Estimates of the increased risk conferred by the *APOE* ε4 vary widely. In a recent study, the lifetime risk of AD at the age of 85 ranged from 51 to 52% for *APOE* ε4/ε4 male carriers to 60–68% for *APOE* ε4/ε4 female carriers and from 22 to 23% for *APOE* ε4/ε3 male carriers to 30–35% for *APOE* ε4/ε3 female carriers. The odds ratio for AD of onset between the ages of 60 and 69 was of 35.1 in *APOE* ε4 homozygotes and of 4.2 in ε4/ε3 heterozygotes (Genin et al., 2011). *APOE* ε4 allele is neither necessary nor sufficient for developing AD (Corder et al., 1993; Farrer et al., 1997).

The early onset forms comprise about 6–7% of all cases of AD (Campion et al., 1999; Nussbaum and Ellis, 2003). Autosomal dominant disease is usually found in early onset AD families (Bertram and Tanzi, 2005). However, almost 40% of the patients with early onset AD are sporadic cases (with a negative family history; van Duijn et al., 1994; Campion et al., 1999). Three genes have been implicated in early onset AD: APP, presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*). The discovery of the first autosomal dominant mutations in *APP* (Goate et al., 1991) was followed by the identification of autosomal dominant mutations in the *PSEN1* (Schellenberg et al., 1992; Sherrington et al., 1995) and *PSEN2* genes (Levy-Lahad et al., 1995a,b; Rogaev et al., 1995). The mutations in any of these three genes result in a shift in the metabolism of APP such that more of a 42 aminoacid form of Aβ is produced (Hardy, 1997). These mutations cause AD with nearly complete penetrance. Nevertheless, they may present with heterogeneous phenotypes (Sherrington et al., 1996; Tedde et al., 2003), and recently an *APP* mutation that causes disease only in

Table 1 | Alzheimer Disease Genetics Division according to the American College of Medical Genetics and the National Society of Genetic Counselors.

	Feature	Definition
Age of onset	Early onset (∼6–7%)*	<60–65 years
	Late-onset (∼93–94%)*	>60–65 years
Family history	Autosomal dominant (<5%)	Disease that occurs in at least three individuals in two or more generations, with two of the individuals being first-degree relatives of the third
	Familial (∼15–25%)	Disease that occurs in more than one individual and at least two of the affected individuals are third-degree relatives or closer
	Sporadic (∼75%)	Isolated case in the family or cases separated by more than three degrees of relationship

**Campion et al. (1999), Nussbaum and Ellis (2003).*

the homozygous state was described (Di Fede et al., 2009). In contrast to mutations in *PSEN1*, mutations in *PSEN2* are a relatively rare cause of familial AD (Sherrington et al., 1996; Campion et al., 1999). The age of symptom onset in patients with *PSEN1* mutations is generally 25–65 years and it is similar among affected members of the same family. In contrast, individuals with *PSEN2* are typically older at presentation (45–88 years) and the age of onset is variable among relatives of the same family (Sherrington et al., 1996). Mutations in *APP*, *PSEN1*, and *PSEN2* are found in up to 82% of patients with autosomal dominant AD. It is likely that additional genes influence the pathophysiology of early onset AD (Janssen et al., 2003; Goldman et al., 2011). *APOE* gene is a risk factor for early onset AD (van Duijn et al., 1994) with odds ratio of 5.6 in ε4 homozygous individuals and of 2.1 in heterozygous ε4/ε3 cases (Genin et al., 2011). A recent study estimates that the early onset AD heritability is of 92–100%, which is compatible with an almost entirely genetically based disease. However, the concordance among siblings is of 21.6% and between parents and offspring of 10% or less. The authors (Wingo et al., 2012) consider that the most likely explanation for these results is that approximately 90% of early onset AD cases are due to autosomal recessive causes.

Since 2009, four GWAS and a three-stage analysis of the GWAS resulted in the identification of nine novel loci associated with late-onset AD: *CLU*, *PICALM*, *CR1*, *BIN1*, *ABCA7*, *MS4A* cluster (*MS4A6A/MS4A4E*), *CD2AP*, *CD33*, and *EPHA1* (Harold et al., 2009; Lambert et al., 2009; Seshadri et al., 2010; Hollingworth et al., 2011a,b; Naj et al., 2011). Other studies replicated some of these associations (Carrasquillo et al., 2010, 2011a,b; Corneveaux et al., 2010; Jun et al., 2010; Antúnez et al., 2011a,b; Lambert et al., 2011; Kamboh et al., 2012). Examining the amount of genetic risk effect attributable to these genes (other than *APOE*), the most strongly associated single-nucleotide polymorphisms at each locus have population attributable fractions between 2.72 and 5.97%, with a cumulative population attributable fraction for non-*APOE* loci estimated to be as much as 35% (Naj et al., 2011).

It has been suggested (Lambert et al., 2009; Lambert and Amouyel, 2011) that, in familial early onset AD, the Aβ peptides accumulate through overproduction and that, in late-onset forms, the Aβ excessive deposition is related to an insidious impairment of clearance of Aβ peptides (Mawuenyega et al., 2010).

Morgan (2011) described three new pathways implicated in late-onset AD:

(1) Immune system function (implicated genes: *CLU, CR1, ABCA7, MS4A* cluster, *CD33* and *EPHA1*). Specific immune responses may be capable of inducing Aβ degradation, avoiding accumulation of these peptides (Lambert and Amouyel, 2011). It was also suggested that AD risk variants may cause changes to the complement system, which can re-ignite programmed synaptic loss (Hollingworth et al., 2011b).
(2) Cholesterol metabolism (implicated genes: *APOE, CLU,* and *ABCA7*). As cholesterol promotes synapse formation, interference with cholesterol processing through AD risk gene activity can be a mechanism of synaptic disintegration (Hollingworth et al., 2011b).
(3) Synaptic dysfunction and cell membrane processes (implicated genes: *PICALM, BIN1, CD33, CD2AP,* and *EPHA1*), including endocytosis (Hollingworth et al., 2011a). Although these processes diverge from the amyloid hypothesis, it was suggested that toxic Aβ may have a modulatory effect on them (Morgan, 2011).

SORL1 is involved in the processing and trafficking of APP into recycling pathways, as demonstrated in a study involving *in vitro* experiments, mice models and human AD samples (Andersen et al., 2005). A recent meta-analysis of genetic data from case-control studies suggests that mutations in *SORL1* may play a role in the pathogenesis of late-onset AD (Reitz et al., 2011), but their effect on the risk of disease seems to be modest (Rogaeva et al., 2007).

Recently, a variable-length poly-T (deoxythymidine homopolymer) polymorphism in the *TOMM40* gene, which is located next to the *APOE* gene in a region of strong linkage disequilibrium, was described and found to be associated with the age of onset of late-onset AD (Lutz et al., 2010; Roses, 2010; Roses et al., 2010). This association is still uncertain and it is unknown whether the poly-T repeat affects risk of AD through an APOE-dependent or a totally independent mechanism (Cruchaga et al., 2011).

GENETIC TESTING

The American College of Medical Genetics and the National Society of Genetic Counselors have recently defined guidelines concerning genetic counseling and testing for AD (Goldman et al., 2011). Tests for genes associated with early onset AD (currently *APP*, *PSEN1*, and *PSEN2*) are useful for: (1) symptomatic patients with early onset AD; (2) individuals with a family history of dementia with one or more cases of early onset AD; (3) individuals with a relative affected by a known mutation of *APP*, *PSEN1*, or *PSEN2*.

In summary, AD genetic risk factors may be divided into: (1) rare autosomal dominant mutations (*APP*, *PSEN1*, *PSEN2*) – genetic tests available in selected circumstances; (2) common mutations with moderate effect (*APOE*) – genetic testing not recommended at present due to limited clinical utility and poor predictive value; (3) common mutations with small effect (e.g., *CLU*, *PICALM*, *CR1*, *BIN1*, *ABCA7*, *MS4A6A*, *MS4A4E*, *CD2AP*, *CD33*, and *EPHA1*) – genes with poor predictive value individually.

Genetic counseling is essential during the process of genetic testing for both symptomatic and asymptomatic patients. Pediatric testing is not recommended (Goldman et al., 2011).

NON-GENETIC RISK FACTORS

AD is a multifactorial disorder, whose causes remain largely unknown. Despite extensive research on genetic factors, the vast majority of AD cases are not directly linked to them. Instead, a complex association between environmental or lifestyle and polygenetic factors seems to play a crucial role in sporadic AD vulnerability (Launer, 2002; Murray et al., 2011).

Aging is, by far, the most well established risk factor for the development of sporadic AD. Several studies are unanimous in showing an exponential growth in incidence rates between the

ages of 65 and 85 years, doubling every 5 years, and no gender differences in the AD incidence (Launer et al., 1999; Fratiglioni et al., 2000; Kawas and Corrada, 2006). In contrast, after the age of 85, the cumulative risk for developing AD seems to decrease only in men. Thus, the female gender is often associated with a higher relative risk of AD (Andersen et al., 1999; Ruitenberg et al., 2001).

Modifiable risk factors have received increasing attention. Epidemiological and clinical studies suggest that vascular and metabolic disorders are important risk factors for AD. Growing evidence has emerged suggesting that raised blood pressure (Qiu et al., 2006) and high levels of serum cholesterol (Kivipelto et al., 2005), particularly at adult age, may precede and increase the risk of dementia, including AD, in late life. The biological pathway linking long-standing hypertension or hypercholesterolemia to AD pathology can be mediated by atherosclerotic lesions and other vascular changes. These lead to chronic or episodic cerebral hypoperfusion and may converge to initiate or accelerate selective neurodegenerative processes in the aging brain, particularly in genetically susceptible hosts (Iadecola and Gorelick, 2003; de la Torre, 2004; Qiu et al., 2006). The hypercholesterolemia's effects in AD incidence may also be due to an increased synthesis of $A\beta_{42}$, through modulation of the cleavage pattern of APP, or to interference with the transport and metabolism of this peptide (Kuller and Lopez, 2011). Cardiovascular disease and carotid artery stenosis are strong risk factors, supporting the view that chronic cerebral hypoperfusion may promote selective neurodegenerative damages in susceptible brain areas (Ruitenberg et al., 2005) and suggesting that peripheral atherosclerosis biomarkers can be early indicators of a subclinical phase of AD (Qiu et al., 2006; Muller et al., 2007). Cerebrovascular disease is an important pathological mechanism adding severity to AD (Knopman, 2006). Similarly to hypertension, overweight and obesity initiated at adulthood seem to increase the susceptibility for AD (Kivipelto et al., 2005), possibly through vascular dysfunction or through the effects of hormonal compounds that are secreted by the adipose tissue (Gustafson, 2006). Diabetes and impaired glucose tolerance have also been associated with increased odds of dementia (Biessels et al., 2006; Qiu et al., 2007). The direct effect of glucose-mediated toxicity and hyperinsulinemia on amyloid metabolism and AD neurodegenerative processes has been emphasized (Biessels et al., 2006), but the exact pathophysiological mechanisms remain unclear.

The vascular hypothesis suggests that midlife vascular risk factors and disorders are involved in neurodegeneration, progression and clinical presentation of AD. The view that sporadic AD is primarily a vascular disease with neurodegenerative consequences (de la Torre, 2010) remains controversial, given that both cerebrovascular disease and AD are very prevalent in the elderly, and thus may coexist in an important proportion of patients. Furthermore, the identification of "pure forms" of AD, i.e., without simultaneous vascular disease, does not support a direct relationship between vascular disease and AD (Román and Royall, 2004).

Concerning tobacco smoking, conflicting outcomes have been reported. Contradicting previous reports, recent studies have found that current smoking is associated with increased risk of AD in older people (Cataldo et al., 2010). With regard to alcohol intake, the outcomes are also controversial, but suggest that light to moderate consumption may decrease the risk of dementia, when compared to abstinence or heavy drinking, in a J-shaped relationship (Xu et al., 2009).

Additional risk factors have been suggested, including migraine (Tyas et al., 2001), high intake of saturated fat (Luchsinger and Mayeux, 2004), high serum homocysteine (Kalmijn et al., 1999) and fibrinogen concentrations (Bots et al., 1998), peripheral inflammation (Engelhart et al., 2004), atrial fibrillation (Duron and Hanon, 2010) and head injury (Guo et al., 2000).

In the elderly population, studies show a strong inverse association between the levels of mental, social and physical activity and the dementia risk (Wang et al., 2002; Rovio et al., 2005). The potential pathway explaining the effects of lifestyle factors on AD risk can be explained by the cognitive reserve hypothesis, which states that educational or occupational stimulation may lead to a more effective and flexible use of brain networks, resulting in an increase of cognitive functional reserve against brain pathology or age-related changes. Thus, stimulating environments and physical exercise can be protective factors and may modulate the threshold of clinical expression of AD pathology (Fratiglioni et al., 2004; Stern, 2006).

EPIDEMIOLOGY

AD is the most common cause of dementia (Fratiglioni et al., 2000; Lobo et al., 2000). By 2005, the Delphi study estimated that there were 24.3 million people worldwide with dementia, with 4.6 million new cases arising every year. Among regional populations of individuals aged $\geq$60 years, those from North America and Western Europe exhibited the highest prevalence of dementia (6.4 and 5.4%, respectively), followed by those from Latin America (4.9%), China and developing Western Pacific (4.0%) and Eastern Europe (3.8–3.9%). The annual regional dementia incidence rates (per 1.000 individuals) were estimated to be 10.5 for North America, 9.2 for Latin America, 8.8 for Western Europe, 8.0 for China and developing Western Pacific and 7.7–8.1 for Eastern Europe. It has been calculated that the number of people with dementia may rise to 81.1 million by 2040 (Ferri et al., 2005).

The estimated lifetime risk of AD is 10–11% in males and 14–17% in females at the age of 85 (Genin et al., 2011). Women bear most of the burden of AD probably due to longer life expectancy and longer post-diagnosis survival duration. However, reports of the association between gender and AD have been controversial and its unclear whether women have a survival advantage or not (Heyman et al., 1996; Lapane et al., 2001; Brookmeyer et al., 2002; Larson et al., 2004; Helzner et al., 2008; Xie et al., 2008). In some studies, age-specific incidence of AD and prevalence controlled for age do not differ significantly by gender (Hebert et al., 2001). Interestingly, a study reported that AD pathology is more likely to be clinically expressed as dementia in women than in men (Barnes et al., 2005).

The prevalence and incidence rates for AD increase exponentially with age. AD rates rise from 2.8 per 1000 person-years in the age group 65–69 years to 56.1 per 1000 person-years in the older than 90-year age group (Kukull et al., 2002).

AD substantially reduces life expectancy and increases the probability of being admitted to a nursing home. The median survival times after diagnosis range from 8.3 years for individuals diagnosed with AD at the age of 65–3.4 years for persons diagnosed

as having AD at the age of 90. Diagnoses of AD at ages 65 and 90 years are associated with approximately a 67 and 39% reduction in median life span, respectively (Brookmeyer et al., 2002). Death from all causes by the age of 80 is expected in 61% of AD patients and in 30% of the general population. Nursing home admission by the age of 80 years is expected for ∼75% of the surviving AD patients, and only for 4% of the general population (Arrighi et al., 2010).

DIAGNOSIS

The clinical diagnosis of dementia caused by AD can approach an accuracy rate of 95%, but only when it is established by highly experienced clinicians observing selected patients who are generally followed up comprehensively over time. Outside of specialized centers, AD dementia is correctly diagnosed only in about 50% of affected individuals (Mayeux et al., 2011). Accurate diagnosis of AD is difficult because of the frequent presence, in older adults, of co-morbidities that can contribute to cognitive impairment. A factor that may further complicate diagnosis is ignorance of the patient's previous baseline, which precludes the clinician from correctly evaluating whether there was cognitive and functional decline (a requisite incorporating MCI and dementia criteria) or not. There may not always be a reliable informant and self-reported estimates of function can be inaccurate (Mayeux et al., 2011).

The diagnosis of AD is frequently based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR; American Psychiatric Association, 2000) and on the National Institute of Neurologic and Communicative Disorders and Stroke – Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). Both sets of criteria require deficits in memory and at least one other cognitive domain. The DSM-IV-TR criteria additionally stipulate that there must be an impact of the cognitive impairment on social function or activities of daily living (ADL). According to the NINCDS-ADRDA criteria, the AD diagnosis is classified as definite (clinical diagnosis with histologic confirmation), probable (typical clinical syndrome without histologic confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histologic confirmation). The NINCDS-ADRDA criteria have been reasonably reliable for the diagnosis of probable AD: across more than a dozen clinical-pathological studies, they have had a sensitivity of 81% and a specificity of 70% (Knopman et al., 2001).

However, using the DSM-IV-TR and the 1984 NINCDS-ADRDA recommendations, the AD cases are discovered late in the disease process. Therefore, substantial efforts have been made to create criteria for the clinical stage preceding dementia, i.e., mild cognitive impairment (MCI; Petersen and Negash, 2008), a state in which, by definition, ADL are essentially normal. Nevertheless, MCI is a heterogenous entity, encompassing not only AD cases, but also patients with degenerative diseases other than AD and individuals with non-degenerative causes of cognitive impairment. This issue was solved with the creation of the concept of prodromal AD, which may be considered a subtype of MCI, by Dubois et al. (2007). The core principle of the research criteria for the diagnosis of AD proposed by this group (Dubois et al., 2007) is based upon the presence of consistent episodic memory disturbance which, together with biomarker positivity, recognizes AD across the full spectrum of the clinical disease. To fulfill criteria for probable AD, a patient must meet the cornerstone clinical criterion A and at least one of the supportive biomarker criteria. Criterion A specifies that there must be an episodic memory deficit within test conditions of encoding specificity. The presence of a biological footprint of the disease is established either by criterion B (structural imaging), criterion C (cerebrospinal fluid), criterion D (molecular imaging), or criterion E (dominant mutation within the immediate family). Apart from the incorporation of biomarkers, two relevant innovations characterize the Dubois criteria: (1) the presence of a progressive memory deficit is considered sufficient to make a diagnosis of AD, even if it is the patient's only cognitive deficit; (2) the declarative memory impairment necessary for diagnosis is of the "medial temporal lobe type" (Carlesimo et al., 2011).

In 2011, the NIA-AA workgroup published recommendations concerning the definition of the preclinical stages of AD (Sperling et al., 2011), the diagnosis of MCI due to AD (MCI-AD; Albert et al., 2011) and the diagnosis of dementia due to AD (AD dementia; McKhann et al., 2011), which also integrated biomarker information. According to the NIA-AA workgroup, the major AD biomarkers can be divided into those related to the process of brain Aβ protein deposition, comprising low cerebrospinal fluid (CSF) $A\beta_{42}$ and positive positron emission tomography (PET) amyloid imaging, and those related to downstream neuronal degeneration or injury: elevated CSF tau, both total tau (t-tau) and phosphorylated tau (p-tau); decreased 18fluorodeoxyglucose (FDG) uptake on PET in the temporo–parietal cortex; and disproportionate atrophy on structural magnetic resonance imaging (MRI) in medial, basal and lateral temporal lobe, and medial parietal cortex; McKhann et al., 2011).

According to the NIA-AA recommendations (Albert et al., 2011), in the presence of a change in cognition, objective impairment in at least one cognitive domain, preservation of independence in ADL (and inherent absence of dementia), clinical syndrome suggestive of AD and examination of potential causes consistent with AD, an individual is classified as having MCI-AD-core clinical criteria in the following situations: (1) in the absence of information on biomarkers; (2) in the event that they are uninformative (neither clearly negative nor positive); or (3) in the case that their information is conflicting (e.g., low Aβ and normal tau in CSF). The "suggestive" clinical syndrome involves typically a prominent impairment in episodic memory, but other patterns, such as visuo-spatial impairment, are also possible manifestations of underlying AD pathology and, as such, are compatible with a diagnosis of MCI-AD. A subject is attributed a diagnosis of MCI-AD with intermediate likelihood if he has one positive biomarker either reflecting Aβ deposition or neuronal injury. A person is diagnosed with MCI-AD with a high likelihood if both biomarkers are positive. An individual is attributed a diagnosis of MCI unlikely due to AD if both biomarkers are negative.

Regarding AD dementia, the NIA-AA workgroup (McKhann et al., 2011) proposes the following terminology: (1) probable AD dementia, (2) possible AD dementia, (3) probable or possible AD dementia with evidence of the AD pathophysiological process. The first two concepts are intended for use in all clinical settings. The third is to be used for research purposes only. The authors underline that dementia from all causes implies the presence of

cognitive decline from previous levels of performance, detected by history taking and objective assessment, involving a minimum of two domains, interfering with ADL and not explained by delirium or major psychiatric disorder. According to McKhann et al. (2011), probable AD dementia is diagnosed when the patient meets criteria for dementia and, in addition, there is clear-cut history of worsening of cognition by report or observation, insidious onset, and the initial and most prominent cognitive deficits are in one of the following categories: memory, language, visuo-spatial function, or executive function. The NIA-AA workgroup recommends that the diagnosis of probable AD dementia should not be applied when there is evidence of substantial concomitant cerebrovascular disease, core features of Dementia with Lewy bodies (DLB; other than dementia itself), prominent features of fronto-temporal lobar degeneration (FTLD), evidence of another concurrent, active neurological disease, or of a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition. In persons who meet the core clinical criteria for probable AD dementia, the authors (McKhann et al., 2011) postulate an increased level of certainty of diagnosis in the presence of: documented decline and/or causative AD genetic mutation. According to the same workgroup, a diagnosis of possible AD dementia is made when there is an atypical course, that is, when there is sudden onset of cognitive impairment, or insufficient historical detail or objective cognitive documentation of progressive decline, or when there is an etiologically mixed presentation.

McKhann et al. (2011) state that, in persons who meet the core clinical criteria for probable AD dementia, biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. However, the authors do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. They indicate the reasons for this limitation: the very good diagnostic accuracy of the core clinical criteria; the need for more research validating the design of the biomarker incorporating criteria; the limited standardization of biomarkers from one site to another; and the limited access to biomarkers in many community settings.

AD VARIANTS

Typically, AD presents with initial episodic memory dysfunction, followed by progressive involvement of other cognitive domains, including praxis, visuo-spatial orientation, language, calculation and executive functions. Deficit progression mirrors the successive involvement of different brain regions, beginning with hippocampal damage and spreading to lateral temporal regions, parieto-occipital cortex and frontal lobe structures. However, AD pathology is also found in patients presenting with different clinical symptoms, caused by initial damage on less frequently involved cortical regions. These atypical cases pose diagnostic difficulties, and are frequently identified as non-AD cases, including FTLD, Lewy-body disease (LBD) and cortico-basal degeneration (CBD), in which non-memory deficits are more frequent. Atypical AD patients present in at least two different patterns. The syndrome of posterior cortical atrophy (PCA) involves dysfunction of the visuo-spatial areas of the occipital and parietal cortices. Primary progressive aphasia (PPA) affects almost exclusively language related structures.

The PCA syndrome, first described by Benson et al. (1988), is characterized by the early appearance (before the age of 60) of alexia with agraphia (the most frequent symptoms, which occur without significant derangement of other language related functions), Balint's syndrome (optic ataxia, ocular apraxia, simultanagnosia, and visual agnosia) and Gerstmann syndrome, with acalculia as the predominant symptom (Galton et al., 2000; Tang-Wai et al., 2004; McMonagle et al., 2006; Alladi et al., 2007). Some cases present with predominant parietal dysfunction (involving the dorsal stream of visual perception – the where stream), manifested by agraphia and apraxia, and others show occipital dysfunction (involving the ventral stream – the what stream), expressed by symptoms of visual agnosia, prosopagnosia, achromatopsia and alexia. A third PCA group has been suggested, consisting of patients with cortical blindness, caused by degeneration of the occipital primary visual cortex (Galton et al., 2000). MRI studies have shown atrophy in regions related to the cognitive deficits found on neuropsychological evaluation, and relative preservation of temporal mesial regions. However, not all cases show conspicuous atrophy on MRI. Functional imaging shows hypofunction of the regions responsible for the cognitive deficits. Many cases evolve to full-blown dementia, including affection of episodic memory and other cognitive domains. Nevertheless, some patients maintain exclusive derangement of posterior cortical functions for many years, and some die without presenting the complete late stage AD pattern (Galton et al., 2000; Alladi et al., 2007). Although PCA is defined as a syndrome, caused by different diseases that affect the posterior cortex (including LBD, prion diseases and CBD), neuropathological examination shows a marked predominance of AD cases (Renner et al., 2004). Renner et al. (2004) were not able to find clinical differences between AD and non-AD PCA cases, although some LBD patients would eventually develop the visual hallucinations and extra-pyramidal symptoms characteristic of the disease (Tang-Wai et al., 2004; McMonagle et al., 2006). AD parietal atrophy cases were also difficult to differentiate from CBD cases.

Primary progressive aphasia was first described by Mesulam as a syndrome consisting of progressive deterioration of language and preservation of other cognitive functions, associated with left temporal and frontal lobe atrophy (Mesulam, 2001). As these cases were primarily associated with the FTLD spectrum of diseases, the existence of early language deficits was usually considered as an exclusion criteria for AD. Further investigation has revealed that AD could underlie a higher percentage of PPA cases than was first considered. The syndrome of primary aphasia was classically divided into two distinct patterns: non-fluent aphasia and semantic dementia. Recently, a third pattern was proposed, consisting of patients who seem to share deficits belonging to the other categories: slow speech and word finding difficulties (as in non-fluent aphasia), with preservation of grammar and phonological functions and presence of deficits in naming (similar to semantic dementia). Difficulty in sentence repetition and in understanding long sentences, with preserved ability to understand single words are also characteristic. This particular kind of PPA, named logopenic aphasia, has been linked by imaging and functional studies to atrophy of the left temporo-parietal junction, including the left posterior superior and middle temporal gyri

and inferior parietal lobule (Henry and Gorno-Tempini, 2010). AD pathology could be present in about 20–30% of patients with PPA. Interestingly, it appears to be linked with particular types of PPA. While atypical Alzheimer cases rarely present with semantic and non-fluent aphasia, AD pathology appears to be common in logopenic patients, as proven by clinical-pathological studies (Alladi et al., 2007; Mesulam et al., 2008) and by imaging studies using Pittsburgh compound B (PiB; Rabinovici et al., 2008).

A frontal variant of AD has also been reported, characterized by prominent executive and behavioral symptoms, mimicking the behavioral variant of FTLD, but presenting with AD pathology and selective deposition of amyloid in frontal regions (Johnson et al., 1999; Alladi et al., 2007). These findings have not been replicated in other studies, and the existence of this variant remains controversial.

The prevalence of AD atypical variants is unknown. In the study by Galton et al. (2000), atypical cases represented 14% of all AD cases followed in the institution. This was, however, a tertiary center of referral, in which atypical cases could be over-represented. In the mentioned study, PCA was present in 6 out of 26 atypical cases, while 20 had the aphasic variant (Galton et al., 2000). Little is known about the relative predominance of AD pathology in the total number of patients presenting with focal cortical symptoms, as compared to FTLD, DLB, and CBD pathology. In a study performed in 100 patients with focal cortical syndromes, AD was present in all PCA cases and in more than half of the mixed aphasic cases (a group which included patients with the logopenic variant). Half of the cortical basal syndrome (CBS) cases, about 40% of the patients with the non-fluent aphasia syndrome and a small percentage with behavioral FTLD and semantic dementia syndromes had AD pathology (Alladi et al., 2007). This suggests that, while a diagnosis of PCA represents a high probability of AD, symptoms characteristic of FTLD (particularly the progressive non-fluent aphasia type) or CBS should not rule out this diagnosis.

FIRST APPROACH TO THE PATIENT

The European Federation of Neurological Societies (EFNS) guidelines for the diagnosis and management of AD (Hort et al., 2010) recommend that the evaluation of a subject suspected of having AD should include history, from the patient and a close informant, focused on the affected cognitive domains, the course of the illness, the impact on the ADL and any associated non-cognitive symptoms.

Global assessment of cognitive functions should be undertaken, using, for example, Mini-Mental State Examination (MMSE; Folstein et al., 1975). Such a screening test is useful for the identification of cases requiring more detailed evaluation. This is done using neuropsychological tests assessing memory, executive functions, language, praxis and visuo-spatial abilities (Hort et al., 2010).

As the differentiation of dementia from MCI rests on the determination of whether or not there is significant interference in the ability to function at work or in usual daily activities, it is useful to assess ADL. However, there is no gold standard available for this purpose (Hort et al., 2010). In a review by Sikkes et al. (2009), out of several systematically reviewed scales, the informant-based questionnaires the Disability Assessment for Dementia and the Bristol ADL were among the most useful. The AD8, a brief informant-based questionnaire that is able to differentiate between non-demented and demented individuals in a trustworthy manner (Galvin et al., 2005), is also helpful.

Behavioral and psychological symptoms, as well as co-morbid conditions, should be identified, since they occur in the majority of AD patients and are associated with decline in cognitive and functional ability (Apostolova and Cummings, 2008), decreased quality of life and increased institutionalization (Hort et al., 2010).

Hort et al. (2010) also consider important to elicit past medical history, co-morbidities, family and educational history. It is stressed that neurological and general physical examination are helpful in distinguishing AD from other primary degenerative and secondary dementias and co-morbidities.

Blood tests, according to the EFNS guidelines (Hort et al., 2010), are useful in excluding co-morbidities and should include vitamin B12, folate, thyroid stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function. Syphilis, *Borrelia* and HIV serological tests should be considered in high risk cases or when there are suggestive clinical features.

Structural brain imaging is useful in excluding potentially surgically treatable diseases and in detecting specific findings for AD. For the former, CT and MRI are similarly good and it is consensual that such an imaging procedure should be carried out once in every patient. However, MRI is more sensitive to subtle vascular changes and to alterations specific of certain conditions. For practice purposes, a standard MRI protocol involving at least coronal T1 and axial T2 or fluid-attenuated inversion recovery sequences should be used (Hort et al., 2010).

Electroencephalography (EEG) may help to differentiate between AD, subjective complaints and psychiatric diagnoses. EEG can also be useful in the differential diagnosis of atypical clinical presentations of AD. Even though reduced alpha power, increased theta power and lower mean frequency are characteristic of AD patients, EEG can be normal early in the course of the disease in up to 14% of cases (Hort et al., 2010).

NEUROPSYCHOLOGICAL EVALUATION

Episodic memory should be assessed because it is the function most commonly impaired early in AD as a result of dysfunction of mesial temporal structures, which are responsible for consolidation. Retrieval, which depends on frontal lobe and subcortical structures, is less affected (Hort et al., 2010).

Impaired delayed recall is not, *per se*, evidence of an AD-related memory disorder. Authentic deficits in encoding and storage processes (features typical of AD) must be differentiated from non-AD deficits that can also affect delayed recall, including attentional difficulties, which may be present in depression, and inefficient retrieval strategies, associated with normal aging, FTLD, or subcortical-frontal dementias (Dubois et al., 2007).

Dubois et al. (2007) proposed the use of a neuropsychological tool – the Grober-Buschke (GB) paradigm (Grober et al., 1988) – which, controlling for elaborative encoding at study and providing a strong category cue at retrieval, should be able to compensate for eventual encoding/retrieval deficits and allow to identify the memory impairment that is caused by reduced efficiency of consolidation of the memory trace (Carlesimo et al., 2011). Within this neuropsychological test paradigm, measures of sensitivity to semantic cueing can successfully differentiate patients with AD from healthy controls (Dubois et al., 2007).

Sarazin et al. (2007) found that the most sensitive and specific test for diagnosis of prodromal AD was the Free and Cued Selective Recall Reminding Test (FCSRT; Grober and Buschke, 1987). Their study showed that impairment of free recall, total recall, and index of sensitivity of cueing can identify prodromal AD in patients with MCI with high sensitivity (79.7%) and specificity (89.9%).

In a series of studies reviewed by Carlesimo et al. (2011), total immediate recall scores on the original or modified version of the GB paradigm achieved levels of sensitivity between 62 and 100% and of specificity between 93.9 and 100% in the discrimination between AD and healthy elderly individuals. However, none of these studies verified the diagnosis of AD using a postmortem histologic examination.

On the other hand, the review by Carlesimo et al. (2011) did not completely corroborate the superiority of the GB paradigm over more traditional neuropsychological tools for analyzing memory disorders in patients suspected of having AD. In fact, controversial results emerged from studies that compared the sensitivity/specificity of the cued recall task in the GB paradigm with the free recall task in the same or a different experimental paradigm in differentiating patients with full-blown AD or amnestic MCI from healthy individuals. The authors (Carlesimo et al., 2011) concluded that the GB procedure was useful for discriminating whether an isolated memory deficit in an elderly person is due to incipient AD or to other causes and for helping in the differential diagnosis between AD and other etiological forms of dementia.

In an interesting study involving 150 patients with an objective history of episodic memory dysfunction (Oksengard et al., 2010), it was found that delayed recall, objectively assessed by Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958), was the most sensitive marker in the detection of AD cases, when compared with MRI, single photon emission tomography (SPECT), CSF t-tau, $A\beta_{42}$, and p-tau.

BIOMARKERS

MAGNETIC RESONANCE IMAGING

Atrophy of the medial temporal lobe atrophy (MTA) is a well-recognized feature of AD, though there are limitations concerning its specificity, because marked hippocampal atrophy has also been shown in fronto-temporal dementia (Galton et al., 2001), dementia with Lewy bodies (DLB; Barber et al., 2000), Parkinson's disease with dementia (Tam et al., 2005), vascular dementia (Barber et al., 2000) and hippocampal sclerosis (Barkhof et al., 2007). However, only one of these studies was in autopsy-confirmed cases (Barkhof et al., 2007) and thus misdiagnosis cannot be ruled out. Indeed, at least two clinical-pathological studies showed high sensitivity and specificity rates in the discrimination between AD and non-AD dementias.

Burton et al. (2009) assessed the diagnostic specificity of MTA, rated visually on MRI using a standardized scale (Scheltens et al., 1992), blind to clinical or autopsy diagnosis, for AD among individuals with AD, DLB and vascular cognitive impairment (VCI). The study group consisted of 46 individuals who had both antemortem MRI and an autopsy. Subjects were pathologically classified as AD, DLB, or VCI. MTA was a highly accurate diagnostic marker for autopsy-confirmed AD (sensitivity of 91% and specificity of 94%).

Vemuri et al. (2011) created atrophy maps using structural MRI and applied them for classification of new incoming patients. They identified 115 pathologically confirmed subjects with a single dementing pathologic diagnosis (AD, LBD or FTLD-TDP-43) who had an MRI at the time of clinical diagnosis of dementia. Leave-one-out classification showed reasonable performance compared to the autopsy "gold standard": in AD, sensitivity was 90.7% and specificity 84%.

A recent study (Karow et al., 2010) showed no evidence that brain FDG PET was more sensitive than MRI to the degeneration occurring in preclinical and mild AD. Thus, MRI, a practical exam, might be used instead of more sophisticated ancillary tests in clinical practice for early detection of AD.

New quantitative methods using MRI are promising biomarkers. These include: functional MRI and diffusion tensor imaging (Hampel et al., 2008); diffusion weighted imaging, magnetization transfer MRI and proton magnetic resonance spectroscopy (Kantarci and Jack, 2003); and MR volumetry methods. The latter encompass cortical thickness measurement, deformation-based and voxel-based morphometry (Hampel et al., 2008), as well as multiple-atlas propagation and segmentation technique (Leung et al., 2010).

SINGLE PHOTON EMISSION TOMOGRAPHY

The EFNS guidelines (Hort et al., 2010) considered that SPECT could increase diagnostic confidence in the evaluation of dementia. However, and even though it is more widely available and cheaper than PET, it was not included in the Dubois criteria (Dubois et al., 2007), because of its poor estimated diagnostic accuracy. It is not mentioned in the recommendations from the NIA-AA workgroup (McKhann et al., 2011), either.

Pooling data in an exploratory manner from two clinical-pathological studies, Dougall et al. (2004) found a weighted sensitivity for a "positive" brain SPECT (that is, one showing a pattern of bilateral temporo-parietal hypoperfusion) of 74% and a weighted specificity of 91% against neuropathology. In theses studies using pathological verification as a gold standard, clinical criteria were more sensitive than brain SPECT (81 versus 74%) and brain SPECT had a higher specificity than clinical criteria (91 versus 70%).

In the context of other clinical-pathological study, by Jagust et al. (2001), the clinical diagnosis of probable AD was associated with an 84% likelihood of pathologic AD. A positive perfusion SPECT scan raised this likelihood to 92%, whereas a negative SPECT scan lowered it to 70%. SPECT was more useful when the clinical diagnosis was possible AD, with a likelihood of 67% without SPECT, increasing to 84% with a positive SPECT, and decreasing to 52% with a negative SPECT.

Dopaminergic SPECT imaging is useful to differentiate AD from DLB with sensitivity and specificity around 85% (Hort et al., 2010).

POSITRON EMISSION TOMOGRAPHY

FDG PET

In vivo brain FDG PET is a minimally invasive diagnostic imaging procedure used to evaluate cerebral glucose metabolism. The pattern of metabolic impairment of the posterior cingulate

and temporo-parietal cortices, including the precuneus, more accentuated than frontal cortex deficits, together with relative preservation of the primary sensorimotor and visual cortices, basal ganglia, and cerebellum, constitutes the distinctive metabolic phenotype of AD (Bohnen et al., 2012).

Hoffman et al. (2000) studied FDG PET imaging in individuals with difficult-to-characterize memory loss or dementia who eventually received pathologic confirmation of diagnosis. The sensitivity, specificity, and diagnostic accuracy of bilateral temporoparietal hypometabolism being associated with AD were 93, 63, and 82%, respectively.

In a study by Silverman et al. (2001), using neuropathological diagnosis as "gold standard," PET was 94% sensitive and 73% specific in identifying AD.

According to a study by Minoshima et al. (2001), PET could distinguish autopsy-confirmed AD and DLB patients with 90% sensitivity and 80% specificity.

Another study, by Jagust et al. (2007), reported results of a mixed sample of subjects with variable levels of cognitive impairment, who eventually underwent autopsy. Results showed that PET had sensitivity of 84% and specificity of 74% for the pathologic diagnosis of AD. The clinical diagnosis of AD was associated with a 70% probability of detecting AD pathology; with a positive PET scan this increased to 84%, and with a negative PET scan this decreased to 31%. A diagnosis of "not AD" at initial clinical evaluation was associated with a 35% probability of AD pathology, increasing to 70% with a positive PET scan. The probability of a postmortem diagnosis of AD for an initial normal cognitive assessment and negative FDG PET findings was 17%.

In a study by Foster et al. (2007), involving patients with pathologically confirmed AD or FTLD, adding FDG PET to clinical information increased the accuracy of AD diagnosis from 86 to 97%.

PiB PET

N-methyl-11C-2-(4-methylaminophenyl)-6-hydroxybenzothiazole, also known as 11C-6-OH-BTA-1 or 11C-PiB, is an amyloid-binding PET tracer.

The topological pattern of PiB binding in preclinical and clinical AD patients comprises prefrontal cortex (PFC), medial parietal cortex, lateral temporal cortex, striatum and posterior cingulate cortex (PCC), with PFC being the region with earliest and most pronounced uptake (Prvulovic and Hampel, 2011).

The diagnostic sensitivity of PiB to accurately classify AD patients and control subjects is reported to average approximately 90% (Prvulovic and Hampel, 2011).

Devanand et al. (2010) evaluated 11C-PiB regional binding potential (BPND, cerebellar reference) in individuals with clinical diagnosis of mild AD, MCI and controls. Using a precuneus BPND cut-point of 0.4087 (values above this considered abnormal), in the differentiation of AD from controls, sensitivity was 0.944 and specificity 0.944. In distinguishing MCI from controls, sensitivity was 0.273 and specificity 0.944.

A puzzling fact is that 10–30% of asymptomatic healthy elderly subjects have increased PiB uptake, a finding that is consistent with several autopsy studies which found AD-typical neuropathological changes in a similar fraction of cognitively intact elderly individuals. On the other hand, a small fraction of AD patients do not show any increase in PiB uptake, which may be explained by inaccurate clinical diagnosis or the fact that PiB does not bind to all fibrillar Aβ conformations (Prvulovic and Hampel, 2011).

CSF ANALYSIS

The typical CSF pattern of AD consists of decreased levels of $A\beta_{42}$ and increased values of t-tau or p-tau. Studies show that CSF $A\beta_{42}$ changes before total tau (Isaac et al., 2011).

In a multicenter-study, CSF baseline concentrations of p-tau predicted conversion to AD in subjects with MCI with high accuracy (80%) during an observation interval of 1.5 years (Ewers et al., 2007; Prvulovic and Hampel, 2011).

A prospective cohort study (Visser et al., 2009) found that the CSF AD profile could identify patients with potential AD type dementia among patients with MCI at sensitivities in the range of 88–91% and specificities between 52 and 90%.

In a large cross-sectional study involving patients with AD, fronto-temporal dementia (FTD) and DLB, CSF concentrations of p-tau-181 discriminated between DLB and AD with a sensitivity of 94% and a specificity of 64%, while CSF concentrations of p-tau-231 performed particularly well in the separation of AD and FTD groups, with a sensitivity of 88% and a specificity of 92% (Hampel et al., 2004).

Welge et al. (2009) found that combining CSF p-tau with $A\beta_{42}/A\beta_{38}$ resulted in a sensitivity of 94% for detection of AD and 85% specificity for excluding non-AD dementias.

In a clinical study by de Souza et al. (2011), the p-tau/$A\beta_{42}$ ratio was the best biomarker for distinguishing AD from behavioral variant FTLD and SD, with a sensitivity of 91.7 and 98.3%, respectively, and a specificity of 92.6 and 84.2%, respectively.

Le Bastard et al. (2010) investigated the utility of CSF in cases that had clinically ambiguous diagnoses, using autopsy-confirmed dementia diagnosis as gold standard. AD and non-AD patients showed no significant differences in CSF $A\beta_{42}$ and t-tau concentrations, whereas p-tau (specifically p-tau-181) concentrations were significantly higher in AD compared to non-AD patients. The biomarker-based diagnostic model correctly classified 82% of the patients.

Interestingly, in a study by Schoonenboom et al. (2012), CSF AD biomarker profile was seen in 47% of DLB cases, 38% of CBD individuals, and in almost 30% of FTLD and vascular dementia patients. Individuals with psychiatric diseases and with subjective memory complaints had normal CSF biomarkers in 91 and 88% of cases, respectively.

CANDIDATE BLOOD-BASED BIOMARKERS

There is evidence of peripheral oxidative damage correlating with the occurrence of AD (Di Domenico et al., 2011). Thus, peripheral oxidative biomarkers might be useful for early diagnosis and prognosis. Complement factor H, alpha-2-macroglobulin, and clusterin have all been consistently associated with Alzheimer's type pathology (Ballard et al., 2011a). Ijsselstijn et al. (2011) identified a significant increase in concentration of pregnancy zone protein (PZP) in pre-symptomatic AD, when compared with controls. At

present, the use of plasma based Aβ cannot be recommended as diagnostic biomarker for MCI and AD (Prvulovic and Hampel, 2011).

ROLE OF BIOMARKERS IN THE CLINICAL SETTING

It is currently difficult to understand the relative importance of different biomarkers when used together, and to interpret results when biomarker data conflict with one another (Albert et al., 2011).

Much work is still needed to determine the sensitivity, specificity, and predictive value of biomarkers for a diagnosis of AD in clinical samples. On the other hand, AD biomarkers allow the detection of AD pathology in living individuals who have no clinically discernible cognitive impairment. Such individuals are considered to have preclinical AD, with the assumption that all eventually will develop symptomatic AD if they live long enough (Mayeux et al., 2011). However, it is known that some older individuals with the pathophysiological process of AD may not become symptomatic during their lifetime (Sperling et al., 2011). Use of biomarkers in the clinical setting is thus currently unwarranted because many individuals who satisfy the proposed research criteria may not develop the clinical features of AD in their lifetime (Sperling et al., 2011).

Nevertheless, biomarkers can be used as optional tools when considered appropriate by the clinician (McKhann et al., 2011).

In our view, biomarkers should be used in MCI and demented patients whose characteristics pose doubt as to etiology. The choice of biomarkers depends on local availability and cost-effectiveness issues, must take into consideration the time dependence of biomarker changes during disease progression and the main alternative differential diagnosis in the case in question.

PREDICTORS OF RATE OF DISEASE PROGRESSION

Factors that seem to increase the rate of disease progression (in terms of cognitive and/or functional status) include: higher education (Bruandet et al., 2008; Musicco et al., 2009, 2010; Roselli et al., 2009); younger onset (Musicco et al., 2009; Tschanz et al., 2011); increased baseline severity (Ito et al., 2011); psychosis (Stern et al., 1994; Lopez et al., 1997); extrapyramidal signs (Mortimer et al., 1992; Stern et al., 1994); lower CSF Aβ 42 levels, higher tau or p-tau-181 levels, lower p-tau-181/tau ratio and higher tau/Aβ 42 ratios (Kester et al., 2009; Snider et al., 2009).

TREATMENT

The particular assembly of symptoms that each patient manifests as a result of AD changes along the course of the disease and is also different between patients. Added to the dynamic influence of co-morbidities and co-medications, this fact may, at least partially, explain why the effect of many treatments may vary both intra and inter individually. Clinical trials, unable to control all variables and limited by the complex task of detecting changes in cognition or behavior, often reflect these heterogeneities by showing a globally small, non-significant or conflicting effect for the treatment they are evaluating (Gauthier et al., 2010). Considering that many drugs (and other treatments) have significant side effects and costs, producing guidelines for the treatment of this disease is not always clear-cut. Despite all this, good level of evidence exists for some effects of a small group of drugs, and for another group of treatments a more or less systematic effect can also be expected, so that it is possible to advise on many aspects of the management of this form of dementia with some degree of certainty (Hort et al., 2010; Ballard et al., 2011a; Massoud and Léger, 2011). Decisions at the level of a single patient, especially in moderate and advanced disease, often have to be, though, based in expert opinions, one's previous experience or extrapolations from other diseases.

The currently available treatments for AD are symptomatic. They are able to, at least transiently, ameliorate some aspects of cognition and function and reduce some neuropsychiatric symptoms, making patients and their entourage suffer less with the disease. If patients under treatment see their therapies removed after a certain time of continuous administration they will be essentially indistinguishable from patients never treated, meaning that this treatments are not intervening in disease progression.

The measures currently advocated to manage this form of dementia involve adapting the patient's environment and treating the patient himself.

The interaction of a demented patient with the environment around him is dysfunctional. Some measures can reduce the consequences of this (Hort et al., 2010). The continuous education of the caregivers, perhaps starting with setting real expectations as to what to expect in terms of long-term evolution of symptoms and treatment effect, is of primordial importance. The ability of patients to correctly use money, medications, transports and home appliances should be assessed and continuous adaptation of the facilities at home and other pertinent environments should be planned. Ability to drive should also be assessed according to global (Iverson et al., 2010) and country-specific guidelines. Information about social security, legal and other related matters should be systematized. The caregivers should be advised of the possibility of their own exhaustion and strategies to avoid it should be foreseen.

Objectives of intervention in the patient himself can be conceptually divided in two: (transiently) revert some cognitive deficits and ameliorate functional capacity; and revert disturbing neuropsychiatric symptoms or behaviors. These treatments may be pharmacological or non-pharmacological.

The mainstay of treatment consists of a small group of drugs that showed consistent, albeit small and variable, benefits in well-designed clinical trials. They are the only currently approved treatments for AD by the authorities of most countries and include the cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine (for a review of the evidence see Herrmann et al., 2011). As stated above for the treatment of AD in general, they show only a "symptomatic" effect, although a neuroprotective potential has also been proposed.

Cholinesterase inhibitors are approved for mild to moderate disease (usually MMSE between 16 and 26), where they proved to have effect in cognition, global outcome and function when compared to placebo (Birks and Harvey, 2006; Loy and Schneider, 2006; Birks et al., 2009). Weaker evidence shows some effect in severe AD (Herrmann et al., 2011) and the FDA has also approved donepezil for moderate to severe disease. These drugs show as well benefit in some neuropsychiatric symptoms, particularly apathy, and somewhat less in psychosis. In clinical practice one can generally expect to observe slight amelioration in cognition and

stabilization in function, parameters which are presumed to return to baseline or start degrading again after 6 to 12 months of treatment. Differences in drug metabolism may justify switching from one cholinesterase inhibitor agent to another in cases of intolerance or lack of effect (Massoud et al., 2011). The most common side effects are gastrointestinal dysfunction, anorexia and sleep disturbances. They can usually be avoided by titrating up the dose. The most concerning side effects of these medications are bradycardia and syncope, reasons for which it is advisable to evaluate preexisting bradycardia or cardiac conduction blocks with an electrocardiogram and monitor blood pressure. Rivastigmine administered in a transdermal patch has fewer side effects than its oral form, maintaining the same benefits (Winblad et al., 2007).

Memantine is approved for moderate to severe AD, where it proved to have beneficial effects in cognitive performance, function and global measures (McShane et al., 2006). Memantine may also be useful in the prevention and treatment of agitation, aggression, irritability and psychosis. As with cholinergic drugs, one should expect stabilization of cognition and function for 6 months after onset of treatment. Memantine is usually well tolerated. Dose-limiting side effects are rare and consist of dizziness, headache, somnolence, and confusion.

There also seem to be additive benefits of combining a cholinesterase inhibitor and memantine (Tariot et al., 2004; Atri et al., 2008; Lopez et al., 2009) albeit not all studies have supported this (Porsteinsson et al., 2008).

The short duration of most trials with these four drugs precludes us from knowing the time for how long a difference from placebo is maintained. The majority of experts advice caution in stopping these drugs, although some reasons for discontinuation may be advocated (Massoud et al., 2011).

Concerning non-pharmacological approaches to help maintain or enhance the cognitive, functional and global status of these patients, current evidence suggests that cognitive training and cognitive stimulation offer modest, albeit significant, benefits. The results are mainly limited to the cognitive domains on which the intervention is focused and, as these interventions are laborious, cost-effectiveness studies are needed (Ballard et al., 2011b).

Another major topic in the treatment of AD is the approach to certain frequent and disturbing neuropsychiatric symptoms like apathy, depression, anxiety, psychosis, agitation, irritability, aggression and sleep disturbances. There are no authority approved treatments for these situations, which is a consequence of lack of data, insufficient or conflicting results and concerns with possible side effects. In general terms, non-pharmacological interventions are advocated first (sleep hygiene measures, for instance). When symptoms are very severe and menacing, pharmacological treatment may be started immediately, accompanied by non-pharmacological measures. Another general rule is that drug treatments employed in this setting should be administered in the minimal efficacious dose and envisaged as transitory. Registering all the events prior to these manifestations helps to identify possible environmental triggers.

For depression, when symptoms are mild and transient, non-pharmacological approaches should be tried, like structured activities, such as day programs and daily exercise (Ballard et al., 2008). Bright light therapy can aid sleep and reduce mood and behavioral disturbance (Gauthier et al., 2010). For severe depression, most clinicians use antidepressive drugs, whose efficacy has been shown in many trials, although not in all. Sertraline (100 mg/day) is the most documented drug, but other SSRI's and other classes can be tried, as long as side effects are considered (Gauthier et al., 2010; Ballard et al., 2011a).

Neuroleptic drugs are commonly used to treat aggression, agitation and psychosis. Efficacy has been demonstrated for risperidone (especially 2 mg/day) when prescribed for aggression, but for agitation and psychosis, and for use of other neuroleptics, results are weak or conflicting. Benefits, which are often moderate, must be weighed against potentially serious adverse events like sedation, parkinsonism, chest infections, ankle edema, and an increased risk of stroke and death. As already stated, minimal effective doses should be used and long-term prescription avoided. Anticonvulsants, like carbamazepine (useful for agitation), and benzodiazepines may be helpful in selected cases. For the first one, potential drug interactions should not be forgotten, and, for the latter, very short term use should be foreseen. Simple non-pharmacological treatments, such as increasing physical and social activity, aroma therapy (lavender and melissa), therapy with animals, music therapy and simulated presence therapy (audio or video tapes with familiars), can be effective alternatives (Ballard et al., 2008, 2011a; Gauthier et al., 2010).

The treatment of AD also involves management of comorbidities. They often cause sudden aggravation of cognitive deterioration or appearance of neuropsychiatric symptoms. In these situations, so called "medical" causes, such as metabolic and infectious diseases, as well as cerebrovascular pathologies, must be actively sought and treated.

Other symptoms which must be dealt with (mostly in advanced disease stages) include parkinsonism, gait instability, myoclonus, seizures, contractures, pressure ulcers, pain, and undernutrition.

Concerning emerging treatment drugs, they are expected to show less inter-individual variability and a more marked effect. For that purpose, they must act directly in the mechanisms of disease and be administered earlier in the course of AD, before significant neurodegeneration has occurred. Hopefully, biomarkers will allow diagnosis before a dementia syndrome is installed and permit testing drugs at a stage when they could be (more) effective.

Several lines of drug investigation are being pursued, some targeting only symptomatic treatment, but the majority aiming to show a disease-modifying effect (for reviews see Potter, 2010; Herrmann et al., 2011; Salomone et al., 2012).

New cholinergic agents in investigation include direct and allosteric muscarinic acetylcholine receptor agonists and also agonists of certain subtypes of nicotinic receptors.

A group of drugs aiming to reduce Aβ production include: rosiglitazone, which, among other modes of action, could inhibit β secretase, was ineffective in a phase 3 trial, despite suggestion of efficacy in earlier data (Gold et al., 2010); semagacestat, a γ secretase inhibitor, was tested in two phase 3 trials that had to be prematurely stopped due to serious systemic adverse events (Schor, 2011); several NSAID, including tarenflurbil, show a weak modulating or inhibiting effect on γ secretase, but the tested ones were not efficacious in AD. Calcium channel blocker nilvadipine could also reduce the production and augment the clearance of

Aβ and is being clinically tested. Investigation of more potent and specific inhibitors of γ secretase and efforts to produce α secretase stimulating drugs are being undertaken. In the line of preventing Aβ aggregation, tramiprosate, which, by binding to Aβ monomers, prevents formation of oligomers, did not show global clinical benefit in a phase 3 trial, although more studies are needed to clarify its effects in some cognitive areas (Saumier et al., 2009). Other drugs that could interfere in this stage of the Aβ cascade are the zinc and copper chelators, curcumin (also proposed to have γ secretase inhibiting properties), epigallocatechin-3-gallate (EGCG) and scyllo-inositol, a compound that promotes dissociation of Aβ oligomers.

Immunotherapy in AD is essentially being tried as a way of clearing Aβ deposits through the use of antibodies against this protein. Active immunization in the form of vaccines has produced severe adverse effects (meningoencephalitis), but different techniques, inducing immunization against only a part of the Aβ molecule and not all of it, are being thought of. Passive immunization with monoclonal antibodies is at present under very active clinical investigation. The most studied antibodies are bapineuzumab, which is under various phase 3 trials with different doses after a higher dose produced cerebral vasogenic edema in almost 10% of the patients (Panza et al., 2011), and solanezumab, also in phase 3 trials. Other strategies are being studied, including the use of intravenous immunoglobulins (IVIG).

Lithium and valproate, besides other modes of action, could reduce hyperphosphorylation of tau, but various clinical studies have shown conflicting results. Other compounds judged to act in tau phosphorylation and aggregation (including methylene blue) are under investigation.

Other therapeutic strategies in development include the use of nerve growth factor, etanercept and phosphodiesterase-5 inhibitors; interventions at the mitochondrial level (for instance with latrepirdine and EGCG); inhibition of the receptor for advanced glycation end products (RAGE); and the use of deep brain stimulation (DBS). The roles of caffeine (or of whole coffee) and of physical activity in the treatment of AD also deserve clarification.

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Rethinking Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder with insidious onset and progressive course, which prevalence increases with the age. It is characterized by neuronal degeneration and death, related to the deposition in the brain of the amyloid β_{1-42} peptide and the hyperphosphorylated tau protein, and initially affects brain areas, namely the hippocampus and other medial temporal lobe structures, which are important for memory processes (Blennow et al., 2006). As a consequence of the aging of the population, the number of patients with AD and other dementias, as well as the number of elderly people who, although not demented, suffer from significant cognitive decline, is growing worrisomely (Alzheimer's Disease International, 2009).

Alzheimer's disease is the most frequent cause for dementia. Indeed, the presence of dementia is presently required for the diagnosis of AD according to established diagnostic criteria, like the *International Classification of Diseases* (World Health Organization, 1992), *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994), or those proposed by the *National Institute of Neurological and Communicative Disorders and Stroke* (McKhann et al., 1984), that is to say, the patient must have deficits in memory and other cognitive domains, representing a decline in relation to a previous level, and interfering significantly with the social and professional life.

However, AD begins insidiously, usually with memory difficulties, many years before the patient has a cognitive and functional decline compatible with the diagnosis of dementia. Furthermore, it is often difficult to appreciate the memory complaints in the initial phase of AD, because healthy people frequently report an unfavorable opinion about their own memory, and there is a slight decline in objective memory performance in the aging process (Mendes et al., 2008).

Several nosologic concepts were proposed, in the last decades, to describe the patients who have cognitive deficits but are not demented. Of these, the one that became more popular was mild cognitive impairment (MCI), as established by Petersen et al. (1999), and subsequently refined (Portet et al., 2006).

Certainly, clinicians interested in memory disorders have been in the last few years consulting younger patients and patients with more subtle complaints. The nosologic concept of MCI has been very useful to establish the probability of progression to dementia and promote an adequate follow-up in these patients. However, the concept of MCI has important limitations. First of all, it represents a stage of cognitive decline between normality and dementia, rather than a disease (Gauthier et al., 2006). In second place, some patients with MCI are intriguingly stable and do not progress to dementia after many years (Petersen et al., 2001). In third place, some patients with cognitive complaints who have no alterations in the neuropsychological testing, and thus do not fulfill MCI criteria, do nevertheless progress to dementia (Nunes et al., 2010). We must thus recognize that the concept of MCI is unsatisfactory both from a diagnostic and prognostic point of view.

However, and very importantly, the studies performed in patients with the diagnosis of MCI allowed a better understanding of the initial phases of AD, and lead to the proposal of new AD criteria that can diagnose the disease at initial stages, before the patient is demented (Dubois et al., 2007; Albert et al., 2011). These criteria are still considered mainly appropriate for clinical research, but their use is certainly spreading to specialized practice. The new criteria are based on the identification of pathological alterations in the brain typical of AD, or biomarkers, namely: (1) decline in episodic memory, confirmed by neuropsychological testing, (2) atrophy of the hippocampus and other medial temporal lobe structures shown by magnetic resonance imaging using volumetric techniques, (3) detection of abnormal CSF biomarkers, namely low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phosphorylated tau concentrations, (4) reduced glucose metabolism in bilateral temporal parietal regions by positron emission tomography. In familial cases, the finding of a causative mutation in the genes responsible for autosomal dominant forms of the disease may establish the definite diagnosis of AD. Other genetic and biochemical biomarkers, as well as neuroimaging using radioligand compounds with affinity for the amyloid β_{1-42} peptide, are presently being developed.

We still do not know the combination of biomarkers most sensitive and specific for the early diagnosis of AD. Large multicentric studies are being conducted to answer this important question, but so far the follow-up times have been generally limited. In the large *Alzheimer's Disease Neuroimaging Initiative* (ADNI) cohort, the use of neuropsychological, brain imaging, and CSF neurochemical biomarkers could only reach a predictive accuracy for MCI conversion to dementia of 64% (Ewers et al., 2010). This is not surprising, since the average follow-up was 2.3 years, and presumably many converters just had not the time to progress to dementia. Longer follow-up times will decisively be needed to find the best combination of biomarkers for an accurate early diagnosis of AD.

In conclusion, the reliable identification of patients with memory complaints who already have Alzheimer's disease opens new frontiers in the management of the disease, since it will allow these patients to undergo interventions that might involve manipulation of risk and protection environmental factors, cognitive rehabilitation procedures, and clinical trials with putative neuroprotective drugs.

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Differences between early and late-onset Alzheimer's disease in neuropsychological tests

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Although patients with Alzheimer disease (AD) share clinical and histological features regardless of age of onset, the hypothesis that early onset AD constitutes a distinct subgroup prevails. Some authors suggest that early attention or language impairment constitute patterns of differentiation in terms of neuropsychological profile, between these groups. However, investigations are not consensual in terms of cognitive domains affected in each group. **Aim:** To investigate whether there is early neuropsychological difference between two types of AD using the conventional dividing line of 65 years. **Methods:** We evaluated the results obtained in the Mini-Mental State Examination (MMSE) and in a comprehensive neuropsychological battery – Battery of Lisbon for the Assessment of Dementia (BLAD), at a Dementia clinic in the University Hospital of Coimbra and a Memory Clinic. The study was developed in consecutive patients with a clinical probable diagnosis of mild to moderate AD, using standard criteria (DSMIV and NINCDS-ADRDA). Statistical analysis was performed using Qui-square and *U*-Mann–Whitney, for categorical and non-categorical variables. The degree of relation between variables, was measured using the coefficient of correlation r_s de *Spearman*. **Results:** The total sample included 280 patients: 109 with early onset AD and 171 with a late-onset form. Groups were comparable in terms of gender, education or severity of disease, and MMSE. In BLAD, for univariate analysis the early onset group had lower scores in Naming ($p = 0.025$), Right–Left Orientation ($p = 0.029$) and Praxis ($p = 0.001$), and better performances in Orientation ($p = 0.001$) and Visual Memory ($p = 0.022$). After application of Bonferroni correction for multiple comparisons only Praxis and Orientation could differentiate the two groups. No significant differences were found in other tests or functions. **Discussion:** The results are suggestive of dissociated profiles between early and late-onset AD. Younger patients have a major impairment in Praxis and a tendency for a great impairment in neocortical temporal functions. AD patients with late-onset forms had a tendency for worse performances in Visual Memory and Orientation, suggesting a more localized disease to the limbic structures.

Keywords: early onset Alzheimer's disease, late-onset Alzheimer's disease, neuropsychological assessment, cognitive domains

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and although its prevalence is much higher in the older population, it is still the most frequent form of dementia under the age of 65 years (Harvey et al., 2003). Early onset dementia conventionally includes patients with onset before 65 years of age (Rossor et al., 2010). This cut-off is an arbitrary division based in sociological aspects and has no biological significance but is considered in diagnostic criteria and is randomly used in clinical practice. Despite neuropathological hallmarks being the same (Khachaturian, 1985), many research groups continue to report phenotypic differences between early and late-onset Alzheimer's disease (EOAD and LOAD), considering age of onset an important determinant of the heterogeneity observed in the disease (Kensinger, 1996). Differences have been reported in rate of progression of the disease (Rogaeva, 2002), perfusion and metabolic deficits in the temporal and parietal lobes (Lantos et al., 1992; Mann et al., 1992; Kim et al., 2005, 2010), grade and distribution of gray matter atrophy (Ishii et al., 2005; Frisoni et al., 2007), and prevalence of the allele ApoE ε4 (van der Flier et al., 2011). Studies have also shown different clinical profiles with higher prevalence of language impairment and other non-memory symptoms as the initial presentation in the EOAD subgroup (Koedam et al., 2010). However, investigations are not consensual in terms of cognitive domains affected in each group (Licht et al., 2007).

The relative low prevalence of AD under 65 years old (McMurtray et al., 2006; Shinagawa et al., 2007), question about the differential diagnosis with other forms of dementia more frequent

in this age level as fronto-temporal dementia, which seems to be responsible for up to 20% of pre-senile dementia cases (Snowden et al., 2002; Weder et al., 2007), and the higher frequency of mutations with more atypical phenotypes (Lucatelli et al., 2009), contribute to divergences in clinical profiles described in literature. Furthermore, although it was generally accepted that Primary Progressive Aphasia (PPA) was a non-Alzheimer type of dementia, some studies have demonstrated that atypical distribution of AD is responsible for 20–30% of cases with various forms of PPA (Alladi et al., 2007). Namely, AD could be the most frequent cause of Logopenic Progressive Aphasia, a subtype of PPA, clinically characterized by slow speech, sentence repetition, and comprehension deficits, with relative sparing of motor speech, grammar, and single-word comprehension (Gorno-Tempini et al., 2008).

The increasing interest in the early forms of the disease because of genetic implications, and the recent biomarker developments will certainly allow a more precise classification in clinical practice.

The aim of this study is to better characterize the neuropsychological profile and cognitive deficits of these subgroups or forms of AD, as this may be relevant to an earlier and accurate diagnosis, as well as to the design of clinical trials.

MATERIALS AND METHODS

PARTICIPANTS AND PROCEDURES

Patients were collected consecutively from January 1990 until June 2009, at the Dementia Clinic of the University Hospital of Coimbra and in a private Memory Clinic in the same city and as purposed; we assigned each patient to one of the two ages of onset groups, using the conventional division line of the 65 years.

Each patient had a structured clinical interview, laboratory routine exams, physical and neurological examination, and structural (CT or MRI) and functional (SPECT or PET) imaging. Laboratory exams included complete blood count, chemistry profile, thyroid function, B12, and folic acid. Age at onset was estimated from caregiver's information using a standard questionnaire and disease duration was established in years, from the estimated age at onset until the date of the first neuropsychological assessment (Sano et al., 1995). Information related to family history was also taken from patient's relatives. Education was calculated considering schooling years of the patients.

Inclusion criteria included (i) clinical probable diagnosis of AD using the of DSM-IV-TR criteria (American Psychiatric Association, 2000) and NINCDS-ADRDA (McKhann et al., 1984); (ii) classification in mild to moderate severity using the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and Clinical Dementia Rating (CDR) Scale considering as a cut-off for mild AD $\geq$17 points and CDR of 1, and moderate severity when scores were from 16 to 10; (iii) cognitive evaluation with a comprehensive neuropsychological battery which includes all the items intended to be assessed – Battery of Lisbon for the Assessment of Dementia (BLAD).

Patients with MMSE score under 10, with relevant psychiatric manifestations and/or sensory or motor deficits that could interfere with the neuropsychological assessment were excluded. All subjects were right-handed.

The present research complied with the ethical guidelines for human experimentation stated in the Declaration of Helsinki and was approved by the Ethics Board of Coimbra University Hospital. An informed consent was obtained from all the participants after the aims and procedures of the investigation were fully explained by a member of the study group. For AD patients who were incapable of providing consent on his/her own behalf, a legal representative provided the informed consent.

MATERIAL AND NEUROPSYCHOLOGICAL TESTING

The instruments for neuropsychological evaluation were applied at the time of the diagnosis by two trained neuropsychologists. A standardized assessment was performed in which a sociodemographic questionnaire and an inventory of current clinical health status were firstly applied, followed by the administration of the MMSE and finally by the comprehensive neuropsychological assessment. MMSE (Folstein et al., 1975) is a widely recognized and used brief screening instrument for detecting cognitive deficits and therefore is not described in detail here. It is in paper-and-pencil format and is scored out of a possible 30 points, with higher scores indicating better cognitive performance. In this project we used the Portuguese adaptation of the MMSE (Guerreiro et al., 1994). The BLAD (Garcia, 1984) is a comprehensive battery adapted and normalized for the Portuguese population that integrates tests with sensitivity and specificity for the explored cognitive domains and critical to outline the clinical profiles of these patients. This battery assesses the following cognitive domains: attention (Cancelation Task); verbal, motor, and graphomotor initiatives (Verbal Semantic Fluency, Motor and Graphomotor Initiative – Luria sequences); verbal comprehension (modified version of the Token Test); sentences repetition; verbal and non-verbal abstraction (Interpretation of Proverbs and the Raven Progressive Matrices); visuoconstructional abilities (Cube Copy); calculation (Basic Written Calculation); immediate memory (Digit Span forward); working memory (Digit Span backward); learning and verbal memory (subtests from de Wechsler Memory Scale-R) (Wechsler, 1987); right–left orientation and praxis.

STATISTICAL ANALYSIS

Statistical analysis was performed using *Statistical Package for the Social Sciences* (SPSS) version 16.0 for Windows.

Non-parametric analyses were performed as there was no equivalence in number, normal distribution, or homogeneity of variances (Qui-square and *U*-Mann–Whitney, for categorical and non-categorical variables, respectively, with Bonferroni correction).

To measure degree of relation between variables, the coefficient of correlation r_s de *Spearman* was applied.

RESULTS

The study sample consisted of 280 patients: 109 with EOAD and 171 with LOAD. The characterization of the study sample and details of both subgroups is provided in **Table 1**. For this description the following variables were considered: sample size, age, gender, education level, age at onset, disease duration, MMSE mean scores and classification in terms of severity of the disease.

Groups were matched for education, gender, MMSE, disease duration, and severity. As expected, significant differences were found for age and age at onset (**Table 1**).

The comparisons of scores obtained in the neuropsychological assessment (BLAD) are presented in **Table 2**. Results suggest that patients with EOAD performed significantly poorly than the LOAD group in Naming ($p = 0.025$), Praxis ($p = 0.001$), and Right–Left Orientation ($p = 0.029$), and had better performances in Orientation ($p = 0.001$) and Visual Memory ($p = 0.022$). After correction for multivariate comparisons only Praxis and Orientation could differentiate the two groups.

In order to investigate in which degree the performances in neuropsychological tests were related to clinical variables, it was conducted a Spearman's correlation. The clinical variables included in the analysis were the mean scores on MMSE, age at onset and disease duration. The neuropsychological variables included

Table 1 | Comparisons of demographic and clinical variables in both groups: EOAD and LOAD.

	EOAD ($n = 109$)	LOAD ($n = 171$)	*U*	χ^2	*p*
Age	58.98 ± 6.45	75.40 ± 4.95	128.5	n/a	<0.001
Education	6.65 ± 4.49	5.76 ± 4.49	3766.5	n/a	0.555
Gender, ♀	56 (51.4%)	101 (59.1%)	n/a	1.59	0.206
MMSE	21.80 ± 5.17	21.19 ± 3.50	3648	n/a	0.358
Age at onset	56.17 ± 6.15	73.34 ± 4.78	15.5	n/a	<0.001
Disease duration	3.36 ± 2.29	4.50 ± 2.70	3449.5	n/a	0.123
Severity	Mild – 71 (65.1%)	Mild – 121 (70.1%)	n/a	0.97	0.323
	Moderate – 38 (34.9%)	Moderate – 50 (29.2%)			

AD, Alzheimer disease; EOAD, early onset Alzheimer disease; LOAD, late-onset Alzheimer disease; MMSE, mini-mental state examination; U, U-Mann–Whitney test; χ^2, Chi-square test.

Table 2 | Comparison of neuropsychological performances on BLAD of EOAD and LOAD groups.

BLAD subtests	EOAD ($n = 109$)	LOAD ($n = 171$)	*U*	*p*
Letter cancelation	3.55 ± 1.72	3.14 ± 1.36	8176	0.788
Digit span	6.16 ± 2.32	6.33 ± 2.83	8619	0.776
Verbal fluency	10.69 ± 4.39	11.08 ± 3.36	8903	0.767
Motor initiative	2.13 ± 0.75	2.21 ± 0.76	8223	0.342
Graphomotor initiative	1.00 ± 0.73	0.96 ± 0.65	7533	0.796
Auditory comprehension	3.91 ± 0.39	3.98 ± 0.13	5689	0.080
Sentence repetition	10.00 ± 1.41	10.41 ± 1.25	7066	0.136
Object naming	6.59 ± 0.79	6.89 ± 0.479	6790	0.025
Auditory comprehension token test	13.92 ± 4.83	614.58 ± 4.36	5868	0.953
Orientation	11.59 ± 3.34	10.56 ± 2.66	6891	0.001*
Information	14.91 ± 4.58	15.02 ± 3.67	8630	0.667
Interference in verbal memory	6.00 ± 2.55	6.51 ± 2.33	8830	0.907
WMS – word pair learning I	6.77 ± 3.49	6.89 ± 2.81	7699	0.809
WMS – word pair learning D	4.88 ± 2.36	5.07 ± 1.78	2358	0.571
WMS – logical memory I	3.03 ± 2.73	2.57 ± 1.94	4419	0.255
WMS – logical memory D	1.22 ± 1.65	0.71 ± 1.11	1987	0.571
WMS – visual memory I	3.88 ± 3.03	3.25 ± 2.22	2945	0.022
WMS – visual memory D	1.25 ± 1.56	0.85 ± 1.07	1802	0.118
Raven progressive matrices	5.44 ± 3.29	5.06 ± 2.50	7814	0.883
Interpretation of proverbs	4.39 ± 2.76	4.45 ± 2.60	8447	0.705
Right–left orientation	5.19 ± 1.40	5.57 ± 1.06	7749	0.029
Praxis	11.47 ± 0.98	11.90 ± 0.46	6964	<0.001*

BLAD, Battery of Lisbon for the Assessment of Dementia; EOAD, early onset Alzheimer disease; LOAD, late-onset Alzheimer disease; WMS, Wechsler Memory Scale (R); word pair learning I, word pair learning immediate; word pair learning D, word pair learning delayed; logical memory I, logical memory immediate; logical memory D, logical memory delayed; visual memory I, visual memory immediate; visual memory D, visual memory delayed.

**p-Values are significant at the 0.05 level adjusted for multiple comparisons with Bonferroni correction.*

the performances in the subtests of BLAD in which were found significant differences in the univariate analysis (**Tables 3** and **4**).

Considering the EOAD group, it was found a significant positive correlation between the Immediate visual memory and Orientation subtests. A positive correlation was also found between Right–left orientation and Visual memory, both immediate and delayed subtests. Although not reaching statistical significance, a higher negative correlation between the Disease duration and the subtests Orientation and Immediate visual memory was noticed.

In the LOAD group it was observed a significant positive correlation between the Praxis subtest, and Object naming, Right–left orientation and Visual memory. In this group, significant correlation was also found for Orientation and Immediate visual memory.

Table 3 | Spearman's correlations between BLAD subtests and clinical variables – MMSE, age at onset and disease duration in EOAD group.

	MMSE	Age at onset	Disease duration	Object naming	Orientation	WMS – visual memory I	WMS – visual memory D	Right–left orientation
Age at onset	0.183							
	0.111							
Disease duration	−0.291	−0.305						
	0.10	0.007						
Object naming	0.305*	0.241	−0.203					
	0.002	0.046	0.094					
Orientation	0.699*	0.233	−0.361	0.228				
	0.000	0.044	0.001	0.026				
WMS – visual memory I	0.431*	0.345	−0.38	0.226	0.351*			
	0.000	0.031	0.017	0.083	0.004			
WMS – visual memory D	0.396	0.362	−0.305	0.263	0.481*	0.73*		
	0.005	0.062	0.129	0.088	0.001	0.000		
Right–left orientation	0.419*	0.303	−0.151	0.286	0.322*	0.316	0.45*	
	0.000	0.009	0.198	0.005	0.001	0.01	0.001	
Praxis	0.417*	0.188	−0.238	0.079	0.304*	0.214	0.32	0.303*
	0.000	0.104	0.038	0.445	0.002	0.087	0.027	0.002

WMS – visual memory I, Wechsler Memory Scale (R) – visual memory immediate; WMS – visual memory D, Wechsler Memory Scale (R) – visual memory delayed.
**p-Values are significant at the 0.0056 level adjusted for multiple comparisons with Bonferroni correction.*

Table 4 | Spearman's correlations between BLAD subtests and clinical variables – MMSE, age at onset and disease duration in LOAD group.

	MMSE	Age at onset	Disease duration	Object naming	Orientation	WMS – visual memory I	WMS – visual memory D	Right–left orientation
Age at onset	−0.032							
	0.752							
Disease duration	−0.071	−0.39*						
	0.482	0.000						
Object naming	0.293*	0.134	−0.089					
	0.000	0.191	0.386					
Orientation	0.719*	−0.12	−0.062	0.215				
	0.000	0.23	0.536	0.007				
WMS – visual memory I	0.371*	−0.213	−0.283	0.05	0.444*			
	0.000	0.086	0.021	0.611	0.000			
WMS – visual memory D	0.221	0.12	−0.294	0.149	0.23	0.416*		
	0.037	0.403	0.036	0.179	0.031	0.000		
Right–left orientation	0.303*	0.056	−0.15	0.286*	0.287*	0.306*	−0.02	
	0.000	0.58	0.135	0.000	0.000	0.001	0.834	
Praxis	0.187	0.243	−0.084	0.244*	0.173	0.209	0.42*	0.353*
	0.014	0.014	0.402	0.002	0.024	0.025	0.000	0.000

WMS – visual memory I, Wechsler Memory Scale (R) – visual memory immediate; WMS – visual memory D, Wechsler Memory Scale (R) – visual memory delayed.
**p-Values are significant at the 0.0056 level adjusted for multiple comparisons with Bonferroni correction.*

The results are presented in the **Table 3** for the EOAD group and in the **Table 4** for the LOAD.

DISCUSSION

Our results are indicative of dissociated profiles between early and late-onset AD. In language domain, initially we found differences in naming, while comprehension and repetition scores were similar in both groups. When multivariate analysis was applied using all the variables considered, this difference was no longer significant. Reviewing the literature, language has shown to be the cognitive domain more useful and consensual to differentiate early from late-onset subgroups (Seltzer and Sherwin, 1983; Filley et al., 1986; Imamura et al., 2005; Suribhatla et al., 2004) In fact, Seltzer and Sherwin (1983) which were the first authors to investigate this hypotheses, found that the major differences between the groups were in a naming task from the *Boston Diagnostic Aphasia Examination* battery, with worst performances in the EOAD group. However, Jacobs et al. (1994) could not find this same difference in naming ability using a modified version of MMSE, and in Koss and Suribhatla studies the EOAD group had even better scores in the *Boston Naming Test* (BNT; Koss et al., 1996; Suribhatla et al., 2004). A justification for these contradictory findings was the possible influence of aging-associated sensorial declines when population samples from different studies were non-equivalent in terms of demographic variables. For instance, a deficit in visual perception or object identification could contribute to worst scores in the naming tasks (Imamura et al., 2005). This interpretation of a dominant deficit in perception and object identification, applied to our results that indicate a tendency for a worse performance in EOAD, can lead us to infer that in this form there is a broader area of cerebral alterations, probably involving posterior regions interfering with normal occipital lobe compensatory strategies (Lawlor et al., 1994). Severity could also be influencing this task performances as naming alterations have been reported in more severe stages of AD (Imamura et al., 2005). This is not an explanation for some asymmetry of our results, because samples in this study were matched for severity.

Even though some authors have observed differences in comprehension and repetition tasks, we have not found significant differences between groups, in comprehension of simple orders, complex orders (*Token Test*) and repetition. We should admit that this controversy results are mainly a reflex of the despair in level of difficulty in the tasks used in each study, nonetheless Frisoni et al. (2007) reported similar results in the Token Test as we did with the same test, reinforcing the similarity of performances in receptive language task for both age of onset groups.

The difference found in the left–right orientation scores, did not reach statistical significance when correction factors were applied, but is consistent with other studies, reveling that younger subjects with AD have more difficulties in eye–hand coordination tasks that require special-motor abilities (Fujimori et al., 1998; Imamura et al., 2005). And in fact, in our data, the praxis task evaluating ideomotor apraxia was the only one, to reach statistical significance after multivariate analysis, with worse performance in the early onset group. This difference was also described by Reid et al. (1996) and supports the hypothesis of left posterior hemisphere susceptibility in EOAD.

Memory is a complex function aggregating many different modalities. The neuropsychological comprehensive battery used in the study, allowed us to investigate the most representative ones, including primary or working memory, and secondary memories, namely remote and episodic memory. Attention/working memory was tested by a cancelation task (letter "A") and the Digit span (Forward and Backward). Many authors have reported attention and working memory deficits to be more pronounced in EOAD (Jacobs et al., 1994; Koss et al., 1996; Suribhatla et al., 2004; Kalpouzos et al., 2005), but our results do not corroborate this because performances of EOAD and LOAD groups were equivalent. To evaluate recollection of very well learned non-autobiographical material we used a BLAD's Information test which is a 20 item multi-thematic cultural task (retrograde memory) and a verbal fluency experiment consisting of food items (semantic memory). Once again the comparison between groups did not reach significance in our patients, corroborating other findings (Suribhatla et al., 2004; Kalpouzos et al., 2005; Frisoni et al., 2007). But this is not a consensual result because Jacobs et al. (1994) have pointed worst performances for the LOAD group in the enunciation of four United States of America presidents in the modified MMSE and Koss et al. (1996) found to be more difficult for EOAD to enunciate animal names, a well-known verbal semantic memory task similar to the one we used in our battery. The evaluation of episodic memory is fundamental in the diagnosis of dementia and especially in AD. The neuropsychological battery used in our study includes the well-known tests of the Wechsler Memory Scale-Revised (WMS-R) version, with immediate and delayed recall of verbal and visual material. For the evaluation of verbal episodic memory we compared the performance of EOAD and LOAD groups in the Associated learning of paired words and Logical memory tasks, evaluation, and differences did not reach statistical significance in immediate or delayed evocation. Our findings are similar to others (Lawlor et al., 1994; Kalpouzos et al., 2005), but some studies have reached different results, with LOAD group presenting lower scores, suggesting more vulnerability of limbic regions (Chui et al., 1985; Jacobs et al., 1994; Koss et al., 1996; Suribhatla et al., 2004). This lack of consensus may be due to intra or inter-study group-differences in duration and severity of disease. Although these variables were well controlled in our study, we could not also get significance for the higher performances in Logic and Visual memory in the EOAD, with multivariate comparisons analysis. In previous studies no differences were found in reproduction of Rey complex geometric figure (Kalpouzos et al., 2005) or LOAD had better performances in visual memory (Suribhatla et al., 2004). Both studies made use of different materials for task execution presenting a single visual stimulus, while in BLAD four drawings are presented.

In our study LOAD individuals had worst performances in Orientation ($p = 0.001$), and the plausible justification is a more pronounced decline in memory, as the observed errors were mainly in questions related to temporal orientation (date and day of the week). Besides, in correlation analysis between Orientation and Visual memory there was a moderate positive association in LOAD group (0.444; $p < 0.0056$), which means that better performance in orientation correlated with higher scores in visual memory. These results and explanatory observations have already been reported in previous studies (Jacobs et al., 1994; Imamura et al., 2005).

So, the lower performance in Orientation task correlated to worst visual memory observed in LOAD can be integrated in the same cognitive deficit, and is consistent with a tendency in literature to point episodic memory as a dissociate factor in AD (Jacobs et al., 1994; Koss et al., 1996; Suribhatla et al., 2004; Kalpouzos et al., 2005; Frisoni et al., 2007).

In the present study visual-constructional abilities were not analyzed properly, because related-tasks in BLAD (clock and cube drawing) were only qualitatively evaluated and no quantitative scoring or analysis was available. This cognitive function has been associated in literature with worst performances in EOAD groups (Koss et al., 1996; Imamura et al., 2005; Mendez, 2006; Frisoni et al., 2007). Other limitation of this study is the lack of a formal assessment of behavioral and psychological symptoms of dementia.

So, in conclusion in this study the younger patients presented a major impairment in Praxis. Despite the strong size sample we failed to confirm a significant difference in language tasks, although there was a tendency for worse performance in naming in the younger set. LOAD patients had inferior performances in Temporal Orientation which is related to a tendency for great impairment in visual memory, suggesting a more localized disease to the limbic structures. This data may contribute to a better recognition of AD in younger patients and suggests atypical clinical presentations to be considered in the differential diagnosis of early onset dementia.

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Cognitive impairment and dementia in Parkinson's disease: clinical features, diagnosis, and management

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Parkinson's disease (PD) is a common, disabling, neurodegenerative disorder. In addition to classical motor symptoms, non-motor features are now widely accepted as part of the clinical picture, and cognitive decline is a very important aspect of the disease, as it brings an additional significant burden for the patient and caregivers. The diagnosis of cognitive decline in PD, namely mild cognitive impairment (MCI) and dementia, can be extremely challenging, remaining largely based on clinical and cognitive assessments. Diagnostic criteria and methods for PD dementia and MCI have been recently issued by expert work groups. This manuscript has synthesized relevant data in order to obtain a pragmatic and updated review regarding cognitive decline in PD, from milder stages to dementia. This text will summarize clinical features, diagnostic methodology, and therapeutic issues of clinical decline in PD. Relevant clinical genetic issues, including recent advances, will also be approached.

Keywords: dementia, diagnosis, diagnostic criteria, mild cognitive impairment, non-motor symptoms, Parkinson's disease, Parkinson's disease dementia, cognition

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, following Alzheimer's disease. Nearly 200 years have gone by since James Parkinson's original clinical depictions in his monograph entitled *An Essay on the Shaking Palsy* (Parkinson, 1817; Goetz, 2011). The text focused mainly on the motor features of PD, overlooking non-motor symptoms, with the notable exception of "melancholy" – but cognitive impairment was at that time completely disregarded. It is currently recognized that the spectrum of non-motor features in PD is broad (Chaudhuri and Schapira, 2009; Tolosa et al., 2009; Massano and Bhatia, 2012), but these may often be missed in clinical practice. Nonetheless, whenever PD is suspected, the routine approach should include a set of questions aimed at exploring their presence, since they may be helpful hints for the diagnosis, although they are non-specific in this regard. On the other hand, it is useful to quantify their severity and impact, as they carry an important additional burden on the patients, leading to significantly deteriorated quality of life (QOL), and warranting specific therapeutic interventions, despite the fact that evidence-based data on treatment are unsatisfactory in many instances (Chaudhuri and Schapira, 2009; Tolosa et al., 2009; Zesiewicz et al., 2010). Braak and coworkers have greatly contributed to the awareness of the association between symptoms and the neuropathological lesions affecting the nervous system (Braak et al., 2003; Hawkes et al., 2010). Indeed, due to long term progression and the mode of pathological spreading, some of the non-motor features of PD may be present before any of the classical motor signs are noticeable, sometimes for years or even decades, which may lend them potential utility as supportive diagnostic features in early disease stages – these include hyposmia, rapid eye movement (REM) sleep behavior disorder, constipation, and depression (Chaudhuri and Schapira, 2009; Lim et al., 2009; Tolosa et al., 2009; Hawkes et al., 2010; Savica et al., 2010; Schapira and Tolosa, 2010). Patients may have these and other symptoms before overt motor signs emerge and the clinical diagnosis is finally established. On the other hand, features like dementia and hallucinations tend to occur later in the course of disease, which might be useful for distinguishing PD from other disorders. Cognitive impairment is a major non-motor feature of PD, but the diagnosis is often complex, remaining based on clinical skills and methods, as no reliable diagnostic biomarkers have been described yet. Mild cognitive dysfunction is apparent in many cases from early stages (Aarsland et al., 2009; Barone et al., 2011; Domellöf et al., 2011; Litvan et al., 2011), but recent research has shown that manifest dementia will occur in over 80% of patients after 20 years of disease (Hely et al., 2008). Accurate cognitive assessment and classification is also paramount in the context of deep brain stimulation for PD, an issue approached in detail in the article by Massano and Garrett (2012), also part of this Frontiers Research Topic. The present manuscript will cover the clinical aspects of cognitive decline in PD, namely mild cognitive impairment (MCI), and dementia (PD-D), including typical features, diagnosis, and management issues.

METHODS

A comprehensive PubMed literature search was conducted for papers published until September 2011, using the keywords "Parkinson's disease," "Parkinson's disease dementia," "mild cognitive impairment." From all the references found, the authors have consensually chosen those most relevant to the review, in

order to obtain a clinically oriented perspective of the state of the art knowledge regarding cognitive decline in PD. Exceptionally, later references of interest, published in the meantime, have also been considered.

EPIDEMIOLOGY OF PARKINSON'S DISEASE DEMENTIA

Due to differences in diagnostic criteria, methodology, and study populations, epidemiological numbers regarding PD-D tend to vary greatly. The prevalence of dementia in community-based studies has been estimated at 30–40% (Aarsland et al., 2005; Aarsland and Kurz, 2010) but figures range from about 10 to 80% of people with PD (Aarsland et al., 2005; Aarsland and Kurz, 2010). Even in young onset PD, defined as symptoms emerging from 21 to 40 years (Schrag and Schott, 2006), dementia affects up to 19% of patients after a median of 18 years of disease duration (Schrag et al., 1998). In addition, cognitive decline is noted in up to 36% of newly diagnosed cases of PD (Reid et al., 1989; Foltynie et al., 2004). From the published literature, it seems clear that the prevalence of dementia increases with age and duration of the disease symptoms (Hughes et al., 2000; Aarsland and Kurz, 2010), although some have suggested that patient age could be preponderant (Aarsland et al., 2007). The Sydney Multicenter Study has been an exceptional initiative in this field of research, as one group of clinicians followed a single cohort of newly diagnosed people with PD over 20 years. Sydney neurologists were asked to refer their newly diagnosed PD patients for a 5-year trial comparing low dose bromocriptine with low dose levodopa/carbidopa (Hely et al., 1994). During this study, neuropsychological assessments were performed at baseline and at 3, 5, 10, and 20 years. At baseline, 26 newly diagnosed PD patients were demented – by current definitions, these would be classified as dementia with Lewy bodies (DLB) cases. A neuropsychological diagnosis of dementia was made on the basis of impairment in memory and at least two other areas of cognitive functioning. A test score at least two standard deviations (SD) below the mean score obtained by the control group was classified as cognitive impairment. The control group consisted of 50 age-, gender-, and education-matched community living people without PD, who were friends or relatives of the patients. If no neuropsychological assessment was carried out, a diagnosis of dementia was based on a Clinical Dementia Rating score of at least 1, with supporting evidence of gradual cognitive decline sufficient to impair daily functioning. This was sustained by performance in Mini-Mental State Examination (MMSE), letter and category fluency, and clock face drawing. At 20 years, 25 of 30 (83%) surviving patients had become demented and 2 others have developed dementia subsequently (Hely et al., 2008).

In an earlier review of 27 studies, Cummings found a mean prevalence of dementia in PD of 40%, even though at that time studies did not include the identification and exclusion of patients with DLB (Cummings, 1988). The incidence of dementia is increased by 2.8- to 6-fold in those with PD when compared to those without the disease (Aarsland et al., 2005; de Lau et al., 2005; Aarsland and Kurz, 2010). The cumulative prevalence is very high – at least 75% of the patients with PD who survive for more than 10 years will develop dementia (Aarsland and Kurz, 2010).

Several risk factors for PD-D have been proposed, including certain predominant motor features such as rigidity and gait instability, MCI, and the presence of visual hallucinations (Goetz et al., 2008). Older age is broadly accepted as a risk factor for dementia in PD. Some authors have found parameters such as disease duration, age of onset, and motor symptom severity to be significant risk factors, but published data are at times contradictory (Aarsland and Kurz, 2010). Interesting findings have been brought to light regarding genetics and cognitive decline in PD, a few of them quite recently, as we will further detail in the text.

PARKINSON'S DISEASE DEMENTIA: CLINICAL FEATURES

Dementia associated with PD holds suggestive phenotypic cognitive features that make it a recognizable and individualized entity. This issue will be further detailed, focusing on its mode of onset, profile of cognitive deficits, behavioral aspects, and motor phenotype, as well as other features. Dementia adds substantially to the burden of disease for the patient, caregiver, and the community (Aarsland et al., 1999, 2000), thus warranting accurate diagnosis and management.

PATTERN OF ONSET AND PROGRESSION

The onset of PD-D is insidious, often making it difficult for the patient and the family to evoke when the first signs of cognitive dysfunction started. The evolution is progressive. In one prospective, 4-year study, the mean annual MMSE decline was 1 point in PD subjects without dementia versus 2.3 points in the PD-D group, a figure similar to that seen in patients with AD (Aarsland et al., 2004). During the 5 year follow-up of the CamPaIGN cohort, researchers have found that MMSE scores declined at a mean rate of -0.3 ± 0.1 points per year over the 5.2 years of average observation (Williams-Gray et al., 2009). Dementia in the early stages of PD is not considered a typical feature of the disease (Massano and Bhatia, 2012); by current consensus definitions, whenever parkinsonism and dementia arise in close temporal relationship, those cases should be classified as DLB, as the diagnosis of PD-D requires the preceding diagnosis of PD followed by the later development of dementia (McKeith et al., 2005; Emre et al., 2007a). Early indicators associated with cognitive decline may include excessive daytime sleepiness (Gjerstad et al., 2002). Visual hallucinations are relatively frequent, as are bizarre but ill-defined misperceptions or psychotic phenomena (such as feeling that there is someone else in the room, when indeed this is not the case). Increasing apathy, impaired attention and concentration, and forgetfulness are also frequent features (Goetz et al., 2008), although memory complaints as initial presentation are less frequent than in DLB and, particularly, AD (Noe et al., 2004). The course of decline in PD-D is relentless and progressive over time. Patients may remain stable for several months, at times with periods of faster worsening with no additional obvious cause (Emre, 2010). Fluctuations occur from day to day and during the same day, which is a similar pattern to that of DLB (Ballard et al., 2002).

Hobson and coworkers have studied a community based cohort of PD patients with and without dementia. They found that standardized mortality ratios (SMR) were significantly higher in PD-D patients than in PD non-demented individuals (SMR 3.10, versus 1.15, $p < 0.001$). Life expectancy in younger-onset PD-D (55–74 years old) was significantly lower than in non-demented patients (average 7.5 versus 12.4 years), and the estimated age

at death was also much lower in the first group (72.4 versus 77.8 years). Differences regarding life expectancy and age at death in older-onset PD-D were less obvious (Hobson et al., 2010). Other authors have also found an increased mortality risk among PD patients with dementia (Levy et al., 2002; de Lau et al., 2005).

COGNITIVE PHENOTYPE OF PARKINSON'S DISEASE DEMENTIA

Assessment of cognition in PD patients can be a demanding and exhausting mission for both the patient and examiner. Disease symptoms such as tremor, bradykinesia, bradyphrenia, pain, fatigue, sleepiness, and mood disorders, as well as medication effects, can interfere with cognitive performance and testing. Also, timed tests can be seriously affected due to motor slowing, and those depending on motor capacity to perform the task, such as drawing, can be interfered by tremor.

Executive functions have been defined as capacities that "enable a person to engage successfully in independent, purposive, and self-serving behavior," and encompass cognitive processes such as initiation, planning, purposive action, self-monitoring, self-regulation, volition, inhibition, and flexibility (Stuss, 2011). Executive dysfunction has been widely recognized as a very important feature of the cognitive phenotype of PD, even in non-demented patients, although published data has been marred by inconsistencies in definitions and research methods (Kudlicka et al., 2011). The most widely used tests to probe executive functioning in PD have been verbal fluency, digit span backward, Wisconsin Card Sorting Test, Stroop Test, and Trail Making Test (Kudlicka et al., 2011). Accumulated research data has shown that executive dysfunction is a prominent feature in PD-D (Tröster, 2008; Kehagia et al., 2010).

There is clinical and electrophysiological evidence of slowed cognition in PD-D, although this may be apparent even in non-dementia stages (Rogers et al., 1987; Owen et al., 1992; O'Mahony et al., 1993; Hanes et al., 1996; Turner et al., 2002). Attentional deficits have been consistently shown in PD-D. In tests such as the letter cancelation test and others, PD-D patients are slower, tend to fluctuate more, and incur on a higher number of errors than AD subjects, whereas the profile of PD-D seems to be similar to that seen in DLB (Ballard et al., 2002; Noe et al., 2004; Bronnick et al., 2007).

Visuospatial function is a term used to describe a wide range of functions that must be assessed by different tests, the unifying feature being that all of them rely on visual function and processing (Jeannerod and Jacob, 2005). Findings from studies pertaining to this matter have shown greater deficits in PD-D than AD patients (Starkstein et al., 1996). It has been shown that visual perception, space-motion, and object-form perception are globally more impaired in PD-D patients than in control subjects, including normal controls and non-demented PD patients, and AD (Mosimann et al., 2004).

In PD-D, short term memory is impaired, both for initial learning and immediate recall. Traditionally, mnesic deficits in PD have been considered to be mainly of retrieval, rather than encoding and storage (Pillon et al., 1993). In PD-D, however, patients may also be impaired on cued recall (Higginson et al., 2005). A large meta-analysis has shown that verbal fluency impairment is more pronounced than that seen in PD non-demented patients; also, semantic fluency seems to be more compromised than phonemic fluency (Henry and Crawford, 2004). Concept formation is also impaired in PD-D (Cahn-Weiner et al., 2002, 2003). The Clock-Drawing Test displays marked changes in PD-D, although it is similar to that found in DLB, and AD. PD-D and DLB patients demonstrate more planning errors, as compared to AD (Cahn-Weiner et al., 2003).

Significant dysphasia is not typically seen in PD-D, and language deficits occur much less frequently in PD-D than in AD (Pillon et al., 1993; Frank et al., 1996; Kramer and Duffy, 1996).

Certain phenotypic characteristics pertaining to cognitive decline have been used to differentiate "cortical" from "subcortical" dementia syndromes (Darvesh and Freedman, 1996; Salmon and Filoteo, 2007; Bonelli and Cummings, 2008). Cortical dementia syndromes display impairments of cognitive domains such as episodic memory, praxis, language, and calculation, whereas subcortical dementias tend to show slowed mental processing speed and frontal lobe changes such as apathy, irritability, and dysexecutive impairment. The "cortical" profile is typical of AD, whereas PD-D and DLB typify the "subcortical" dementia type, but many cases fit the opposite prototype (Janvin et al., 2006). Characteristically, early impairment of episodic memory is seen in AD, in accordance to the pathological changes seen in this disorder (Weintraub et al., 2012). For more details on the clinical features of AD please refer to the manuscript by Alves et al. (2012) included in this Frontiers Research Topic.

BEHAVIORAL OR NEUROPSYCHIATRIC SYMPTOMS

Psychotic symptoms

Hallucinations occur in 45–65% of PD-D patients, a higher rate than in the general population of PD; these come about usually in the visual perceptual modality (Aarsland et al., 2001a,b,c). In PD patients without dementia, hallucinations are an important predictor for the development of dementia and institutionalization (Giladin et al., 2000). Hallucinations tend to be more common in DLB than in PD-D and in these more frequent than in AD (Hirono et al., 1999; Aarsland et al., 2000, 2001a,b; Benoit et al., 2005). Hallucinations in PD-D and DLB tend to present similar characteristics, as they are usually complex and well formed, often colorful moving images, with people and animals being a frequent motif (Williams and Lees, 2005; Janvin et al., 2006). Brief, ill-defined peripheral images (*de passage*) may also occur and be less appreciated by the patient (Fenelon et al., 2000). Delusions seem to be less frequent than hallucinations in PD-D, and are estimated to occur in about 30% of patients; this rate is greater than in AD but lower than in DLB (Aarsland et al., 2001b). Delusional activity in PD-D includes "feeling of presence," phantom boarder (the delusional belief that there are foreign people in the house, who may even interfere with the patient's life, e.g., eat their food or misplace their objects), paranoid, or grandiose delusions; delusional activity may be broad or isolated to a single subject.

Mood and anxiety

Aarsland and coworkers have conducted a community-based study and have documented major depression in 13% of PD-D subjects, compared with 9% of non-demented PD patients. This rate is lower than in DLB, but greater than in AD (Starkstein et al., 1996; Aarsland et al., 2001a). Dysphoric mood with depressive

symptoms occurs with approximately the same frequency in PD-D and AD (40–58%) patients (Aarsland et al., 2001b). Anxiety occurs at a similar frequency (30–49%) as depressed mood, and these symptoms may frequently co-exist in the same patient (Menza et al., 1993; Bronnick et al., 2005). Irritable mood, anger, and aggression are common in AD, but uncommon in PD-D (Engelborghs et al., 2005). Manic or hypomanic mood is infrequently seen in PD-D (Starkstein et al., 1996).

Apathy

It has been reported in 54% of patients in a large sample of mild to moderate PD-D (Aarsland et al., 2001b). Prominent apathy is very common in other forms of dementia, including frontotemporal dementia (Kertesz, 2003), progressive supranuclear palsy (Aarsland et al., 2001c), AD (Benoit et al., 2005), and DLB (Engelborghs et al., 2005); thus, this feature is not specific enough to guide diagnosis.

NON-COGNITIVE FEATURES OF PARKINSON'S DISEASE DEMENTIA

Non-motor complications of PD-D are frequent, and those features are now assumed to be an intrinsic part of the pathological processes involved. Therefore, it seems legitimate to assume that motor and non-motor features must be interrelated. PD-D neuropathological findings are detailed in the manuscript by Taipa et al. (2012), included in this Frontiers Research Topic.

MOTOR PHENOTYPE

There is the notion that certain motor features, such as postural instability and gait disorder (PIGD) are associated with a faster progression rate of cognitive decline in PD, being a risk factor for dementia (Burn et al., 2006). Levy et al. (2002) have documented that older patients with more severe parkinsonian signs had a relatively increased risk for incident dementia than younger and mildly affected subjects. Tremor predominance as the initial presentation has been associated with a lower risk for cognitive decline in some studies. These patients seem to remain protected against cognitive decline, unless they evolve to the PIGD phenotype (Elizan et al., 1986; Reid et al., 1989; Wood et al., 2002). Clinicopathological studies have shown that dementia is most common in PD patients with akinesia/rigidity than in the tremor dominant and mixed phenotypes (Rajput et al., 2009; Selikhova et al., 2009). Poorer cognitive performance is also associated with poorer outcomes in motor and non-motor domains, as a study by Papapetropoulos et al. (2004) has shown. PD-D also seems to be an independent risk factor for falls; other predictors of cognitive decline include previous falls, longer time from disease onset, and decreased arm swing (Wood et al., 2002; Pickering et al., 2007). For levodopa responsivity, data are inconsistent in showing any pattern that differentiates PD-D patients from PD patients without dementia (Stern et al., 1993; Bonelli et al., 2004). A 3-year longitudinal study, however, documented greater cognitive decline in PD patients with less than a 50% levodopa-induced improvement at baseline (Caparros-Lefebvre et al., 1995). Furthermore, an autopsy study has suggested that loss of levodopa responsivity is correlated with dementia due to greater loss of striatal D3 receptors (Joyce et al., 2002). Although fewer dyskinesias were reported in PD-D patients in a cross-sectional study, a longitudinal study found greater mental deterioration in those PD patients with baseline levodopa-induced dyskinesias (Elizan et al., 1986; Caparros-Lefebvre et al., 1995).

SLEEP DISORDERS

REM sleep behavior disorder (RBD) is characterized by dream enacting behavior, such as jumping out of bed, talking, or kicking. While in REM sleep, abnormal electromyographic activity is present, thus demonstrating the anomalous absence of muscle atonia during this stage of sleep (Olson et al., 2000; Iranzo et al., 2006; Frauscher et al., 2008). The pathophysiology is thought to be related to lesions inflicted on the brainstem REM sleep centers that inhibit the spinal cord motoneurons and their connections, as these structures are usually damaged in PD (Boeve et al., 2009; Iranzo, 2011).

REM sleep behavior disorder may be idiopathic or linked to several neurodegenerative diseases such as PD, DLB, and multiple system atrophy. A study by Iranzo and collaborators has reported that 45% of the idiopathic RBD patients studied developed a neurological disorder after a mean of 11.5 years from the reported onset of RBD – PD in nine patients (two of them with dementia), DLB in six, MSA in one, and MCI in four by the end of the 5 year follow-up period. Neuropsychological evaluation disclosed cognitive decline of various degrees of severity; three of the four MCI patients showed visuospatial deficits and short term free recall impairment that benefited from external cues (Iranzo et al., 2006).

Patients with idiopathic RBD usually do not report cognitive problems, but Terzaghi et al. (2008) demonstrated that a visuospatial construction deficit was present in 44% of the patients who suffered from idiopathic RBD. The cognitive profile found in patients with idiopathic RBD usually comprises visuospatial capacities, verbal memory, attention, and executive function impairment. Usually these subjects show no impairment in semantic memory and language, deficits commonly seen in AD (Ferrini-Strambi et al., 2004; Weintraub et al., 2012). Similarities have also been found between EEG patterns of idiopathic RBD, with cortical EEG slowing (abundant delta and theta waves) in frontal, temporal, and occipital regions, also found in PD and DLB patients (Kai et al., 2005; Caviness et al., 2007b). Some studies have tried to characterize RBD patients with MCI. Gagnon and coworkers have found that most PD patients (73%) with RBD display MCI, while many patients with idiopathic RBD (50%) also show MCI. The main subtypes of MCI seem to be single domain non-amnestic and amnestic in PD, while in idiopathic RBD the predominant subtype was non-amnestic MCI; all these patients displayed predominantly executive-attentional impairment (Gagnon et al., 2009). It is currently accepted that RBD occurs in PD patients with associated MCI and dementia, however RBD may also occur in PD patients with no associated cognitive deficits (Iranzo et al., 2005; Gagnon et al., 2009).

AUTONOMIC SYMPTOMS

Dementia and significant autonomic features may develop in the course of PD, especially in later stages (Hely et al., 2005; Hawkes et al., 2010), hence one could presumably postulate an association between autonomic symptoms and PD-D. This is however yet to be proven by comprehensive studies. The amount of data on the

relative frequency of autonomic features in demented compared to non-demented PD patients is scarce. Idiaquez and collaborators have assessed 40 PD patients and 30 age matched controls for cognitive and behavioral manifestations using standardized neuropsychological tools. These subjects were assessed for orthostatic hypotension, heart rate, and responses to deep breathing (SCOPA-AUT): 11 of these patients fulfilled the DSM-IV criteria for dementia and a higher incidence of cardiovascular dysfunction were found amongst demented patients (Idiaquez et al., 2007). The presence of autonomic dysfunction has also been reported in the Sydney multicenter study, after 15 years follow-up. Orthostatic hypotension was found in 35% and urinary hypotension has also been reported in 41% of PD patients and these were most frequent among those with higher Hohen and Yahr scores (Hely et al., 2005). In this study, however, it was not specified whether or not autonomic symptoms were more frequent in demented patients.

The pathophysiological mechanisms of autonomic dysfunction seem to be related to typical synuclein deposits throughout the central and peripheral autonomic nervous systems. The extension of these deposits to the limbic and cortical areas may be the cause for the associated development of dementia. Trying to define the neural substrate of autonomic dysfunction is difficult, as both systems may be implicated. Comorbidities are also important, as the presence of symptoms, such as orthostatic hypotension, constipation, and urinary incontinence may be due to other causes besides autonomic dysfunction. For instance, dopaminergic drugs may also cause dysautonomic symptoms, leading to constipation, and urinary incontinence (Winge and Fowler, 2006; Allan et al., 2007).

In summary, PD-D patients typically present with dysexecutive syndrome, fluctuating attentional deficits, visuospatial impairment, and memory dysfunction, associated with behavioral symptoms (Emre et al., 2007a), which include depression, anxiety, apathy, delusions, and recurrent prominent complex visual hallucinations that may seem disproportionate to the severity of dementia. PD-D is most frequently associated with the postural imbalance gait disability motor phenotype of PD. The evolution is progressive. These clinical features are in many aspects similar to those seen in DLB, and distinguishing both disorders from each other can be challenging (McKeith, 2005; Metzler-Baddeley, 2007).

DIAGNOSTIC CRITERIA FOR PARKINSON'S DISEASE DEMENTIA

For a long time, specific diagnostic criteria did not exist for PD-D. Clinicians and researchers had to formally support this diagnosis with the help of generic criteria for dementia, such as those set by the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV; American Psychiatric Association, 1994). Finally, criteria aimed specifically at the diagnosis of PD-D have been published in 2007, proposed by a Movement Disorder Society task force. Two levels of clinical diagnostic certainty have been defined: possible and probable PD-D (Emre et al., 2007a). According to this document, the essential defining feature of PD-D is the emergence of dementia in the setting of established PD, as diagnosed according to the Queen Square Brain Bank criteria. Dementia is defined as a syndrome of insidious onset and progressive decline of cognition and functional capacity from a premorbid level, that is not attributable to motor or autonomic symptoms.

Impairment in at least two of the four typically involved cognitive domains (impaired and often fluctuating attention; dysexecutive changes; impaired visuospatial abilities; and impaired free recall that improves with cueing) must be documented without prominent language dysfunction, as demonstrated by clinical and cognitive examination. The authors take into account that the main behavioral or neuropsychiatric symptoms seen in PD-D include visual hallucinations, delusions, apathy, depressed mood, anxiety, and excessive daytime sleepiness. These features are frequent in PD-D, but their presence is not invariable. The presence of at least one symptom from this set supports, but is not required for, the diagnosis of PD-D. Further details on diagnostic criteria for PD-D can be found in Emre et al. (2007a) and the proposed neuropsychological assessment methods to be carried out with these patients have been published in Dubois et al. (2007), from the same workgroup.

Clinical validation efforts have been carried out from experienced groups in this field, regarding this proposal. Dujardin and coworkers have enrolled 188 PD patients, which have been assessed using the two-step cognitive evaluation recommended by the MDS task force (shorter battery followed by longer comprehensive cognitive assessment battery), recording also the presence or absence of dementia after each step had been taken. After the short battery had been applied 18.62% of PD patients were suspected of having dementia, whereas 21.81% fulfilled criteria for probable PD-D following the longer battery. The authors have found that the short battery's sensitivity and specificity were 65.85 and 94.56%, respectively – but using specific cutoff scores the sensitivity would increase considerably without significant loss of specificity, thus suggesting that PD-D can be diagnosed accurately with the shorter battery as well as the longer assessment method. Specifically, an MMSE score <27, the inability to recall five words immediately after learning, being unable to generate >7 words beginning with "S" within 60 s, the lack of full personal independence in managing antiparkinsonian medications, and age >69 years seem to be associated with a high probability of PD-D (Dujardin et al., 2010).

Martinez-Martin and coworkers have compared the MDS criteria for the diagnosis of PD-D with dementia criteria established by the DSM-IV. In this study, 299 PD patients have been enrolled, and the authors have found out that the DSM-IV criteria failed to identify 22% of patients fulfilling the MDS criteria. False negative cases were older and had more severe motor symptoms, but less psychosis than those true non-demented PD. False positives had less severe motor symptoms than true PD-D, although the difference did not reach statistical significance. These findings suggest that the MDS criteria are more sensitive than DSM-IV for diagnosing PD-D, and that it could be more difficult to diagnose PD-D in older patients, as well as those with less psychotic symptoms or severe motor impairment (Martinez-Martin et al., 2011).

Another clinical study aimed at comparing the diagnostic acuity for PD-D of the eight-item screening checklist proposed by the MDS task force, as compared to full neuropsychological assessment. This is an important issue since comprehensive neuropsychological testing is not widely available in every practice setting, thus short screening tools would be most welcome. The authors have assessed 91 PD patients – of these 7 (7.7% of all subjects) met criteria for probable PD-D based on the screening

checklist, whereas 15 patients (16.5%) were detected using full neuropsychological testing; of note, all patients that met criteria for PD-D according to the screening checklist also did with longer neuropsychological testing (100% specificity). These results imply that the screening checklist performed at 46% sensitivity for the diagnosis of PD-D, although agreement was moderate between both methods (κ 0.59, $p < 0.001$). The most common reasons for false negative misclassification by the screening checklist were that subjects were not deemed to be free of depression (5 patients), they had an MMSE score of at least 26 (6 patients), and they were not rated as impaired in activities of daily living (1 patient). Altogether, these results suggest that the screening checklist proposed by the MDS task force for the diagnosis of PD-D is specific when all eight items are met, but sensitivity is low, thus a significant number of false negative cases are to be expected. Therefore, this does not seem to be an ideal screening instrument. The authors have also demonstrated that the sensitivity of this tool could be largely increased if two problem items would be removed (absence of depression, abnormal MMSE score), something that should be considered in future research (Barton et al., 2012).

Ideally, clinicopathological validation studies should also be carried out in the future using the MDS criteria for the diagnosis of PD-D, in order to promote in-depth understanding of their diagnostic acuity. Hopefully, the proposal from the MDS task force will at least bring uniform definitions and methods into clinical care and research in the setting of PD-D.

MILD COGNITIVE IMPAIRMENT IN PD

In a way somewhat analogous to what can be perceived in the course of Alzheimer's disease, a pre-dementia period exists in PD (see **Figure 1**). In a wide-ranging manner, MCI can be defined as a cognitive decline from a previous performance baseline, that is considered abnormal for the patient's age, but with retention of normal daily functioning. Such a condition appears to be quite frequent in PD, even in early stages and also prior to the initiation of dopaminergic therapy (Muslimovic et al., 2005; Caviness et al., 2007a; Domellöf et al., 2011; Litvan et al., 2011). In clinical and research settings, the term is applied to PD patients who present cognitive complains and whose neuropsychological examinations confirm the deficits, but PD-D criteria cannot be fulfilled due to the lack of overt functional decline related to cognitive impairment.

Deterioration can occur in a range of cognitive domains. However, non-amnestic single domain MCI seems to be more common than amnestic single domain MCI (Pillon et al., 1993; Caviness et al., 2007a; Litvan et al., 2011). Nonetheless, the predictive value regarding the future risk of dementia of each of the MCI subtypes has not been thoroughly assessed in prospective studies (Barone et al., 2011).

From the published data, it is apparent that most PD patients will develop dementia, provided that enough time elapses since disease onset. Since PD-MCI precedes PD-D, one could postulate that the lifelong cumulative prevalence of PD-MCI must be at least as high as that of PD-D. Approximately 27% of PD patients will meet criteria for PD-MCI at any given time (Litvan et al., 2011). Aarsland et al. (2010) have reported that PD-MCI affects 25.8% of PD patients (ranging between 23.5 and 28.8%). There is significant variability among the numbers reported, which may be justified by methodological differences, namely definitions used, the cognitive domains assessed, how impairment was defined for the test, and the fact that different patient populations have been enrolled.

An interesting population based study using a sample of 239 newly diagnosed PD patients has found an incidence rate of cognitive impairment of 36%. From this subgroup, 21% scored 1 or more SD below the mean on a pattern recognition memory test, being subsequently classified as having temporal lobe impairment. Thirteen percent scored below the cut off score on a test evaluating frontostriatal deficit, and 15% were impaired in both tests, suggesting a more global impairment (Foltynie et al., 2004). A second study used an extensive neuropsychological test battery to compare the performance of a sample of 115 newly diagnosed PD-D patients (mean disease duration of 19 months) and 70 healthy controls. Using a definition for impairment as <2 SD below the normative sample mean score on at least 3 tests, PD patients performed significantly worse across most tests, and 24% of them were deemed cognitively impaired. The patient group performed worse in executive function, memory, complex attention, and psychomotor speed tests (Muslimovic et al., 2005). Several studies have found that increasing age, late disease onset, severity of PD, and lower educational level are risk factors associated with PD-MCI (Pai and Chan, 2001; Foltynie et al., 2004; Muslimovic et al., 2005; Mamikonyan et al., 2009).

The complexity of defining MCI in early stages of PD is high, for significant confusion with early DLB should be anticipated. On the other hand, there is a concern that the definitions used to determine MCI may lack sensitivity to detect early cognitive decline in high functioning people, as these have to suffer added decline before they reach the defined cutoff below normative means. Hence they may potentially be classified cognitively unimpaired when in fact a decline from baseline performance has already occurred. It is commonly argued that high functioning people may have additional protection from dementia – but their work and social settings also tend to be more demanding, and subtle cognitive decline may thus become more apparent. Importantly, the clinical definition of MCI requires that the person has experienced a change in cognition, compared to baseline (Litvan et al., 2011).

PROFILE OF COGNITIVE IMPAIRMENT

A number of studies assessing cognitive functioning in non-demented PD have been published. Cognitive deficits in PD are traditionally seen as subcortical in their nature, as several studies have demonstrated that there is a significant impairment in executive functions such as poor planning, sequencing, cognitive flexibility, and problem solving capacities (Pai and Chan, 2001; Muslimovic et al., 2005; Barone et al., 2011). Memory impairments, including encoding, recall, and procedural memory are also affected (Foltynie et al., 2004). Recognition is thought to remain relatively well preserved (Foltynie et al., 2004). Language dysfunction is rarely reported, with an exception of deficits in phonemic and semantic tasks, which exist and tend to decline over time and with disease severity, as evaluated by the Hoehn and Yahr stage, predicting also a future diagnosis of dementia (Barone et al., 2011).

Identifying PD-MCI is clinically relevant, given that these patients appear to be at increased risk for developing PD-D

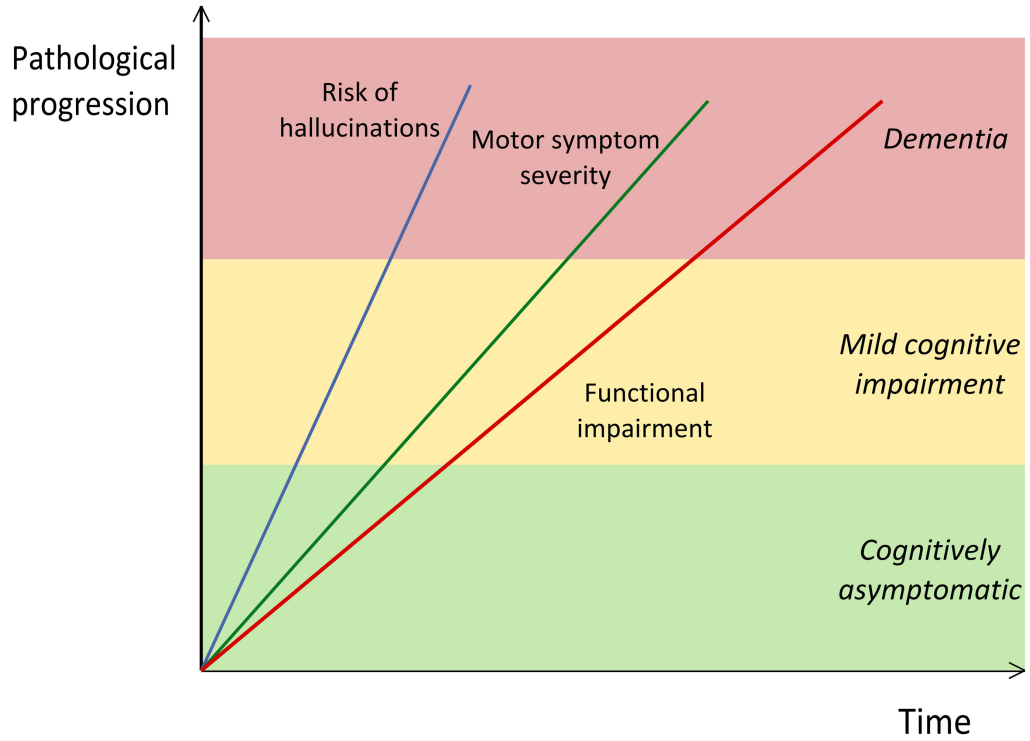

FIGURE 1 | schematic representation of the progression of PD patients until the stage of dementia. Functional impairment in PD is multifactorial (motor symptoms, cognitive decline, other non-motor symptoms). Please note that this graph is merely pictorial; it is not intended to represent proportions between variables nor is the progression linear, despite the drawing.

(Litvan et al., 2011). On the other hand, one wonders if drug therapy known to be effective in PD-D could be also of benefit at the stage of MCI, although this has not been formally studied in large trials. A contributing factor for this might be the lack of broadly accepted definitions and efficacy endpoints. In this regard, a very recent advance has been achieved, as the first set of consensus diagnostic criteria for PD-MCI have been proposed (Litvan et al., 2012).

DIAGNOSTIC CRITERIA FOR MCI IN PARKINSON'S DISEASE

The clinical validity of PD-MCI has found strong support in the published literature (Litvan et al., 2011). This concept has been formally accepted and used for several years, but only very recently has the first set of criteria for the formal diagnosis of PD-MCI been proposed (Litvan et al., 2012). A great contributor to a stagnant state regarding concrete definitions and criteria has been the scarcity of long term in-depth prospective studies that would allow better characterization of the phenotype of PD-MCI, to establish biomarker correlates, and to clearly define the progression and risk of dementia for PD-MCI patients. The MDS task force on PD-MCI has built this concept on the previous classic definitions of MCI and made the necessary adjustments regarding the specificities of PD. The diagnosis of this condition requires a few key points. First of all, the diagnosis of PD should be well established. Then, cognitive decline must be reported by the patient or caregiver, or documented by the clinician. These are subsequently documented by means of formal cognitive assessment. Lastly, cognitive impairment must not cause significant functional decline. Exclusion criteria have also been described and two levels of assessment and diagnostic certainty have been proposed (Litvan et al., 2012). The manuscript issued by this task force also proposes specific assessment tests and scales, which will hopefully expedite the homogenization and alliance of procedures throughout practice and research settings all over the world. However, no biomarkers could be recommended at this stage to incorporate the diagnostic criteria, as evidence is still scarce concerning this matter in the field of PD-D (Litvan et al., 2012).

GENETICS AND COGNITIVE DECLINE IN PD

HEREDITARY FORMS OF PARKINSON'S DISEASE AND COGNITION

Ten to 15% of PD patients disclose a family history suggesting Mendelian inheritance, either autosomal dominant or recessive. These tend to be younger than the typical PD patients (Schrag and Schott, 2006; Tan and Jankovic, 2006). A number of levodopa responsive parkinsonian syndromes have been described and linked to a specific locus or gene, and 18 of these so far have been classified as PARK syndromes (Klein and Westenberger, 2012). While some of these represent true PD, others denote more complex phenotypes and different diseases (Gasser, 2007; Klein et al., 2009), which we will not address in this manuscript.

Several autosomal dominant forms of PD have been described, the most important being PARK1/PARK4 (gene *SNCA*, α-synuclein) and PARK8 (gene *LRRK2*, leucine-rich repeat kinase 2). In PARK1/PARK4, which are infrequent forms of PD, symptoms

usually emerge in the fourth or fifth decades, and patients display typical PD features, except that early prominent cognitive decline and dementia is a common event. Hence, the clinical picture may resemble DLB, although age at onset is much lower than in the classical cases. PARK1 and PARK4 are due to *SNCA* mutations and duplications/triplications, respectively (Polymeropoulos et al., 1997; Spira et al., 2001; Zarranz et al., 2004). PARK8 is probably the most common type of inherited PD. It has been reported that mutation frequency is about 40% in North African Arabs and Ashkenazi Jewish populations; high mutation frequency has also been reported in populations from southern Europe (Healy et al., 2008). The clinical picture resembles that of classical sporadic PD (Wszolek et al., 2004; Healy et al., 2008), and cognitive singularities have not been reported in this form of the disease, with a dementia prevalence of about 11% (Kasten et al., 2010).

Three forms of autosomal recessive PD have been described: PARK2 (gene *Parkin*), PARK6 (gene *PINK1*, PTEN-induced putative kinase 1), and PARK7 (gene *DJ-1*), here listed by decreasing order of frequency. The clinical pattern of PARK2 includes, in addition to typical PD features, a variety of symptoms such as hyperreflexia, prominent dystonia, sensory axonal neuropathy, increased sensitivity to levodopa induced dyskinesias, and psychosis (Abbas et al., 1999; Klein et al., 2000; Lücking et al., 2000; Gouider-Khouja et al., 2003; Khan et al., 2003; Deng et al., 2006; Wickremaratchi et al., 2009). Notably, non-motor symptoms seem to be less prevalent than in sporadic PD, except anxiety (Kägi et al., 2010). Therefore, cognitive decline is apparently less frequent, as compared to sporadic PD. Lewy bodies were absent in most patients that came to autopsy (Farrer et al., 2001; Gouider-Khouja et al., 2003). Age at onset of symptoms ranges from childhood to mid-fifties. It accounts for most PD cases under the age of 30 years. PARK6 and PARK7 share many common clinical features with PARK2, including early onset, excellent response to levodopa, and frequent levodopa induced dyskinesias, but psychiatric features may be more prominent in PARK6 (Valente et al., 2001, 2002, 2004; van Duijn et al., 2001; Abou-Sleiman et al., 2003; Dekker et al., 2003; Bonifati et al., 2005; Ibáñez et al., 2006; Leutenegger et al., 2006; Steinlechner et al., 2007; Kasten et al., 2010).

GLUCOCEREBROSIDASE MUTATIONS: MORE THAN A SIMPLE RISK FACTOR FOR PD

Interesting observations have been made in the last few years in families with members suffering from Gaucher's disease, an autosomal recessive disorder caused by homozygous mutations in the *GBA* gene encoding the lysosomal enzyme glucocerebrosidase. Some years ago, heterozygous *GBA* mutations have been associated with a higher risk of PD (Aharon-Peretz et al., 2004; Sidransky et al., 2009), and data even suggested that these patients could have an increased risk for cognitive impairment. For instance, Brockmann et al. (2011) have found that non-motor symptoms, among them dementia, seem to be more prevalent in *GBA*-associated PD than in mutation non-carriers. Two pathogenic mutations (L444P and N470S) seem to be particularly prevalent, but others have been described (DePaolo et al., 2009; Neumann et al., 2009; Sidransky et al., 2009; Velayati et al., 2010). Interestingly, *GBA* heterozygosity has also been associated with DLB, another synucleinopathy that shares clinical and pathological features with PD-D (Clark et al., 2009). Further clarifying these issues, Setó-Salvia and coworkers have recently investigated *GBA* mutations in DLB and PD-D, by fully sequencing the gene in 225 PD patients, 17 pathologically proven DLB patients and 186 controls. Mutations were significantly more frequent in PD and DLB as compared to controls, and PD patients carrying *GBA* mutations were at higher risk of dementia, with an estimated adjusted odds ratio of 5.8, $p = 0.001$ (Setó-Salvia et al., 2012). In fact, previous research has shown that *GBA* mutations are associated with more diffuse Lewy body neuropathology and greater neocortical involvement, which might explain the higher risk of cognitive decline in these PD patients (Neumann et al., 2009; Nishioka et al., 2011). Speculation has been brought to light about the putative association of other lysosomal disorders and parkinsonism (Shachar et al., 2011). For further details on this topic please refer to the manuscript by Almeida included in this Frontiers Research Topic (Almeida, 2012).

A word of caution should be given regarding *GBA* testing in clinical practice. Current evidence clearly shows that heterozygous pathogenic mutations are a risk factor for PD and DLB. Thus, it has not been demonstrated that *GBA* mutations cause a monogenic form of PD or DLB. Therefore, similarly to what has been suggested for ApoE genotyping in AD (Goldman et al., 2011), testing for *GBA* mutations is not currently recommended with clinical diagnostic purposes. Similarly, testing cannot be recommended for the diagnosis of PD-D. Nonetheless, further scientific research should be encouraged regarding *GBA* in PD, as many aspects remain enigmatic.

MICROTUBULE ASSOCIATED PROTEIN TAU AND COGNITIVE DECLINE IN PD

Traditionally, microtubule associated protein tau (MAPT) gene mutations have been linked to autosomal dominant frontotemporal dementia, usually the behavioral variant, in particular the clinical forms also displaying parkinsonism (Galimberti and Scarpini, 2012). In addition, *MAPT* haplotype H1 has been associated with increased susceptibility for the development of PD (Elbaz et al., 2011; Trotta et al., 2012). In recent years, an interesting relationship has been acknowledged between *MAPT* haplotype H1 and clinical progression in PD, specifically with regard to cognitive decline. Williams-Gray and coworkers have followed up their incident community PD CamPaIGN cohort and at 5 years ($n = 162$) have found that 17% of patients had developed dementia. In this study *MAPT* haplotype H1 was associated with accelerated cognitive decline, and was also a significant independent predictor of dementia, along with older age, and poor performance on semantic fluency and pentagon copy at diagnosis. The authors have conducted additional postmortem research using brain bank tissue, demonstrating that the H1 haplotype was also associated with 20% more deposit load of 4 repeat tau in Brodmann area 46 in Lewy body disease brains (PD or DLB), as compared to the H2 haplotype (Williams-Gray et al., 2009). The same working group subsequently assessed a representative group of 132 PD patients from this cohort for up to 7.9 years from diagnosis, and tau haplotype H1 remained a strong risk factor for dementia at this time point (Evans et al., 2011).

In a Spanish case-control study *MAPT* haplotypes were determined in 202 PD patients (48 of these with dementia), 41 patients with DLB (pathologically confirmed in 17), 164 patients with AD, and 374 controls. The authors have found that the haplotype H1 is significantly overrepresented in PD patients compared with controls and that the association was significantly stronger in PD-D than in non-demented PD patients, suggesting that *MAPT* H1 haplotype seems to be a strong risk factor for PD and for dementia in PD patients. In addition, no association could be found between any of the *MAPT* subhaplotypes and DLB or AD (Setó-Salvia et al., 2011).

The groups led by Andrew Siderowf has studied genotypic variants of apolipoprotein E (*APOE*), catechol-*O*-mehyltransferase (*COMT*), and *MAPT*, and whether these could be correlated with cognitive decline in PD in 212 clinically diagnosed patients followed up prospectively. *APOE* allele E4 was associated with faster decline, and *MAPT* and *COMT* could be correlated with performance in memory and attention, respectively, but not with the rate of general cognitive decline, as assessed with the Mattis Dementia Rating Scale version 2. Of note, 96% of patients in this cohort were assessed no later than at 3 years of follow-up (Morley et al., 2012).

MANAGEMENT OF PD-D: GENERAL PRINCIPLES

Parkinson's disease patients suffer significant decline in their QOL, due to motor symptoms, motor complications induced by progressive neurodegeneration and medication effects, and non-motor symptoms (Chaudhuri and Schapira, 2009; Lim et al., 2009; Tolosa et al., 2009; Calabresi et al., 2010; Hawkes et al., 2010; Savica et al., 2010; Schapira and Tolosa, 2010). Among these, dementia is a particularly important aspect, since it brings an additional and important burden of functional impairment associated with significant cognitive deterioration and further loss of QOL. The achievements in the last few decades regarding cognitive and behavioral issues in PD have been important scientific progresses (Weintraub and Burn, 2011), but research on clinical management is still scarce, particularly concerning randomized trials. There are no known disease modifying strategies in PD-D and every therapy here mentioned is currently seen as purely symptomatic.

Treating physicians should encourage an open dialog with the patient and family regarding the issue of cognitive decline in PD, especially when symptoms are brought to light by the patient or the caregivers, or uncovered by the clinician. Subjective cognitive complains should be noted and delved in detail. Functional impairment due to cognitive deterioration should be searched for in the several daily life environments, such as at home or at work, by questioning the patient and significant others. Sensitive and user friendly screening scales like the Montreal Cognitive Assessment (MoCA; Dalrymple-Alford et al., 2010) can be used to quickly probe the severity of cognitive decline, although comprehensive neuropsychological assessment is the best way of defining the profile of impairment in detail. Associated neuropsychiatric symptoms should be searched for, so that they can be properly addressed.

Common sense advises that, as in other circumstances when cognitive decline is apparent, with or without concomitant functional impairment (i.e., dementia), treatable causes should be ruled out through suitable laboratory testing, such as hypothyroidism, vitamin B12 or folate deficiencies, renal, or liver failure, anemia, and exceptionally even VDRL or HIV antibodies in the appropriate setting (i.e., classical risk factors). Structural brain imaging should be considered in the context of new onset cognitive decline, including when brain vascular disease or atypical degenerative parkinsonian disorders are suspected; magnetic resonance imaging would be the modality of choice in this regard (Bohnen and Albin, 2011; Wattjes, 2011). Exceptionally, genetic testing can be considered, in carefully selected circumstances above mentioned in the text.

Marked cholinergic deficits can be found in the brain of PD-D patients (Kehagia et al., 2010), thus providing the rational basis for cholinesterase inhibitor therapy in this condition. Only one large randomized placebo-controlled trial has been published so far regarding the use of cholinesterase inhibitors in PD-D (Emre et al., 2004). Emre and collaborators have demonstrated that rivastigmine, a dual inhibitor of acetylcholinesterase and butyrylcholinesterase, brings modest but significant improvements in mild to moderate PD-D. As expected, gastrointestinal adverse events such as nausea and vomiting were more common in the group treated with rivastigmine. One wonders whether newer formulations (i.e., transdermal patch) would reduce gastrointestinal adverse events as compared to capsules, which has already been demonstrated for AD in the large randomized, controlled, double-blind, double-dummy IDEAL trial (Winblad et al., 2007). Interestingly, visual hallucinations seem to predict better clinical outcomes under rivastigmine, as a mean statistically significant difference of 2.3 points on the Progressive Deterioration Scale has been documented in rivastigmine- versus placebo-treated patients without hallucinations at baseline, compared with a mean statistically significant difference of 5.3 points in patients with hallucinations at baseline (Emre et al., 2007b). Memantine has also been studied in PD-D, with two randomized double-blind placebo-controlled trials published thus far. One trial demonstrated marginal efficacy of memantine over placebo, regarding global clinical impression, and attention, whereas it failed to establish significant improvements in other secondary outcome measures (Aarsland et al., 2009). The second trial has shown clinical benefits of memantine on global clinical status and behavioral symptoms, but activities of daily living and caregiver burden did not improve (Emre et al., 2010). Both trials enrolled a mixed population of PD-D and DLB patients.

Behavioral or neuropsychiatric symptoms are common in PD-D and often exceedingly disturbing for the patient and caregivers. They must be properly explored and managed. Thorough questioning of both the patient and caregiver is paramount in this regard. For instance, visual hallucinations are commonly uncovered in clinic during patient interview, which were previously not suspected at all by the astonished family.

No randomized controlled trials have been conducted regarding the treatment of depression in PD-D. Tricyclic antidepressants have been found superior to placebo in PD (Devos et al., 2008; Menza et al., 2009), but their anticholinergic effects advises against their use in PD-D, since the risk of additional cognitive deterioration and new onset confusion would be significantly increased (Labbate et al., 2009). Thus, depression in PD-D is usually treated with serotonin selective reuptake inhibitors (SSRIs), such as sertraline and citalopram, although evidence in favor of this practice

is scarce (Wermuth et al., 1998; Leentjens et al., 2003; Weintraub et al., 2006; Devos et al., 2008). Noradrenaline and serotonin reuptake inhibitors like venlafaxine could be an alternative, but no trials have been published so far in this setting. Nonetheless, clinical practice has brought an overall positive experience with these drugs. Bupropion, that inhibits the reuptake of dopamine and noradrenaline, has been suggested by some to have a role in the treatment of depression in PD (Raskin and Durst, 2010; Zaluska and Dyduch, 2011), but controlled trials are also lacking. In any case, it appears that sedation and sexual dysfunction are lower with bupropion, when compared to SSRIs (Labbate et al., 2009). Recent research has found that pramipexole, a dopamine agonist widely used in the treatment of PD motor symptoms, improves depressive symptoms in PD (Barone et al., 2010), but the prescription should be carefully considered in PD-D due to the risk of visual hallucinations and confusion with this drug class.

Psychotic symptoms can be a challenging clinical problem in PD-D. Patients should be questioned about the content of their visual hallucinations and whether these are disturbing or not. They can be a source of significant anxiety and agitation or, on the other hand, be felt by the patient as friendly or at least non-threatening. At times the diagnosis of delirium is considered in PD-D, as patients may appear confuse and attention may become more volatile than usual. In this case, comorbid medical conditions should be searched for and treated, such as urinary tract infections, pneumonia, gastroenteritis, dehydration, or aggravated pre-existent disorders (e.g., renal or cardiac failure). Certain drugs seem prone to cause psychosis and confusional states, thus pharmacological therapy should be thoroughly reviewed and optimized. Antiparkinsonian drugs are often implicated – anticholinergics, selegiline, amantadine, dopamine agonists, and catechol-*O*-methyltransferase inhibitors should be discontinued, and lastly, a reduction in levodopa dosage should be considered. However, this approach is also not evidence-based. Antipsychotics should be used only as a last resort in PD-D. Atypical agents such as quetiapine can be used, despite the fact that trial results do not support this strategy (Ondo et al., 2005; Rabey et al., 2007; Shotbolt et al., 2009). Clozapine has been studied with a few positive results in PD patients (The Parkinson Study Group, 1999; Fernandez et al., 2004), but the hematological safety profile and significant muscarinic receptor affinity (Bymaster et al., 2003; Gareri et al., 2008) advise against its use in PD-D. Ondansetron, a 5-HT3 receptor antagonist used for the treatment of severe vomiting, especially in the setting of cancer chemotherapy, has also been tried as an antipsychotic agent, based on the rational that psychotic symptoms could be due to central serotoninergic overstimulation; Zoldan and coworkers conducted an open-label trial for 4–8 weeks, enrolling 16 PD patients with psychosis (daily dose 12–24 mg). They have found that psychotic symptoms were significantly improved, with good tolerability and no repercussion on PD motor symptoms, levodopa efficacy, or general cognitive state (Zoldan et al., 1995). However, this line of research has not been followed subsequently by any other group, probably due to the high cost of the drug. Coping strategies to deal with hallucinations might be helpful for patients and caregivers (Diederich et al., 2009).

CONCLUSION

Parkinson's disease is much more than a motor disorder and a wide range of non-motor symptoms have been recognized along the years, especially in the last decades. Among them, cognitive decline, in a wide range of severity, is particularly important to recognize, due to the meaningful impact on the life of patients and caregivers, as well as the social and economic burden brought about by this condition. Expert consensus guidelines have been recently issued specifically for the diagnosis of MCI in PD and PD dementia. These have not been prospectively assessed so far, but might prove useful both in clinical and research settings, as clinical decisions and research methods will hopefully become more homogeneous. An array of cognitive and behavioral symptoms has been associated with PD-D, which should be properly characterized and managed, as patients benefit from specific interventions. Nevertheless, many clinical decisions and practices do not find solid support on evidence-based data, and rely on the older and less objective "experience-based medicine" practices. This is an important point to be addressed in the future, as multicenter randomized trials using recent consensus definitions should be considered in relevant clinical areas.

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Glucocerebrosidase involvement in Parkinson disease and other synucleinopathies

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Mutations in both copies (homozygous or compound heterozygous) of the gene encoding the lysosomal enzyme glucocerebrosidase, which cleaves the glycolipid glucocerebroside into glucose and ceramide cause Gaucher disease. However, multiple independent studies have also reported an association between *GBA* mutations and Parkinsonism with an increased frequency of heterozygous *GBA* mutations in various cohorts of patients with parkinsonism and other Lewy body disorders. Furthermore, *GBA* mutation carriers exhibit diverse parkinsonian phenotypes and present a diffuse pattern of Lewy body distribution in the cerebral cortex. This review provides an overview of the genetic basis for this association in various diseases with dysfunction of the central nervous system in which affected individuals developed Parkinsonian symptoms. The emerging clinical, pathological, and genetic studies in neuronal synucleinopathies suggest a common underlying mechanism in the etiology of these neurodegenerative disorders.

Keywords: glucocerebrosidase gene, Parkinson disease, synucleinopathies, Lewy body pathology

INTRODUCTION

GAUCHER DISEASE

Mutations in the glucocerebrosidase gene (OMIM #606463), which encodes the lysosomal enzyme glucocerebrosidase, which breaks down the glycolipid glucocerebroside (also called glucosylceramide) into glucose and ceramide, result in Gaucher disease (GD; Brady et al., 1965). This is the most common lysosomal storage disorder (LSD) and follows an autosomal recessive mode of inheritance. The accumulation of glucosylceramide primarily occurs in cells of the reticulo endothelial system. The classic cellular hallmark of Gaucher patients is the characteristic morphology of their macrophages with a "wrinkled tissue paper" appearance on cytoplasm, which contains lysosomal inclusion bodies, referred as Gaucher cells (Westbroek et al., 2011). These macrophages accumulate in the liver, spleen, and bone marrow, and patients can present with organomegaly (Beutler and Grabowski, 2001; Sidransky, 2004). Patients with GD can present with a broad range of phenotype and the spectrum of the disease correlates, at least in part, with residual enzyme activity (Cox and Schofield, 1997). Based on the age at onset and neurological manifestations, the disease is classified into three subtypes (type 1, OMIM #230800; type 2, OMIM #230900; and type 3, OMIM #2301000; Velayati et al., 2010). The most common phenotype is non-neuronopathic type 1, sometimes referred as "adult Gaucher disease," although it can affect individuals of all ages. There is enough residual enzyme activity to prevent subtract storage in other cells rather than macrophages. Type 1 GD is relatively common in all ethnic groups, it presents the highest carrier frequency among Ashkenazi Jews population of 1 in 15 and an incidence of about 1 in 1,000. Although type 1 disease is traditionally considered non-neuronopathic, a subset of patients developed neurological alterations and subclinical peripheral neuropathy (Capablo et al., 2008). Patients with neuronopathic forms of the disease, present with either an acute course (type 2) or subacute course (type 3). Type 2 phenotype is the most severe form, often presenting in the first 6 months of life and the complete deficiency in glucocerebrosidase activity result in glucosylceramide accumulation in a variety of cell types, including neurons, which leads to rapidly fatal consequences either prenatally or shortly after birth (Cox and Schofield, 1997; Sidransky, 2004). Elevations in brain glucosylsphingosine have been detected in patients with neuronopathic GD, but not with type 1 (Orvisky et al., 2002). Type 3 tends to progress more slowly than type 2 and usually appears in adolescence. Affected individuals may survive into their 30 years. While not limited to any particular ethnic group, the largest group of patients with GD type 3 has been reported from the province of Norrbotten in Sweden (Dahl et al., 1990) and increased prevalence rates have also been reported in Japan and Spain. Although the *GBA* genotype plays a role in determining the type of GD, genotype–phenotype correlations are difficult to be established, due to the enormous clinical variation concerning the disease manifestations, clinical course, and response to therapy exhibited between patients who share the same genotype (Lachmann et al., 2004; Sidransky, 2004). Differences are even observed among siblings and twins (Amato et al., 2004; Lachmann et al., 2004).

GLUCOCEREBROSIDASE GENE (*GBA*)

The human *GBA* gene is located on chromosome 1q21 and is composed by 11 exons and 10 introns, spanning 7.6 kb of sequence. A highly homologous pseudogene (*GBAP*) is located 16 kb downstream and is 5.7 kb in length (Horowitz et al., 1989). The presence of this highly homologous pseudogene at the same locus, which shares 96% exonic sequence homology explains the high number of complex recombinant alleles between *GBA* and *GBAP* which have been detected in several GD, Parkinson's disease (PD), or Lewy body dementia (LBD) patients (Hruska et al., 2008).

To date, approximately 300 pathogenic mutations scattered throughout the *GBA* gene have been reported and their frequency varies significantly according to the different ethnicity. For example, the common c.1226A > G (N370S) allele is quite frequent among patients of European, American, and Middle East origin and it is not seen in Chinese and Japanese cohorts. Moreover, this particular mutation accounts for approximately 70% of the mutant alleles in an Ashkenazi Jewish subjects with type 1 GD and with c.84dupG mutation accounts for about 10%. Therefore, focusing the mutation analysis only to these two mutations in Ashkenazi Jewish populations of GD type 1 could be considered a cost-effective procedure. However to other non-Ashkenazi Jewish populations, especially in patients with neuronopathic GD forms, the whole gene sequencing is required for an accurate genotyping (Hruska et al., 2008). Furthermore, to populations of European origin, two mutations, N370S and L444P contribute to two-thirds of the disease alleles found (Kaplan et al., 2006; Hruska et al., 2008). The allelic distribution of these two prevalent mutant alleles can be confused because many laboratories do not distinguish between the point mutation c.1448T > C (L444P) and recombinant alleles that include this mutation such as RecNciI (Hruska et al., 2008).

GAUCHER DISEASE AND PARKINSONISM

Clinical reports of patients with GD recognized a small subset of patients who develop parkinsonian symptoms including tremor, rigidity, and bradykinesia (Neudorfer et al., 1996; Machaczka et al., 1999; Bembi et al., 2003). In the majority of these cases, the onset of parkinsonian manifestations was noted in their 40 years, and cognitive changes had also occurred (Tayebi et al., 2003). Postmortem brain tissue of several of these subjects was examined, and Lewy bodies appeared in cortical areas corresponding to Braak stages 5–6, in addition to the classic PD pathology (Neumann et al., 2009). The substantia nigra showed a marked loss of pigmented neurons while numerous Lewy bodies were detected and were specifically associated with brain regions affected by GD, including the CA4–CA2 hippocampal regions (Wong et al., 2000, 2004). In order to investigate the underlying dopaminergic dysfunction in *GBA* mutation carriers with and without parkinsonism, Kono et al. (2010) used positron emission tomography (PET) and demonstrated presynaptic dopaminergic dysfunction in the *GBA* carriers with parkinsonism identical to PD.

Moreover, a higher frequency of PD has also been reported in relatives of patients with GD, many of whom were demonstrated to harbor a heterozygous mutation in *GBA*. Families of probands with GD were surveyed for the presence of PD among obligate *GBA* carriers, and a higher rate of PD has been observed compared to the putatively non-carriers cohort. These clinical observations, strengthen the association between these two disorders and provided evidence that mutant glucocerebrosidase, even in heterozygosity may be a risk factor for the development of parkinsonism (Goker-Alpan et al., 2004; Halperin et al., 2003). Furthermore, a recent study was able to estimate the PD penetrance in *GBA* mutation carriers. The authors considered *GBA* as a dominant causal gene with reduced penetrance which should be taken into consideration for genetic counseling in relatives of patients with GD and patients with GBA associated PD (Anheim et al., 2012).

GBA MUTATIONS IN PD COHORTS

The clinical observations of GD patients and their relatives prompted an examination of the *GBA* mutations among different cohorts of PD worldwide. The first description of the relationship between alterations in the *GBA* and PD has reported alterations in *GBA* in 12 (21%) autopsy samples of PD patients. These alterations were more frequent among the younger subjects. These included eight with mutations (N370S, L444P, K198T, and R329C) and four with probable polymorphisms (T369M and E326K; Lwin et al., 2004). Subsequently, the six *GBA* mutations (N370S, L444P, 84GG, IVS + 1, V394L, and R496H) which are most common among Ashkenazi Jews were screened for a clinic-based case series of 99 Ashkenazi patients with idiopathic PD and 1,543 healthy Ashkenazi Jews. Mutations were found in 31.3% of PD patients *versus* 6.2% of controls ($P < 0.001$). Once more, patients who were carriers of *GBA* mutations were younger than those who were not carriers (Aharon-Peretz et al., 2004).

Since then, multiple studies were conducted, in which these findings were replicated in various cohorts of PD patients with different geographical or ethnical origins. These studies reported higher *GBA* mutation frequencies among the Ashkenazi Jewish PD population, which varied in different centers, between 10.7 and 31.3% contrasting, with the lowest carrier frequency reported, 2.3% in a series of Norwegian patients with PD *versus* 1.7% in controls (Toft et al., 2006). To accurately ascertain the frequency of *GBA* mutations in Europe, several European non-Ashkenazi Jewish individuals with PD and ethnicity-matched controls were screened and *GBA* alterations have been found in 6.1% of Portuguese (Bras et al., 2009), 9.8% of Spanish (Setó-Salvia et al., 2011), 4.2% British (Neumann et al., 2009), 4.7% of Greek (Kalinderi et al., 2009), 6.7% of French (Lesage et al., 2010), and 2.8% of Italian (De Marco et al., 2008). Importantly, some of the previous studies have focused the mutation analysis only in the two most common mutations, N370S and L444P, whereas some others extended the mutations search to the entire coding region of the gene. Overall, the definitive study on this topic was published in 2009, when an international collaborative study of *GBA* mutations in PD patients was undertaken by pooling data for individual persons from 16 centers, in 12 countries, including 5,691 patients and 4,898 controls. The data collected demonstrated a strong association between *GBA* mutations and PD. This finding was not exclusive to a specific ethnic group or a specific *GBA* mutation. In addition, the age at onset of PD was found to be significantly lower among patients with *GBA* mutations as compared with those without mutations ($P < 0.001$; Sidransky et al., 2009).

Concordant results have been observed in familial PD cases. A large comprehensive study of all *GBA* exons in one patient with PD from each of 96 PD families selected, based on the family-specific lod scores at the *GBA* locus revealed nine different variants identified in 21 of the 96 PD cases (21.8%). These variants have been further tested in 1,325 PD cases from 566 multiplex PD families and in 359 controls and were present in 161 of these patients (12.2%) *versus* 5.3% of controls (Nichols et al., 2009). Similarly, a Japanese group identified eight multiplex PD families with patients with PD heterozygous for pathogenic mutations in *GBA* (Mitsui et al., 2009). Therefore, it is conceivable that *GBA*

mutations underlie not only sporadic PD but also familial PD, and are associated with significantly earlier age at onset of disease.

GBA MUTATIONS IN OTHER SYNUCLEINOPATHIES

There is a line of evidence for the association of *GBA* mutations with other synucleinopathies rather than PD, such as dementia with Lewy bodies (DLB) and Lewy body variant Alzheimer disease (LBV-AD) but not in multiple-system atrophy (MSA).

Initially, Goker-Alpan et al. (2006) performed full genotyping of *GBA* in DNA from brain samples of 75 autopsy cases with pathologically confirmed Lewy body disorders including 28 PD, 35 cortical LBs (DLB or LBV-AD), and 12 MSA. Mutations in *GBA* gene were identified in 4% of cases with PD, 23% of cortical LBs, and none with MSA. A low frequency of *GBA* mutations, similar between cases (0.9%) and controls (1.2%) was also reported in a series of 108 British MSA pathologically confirmed cases and 257 controls (Neumann et al., 2009). Similarly, two additional studies did not identify *GBA* pathogenic mutations among MSA patients. One of the studies involved the sequencing of *GBA* in 27 MSA cases (Nishioka et al., 2011) and in the other one, the two most common mutations, L444P and N370S were tested in 66 MSA cases (Jamrozik et al., 2009). These data suggested a different mechanism to the α-synuclein aggregation in MSA cases in which its principal cellular target is the oligodendrocytes. The evolved concept that MSA may not just be related to PD but also share traits with the family of demyelinating disorders has been recently reviewed (Wenning et al., 2008).

As with the first study, an increased frequency of *GBA* mutations has also been detected in 2 (3.5%) of 57 clinical DLB patients of European Caucasian ancestry compared with control subjects (0.4%; Mata et al., 2008). In this latter study, only the two mutations, N370S and L444P were tested. Also, Farrer et al. (2009) reported mutations in *GBA* in 6% of 50 brain samples from subjects with pathologically confirmed diffuse LBD. Conversely, another study found *GBA* mutations in 28% (27 of 95) of patients with primary pathological diagnoses of LB disorders, compared with 10% (6 of 60) of cases with primary AD and 3% (1 of 32) of control cases (Clark et al., 2009). In this latter study, the presence of *GBA* mutations appeared to be related more to the presence of cortical LBs than to LBs confined to the subcortical regions. Moreover, *GBA* mutations were also detected in 6.8% (4/59) of cases with a pathological diagnosis of diffuse Lewy body disease. Taken with previous studies, it appears that *GBA* mutations are associated with a more diffuse pattern of Lewy body distribution involving the cerebral cortex than the brainstem/limbic distribution observed in typical PD (Nishioka et al., 2011). Also Setó-Salvia et al. (2011) reported more recently, 12% of LBD brains carrying a mutated *GBA* allele.

GBA MUTATIONS AND COGNITIVE DECLINE

Given the distribution of Lewy bodies into the neocortical regions, subsequently studies were conducted to rule out the influence of *GBA* mutations in the clinical course of PD, including cognitive decline and dementia. A prospectively evaluation at the NIH Clinical Center with detailed neurological examinations reported cognitive changes in half of the subjects (Goker-Alpan et al., 2008). In addition, the clinical features of a British PD patient group who carried *GBA* mutations comprised, an early-onset of the disease, the presence of hallucinations in 45% (14/31) and symptoms of cognitive decline or dementia in 48% (15/31) of the patients (Neumann et al., 2009). The effect of *GBA* on susceptibility to dementia was reinforced in Spanish PD patients with *GBA* mutations, in which half of the patients developed dementia during the clinical course of PD (Setó-Salvia et al., 2011).

OTHER LYSOSOMAL STORAGE DISORDERS AND PARKINSONISM

Glucocerebrosidase has been identified as a component of the Lewy body's inclusions in patients with *GBA* mutations (Goker-Alpan et al., 2010) and it colocalized with lysosomal-associated membrane protein 1 (LAMP1) marker, which suggested an impairment of the lysosomal activity in LB pathology. This observation is supported by the emerging reports of PD across a range of LSDs. Over two-thirds of LSDs involve central nervous system dysfunction (progressive cognitive and motor decline) whereas affected individuals developed frequently parkinsonism with deposits of α-synuclein in the brain and substantia nigra pathology (Shachar et al., 2011; Schultz et al., 2011). For the first time, it was recently demonstrated accumulation of the α-synuclein in the cortical tissue of two postmortem cases of Sanfilippo syndrome (mucopolysaccharidosis type III, MPSIII; Winder-Rhodes et al., 2012). MPSIII is an autosomal recessive neurodegenerative storage disease caused by mutations in *N*-acetylglucosaminidase (*NAGLU*) gene. Additional case reports of LSDs have described parkinsonism features among patients and in postmortem tissues, Lewy body's inclusions have been observed. Thus, patients with GM1 gangliosidosis (caused by defective β-galactosidase activity), GM2 gangliosidoses, including Tay–Sachs and Sandhoff diseases (caused by defective β-hexosaminidase activity) and Fabry–Anderson disease (caused by the defective activity of α-galactosidase) as well as some family members, developed various PD symptoms including bradykinesia, rigidity, and resting tremor (Argov and Navon, 1984; Inzelberg and Korczyn, 1994; Orimo et al., 1994; Muthane et al., 2004; Roze et al., 2005).

Also relatives and patients with Niemann–Pick C disease (caused by the defective activity of either NPC1 or NPC2) presented with parkinsonian tremor and an α-synucleinopathy in human NPC brain was observed in the midbrain and amygdale of a postmortem tissue (Saito et al., 2004).

Therefore, the link of PD and LSDs suggested a common underlying mechanism compromising the lysosomal and proteasomal degrading systems, resulting to the α-synuclein pathology shared by several of these disorders (Settembre et al., 2008). This association, as described above is not limited exclusively to changes that occur in GD, such as changes in glucocerebrosidase activity or in glucosylceramide levels, but rather include changes that might be common to a wide variety of LSDs. So it may be interesting in a near future to investigate the frequency of mutations in genes encoding lysosomal proteins in the patients who display Parkinson's symptoms.

GBA MUTATIONS AND CERAMIDE METABOLISM

Although *GBA* mutations and consequently glucocerebrosidase deficiency show a clear and, potentially direct risk association with α-synucleinopathies and PD, it was suggested that this link is

due to its subtract accumulation, glucosylceramide excess, rather than the decrease levels of its subproduct, ceramide. Several studies have been conducted and no evidence of ceramide deficiency has been detected in patients with GD, even in those severely affected. This finding supported the existence of a tightly regulated ceramide levels resultant from many different degradative and synthetic pathways. So, the link between *GBA* heterozygosity and PD or other synucleinopathies may not be determined by ceramide metabolism dysfunction. In fact, the use of inhibitors of the glucocerebrosidase function has been shown to modulate α-synuclein levels (Manning-Bog et al., 2009). In addition, the α-synuclein aggregation and glucosylceramide accumulation occurred in a chemically induced glucocerebrosidase deficiency. These studies demonstrated a relationship between glucosylceramide accumulation and α-synuclein aggregates, and implicate glucosylceramide accumulation as risk factor for the α-synucleinopathies (Xu et al., 2010). Nevertheless, it was proposed that the abnormal α-synuclein pathology presented in neurodegeneration with brain iron accumulation 1 and 2 (NBAI-1, NBAI-2) caused by mutations in the pantothenate kinase type 2 (*PANK2*) and phospholipase A2, group VI (*PLA2G6*) genes, respectively, could be connected to ceramide metabolism (Bras et al., 2008). However, very recently, it was demonstrated that *PLA2G6* mutations were the second common genetic cause after *PARK2* gene mutation in cohorts of Chinese and Taiwanese young-onset parkinsonism with Chinese ethnicity (Shi et al., 2011; Lu et al., 2012). Additionally, the postmortem study on a series of patients with *PLA2G6* mutations, demonstrated widespread α-synuclein positive Lewy pathology particularly severe in the neocortex (Paisán-Ruiz et al., 2012). Therefore, in order to rule out the pathogenic mechanism by which, mutations in *PLA2G6* gene cause PD, it will be interesting to measure the ceramide levels in these early-onset PD patients carrying mutations in the *PLA2G6* gene.

POSSIBLE MECHANISMS LINK GBA AND PD AND α-SYNUCLEINOPATHIES

GBA mutations act as a strong risk factor to α-synucleinopathies and Parkinson disease interfering with the clearance of or promote the aggregation of α-synuclein. Mazzulli et al. (2011) have shown that intracellular glucosylceramide levels control the formation of soluble toxic α-synuclein assemblies in cultured neurons and mouse and human brain, leading to neurodegeneration. The elevation and formation of α-synuclein assemblies inhibits the lysosomal activity of normal glucocerebrosidase in neurons and idiopathic PD brain, resulting in additional glucosylceramide accumulation and augmented α-synuclein oligomer formation. This self-propagating positive feedback process, proceeds until a pathogenic threshold is reached, resulting in neurodegeneration (Mazzulli et al., 2011). The frequently reported lysosomal proteolytic dysfunction in PD as well is in other LSDs is one of the common mechanisms underlying the α-synuclein pathology shared by various of these disorders (Shachar et al., 2011; Yap et al., 2011). Indeed, the disruption of autophagy-lysosomal process has been proposed as the mechanism by which *LRRK2* mutations, the gene responsible for the autosomal dominant forms of PD, may exert its effects (Tong et al., 2010). The autophagy degrading pathway is considered the primary mechanism through which α-synuclein is degraded and its impairment is reinforced by the involvement of another gene associated with familial forms of PD, *ATP13A* gene, which encodes a lysosomal ATPase responsible for maintaining intralysosomal pH and suppresses α-synuclein toxicity in *C. elegans*, yeast, and primary neuronal cultures (Gitler et al., 2009). In addition, the dysfunction of the ubiquitin–proteasome system also underlies many of these α-synucleinopathies. Again, *Parkin* gene which has been associated mostly with the early-onset PD recessive familial cases encodes the E3 ubiquitin ligase, and is involved in the ubiquitination pathway of misfolded glucocerebrosidase in dopaminergic neurons. The absence of normal parkin leads to improper degradation of some of its subtracts, such as α-synuclein and to their accumulation (Ron et al., 2010).

A distinct α-synuclein degraded pathway within lysosomes is the chaperone mediated autophagy (CMA), whereas SNCA mutants Ala53Thr and Ala30Pro bind to LAMP2A but fail to translocate into the lysosomal lumen for breakdown (Cuervo et al., 2004; Cullen et al., 2011). Subsequently, further CMA-mediated degradation substrates are blocked, which contributes to their accumulation (Westbroek et al., 2011). Likewise, defects in mitochondrial activity are reported in many of α-synucleinopathies which results mainly in decrease levels of the ATP synthesis, causing the formation of free radicals leading to oxidative stress and impairment of the membrane potential (Schapira, 2011). Several studies have demonstrated the effect of PD causative genes also on mitochondrial depolarization and their interference in the electron transport chain (Schapira and Gegg, 2011).

Additionally, *GBA* haploinsufficiency alters the lipid metabolism and composition of the cell membranes which is also considered a common impaired pathway in many of these disorders. The helical binding of α-synuclein to lipid membranes prevents the formation of fibrillar protein structures. It has been demonstrated that α-synuclein does bind to brain-derived glycosphingolipids that contain glucosylceramide in their core. Therefore, deficiency of glucocerebrosidase leads to the accumulation of its substrates glucosylceramide and/or glucosylsphingosine and alter sphingolipid composition of the cell membranes, which may disrupt the membrane binding of α-synuclein, enhancing its aggregation in the cytoplasm (DePaolo et al., 2009).

In this article, an extensive literature review has documented clinical, pathological, and genetic studies which have contributed to our growing understanding of the involvement of the glucocerebrosidase as a susceptibility factor to PD and other synucleinopathies. The rapid pace of investigation of the *GBA* function has been stimulated by the identification of mutations in this gene, not only in GD patients, but also in sporadic and familial PD cohorts as well as in different α-synucleinopathies. The clinical and pathological studies have accompanied and complement the genetic analysis of *GBA* gene in different patient's cohorts, adding a crucial value toward the delineation of the different molecular pathways underlying the pathogenesis of these conditions. Curiously, an attempt to integrate the different molecular pathways and functions in a unique mechanism indicates a considerable overlap between them, suggesting interactions of pathological proteins engaging common downstream pathways which is not only relevant for the familial forms, but also to the more common sporadic PD cases.

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Deep brain stimulation and cognitive decline in Parkinson's disease: a clinical review

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Parkinson's disease is a common and often debilitating disorder, with a growing prevalence accompanying global population aging. Current drug therapy is not satisfactory enough for many patients, especially after a few years of symptom progression. This is mainly due to the motor complications that frequently emerge as disease progresses. Deep brain stimulation (DBS) is a useful therapeutic option in carefully selected patients that significantly improves motor symptoms, functional status, and quality of life. However, cognitive impairment may limit patient selection for DBS, as patients need to have sufficient mental capabilities in order to understand the procedure, as well as its benefits and limitations, and cooperate with the medical team throughout the process of selection, surgery, and postsurgical follow-up. On the other hand it has been observed that certain aspects of cognitive performance may decline after DBS, namely when the therapeutic target is the widely used subthalamic nucleus. These are important pieces of information for patients, their families, and health care professionals. This manuscript reviews these aspects and their clinical implications.

Keywords: Parkinson's disease, cognitive impairment, deep brain stimulation, dementia, functional impairment, globus pallidus interna, quality of life, subthalamic nucleus

INTRODUCTION

Parkinson's disease (PD) is a common, potentially disabling neurodegenerative disease (Massano and Bhatia, 2012). It was estimated that, in 2005, more than 4 million people in the world suffered from this disorder, and disease prevalence is estimated to escalate in the future, as the mean age of the population increases at a worldwide level (Dorsey et al., 2007). Following the original clinical depictions by Parkinson (1817) in the nineteenth century, motor features of the disease, such as bradykinesia, resting tremor, rigidity, and gait and postural changes, were regarded for a long time as the major features of PD. This view has changed in the past few decades, as a growing number of clinicians and researchers have studied and reported in detail on the important non-motor characteristics of the disease (Chaudhuri and Schapira, 2009; Gallagher et al., 2010). Among them is cognitive decline, ranging from mild impairment to overt dementia – a contemporary review on this topic can be found included in the present Frontiers Research Topic collection (Meireles and Massano, submitted).

The treatment of PD is not a straightforward task, especially when dealing with newly diagnosed patients and, especially, in advanced disease stages. In the early stages there is controversy regarding the timing of therapy initiation and which specific strategies should be used. Many clinicians tend to initiate drug therapy as soon as symptoms interfere with the patient's lifestyle, usually prescribing monoamino oxidase B inhibitors or dopaminergic agonists, especially in younger patients, but this approach is under dispute within the scientific community – for instance, opposite views support the notion that levodopa is the drug of choice regardless of patient age or disease stage (Lang, 2009; Lees et al., 2009; Schapira, 2009). Deep brain stimulation (DBS) has become a standard of care for a significant minority of patients in advanced disease stages, with controlled trials and large clinical series supporting its use, as both benefits and safety have been well established (Krack et al., 2003; Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Weaver et al., 2009; Follett et al., 2010; Moro et al., 2010; Smeding et al., 2011). Patients selected for the procedure are typically not satisfied with the severity of their symptoms and disability even under optimized medical therapy, especially due to the quite incapacitating and frustrating motor complications, such as peak dose dyskinesias, prolonged off periods, or sudden off states (Lang et al., 2006; Massano and Bhatia, 2012). In most occasions, one of two different brain regions is currently targeted for DBS in PD: the subthalamic nucleus (STN) or the *globus pallidus interna* (GPi). The ventral intermediate (VIM) nucleus of the thalamus was the first electrically stimulated region for the treatment of PD (Benabid et al., 1987), but it is now targeted in uncommon and much selected circumstances, as tremor is apparently the only clinical feature improving significantly with the procedure (Walter and Vitek, 2004; Moro and Lang, 2006; Pahwa et al., 2006). The choice of brain target for DBS should probably be carried out according to each patient's characteristics, as we will further detail in the text.

Cognitive impairment plays an important role in PD patients who are potential candidates for DBS, as this may be a limiting factor during patient selection. Also, evidence has been accumulating regarding changes in cognitive performance after DBS, and both physicians and patients should be well aware of this prior to

the procedure. This review will approach these matters, and the implications for clinical management.

METHODS

The authors conducted a PubMed search for papers published between 1990 and August 2011. Keywords used were "PD," "cognition," "cognitive decline," and "DBS." Relevant references were chosen and an additional manual reference search was carried out on the reference list in retrieved manuscripts; articles were included for analysis only if the research enrolled at least 15 subjects undergoing DBS, except where evidence was much scarcer and only smaller series were available. The final reference list was produced on the basis of importance to the topics covered in this review. Data were extracted from relevant sources and the text was devised according to a predefined structure.

COGNITIVE STATUS AS A KEY FACTOR FOR PATIENT SELECTION FOR DBS IN PD

Accurate PD patient selection is paramount in DBS. This has been acknowledged in the widely used core assessment program for surgical interventional therapies in PD (CAPSIT-PD) protocol, a landmark document in this field (Defer et al., 1999). Patient cognitive status is of utmost importance when considering DBS as a potential therapy for PD, as patients displaying significant cognitive decline are generally not considered good candidates for the procedure (Pillon, 2002; Lang et al., 2006; Moro and Lang, 2006; Okun et al., 2007; Rodriguez et al., 2007; Bronstein et al., 2011). This is due to several reasons, with ethical imperatives always in mind as a background for clinical thinking and action. First, it must be assured that the procedure is expected to help the patients (beneficence) and not harm them (non-maleficence). Moreover, effective and safer therapies should be thoroughly tried before proceeding with DBS, and benefits should be wisely balanced against risks (proportionality and subsidiarity; Clausen, 2010; Schermer, 2011). Such equilibrium may at times be difficult to perceive when considering specific therapeutic interventions, such as DBS, which is often a publicly glorified intervention, and commonly understood as a last resort (Bell et al., 2011). Another important issue is that of autonomy, meaning that the patient must be able to decide freely and in a fully informed manner whether he/she wishes to proceed with the therapy (Clausen, 2010; Schermer, 2011). This principle implies that the patient must have a cognitive status that makes him/her able to understand the information given by the clinicians, and carry out every relevant decisions in this regard. These important ethical imperatives should be actively safeguarded by the team involved in patient care at all times. On the other hand, cognitive status is also important from a practical perspective, as patients must be able to go through all required presurgical selection procedures, to collaborate with the team in the operating theater (patients are awake during surgery in most centers), and to comply with the postsurgical follow-up program, including serial DBS parameter adjustments. This can be very demanding, due to the high number of visits often required and the amount of time consumed, as well as the need for a skilled and persistent programmer (Volkmann et al., 2006).

Despite the amount of knowledge gathered in the past decades in the field of DBS, several caveats, and important uncertainties still remain. When someone is clearly demented it is straightforward that he/she should not be offered the procedure. Nevertheless, milder forms of cognitive decline occur in PD, even at early disease stages (Caviness et al., 2007; Barone et al., 2011; Domellöf et al., 2011; Meireles and Massano, submitted) and this should be taken into account when selecting patients for DBS, but drawing safe selection boundaries with regard to cognitive capacities is not an easy assignment. Even a recent international multidisciplinary expert consensus meeting was unable to come up with firm recommendations regarding the best way of assessing these patients and the cutoff scores that should be used in neuropsychological testing (Bronstein et al., 2011). Some cognitive features have been clearly associated with PD (Emre et al., 2007; Goetz et al., 2008; Williams-Gray et al., 2009; Barone et al., 2011), while others should rise suspicion about concomitant pathologies, such as the characteristic early and predominant decline of episodic (hippocampal) memory seen in Alzheimer's disease (Mayeux, 2010; Ballard et al., 2011; McKhann et al., 2011). Physicians should be extraordinarily cautious in these circumstances, as accelerated cognitive decline would probably be expected in such patients, as compared to those with isolated PD pathology. Concurrent mixed pathology might not be an uncommon happening (Jellinger and Attems, 2008; Kovacs et al., 2008), and imaging research has shown that a pattern of atrophy typical of AD may predict cognitive decline in PD (Weintraub et al., 2012). Therefore, it is imperative that detailed neuropsychological testing is performed and data thoroughly reviewed and interpreted before a final decision is reached about DBS in a particular patient. Normalized tests and data should be used whenever possible, thus aiming at the highest standards and accuracy of cognitive testing and interpretation.

COGNITIVE DECLINE FOLLOWING DEEP BRAIN STIMULATION IN PD

STN VERSUS GPi

A number of studies have looked at how cognition might be affected following DBS in PD, especially when STN is the target. Cognitive changes have been reported despite the fact that patients undoubtedly improve from the motor standpoint and quality of life (QOL; Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Follett et al., 2010; Smeding et al., 2011). This implies that DBS produces effects both on motor and cognitive neural networks, probably due to the fact that the targeted nuclei are also involved in associative processes, thus explaining the impact of DBS on cognition (Temel et al., 2005; Mallet et al., 2007; Utter and Basso, 2008; Rodriguez-Oroz et al., 2009).

Interesting data comparing cognitive performance following DBS using the STN or the GPi can be collected from recently published randomized trials. The COMPARE trial randomized 52 PD patients to receive unilateral DBS of either the STN or GPi in a single center where staged surgery is customarily performed (Okun et al., 2009). Forty-five patients were assessed using a preplanned protocol before and 7 months after surgery, showing that no differences could be observed between both targets regarding cognitive outcomes, as assessed by verbal fluency (VF) tasks (letter and category). However, when analyzed independently, letter VF declined more on the STN group as compared to the GPi group, although no statistical significance was reached ($p < 0.03$,

predefined significance <0.025). Moreover, patients were tested under four different stimulation conditions: optimal (i.e., active contact on target), dorsal (i.e., active contact dorsal to the nucleus), ventral (i.e., active contact ventral to the nucleus), and switched off. No differences could be observed between the several conditions and, interestingly, letter VF has been found to be worse in the STN group regardless of the stimulation condition. Taken together, these results suggest that surgical microlesion effects could play an important role concerning cognitive outcomes in this setting. On the other hand, the interesting issue of laterality has been approached in this trial: an approximately equal number of right and left-sided electrode implantations were performed, and no significant differences could be observed between groups concerning cognitive outcomes. Nonetheless, this trial does not reflect usual clinical practice, as bilateral DBS of any of those targets is the rule, so caution should be used when drawing predictions from these data for most PD patients undergoing DBS.

Robust and clinically useful evidence on this matter is derived from the work by Follett and colleagues, who conducted a large randomized double-blind trial of STN DBS ($n = 147$) versus GPi DBS ($n = 152$) in advanced PD. Patients were observed up to 24 months after surgery, showing that both groups improved, and that no differences could be found between them regarding motor outcomes, self-reported function, QOL, and adverse events. Cognitive performance declined in both groups equally except for processing speed index, which declined more for the subthalamic than for the pallidal stimulation patients ($p = 0.03$). Interestingly, mood was also differentially affected, with GPi patients faring better as mood improved slightly in the GPi DBS group, whereas it worsened slightly in the STN DBS group. Medication was significantly reduced after surgery only in the STN DBS group (Follett et al., 2010).

Another recent publication disclosed data on DBS using either target. This international collaborative effort was firstly designed as an open, non-randomized, prospective multicenter clinical trial aimed at evaluating safety and effectiveness of bilateral STN and GPi stimulation in advanced PD. Randomized double-blind assessments with crossover on the second day of the 3-month follow-up visit and unblinded assessments at 1-, 6-, and 12-month follow-up were planned. An extension period was carried out to collect data from the long-term (3–4, 5–6 years) and from a double-blind randomized crossover evaluation at 5–6 years. At this time point, 35 patients from the STN DBS group and 16 included in the GPi DBS group were assessed and compared with the stimulation randomly turned on and off. Double-blind assessments confirmed the effectiveness of stimulation in both groups concerning motor outcomes. Dyskinesias and activities of daily living were also significantly improved, and medication had been significantly reduced in the STN group only. However, adverse events were more common in the STN group, including cognitive decline and speech difficulties, but further details have not been provided in the manuscript (Moro et al., 2010).

A French collaborative research assessed patients undergoing bilateral DBS (49 STN and 13 GPi) at baseline and 3–6 months after surgery. Neuropsychological testing included the Mattis Dementia Rating Scale (MDRS), the Grober and Buschke Verbal Learning Test, the Wisconsin Card Sorting Test, category and literal fluency, graphic and motor series, the Stroop Test, and the trail making test (TMT). Motor improvements were noticeable in both groups after DBS, but lexical fluency declined in the STN DBS patients. However, these were not noticed by the patients or their families, suggesting that this decline might be very subtle. On the other hand TMT A and B, which evaluate selective attention and cognitive flexibility, improved in the STN DBS patients (Ardouin et al., 1999).

Extending their work, the same research group assessed whether turning the stimulation on and off would affect cognitive performance in subthalamic and pallidal DBS. With the stimulation on, STN patients showed a mild but significant improvement in psychomotor speed and working memory; they also showed a deficit of lexical fluency at 12 months after surgery. Stimulation status did not seem to influence cognitive performance in the GPi group (Pillon et al., 2000).

Volkmann and coworkers have conducted a retrospective study aimed at comparing safety and efficacy of subthalamic ($n = 16$) and pallidal ($n = 11$) stimulation. Again, motor outcomes were similar in both groups, with slight advantage to the STN patients regarding off period symptom severity. Furthermore, antiparkinsonian medication was significantly reduced in the latter patients, who also required less energy delivery, but this group suffered a higher frequency and severity of adverse events. Cognitive status, as assessed by mini-mental state examination (MMSE) and the Cambridge Examination for Mental Disorders Cognitive Subscale, remained unchanged in both STN and GPi groups (Volkmann et al., 2001).

Anderson et al. (2005) reported on the outcome in STN ($n = 10$) versus GPi ($n = 10$) stimulation in PD at 12 months after surgery, finding similar motor benefit in both groups, although bradykinesia has suffered additional improvement with STN DBS. Significant cognitive decline was observed in two STN patients, as compared to none in the GPi group.

Rothlind and collaborators conducted a complex study randomly assigning 42 PD patients to DBS of either STN ($n = 19$) or GPi ($n = 23$). Moreover, surgery was staged (i.e., unilateral stimulation initially, with contralateral surgery performed later), thus allowing intermediate cognitive assessment, on average 6 months after the first lead was implanted. Twenty-nine patients subsequently underwent a second surgery for contralateral lead implantation, and completed a second neuropsychological evaluation on average 15 months later. The authors have found that unilateral surgery induced slight but statistically significant decays of VF and working memory, which has also been observed after the second surgery. However, VF was significantly affected only after left-sided implantation. There were few differences regarding cognitive performance when considering each target, and these were observed both in unilateral and bilateral DBS: visuomotor coordination and manual dexterity declined slightly more in the STN group, whereas auditory working memory was somewhat more affected in the GPi group (Rothlind et al., 2007).

Hariz et al. (2008) brought further data on this matter, by assessing adverse events in STN ($n = 49$) and GPi ($n = 20$) stimulated patients at 4 years of postsurgical follow-up from eight centers. Adverse events were significantly more frequent in the STN group as compared to GPi, with neuropsychiatric disorders

(including cognitive decline) leading the list, but no details can be extracted from the manuscript with regard to the type of mental deterioration.

Overall, evidence on cognitive performance following pallidal DBS in PD is shorter than the one available for subthalamic DBS. However, the available data clearly suggests that the risk of cognitive decline is lower whenever the GPi is target of choice, unlike what has been observed for the STN. Pursuing this line of thought, Rouaud and collaborators have recently looked at the GPi as a potential alternative for subjects with cognitive deficits advising against performing subthalamic DBS. Seventeen patients were submitted to bilateral GPi DBS, nine of these exhibiting significant cognitive deterioration at the time of surgery. Final assessment was carried out 6 months after surgery. Taking the group as a whole there were significant improvements in parkinsonian symptoms (including axial features), fluctuations, and dyskinesias. A significant benefit on activities of daily living has also been documented. On the other hand, neuropsychological assessment remained unchanged. The authors argue that bilateral GPi DBS is both effective and cognitively safe in advanced PD patients for whom STN DBS is not a viable option due to cognitive decline or dopa-resistant axial motor signs (Rouaud et al., 2010).

Taken together, these data suggest that STN and GPi possess differential profiles of cognitive risk, thus favoring tailoring of the surgical approach. In other words, until fresher data advises otherwise, each patient should be assessed in detail and the target chosen according to his/her specific characteristics, including cognitive status.

A limited amount of data has been published regarding cognition in PD patients undergoing DBS using the VIM nucleus of the thalamus, probably due to the fact that this target is now seldom used and earlier series where much smaller than those published with STN or GPi stimulated patients. Caparros-Lefebvre and collaborators approached this issue in nine PD patients submitted to VIM stimulation. Tremor response was quite satisfactory and neuropsychological testing disclosed similar results before and after surgery (Caparros-Lefebvre et al., 1992). Tröster and coworkers have reported on a single case undergoing left unilateral VIM stimulation, with testing carried out at 3-, 6-, and 18-months. They have found that semantic VF was subtly improved while the stimulation was on, but in the very same condition short-term verbal memory became impaired (Tröster et al., 1998). Woods et al. (2001) analyzed cognitive performance of six PD patients at baseline and 1 year after unilateral DBS of the VIM; the authors have found that conceptualization and verbal memory suffered significant postsurgical decline, despite the improvements in QOL and emotional functioning. Loher and coworkers analyzed cognitive outcomes following VIM DBS in five PD patients, two essential tremor patients, and two MS patients. Detailed neuropsychological testing was carried out on and off stimulation, with a mean follow-up of 9 months. The authors found mild memory changes while the stimulation was on but not when it was turned off, suggesting that this change is related to the stimulation and not due to microlesion effects (Loher et al., 2003).

In view of the results extracted so far from published data, we will further detail on cognitive outcomes following subthalamic DBS, as this seems a topic deserving further consideration.

DBS OF THE SUBTHALAMIC NUCLEUS: OUTCOME BY COGNITIVE DOMAIN

Evidence collected so far has clearly demonstrated that DBS of the STN in advanced PD is beneficial regarding motor symptoms, activities of daily living, and QOL, while levodopa equivalent daily dose (LEDD) is significantly reduced (Limousin et al., 1998; Krack et al., 2003; Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Witt et al., 2008; Follett et al., 2010; Williams et al., 2010; Smeding et al., 2011). However, as mentioned above, data has been accumulating that shows the potential for cognitive changes following the procedure, and several cognitive domains have been separately explored in this regard. Defining and assessing independent cognitive domains is not a straightforward task, as several definitions are often used for the same domain, and it is hard to independently assess each cognitive function, for neural processes and behaviors are inextricably intertwined. Frontal executive functions (FEx), for instance, encompass several cognitive functions and processes, for which various assessment tests have been devised (Funahashi, 2001; Godefroy, 2003; Miller and Cummings, 2007; Stuss and Alexander, 2007). This might bring some interpretation problems, as the different aspects of FEx may be differentially affected following STN DBS, something that has in fact been observed in a few studies. A well-structured list of tests used for cognitive assessment in DBS research can be found in the work by Parsons et al. (2006).

Various studies have assessed global cognitive performance before and after surgery, usually by means of the MMSE test or the MDRS. Most authors have found no significant postsurgical changes, thus suggesting that the procedure is generally safe regarding cognition in well selected patients (further details can be found in **Table 1**). The fact that different measures of global cognition have been used could be potentially relevant, since it has been shown that MMSE, a classically used instrument, has shown low sensitivity to detect cognitive deterioration in PD (Hoops et al., 2009; Kulisevsky and Pagonabarraga, 2009; Chou et al., 2010; Kaszás et al., 2012). On the contrary, MDRS seems to have good sensitivity and specificity scores for this purpose, which might be due to the fact that it explores further cognitive domains and deficits in comparison to the MMSE, including frontal lobe and fronto-subcortical cognitive decline, although it is more time consuming than MMSE (Kulisevsky and Pagonabarraga, 2009; Chou et al., 2010; Kaszás et al., 2012). In fact, the MDRS Nonetheless, MMSE has been recognized by the Movement Disorder Society PD dementia workgroup as a potentially useful instrument in the diagnostic process of PD dementia, but should not be used in isolation with this purpose (Emre et al., 2007).

Several studies have found a significant decline in phonemic (letter) VF, while semantic VF seemed to remain relatively spared after DBS (Castelli et al., 2007; Okun et al., 2009; Zangaglia et al., 2009), but others have observed significant declines in both VF modalities (Witt et al., 2008). Some studies convey information of special interest, due to the fact that a control group has also been included. Okun et al. (2009) have found interesting results, as phonemic VF declined after unilateral STN DBS, regardless of the active contact used and even with the stimulation turned off. This suggests that such an impairment might arise even after unilateral procedures and could result from microlesion or

Table 1 | Publications concerning cognitive functioning after deep brain stimulation of the subthalamic nucleus in Parkinson's disease, at the time of last cognitive assessment.

Publication	Number of patients[a]	Follow-up[b]	Age[c]	Symptom duration[c]	Improvement	Worsening	Unchanged
Limousin et al. (1998)	24	12 months	56	14.0	–	–	A/FEx, GCP
Ardouin et al. (1999)	49	3–6 months	54.7	15.1	A/FEx	L	GCP
Pillon et al. (2000)	63	6–12 months	55.2	14.8	A/FEx, PMS	L	M
Alegret et al. (2001)	15	3 months	61.1	16.1	A/FEx, PMS	L, M, VS	–
Lopiano et al. (2001)	16	3 months	60.7	15.4	–	–	A/FEx, L, M
Perozzo et al. (2001)	20	6 months	61.6	15.4	–	–	A/FEx, L, M, PMS
Volkmann et al. (2001)	16	12 months	60.2	13.1	–	–	GCP
Daniele et al. (2003)	20	12–18 months	57	14.2	GCP, A/FEx	L	M
Funkiewiez et al. (2003)	50	3–48 months	54.6	NR	–	–	A/FEx, GCP
Krack et al. (2003)	49	5 years	55	14.6	–	A/FEx	GCP
Funkiewiez et al. (2004)	77	12–36 months	55	15	–	L	A/FEx, GCP
Hershey et al. (2004)	24	2–15 months	63	13	–	A/FEx	–
Morrison et al. (2004)	17	13.3 weeks (average)	59.9	10.8	–	A/FEx, L	GCP, M, VS
Witt et al. (2004)	23	6–12 months	57.4	15.1	A/FEx (cognitive flexibility)	A/FEx (response inhibition)	GCP, L
Schüpbach et al. (2005)	37	60 months	54.9	15.2	–	A/FEx, GCP	–
Castelli et al. (2006)	72	15 months (average)	60.5	15.1	A/FEx (set shifting)	L	A/FEx (attention, reasoning), M
De Gaspari et al. (2006)	26	15 months (average)	59.8	15.8	–	L	GCP
Deuschl et al. (2006)	78	6 months	60	NR	–	–	GCP
Erola et al. (2006)	29	12 months	60	13	–	L	A/FEx
Smeding et al. (2006)	103	6 months	57.9	13.7	–	A/FEx, L, M	–
Temel et al. (2006)	39	13.6 months (average)	60	15.5	PMS	–	–
Aybek et al. (2007)	57	34.3 months (average)	63.8	15.7	–	A/FEx, C, M, P (constructive)	L, VS, P (ideomotor)
Castelli et al. (2007)	19	17 months (average)	62.1	14.7	–	L (phonemic VF)	A/FEx, M, L (semantic VF)
Ory-Magne et al. (2007)	45	24 months	60	13.5	–	–	A/FEx, L, M
Rothlind et al. (2007)	19	15 months	61.4	12.9	–	A/FEx (attention, working memory), L	A/FEx (executive functions), M
York et al. (2008)	23	6 months	59.5	12.0	–	L, M	GCP, A/FEx, VS
Heo et al. (2008)	46	12 months	58	11.4	–	A/FEx (attention, interference sensitivity), L, M	GCP, A/FEx (reasoning), PMS
Witt et al. (2008)	60	6 months	60.2	13.8	–	A/FEx, L	GCP, M, VS
Denheyer et al. (2009)	16	16 months (average)			–	L	A/FEx
Okun et al. (2009)	26	7 months (average)	59.8[d]	13.3[d]	–	L (phonemic VF)	L (semantic VF)
Zangaglia et al. (2009)	32	36 months	58.8	11.8	–	A/FEx[e], L	GCP, M
Fasano et al. (2010)	20	96 months (average)	56.9	13.7	–	A/FEx, L, M	GCP
Kishore et al. (2010)	45	5 years	55.4	11.1	–	–	A/FEx, GCP, L, M, VS

(Continued)

Table 1 | Continued

Publication	Number of patients[a]	Follow-up[b]	Age[c]	Symptom duration[c]	Improvement	Worsening	Unchanged
Merola et al. (2011)	19	7.9 years (average)	61.5	22.8	–	A/FEx, L, M	–
Smeding et al. (2011)	105	12 months	58.4	13	–	A/FEx, GCP, L, M	–
Williams et al. (2011)	19	2 years	62.1	10.1	–	L, M	A/FEx, GCP, VS

Results presented here exclude any cognitive deficits directly attributed to well-defined adverse events (e.g., intraparenchymal hematoma). Further details are provided whenever diverse aspects of the same cognitive domain are differentially impaired in the same study. Legend: [a]included at baseline; [b]time after DBS for the last cognitive assessment; [c]mean or median, at the time of DBS; [d]refers to those assessed cognitively only ($n = 22$); [e]decline seen 6 months after DBS, but same performance as controls after 12 months; NR, data not reported; A/FEx, attention and frontal executive functions; C, calculation; GCP, global cognitive performance; L, language; M, memory; P, praxis; PMS, psychomotor speed; VF, verbal fluency; VS, visual/spatial capabilities.

insertion effects. Witt and collaborators have conducted a multicenter controlled study enrolling patients for either STN DBS ($n = 60$) or best medical therapy ($n = 63$). By the end of the 6-month study period following DBS, they have found that VF (both phonemic and semantic) and executive functions had declined significantly in the surgical group, but this finding was independent of the observed improvement in QOL, and global cognition remained unaffected (Witt et al., 2008). In their series of 77 consecutive PD patients undergoing subthalamic DBS Funkiewiez et al. (2004) have observed that semantic fluency was significantly worse 1 and 3 years after surgery, when compared with the preoperative score. However, the difference between 1 and 3 years after surgery is not significant, suggesting that this is an early adverse effect of the therapy. Zangaglia and coworkers have observed results somewhat different from those found by other authors. In their study, 32 patients underwent STN DBS while 33 were enrolled as controls, after having refused surgery, choosing medical treatment instead. Six months after surgery, DBS patients had shown significant declines in both phonemic VF and FEx; however, the cognitive profile had returned to the values obtained before the surgical procedure by 12 months, remaining stable 3 years after surgery (Zangaglia et al., 2009). These findings seem to be in conflict with other publications, but comparing results is a challenging task, since the few studies controlled by a medical treatment group conducted so far had shorter follow-up periods. A 12-month long study was conducted by Smeding et al., who enrolled 105 STN DBS patients and 40 medically treated controls. In the surgical group a decline in cognitive performance has been noted in 36% percent of patients; significant changes were seen in global cognitive performance, VF, verbal memory, and executive functions. The authors argue that this does not seem to be a transient consequence, since effect sizes of most cognitive changes had become even larger from 6 to 12 months. Despite experiencing cognitive decline, 9% of these patients reported improvements in QOL, suggesting that cognitive decline does not necessarily mean a loss of clinical benefits gained from the surgical procedure (Smeding et al., 2011). The study by Williams et al. (2011) included 19 patients undergoing STN DBS and 18 medically treated PD controls; the final cognitive assessment was performed 2 years after surgery. Patients undergoing DBS displayed significant decline of phonemic and semantic VF, as well as non-verbal recall and information processing speed.

An array of data regarding FEx following STN DBS has been published, but conclusions are considerably harder to analyze than for VF. Several studies have reported that FEx worsen after STN DBS, whereas an approximately equal number has found unchanged scores after the procedure (see **Table 1** for details). Of course, there are methodological differences between studies, and this might contribute for the disparities, but one must keep in mind that research groups have used widely accepted criteria for surgical patient selection, and the tests used for cognitive assessment are similar in many studies. Also, mean age at time of DBS and disease duration do not seem to differ significantly amongst most studies (**Table 1**). Hence, other factors probably account for the differences. FEx are particularly difficult to define and assess, as several different processes are encompassed under this umbrella term (Funahashi, 2001; Godefroy, 2003; Miller and Cummings, 2007; Stuss and Alexander, 2007). Therefore, strict definitions and assessment uniformization would clearly be useful in order to allow effective comparison of data published by the different study groups and eventually produce future meta-analyses of results. Other cognitive domains have been assessed, and **Table 1** qualitatively summarizes the findings from each study.

Longer term data has also been published. Fasano et al. have reported their findings on a group of 20 STN DBS patients followed up for 8 years after surgery. The authors have found that part of the motor benefit had been lost since the previous assessment 3 years before, due to levodopa- and stimulation-resistant symptoms. On the other hand, they have found significant declines in VF, episodic memory, and executive functions, but only memory had significantly declined from 5 to 8 years of follow-up. Executive functions correlated significantly with postural instability (PI), which is not a surprising result, as both cognitive deterioration and PI are to be expected along disease progression – however, questions remain regarding putative common pathophysiological mechanisms or interactions. One patient had developed dementia at 5 years after DBS, with further progression at 8 years (Fasano et al., 2010).

The mechanisms leading to cognitive changes following STN DBS remain both intriguing and enigmatic. The STN seems to play an important role not only in motor function, but also in limbic and associative neural networks (Mallet et al., 2007; Rodriguez-Oroz et al., 2009; Volkmann et al., 2010). This nucleus

incorporates the basal ganglia circuitry, and has traditionally been included in the so-called "indirect-pathway" inhibiting thalamocortical excitability (Obeso et al., 2008). It has been recognized that the dorsolateral portion of the STN is involved in motor function, while the intermediate part is important for cognitive processes and the anteromedial portion seems to be implicated with emotion (Mallet et al., 2007; Rodriguez-Oroz et al., 2009; Volkmann et al., 2010). Conceivably, although electrical stimulation in PD is meant to modulate motor circuitry, the energy pulse could extend to nearby non-motor regions in the STN and affect both emotion and cognitive performance, including VF. This also implies that the STN must play an important role with regard to cognitive processes, with a special clinical relevance for those involved in VF. This has also been suggested by functional neuroimaging research, namely PET scan, such as the work from Schroeder et al. (2003), who demonstrated that regional cerebral blood flow (rCBF) of the right orbitofrontal cortex and VF-associated rCBF within left-sided frontotemporal regions became notoriously reduced during STN stimulation compared with the off stimulation condition, which suggests that STN stimulation reduces the activation of a VF-related frontotemporal network.

In any case, the mechanisms underlying postsurgical cognitive decline remain obscure, and could be multifactorial, with the possible implication of individual and therapy-related risk factors. For example, it is currently unknown whether the trajectory of the electrodes, which are inserted through the frontal lobes and often cross the caudate nucleus, influences the cognitive outcome (Volkmann et al., 2010).

DEMENTIA FOLLOWING SUBTHALAMIC DBS IN PD PATIENTS

It would be important to know the incidence rate of dementia after DBS and whether this is in consonance with the natural history of the disease or if, on the other hand, there is an influence exerted by the surgical procedure itself or the stimulation. So far, data have not been conclusive, as there is a paucity of controlled and long-term studies aimed at looking into this issue. The studies considered here have demonstrated significant benefits with regard to motor symptoms and QOL, in accordance to what has been described by other authors.

The experienced Grenoble group has analyzed outcomes of STN DBS in 49 PD patients 5 years after surgery, and has found that three patients developed dementia (according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition criteria) 3 years after surgery, which corresponds to a prevalence of 6% (Krack et al., 2003). Importantly, two of these patients had become demented within 3 months after surgery, which is a matter of concern, since neuropsychological testing and clinical observation had been rigorously carried out preoperatively.

Castelli et al. (2007) have published their findings from 19 patients submitted to STN DBS, assessed at baseline and at a mean of 17 months after surgery. None of the patients developed dementia in this series.

York and coworkers designed a 6-month controlled study, and included 23 PD patients who underwent STN DBS, as well as 28 medically treated PD controls. The authors have found that one patient (4%) had developed dementia 6 months after surgery, and two others had significant cognitive decline but did not fulfill criteria for dementia (York et al., 2008). The former patient was 14 years older than the average age in the series, had several vascular risk factors, and preoperative MRI had shown small vessel subcortical ischemic lesions. However, his cognitive, clinical, and psychiatric assessments did not contraindicate DBS. Postoperative CT scan has shown a small intraventricular hemorrhage and the patient suffered from transient postoperative confusion.

The study by Ory-Magne et al. (2007) has shown that 3 out of 45 patients developed dementia after a follow-up period of 24 months.

From Switzerland, Aybek et al. (2007) have obtained quite different results, as they prospectively assessed 57 patients submitted to STN DBS over 3 years. In this series, 24.5% of patients developed dementia over 3 years, whereas the remainder maintained stable cognitive scores. Those who became demented were on average older, displayed poorer executive performance, and a higher frequency of hallucinations. The average age of this series is somewhat higher than what can been observed in others, where lower incidence rates of dementia have been found. The authors argue that the incidence rate of dementia in this cohort is similar to what has been observed in medically treated patients, thus in keeping with the natural history of PD. Nonetheless, they agree that further studies should be conducted in order to define risk factors for developing dementia after DBS, especially because 36% of patients developing dementia did so within 6 months after surgery, suggesting a triggering effect of the procedure or the stimulation. From the same group, a longer observation period which included additional subjects has shown that 20% of patients (14/70) developed dementia on average 25 months after surgery (Aybek et al., 2009).

Zangaglia and collaborators where able to conduct a 3-year prospective study of STN DBS patients ($n = 32$) and medically treated controls who declined surgery ($n = 33$); at the time of last assessment one patient had become demented and one other had developed mild cognitive impairment in the surgery group only. The former patient had long disease duration (>21 years) at the time of DBS, when she was 60. Her MMSE score was at the lower limits of normal (24/30), and her preoperative L-dopa test had shown improvement of 56–36 in the Unified PD Rating Scale part III score (Zangaglia et al., 2009).

In the above mentioned series by Fasano et al. (2010) which included 20 patients with a follow-up of 8 years, only one patient developed dementia.

Kishore and colleagues have published results on 49 patients, 29 of them assessed at 5 years. At this time point five patients had become clinically demented; all of these had shown mild cognitive changes in baseline neuropsychological testing (Kishore et al., 2010).

The study by Castrioto et al. reveals data extracted during longer follow-up, as 18 patients were assessed 10 years after surgery. The authors have shown that motor benefits are still significant by this time as compared to baseline, although progressive decline has been observed, especially with regard to axial features. Three patients developed dementia in this series (Castrioto et al., 2011).

Williams et al. (2011) conducted a 2-year long controlled study, which enrolled 19 STN DBS patients and 18 medically treated PD controls. Two patients fulfilled criteria for dementia 6 months after surgery, and six patients at 2 years, twice as much as in the

control group, but based on frequencies this was statistically not significant ($p = 0.21$). In addition, the authors have analyzed MCI frequency in this study, defined by a deficit of at least 2 SDs below the age corrected mean in one of the four cognitive domains identified in a recent expert consensus (Emre et al., 2007). Baseline MCI frequencies were similar in both groups. Three of the five stimulated patients who met criteria for MCI at baseline, had developed dementia, whereas the remaining two still fulfilled criteria for MCI at 2 years. In the control group all three PD patients with MCI at baseline had developed dementia by the time of the 2-year postsurgical evaluation. Moreover, at 2 years, four additional STN DBS patients fulfilled criteria for MCI, compared to three controls. When combining MCI and dementia patients, a trend has been observed toward higher cognitive deterioration in the surgery group ($p = 0.06$).

In summary, data coming from these studies seems somewhat divergent, but one must keep in mind methodological differences. Some studies suggest that cognitive decline follows the natural history of PD, whereas others have shown that a significant number of patients develop dementia in the first few months after implantation. This is an intriguing finding, and one may wonder if certain patients have some sort of specific vulnerability to accelerated postsurgical cognitive decline.

COGNITIVE OUTCOME FOLLOWING DBS OF THE SUBTHALAMIC NUCLEUS: PREDICTIVE FACTORS

A few studies have tried to delineate predictors of cognitive decline. However, the evidence published on this matter is limited.

Funkiewiez et al. (2004) have studied 77 PD patients up to three 3 years after surgery; category VF was found to have significantly declined in this series. Patient preoperative age correlated significantly with the decay of a previously described frontal lobe score (Pillon et al., 1986) and the initiation subtest of MDRS.

The study by Ory-Magne and coworkers explored a possible role of age on clinical outcome following subthalamic DBS; 45 patients with a mean age of 60 years (range 40–73) were enrolled, 43 were reassessed at 12 months, and 39 at 24 months. The authors have found that cognitive and motor outcomes were unrelated to patient age at the time of DBS, but younger patients sustained greater improvements in QOL (Ory-Magne et al., 2007).

The study carried out by Rothlind et al. (2007) has failed to demonstrate any relation between postoperative cognitive changes and age or reductions in levodopa equivalent dose after surgery.

Heo and colleagues studied cognitive changes after STN DBS in 46 PD patients, who were assessed at 6 months and 1 year after surgery. At these time points VF had declined; mild declines have also been found in memory and executive functions. Higher formal education, higher levodopa equivalent dose, and younger age at onset correlated with cognitive worsening, but age at the time of DBS has not been found to be a predictor of decline (Heo et al., 2008).

Aybek and coworkers have found that, in their series of 70 PD patients, 14 developed dementia after an average of 25 months postsurgery. These were compared with 14 controls and the authors have found that hippocampal atrophy is a predictor of dementia in PD patients converting to dementia after subthalamic DBS (Aybek et al., 2009).

The above mentioned study by Smeding et al. also approached the issue of predictors of postsurgical decline. This controlled study has found that patients with advanced age, impaired baseline attention, and poorer levodopa response are at greater risk for postsurgical cognitive decline; importantly, the correlation between these factors was low, and multicollinearity was not significant, suggesting that their correlation with postsurgical cognitive deterioration is probably independent (Smeding et al., 2011).

In summary, the amount of evidence specifically concerning the issue of predictors of cognitive decline following DBS is somewhat small. Keeping in mind the natural history of PD (Lim et al., 2009; Rajput et al., 2009; Hawkes et al., 2010), one could postulate that certain factors would eventually predict cognitive decline following STN DBS, such as advanced age, axial signs, levodopa resistant symptoms, visual hallucinations, vascular lesion load, and poor baseline cognitive performance. Although the intuitive notion that, for instance, age would predict cognitive decline seems logical, the findings from the several studies published so far have not settled this question. This is also valid for other variables; importantly, many of them have not even been tested in the published research literature.

PSYCHIATRIC AND BEHAVIORAL EFFECTS OF DBS IN PD

Deep brain stimulation in PD has been frequently associated with behavioral and psychiatric symptoms, which have been mostly reported in association with STN DBS (Voon et al., 2006; Volkmann et al., 2010). Although this is not the main focus of the present manuscript, this matter should be here briefly mentioned, due to its clinical relevance.

Apathy is frequently diagnosed in PD patients, but the overlap and confusion with depression and cognitive impairment (including dementia) are common (Starkstein, 2012). Data on postsurgical apathy is quite variable, but this seems to be a frequent adverse event following STN DBS (Voon et al., 2006; Volkmann et al., 2010; Starkstein, 2012).

Elevation of mood has been reported following STN DBS; euphoria; or hypomania have been described in up to 15% of patients, whereas mania probably occurs in less than 2% of cases (Voon et al., 2006; Volkmann et al., 2010). A decrease in stimulation levels or dopaminergic drugs may be necessary for symptom remission; alternatively, switching the active contact to a more dorsal position could be tried. Depression has been reported in up to 25% of patients during postsurgical follow-up (Voon et al., 2006; Volkmann et al., 2010). Results from the COMPARE trial have suggested that more ventral contacts carry the ability to induce depressive feelings, as compared to more dorsal contacts (Okun et al., 2009). The recent randomized trial conducted by the CSP 468 Study Group has shown that depression worsened after STN stimulation, whereas it improved after pallidal stimulation ($p = 0.02$), despite the fact the both groups of patients improved similarly regarding motor symptoms and self-reported function (Follett et al., 2010). Interestingly, mood disorders tend to occur in the first few months after surgery (Voon et al., 2006; Volkmann et al., 2010).

Postsurgical suicide is a leading concern in the setting of STN DBS. A large international multicentre study involving more than 5000 patients has shown that the attempted and completed suicide

rates can be estimated at 0.90 and 0.45%, respectively (Voon et al., 2008). Suicide rates were higher in the first postoperative year and remained high in the fourth year, as compared to the adjusted World Health Organization suicide rates. The excess death number was 13 in the first year, declining to one in the fourth. Attempted suicide risk has been related to postoperative depression, being single, a previous history of impulse control disorders, or compulsive medication use, being younger, younger PD onset, and a previous suicide attempt. Completed suicides were associated with postoperative depression, which remained a significant factor associated with attempted and completed suicides even after statistical correction (Voon et al., 2008). Also, it has been shown that impulsivity scores following STN DBS increase (Hälbig et al., 2009). However, the implications for suicide have not been adequately established, although one might speculate that this could cause greater propensity for impetuous self-destructive behaviors.

A range of impulsive compulsive behaviors (ICBs) have been described in PD, in association with dopaminergic drug therapy (Evans et al., 2009; Djamshidian et al., 2011). One would expect that STN DBS could improve ICBs by facilitating a decrease of postoperative dopaminergic medication. Unfortunately, the available evidence concerning this issue is not robust, and the outcomes regarding the effect of DBS on ICBs are conflicting, as published data have disclosed mixed results (Broen et al., 2011).

In most studies a decrease in anxiety levels has been reported (Volkmann et al., 2010).

It remains unclear which mechanisms underlie, and which risk factors associate with, the behavioral and psychiatric disorders observed after STN DBS. For instance, it has been suggested that the common postoperative reduction of dopaminergic drugs might play a role in the case of apathy or depression, but surgery itself or electrical stimulation could also be involved (Voon et al., 2006; Volkmann et al., 2010). On the other hand, an array of factors such as previous psychiatric disorders, personality traits, and psychological and psychosocial aspects might also play an important role.

Psychiatric symptoms warrant dedicated management before and after surgery, and their nature or severity may even advise against STN DBS in PD. Useful recommendations regarding management have been issued by experts in the field (Lang et al., 2006; Voon et al., 2006). This is an area of major concern and it has become clear that patient selection for DBS should be carried out by incorporating also psychiatric symptoms as important variables. In any event, patients should be informed beforehand of the expected risks in association with the procedure, especially suicide. As mentioned above, the choice of brain target for stimulation should probably be considered on a tailored perspective.

CONCLUSION

From the evidence collected so far, it seems reasonable to consider that DBS is generally safe from the cognitive standpoint in well selected PD patients, especially when looking at measures of global cognition. Nonetheless, there is a clear risk of postsurgical cognitive decline, which seems greater whenever the STN is used, although data concerning other targets is scanter. On the other hand, robust evidence based data is not prolific, with only one large randomized, double-blind trial conducted thus far, which has focused mainly on motor efficacy issues of STN DBS versus GPi DBS (Follett et al., 2010).

Postsurgical decline in VF has been the most consistently reported cognitive adverse effect in patients undergoing subthalamic DBS. Interestingly, our experience over the last decade, after around 200 PD patients already treated with DBS, suggests that patients are willing to accept such a tradeoff, as the motor benefits gained from the procedure seem, from their subjective point of view, to compensate for the VF changes observed. It would probably also be pertinent to systematically and objectively collect the opinions from families and caregivers on this matter, in order to confirm this impression, as frontal lobe dysfunction could bias patient self-assessment.

Several questions remain unanswered. First, it is difficult to demonstrate long-term effects of the surgical procedure or stimulation, and to differentiate these from the natural progression of the disease, as well as other confounding variables (e.g., effects of drug therapy, brain vascular lesions, PD progression, and concurrent degenerative pathology). Short-term clear cut changes (e.g., 6–12 months after surgery) are most probably due to the surgical procedure itself and/or the electrical stimulation – some small controlled studies, above mentioned, have suggested this. On the other hand, available data suggests that some aspects of cognitive functioning remain unchanged or even improve. Finally, so far it has not been explored what these postsurgical cognitive changes imply in terms of QOL and daily functioning. This seems to be an important issue, since medical decisions, as well as presurgical patient information and choices would largely benefit from this kind of evidence.

In some studies, dementia cases have been detected a few months after the surgical procedure, which is an intriguing and disturbing fact. Nonetheless, there is large heterogeneity between study results concerning this matter. Dementia cases should be systematically recorded and published, using well recognized diagnostic criteria – currently, the proposal by Emre et al. (2007) seems the most comprehensive one, and conveys the first diagnostic recommendations aimed specifically at PD dementia, although, to the best of our knowledge, prospective validation in large cohorts has not been reported so far.

In addition, research on predictive factors of postsurgical decline remains unsatisfactory, as this topic has not been approached in detail, and even at all, in most studies. Anyhow, the identification of predictive factors of outcome would be of great help, since it would allow better patient selection and information concerning the risk of poor cognitive outcome after DBS. Emphasis should probably be placed in risk factors for cognitive decline in PD (Williams-Gray et al., 2007; Aarsland and Kurz, 2010) but maybe also for dementia, broadly speaking (Korczyn and Vakhapova, 2007; Qiu et al., 2007). Notably, age, years of formal education, PD duration, disease phenotype, axial symptoms, levodopa responsiveness, hallucinations, and baseline cognitive performance seem good research candidates. One wonders if certain genetic factors may also play a role, such as apolipoprotein E polymorphisms or glucocerebrosidase mutations, and it would be very exciting to explore this matter through large multicenter collaborative research initiatives. Preoperative imaging markers such as vascular lesion load and atrophy of specific brain regions or

whole brain volume would also probably deserve further exploration. It would certainly be an interesting and useful achievement to be able to stratify patients according to their risk based on a number of features, eventually even using objective mathematical and statistical models.

A large international agreement is clearly needed concerning detailed cognitive assessment methodology and cutoff scores in the setting of DBS for PD, for it seems difficult to devise strict recommendations based solely on the currently available data. It seems that expert analysis and common sense are still paramount at this point. Ideally, well founded consensus guidelines should be issued and prospectively assessed in large well designed multicenter trials.

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Clinico-pathological correlations of the most common neurodegenerative dementias

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Neurodegenerative dementias are a group of neurological disorders characterized by deterioration in several cognitive domains in which there is selective and progressive loss of specific populations of neurons. The precise neurobiological basis for the different neurodegenerative dementias remains unknown. It is expected that different pathologies reflect different mechanisms, at least early in the neurodegeneration process. The next decades promise treatments directed to causes and mechanisms, bringing an outstanding challenge to clinicians due to heterogeneous clinical presentations with the same molecular pathology. The purpose of this brief review is to describe the key neuropathological features of the most common neurodegenerative dementias (Alzheimer disease, dementia with Lewy bodies and Parkinson's disease dementia, and frontotemporal lobar degeneration) and the relationship with the clinical syndromes described in clinico-pathological studies. We expect this overview contributes for the understanding of this broad topic integrating the two ends of the spectrum: clinical and pathological.

Keywords: neurodegenerative dementia, neuropathology, clinical syndromes

INTRODUCTION

Neurodegenerative dementias are a group of neurological disorders characterized by deterioration in several cognitive domains in which there is selective and progressive loss of specific populations of neurons (Dickson, 2011). The precise neurobiological basis for the selective vulnerability in the different neurodegenerative dementias remains unknown. Furthermore, recent research data showed that dementia is not only caused by "neuronal cell death"/cell loss but predominantly by dysfunction and loss of synapses in Alzheimer disease and in dementia with Lewy bodies (DLB; Jellinger, 2009). These changes cause disconnections of important nervous circuitries which can contribute to the clinical manifestations. An increasing number of hypotheses to explain the pathogenesis of Alzheimer's disease, for instance, have been proposed but it remains a mystery a century after this dementia was first described (de la Torre, 2011). In the most common neurodegenerative disorders there are biochemical changes in a specific protein that often promotes their deposition (Dickson, 2010). Over the last decade, many researchers have investigated the neuropathological background of the phenotypic variability in neurodegenerative dementia and identified a wide spectrum of associations between clinical syndromes and molecular pathologies. The classification of neurodegenerative diseases, previously based on the anatomical systems involved, has been progressively replaced by molecular diagnosis (Jellinger and Kovacs, 2011b).

The next decades promise treatments that are directed at changing pathogenesis, increasing the importance for clinicians' awareness of the full clinical spectrum under the umbrella of the same molecular pathology.

The purpose of this brief review is to describe the key neuropathological features of the most common neurodegenerative dementias [Alzheimer's disease, DLB and Parkinson's disease dementia (PDD), and frontotemporal lobar degeneration (FTLD)] and the relationship with the clinical syndromes described in clinico-pathological studies.

ALZHEIMER DISEASE

Alzheimer's disease (AD) is the most frequent cause of dementia worldwide, and its prevalence increases steeply after age 65 years, representing a significant health-care cost in developed countries (Reitz et al., 2011). Despite significant advances have been made in the understanding of AD pathogenesis, it remains largely unknown. Monogenic causes of familial early onset AD include autosomal dominant mutations in the β-amyloid precursor protein (APP), presenilin 1, and presenilin 2 protein genes, but represent less than 5% of AD cases (Bertram, 2008). Together with identification of apolipoprotein E ε4 allele as a genetic risk factor for late onset AD (Saunders et al., 1993) and neuropathology findings (see below), this evidence supports the amyloid cascade hypothesis as an important contributor in AD pathogenesis (Hardy and Higgins, 1992), even though other converging mechanisms most certainly play important roles in non-Mendelian forms of AD. More recently, genome-wide association studies have identified multiple genetic polymorphisms which are associated with late onset, non-Mendelian AD, and suggest involvement of other molecular pathways, namely implicating immune system, synaptic, and cell membrane function (Bertram, 2011; Morgan, 2011). AD pathogenesis theories must also recognize contribution of environmental factors, since several risk factors and modifiers of disease expression such as age (Ferri et al., 2005), cognitive reserve (Roe et al., 2007), physical activity (Podewils et al., 2005), smoking (Anstey et al., 2007), obesity (Lee, 2011), diabetes (Biessels et al.,

2006), and intracranial atherosclerosis (Dolan et al., 2010) have been found. Core classical clinical characteristics of AD include a gradual and progressive decline of cognitive function which affects episodic memory, involves other cognitive domains, and is not explained by other medical or psychiatric conditions. Several diagnostic criteria have been proposed, namely the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders criteria (McKhann et al., 1984), and the Diagnostic and Statistical Manual of Mental Disorders fourth edition criteria (American Psychiatric Association, 2000), but increasing evidence concerning magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), and functional neuroimaging findings has led to a new proposal of research criteria for the diagnosis of AD (Dubois et al., 2007), in which is implied a reformulation of classic concepts in AD and mild cognitive impairment (Dubois et al., 2010). In all these criteria, neuropathological findings consistent with AD are required for a definite diagnosis, since it is assumed that a clinical diagnosis, even though may have high accuracy, is probabilistic.

PATHOLOGY

Brain pathology abnormalities in AD may be classified as "positive" or accumulation lesions (Aβ peptide deposits and tau protein accumulation), "negative" lesions (neuronal loss, loss of synapses), or a third type of lesion which include dendritic and axonal changes and inflammatory reaction lesions (Gomez-Isla et al., 2008).

Aβ peptide is cleaved from APP by β-secretase and γ-secretase enzyme complexes, and it is accumulated in AD, taking the form of mature neuritic plaques (senile plaques) or different types of extracellular deposits in brain parenchyma (**Figures 1A–C**). Neuritic plaques, stained by Congo red, are complex lesions formed by extracellular focal deposits of Aβ, neuronal processes (axonal or dendritic), microglial cells, and astrocytic processes (Duyckaerts et al., 2009). Neuritic plaques are found evenly distributed through the isocortex, preferentially in layers II and III, with high density in associative cortices, are relatively sparse in hippocampal and parahippocampal areas and are nearly absent in striatum and presubiculum (Duyckaerts and Hauw, 1997). Diffuse Aβ deposits are weakly immunoreactive and may be found in specific regions, such as the presubiculum (Wisniewski et al., 1998) and entorhinal cortex (Thal et al., 1999). Other focal and stellate Aβ deposits were also described, with different distributions through the cortical layers (Delaère et al., 1991). In 1991, the Consortium to establish a registry for AD (CERAD) established a neuropathologic method for diagnosing "definite," "probable," or "possible" AD, primarily based on a semiquantitative assessment of the number of neuritic plaques and its correlation with age (Mirra et al., 1991).

In AD, tau protein accumulation (three repeat and four repeat isoforms) takes the form of neurofibrillary tangles (cell body), neuropile threads (dendrites), and is also identified in the corona of neuritic plaques (**Figures 1C,D**). Neurofibrillary tangles, flame-, or globose-shaped silver positive intracellular inclusions, tend to accumulate in the entorhinal cortex, hippocampus, amygdala, basal nucleus of Meynert, and layers III and V of the isocortex, predominantly affecting neurons responsible for cortico-cortical projections (Arnold et al., 1991). Neuropil threads represent swollen dendrites with tau accumulation, occur in the same topography as

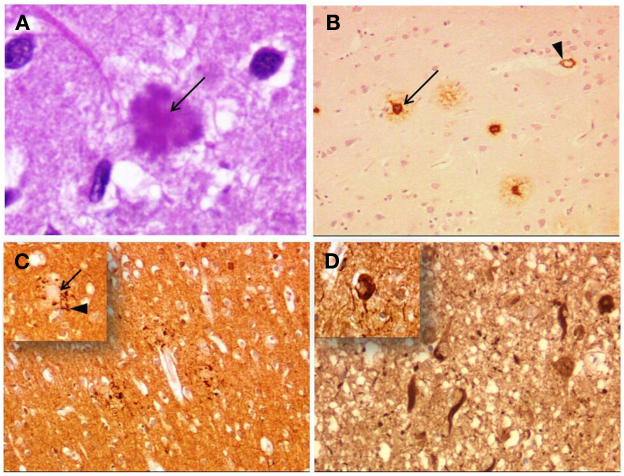

FIGURE 1 | Alzheimer's disease neuropathology. (A) Senile plaque (hematoxylin–eosin) with amyloid core (*arrow*). **(B)** Senile plaques with anti-Aβ antibody. The amyloid core (*arrow*) is surrounded by a corona of lightly labeled Aβ peptide. *Arrowhead* indicates vascular amyloid deposition in a capillary (Cambridge Bioscience, 4G8). **(C)** Neuritic plaques immunostained with tau antibody. The *arrow* indicate the core of the plaque and *arrowhead* the tau-positive processes of the neuritic crown (inset). **(D)** Flame-shaped neurofibrillary tangles. Inset shows a globose neurofibrillary tangle (Autogen Bioclear, AT8). Magnification, 400× **(A)**, 100× **(B,C)**, and 200× **(D)**.

neurofibrillary tangles and predominate in the earlier stages of the disease (Giannakopoulos et al., 2007). The neuritic plaque is where amyloid and tau pathology coincide, since the dystrophic large axonal processes in the corona at the periphery of the plaque core are tau-positive (Wang and Munoz, 1995). Despite the classical hypothesis that amyloid deposition drives the disease, neurofibrillary tangles have been shown to occur before amyloid lesions (Braak and Tredici, 2004), which highlights the poor understanding of tau–amyloid relationship, and of the role of other factors in AD pathogenesis. Braak and Braak (1991) proposed six stages for AD neuropathology, based on distribution and severity of neurofibrillary tangle pathology, and it has been demonstrated that these stages are closely related to clinical symptoms and deterioration (Riley et al., 2002). Interestingly, progression of tau pathology through a relatively predictable topography, a process which underlies progression of clinical symptoms, may result from a prion-like mechanism of neuron to neuron propagation of pathology (Braak and Tredici, 2011).

Neuronal loss is possibly the most significant microscopic correlate of gross macroscopic cerebral atrophy in patients with AD, occurring markedly in layer II of entorhinal cortex even in early clinical phases (Gomez-Isla et al., 1996), CA1, superior temporal gyrus, and supramarginal gyrus (Grignon et al., 1998).

Synaptic loss is reported to be an early event in the neurodegenerative process occurring in AD, and it is thought to be the major correlate of cognitive decline (Arendt, 2009). Distribution and degree of synapse degeneration is coincident with neurofibrillary tangle accumulation, suggesting a link between tangles and loss of synapse markers (Callahan et al., 1999).

Other neuropathology findings include local spine loss, axonal swellings, dysmorphic neurites, aberrant dendritic sprouting, inflammatory changes with activated microglia, astrocytosis, spongiosis, and Lewy bodies (LBs; Duyckaerts et al., 2009).

Recently, a new and comprehensive proposal for the neuropathological evaluation of AD was proposed by the National Institute on Aging-Alzheimer's Association, in which there is emphasis on identification of amyloid deposits, staging of neurofibrillary tangles, scoring of neuritic plaques, and systematic search for other neurodegenerative dementia pathologies (Montine et al., 2012).

CLINICO-PATHOLOGICAL CORRELATIONS

Classical AD clinical phenotype is characterized by: (1) decline from a previous level of function; (2) interference in daily living, work, and social interaction; (3) cognitive impairment with significant emphasis on episodic memory, accompanied by progressive and increasing involvement of other cognitive domains (visuospatial function, executive skills, attention, praxis, language); (4) progressive behavioral deterioration (depressive symptoms, disruptive behavior, apathy, anxiety, psychosis). This typical phenotype is the basis for the currently accepted diagnostic criteria. Clinical NINCDS-ADRDA criteria for AD has a reasonable sensibility and specificity for differentiating AD from normal controls, but accuracy for the differential diagnosis of neurodegenerative dementias may be very low (Ballard et al., 2011). The most recent research criteria for diagnosing AD (Dubois et al., 2007) have not been validated and there is debate on which neurocognitive tests should be used for characterization and quantification of cognitive deficits, and which are the best auxiliary biomarkers, definition of their pathological threshold and their clinical value in single patients (Oksengard et al., 2010).

Growing evidence from neuropathologic studies and new *in vivo* biomarkers allowed for identification and further characterization of atypical or focal presentations of AD and also an increased understanding about other neurodegenerative dementias. AD atypical presentations include posterior cortical atrophy (PCA), primary progressive aphasias (PPA), corticobasal syndrome (CBS), and frontal lobe syndrome (FLS).

Posterior cortical atrophy was first identified by Benson et al. (1998). Clinical phenotype is characterized by a progressive deterioration in complex visual functions, leading to a perceptual agnosia, Bálint syndrome, Gerstmann syndrome, and ultimately visual field defects, with no or residual impairment of other cognitive functions at least in early stages. Neuropathological studies support the hypothesis of dysfunction of the dorsal occipito-parietal visual pathway, and in the majority, AD pathology is found. Some studies have found a characteristic distribution of neuritic plaques and neurofibrillary tangles, with antero-posterior gradient in occipito-parietal regions (lower density in primary visual cortex), and relative sparing of frontal cortex (Levine et al., 1993; Hof et al., 1997). When comparing PCA and typical AD phenotype, it was found that the former had higher density of neuritic plaques and neurofibrillary tangles in visual association cortex and the later had higher density of lesions in hippocampus and subiculum, but there were no differences in other cortical areas (Tang-Wai et al., 2004). Clinical progression may disclose clues to underlying pathology: development of episodic memory impairment and involvement of other cognitive domains suggests AD; visual hallucinations, delusions, and parkinsonism may indicate DLB; asymmetric parkinsonism and ideomotor apraxia may suggest corticobasal degeneration, CBD; rapid progression of global disability, myoclonus, and cortical blindness with Anton syndrome suggest prion disease (namely the Heidenhain variant of Creutzfeldt–Jakob disease). It should be noted, however, that despite the etiological diversity of PCA, in over 75% of cases, AD pathology was shown (Renner et al., 2004; Tang-Wai et al., 2004).

Clinically, PPA may be subclassified in logopenic progressive aphasia (LPA; slow speech, impaired word retrieval, comprehension, and repetition), progressive non-fluent aphasia (PNFA; effortful speech, agrammatism, speech apraxia, dysprosody), and semantic dementia (SD; fluent, impaired confrontation naming, and word comprehension, surface dyslexia; Gorno-Tempini et al., 2011). LPA is the PPA subtype more strongly correlated with AD. Mesulam et al. (2008) found AD pathology in 7/11 patients with LPA. Even though LPA patients show atrophy in left posterior temporal and inferior parietal regions (Gorno-Tempini et al., 2008), distribution of neurofibrillary tangles did not show consistent hemispheric asymmetry in PPA/AD patients when using the CERAD protocol, while a stereological tangle quantification in four PPA/AD cases revealed higher tangle density in left hemisphere and similar entorhinal tangle density as typical AD cases (Mesulam et al., 2008). PNFA is classically associated with tau pathology but a significant proportion of patients who have come to autopsy have AD pathology (Grossman, 2010), and atypical distribution of lesions was described, with prominent involvement of left anterior perisylvian regions (Greene et al., 1996). SD is characteristically associated with TAR DNA binding protein (TDP) pathology (Seelaar et al., 2011), but 2/20 patients with SD had neuropathologic findings of AD (Alladi et al., 2007), and among 15 patients with fluent progressive aphasia, 33% had AD pathology, with striking atrophy and extensive neuritic plaque and tangle deposition in left anterior temporal and frontal lobes (Knibb et al., 2006).

Corticobasal syndrome is characterized by a slowly progressive constellation of manifestations which include asymmetric parkinsonism, asymmetric apraxia, unilateral useless limb, alien hand syndrome, cortical sensory loss, action myoclonus, and visuospatial deficits. It is now known that CBS is a neuropathological heterogeneous entity, and AD pathology was shown to be present in 24–50% in autopsy studies. Visual neglect, visual memory impairment, episodic memory deficits, and posterior extension of atrophy into precuneus and temporoparietal cortex are possible clinical indicators of CBS/AD (Alladi et al., 2007; Ling et al., 2010; Lee et al., 2011b).

Frontal lobe syndrome is dominated by deterioration of frontal functions, with dysexecutive syndrome, apathy, or disinhibition, changes in behavior, and social interaction. Initially, episodic memory impairment is absent or residual (Taylor et al., 2008), but usually progresses. Compared to typical AD, FLS/AD patients were reported to have greater impairment in Trail Making Test, phonemic fluency, and visuoconstructive skills (Johnson et al., 1999). In the previously mentioned cohort of focal dementia syndromes, among 28 patients with FLS, two had pathological

findings consistent with AD (Alladi et al., 2007). In terms of neurofibrillary tangle load, entorhinal, temporal, and parietal cortex in typical AD is similar to FLS/AD, but the later have a significantly higher tangle density in frontal cortex (Johnson et al., 1999). No β-amyloid pathology distribution differences were found in this study.

In summary, AD pathology is associated principally to the classical clinical phenotype of Alzheimer's disease with loss of episodic memory, but it should be noted that focal presentations of AD are part of the spectrum of the AD pathology (i.e., PCA, PPA, CBS, and FLS).

PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

Parkinson disease dementia and DLB represent two clinical phenotypes of the neurodegenerative dementia disorders diagnosed by the presence of LBs and Lewy neurites (LN).

Parkinson's disease (PD) is one of the most frequent neurodegenerative diseases of the elderly. It is characterized clinically by bradykinesia, rigidity, resting tremor, and postural instability. The clinical diagnostic criteria require the presence of two of the four cardinal signs that are responsive to levodopa therapy (Gelb et al., 1999). The diagnosis of definitive PD requires histopathological confirmation, namely the presence of LBs in association with loss of substantia nigra neurons (Dickson et al., 2009). Clinical cohorts of patients identified with early PD are heterogeneous when referring to symptoms (resting tremor vs. akinesia and rigidity and/or postural instability and gait disorder), rates of progression (rapid vs. slow), and ages of onset (early vs. late onset), often with overlap between these phenotypes (Halliday and McCann, 2010). The prevalence of dementia in PD (i.e., PDD) is close to 30% and at least 75% of PD patients who survive for more than 10 years will develop dementia (Aarsland et al., 2005; Aarsland and Kurz, 2010). Age is an essential factor, and dementia is infrequent in patients with young onset and who are chronologically still young at the time of assessment, despite very long disease duration. The principal risk factors are older age, more severe parkinsonism (rigidity, postural instability, and gait disturbance), and mild cognitive impairment at baseline (Emre et al., 2007).

Dementia with Lewy bodies is considered to be the second most common type of degenerative dementia in the elderly, accounting for 10–15% of cases at autopsy (McKeith et al., 1996). Clinically it is characterized by prominent visuoconstructive and frontal-subcortical impairment, associated with core clinical neuropsychiatric features of fluctuating cognitive function, visual hallucinations, and spontaneous parkinsonian motor signs (McKeith et al., 2004, 2005). Both conditions have been associated to higher rates and more severe depression when compared to AD (Fritze et al., 2011).

For research purposes an arbitrary cut-off of 1 year is used to distinguish PDD from DLB. When PD develops first and dementia develops 1 year or more lately the diagnosis of PDD is made, if the cognitive impairment precedes motor symptoms or develops earlier the diagnosis is of DLB (Lippa et al., 2007).

There are no definite pathological criteria that separate the two disorders (Lippa et al., 2007) and the separation between PDD and DLB is considered by some to be artificial (Halliday et al., 2011).

PATHOLOGY

There is no "gold standard" for the pathological diagnosis of DLB or PDD. The hallmark pathology is α-synuclein (αSyn) in form of LBs (both classical and cortical types) and LN (Halliday et al., 2011; Ince, 2011). Classical LBs (**Figure 2A**) are easily recognizable by standard histological methods as large, spherical, highly eosinophilic intracytoplasmatic inclusions with a clear halo in the dopaminergic neurons of substantia nigra and the locus coeruleus (McKeith et al., 1996; Kövari et al., 2009). Cortical LBs (**Figures 2B,C**) are seen in limbic and neocortical regions, predominantly in the small neurons of deep layers of the cortex. Because of their small size they are easily identified using immunohistochemistry with αSyn antibodies (**Figures 2E,F**; Kövari et al., 2009). LN are curvilinear or dot-like processes (**Figures 2D–F**) that are found in regions with the highest density of LBs, such as limbic cortex and amygdala (Saito et al., 2003; Dickson, 2010).

In spite of being the hallmark of DLB and PD, LBs they can be detected in the amygdala in up to 50% of patients with clinically and pathologically confirmed AD (Hamilton, 2000) and in up to 10% of neurologically normal elderly individuals over age of 60 years (Gibb and Lees, 1998). α-synuclein is a small, presynaptic protein without a well-defined function. Some data implicate the misfolding or aggregation of αSyn in the disease pathogenesis, but the mechanisms that underlie the aberrant functions of α-synuclein and how these impacts on disease pathogenesis remain poorly understood (Forman et al., 2004; Vekrellis et al., 2011).

CLINICO-PATHOLOGICAL CORRELATIONS

A staging system, based on the number and location of LBs, with a caudal to rostral six-stage progression has been proposed for sporadic PD (Braak et al., 2003). The first two stages, with LB pathology involving medulla oblongata and pontine tegmentum, are considered asymptomatic or presymptomatic and may explain the early non-motor symptoms (autonomic and olfactory). Stages 3 and 4, with extension of LB pathology to midbrain and basal prosencephalon and mesocortex, have been correlated to clinical symptomatic stages. The terminal stages 5 and 6, characterized by widespread neocortical LB degeneration, are correlated with significant cognitive decline associated with severe parkinsonism (Hurtig et al., 2000). Although there is an acceptable correlation between pathological findings and clinical data in this staging system, mainly in a subgroup with early onset and prolonged duration (Halliday et al., 2008), recent studies revealed exceptions to the general order of progression suggested by Braak and colleagues (Jellinger, 2008; Parkkinen et al., 2008; Dickson et al., 2009; Kalaitzakis et al., 2009). Another interesting observation from a number of recent clinico-pathological studies that assessed the progression of pathology in subtypes of PD is that in patients with non-tremor-dominant and postural instability and gait dominant clinical pictures there are significantly more cortical LBs and amyloid β plaques compared with tremor dominant or younger onset patients (Selikhova et al., 2009; Halliday et al., 2011). Furthermore, PD patients with dementia have higher amounts of cortical αSyn pathology as compared to those without dementia and a correlation between its severity and AD pathology is also present in such patients (Halliday et al., 2011).

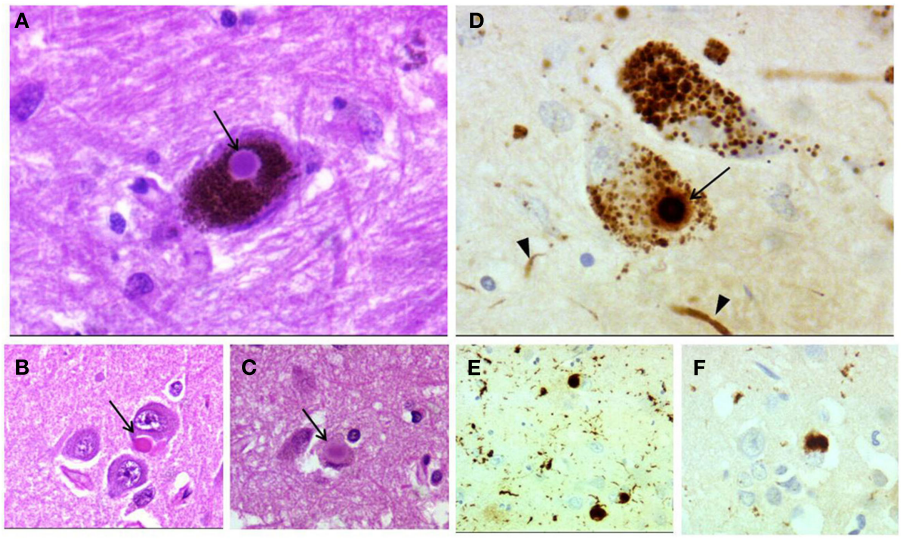

FIGURE 2 | Dementia with Lewy bodies neuropathology. Lewy body in a neuron of the substantia nigra **(A)**, in a pyramidal cell of CA1 area of the hippocampus **(B)**, and in cingulated cortex **(C)** (*arrows*). Lewy body (*arrow*) and Lewy neurites (*arrowheads*) in the substantia nigra **(D)**. Cortical Lewy bodies **(E,F)**. **(A–C)** hematoxylin–eosin; **(D–F)** anti-α-synuclein immunostaining. Magnification, 400× **(A–C,F)** and 200× **(E)**.

According to the consensus pathologic guidelines for DLB, LBs are scored semiquantitatively according to the severity and anatomical distribution, separating brainstem-predominant, limbic (or transitional), and neocortical types, depending on the anatomical distribution of the αSyn pathology (McKeith et al., 1996, 2005). More recently, a new protocol for assessing αSyn pathology and currently recommended by the DLB Consortium, showed higher inter-observer agreement for both the assignment to brainstem, limbic, neocortical and amygdala-predominant categories of synucleinopathy, and Braak stages (1–6; Alafuzoff et al., 2009). Alzheimer's disease pathology is the most common co-occurring pathology that accompanies Lewy body pathology (PDD or DLB; Dickson et al., 2009) and most cases with cortical LBs show in some degree concomitant AD pathology (i.e., NFTs and neuritic plaques; Kövari et al., 2009). The methods proposed by the third Consortium for DLB (McKeith et al., 2005) recommend the description of Alzheimer disease-type pathology using the National Institute on Aging-Reagan Institute criteria (Hyman and Trojanowski, 1997). It is proposed that the DLB clinical syndrome is directly related to the severity of Lewy-related pathology, and inversely related to the severity of concurrent AD-type pathology (McKeith et al., 2005). In cases of "pure" DLB (i.e., without excessive tau neuritic pathology) clinical picture appears more similar to the dementia phenotype of PD than to AD (Emre et al., 2007). There is evidence suggesting that the increase of neocortical αSyn is associated with cognitive decline in DLB and PD (Hurtig et al., 2000; Kövari et al., 2003) and some clinico-pathological studies demonstrated that visual hallucinations are strongly related to the αSyn burden in the amygdala in both (Casanova et al., 2011).

Within the DLB phenotype spectrum, some clinico-pathological studies and case reports disclose a subset of DLB patients with rapid symptoms progression to death within 1–2 years (Armstrong et al., 1991; Haik et al., 2000). These patients can fall within the differential diagnosis of rapid progressive dementias such as Creutzfeldt–Jakob disease, and more recent data show that 7–10% of autopsy confirmed diffuse Lewy body disorder cases can have a rapid PD and dementia progression (Gaig et al., 2011; Jellinger and Attems, 2011a). The neuropathology of these cases did not show particular features that could differentiate rapidly progressing from classical forms.

In summary, PDD and DLB refers to a form of dementia that has the pathological signature of abnormal aggregates of α-synuclein in the form of LBs and LN. There is a considerable clinical heterogeneity explained, at least partially, by topographic distribution of αSyn aggregates and the presence of additional neuropathologies such as AD pathology. In fact, large autopsy series show that although the specificity of *ante-mortem* diagnosis of DLB when correlated to pathological diagnosis was over 95%, the sensitivity of the clinical diagnoses was quite low (32%). Furthermore, these studies show that that in late-stage cognitive impairment, specifically documented signs and symptoms associated with DLB (visual hallucinations, extrapyramidal signs, and fluctuating cognition) do not contribute for predicting the presence of neocortical LBs at autopsy. Consequently, while these clinical symptoms may be useful in milder cases of dementia, caution should be used when providing a diagnosis of LBD in patients with more advanced dementia (Nelson et al., 2010).

FRONTOTEMPORAL LOBAR DEGENERATION

Frontotemporal lobar degeneration refers to a clinical, genetic, and pathological heterogeneous group of disorders that constitute a common cause of dementia with onset usually before 65 years of age (Cairns et al., 2007; Pickering-Brown et al., 2008). FTLD is a macro-anatomical descriptive term reflecting the relatively selective involvement of frontal and temporal lobes that characterizes most cases (Rohrer et al., 2011). Epidemiological studies

suggest that FTLD is the second most common cause of young onset dementia after AD (Ratnavalli et al., 2002; Rosso et al., 2003). The clinical spectrum of FTLD encompasses three canonical syndromes that are distinguished by the presenting symptoms and regional pattern of atrophy: the behavioral variant frontotemporal dementia (bvFTD), with predominant behavioral symptoms; PNFA, a disorder of expressive language; and SD, a disorder of conceptual knowledge (Neary et al., 1998; Kertesz et al., 1999, 2005). There is also overlap of FTLD with motor neuron disease (FTD–MND), as well as the parkinsonian syndromes progressive supranuclear palsy and CBD (Litvan et al., 1996; Neary et al., 1998; Boeve et al., 2003).

A positive family history is common in FTLD, with up to 40% cases showing a pattern of inheritance consistent with autosomal dominant transmission of disease (Neary et al., 2005; Seelaar et al., 2011). Genetic heterogeneity of FTLD is reflected by the identification of seven different genes that are associated with FTLD. Mutations in genes encoding for microtubule-associated protein tau (*MAPT)* and progranulin (*GRN*) are responsible for approximately 50% of the familial cases, where other genes associated with FTLD pathology are extremely rare and include mutations in the valosin-containing protein (VCP) gene, the charged multivesicular body protein 2B (CHMP2B) gene, the TAR DNA binding protein 43 (TARDBP) gene and the fused in sarcoma (FUS) gene (Josephs et al., 2011; Seelaar et al., 2011). More recently, an expansion in chromosome 9 (C9ORF72 gene) was identified as cause of Chromosome 9p21-Linked FTD–MND (DeJesus-Hernandez et al., 2011; Renton et al., 2011).

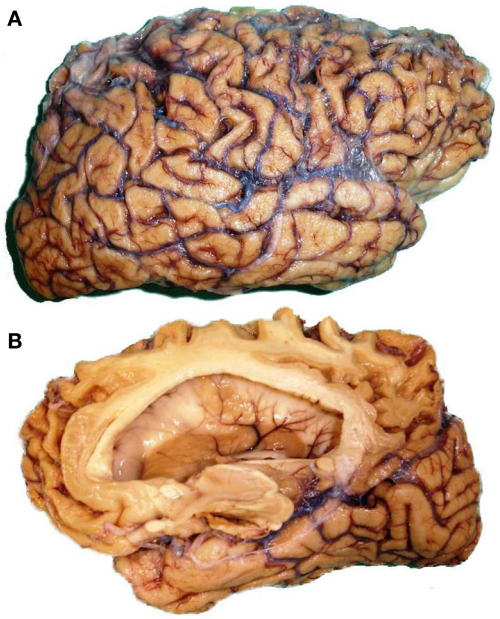

FIGURE 3 | Macroscopical findings of a FTLD–TDP brain. Lateral **(A)** and medial view **(B)** showing cortical atrophy that involves frontal, temporal, and parietal lobes, with better preserved sensorimotor cortex and occipital lobe.

PATHOLOGY

The pathology of the group of disorders under the FTLD umbrella term overlaps in gross and histological features. All share the findings of selective atrophy of the frontal and temporal cortex (**Figure 3**), with neuronal loss, gliosis and spongiosis of the superficial layers, especially of layer II. In some patients there is asymmetry of atrophy, typically reflected in perisylvian loss on one side of the brain. Specific diagnosis of the neurodegenerative disease within the FTLD group is established by the identification of the protein that constitutes the cellular inclusions (Cairns et al., 2007). Three proteins have been identified as important players in the mechanism of neurodegeneration of the FTLD: MAPT, the transactive response DNA binding protein of 43 kD (TDP-43), and the tumor associated protein FUS (Josephs et al., 2011). Therefore, the majority of FTLDs can be subclassified at molecular level as FTLD–tau, FTLD–TDP, and FTLD–FUS (Mackenzie et al., 2010a). However, the exact mechanisms by which cell death occurs are not known. We will use this subclassification to characterize further the pathology features within each subgroup and, in the next section, to serve as basis for the clinico-pathological correlates reported in the literature.

FTLD–tau

In this group the major abnormal protein identified by immunohistochemistry is the tau protein. This group includes Pick's disease (Dickson, 2001) and the pathological entities CBD and progressive nuclear palsy, which can fall under the FTLD clinical presentation (Litvan et al., 1996; Boeve et al., 2003; Kertesz, 2003; Scaravilli et al., 2005; Josephs et al., 2006). Tau is a phosphoprotein that promotes microtubule polymerization and stabilization. The discovery of multiple mutations in the tau gene that lead to the abnormal aggregation of tau and cause FTLD demonstrates that tau dysfunction is sufficient to produce neurodegenerative disease, but the precise mechanisms remain to be completely elucidated (Lee et al., 2001). The microtubule binding domain of the tau protein contains three of four repeat regions (tau 3R and 4R) depending on the splicing of the RNA. There is preferential accumulation of 3R or 4R tau in the different tauopathies, allowing a biochemical subclassification within this group.

In Pick's disease (PiD), the most characteristic neuropathological feature is the presence of Pick bodies. Pick bodies are spherical cytoplasmatic neuronal inclusions, that are well demarcated, amorphous, and faintly basophilic on hematoxylin–eosin staining (**Figures 4A,B**). They are strongly argyrophilic but do not stain with Gallyas (Dickson et al., 2011b). They are abundant in the dentate gyrus of the hippocampus and also common on the cerebral cortex, particularly in layers II and III (Munoz et al., 2011). Pick bodies contain deposition of tau protein (**Figures 4C,D**) that is abnormally hyperphosphorylated and biochemistry analysis showed that most of the tau consists of 3R tau (Delacorte et al., 1998; Bronner et al., 2005). Mutations in the tau gene (*MAPT*), most commonly associated to bvFTD-like phenotype in which extrapyramidal features may also be present (Josephs et al., 2011), account for the most pathologically confirmed cases of familial PiD (Dickson et al., 2011b). The neuropathological characteristics associated to *MAPT* gene mutations vary substantially, but the hallmark is the presence of tau protein deposits in neurons and/or glia (Ghetti et al., 2011). The pathology can resemble other

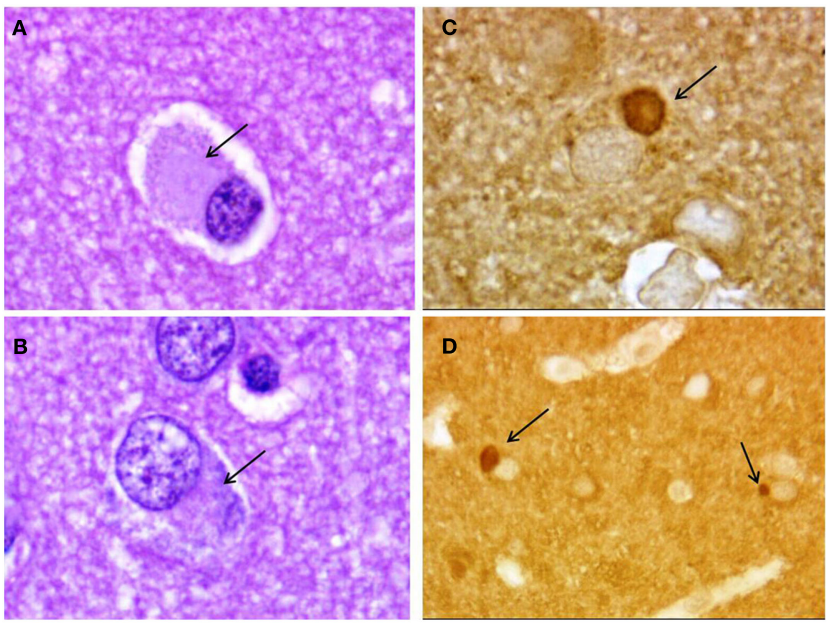

FIGURE 4 | Neuropathology of Pick's disease. Pick bodies (*arrows*) in frontal cortex. **(A,B)** Hematoxylin–eosin; **(C,D)** tau immunostaining. Magnification, 1000× **(A–C)**, 400× **(D)**.

tauopathies as PiD, PSP, or CBD and, for instances, neuropathological criteria for CBD states that for differentiate it from *MAPT* gene mutation cases additional clinical or molecular genetic information is required to make an accurate diagnosis (Dickson et al., 2002).

Corticobasal degeneration, as a pathological entity, is associated to a wide range of clinical presentations (see below). CBD is a 4R tauopathy (Dickson et al., 2011b). The characteristic pathology in CBD is tau immunoreactive inclusions in the cell processes of neurons and glia in the cortex, basal ganglia, thalamus, and brainstem. Tau-reactive thin, thread-like processes of glial and neuronal origin are also seen throughout the gray and white matter and are an important feature of the pathology of CBD. The most specific histopathological lesion in CBD is the astrocytic plaque, a distinctive annular cluster of thick, short tau immunoreactive deposits within the distal processes of astrocytes (Dickson et al., 2002). Ballooned neurons, described since the first report of the disease under the name "corticodentatonigral degeneration with neuronal achromasia" (Rebeiz et al., 1967), are swollen cortical neurons, eosinophilic in hematoxylin–eosin staining, most often found in the third, fifth, and sixth cortical layers. They are immunoreactive to phosphorylated neurofilaments and alpha–beta-crystallin (Dickson et al., 2002). Despite of being one of the histological hallmarks of CBD, this type of neuronal degeneration itself is known to be a non-specific change and can be seen in other pathological conditions (Ikeda, 1997).

Progressive supranuclear palsy is also a 4R tauopathy. The most characteristic neuronal lesion on histopathology is the globose neurofibrillary tangle, while the most significant astrocytic lesion is the tufted astrocyte (Nishimura et al., 1992; Yamada et al., 1992), characterized by a tuft like arrangement of cell processes around the astrocyte cell body. They are both best appreciated with Gallyas silver stain or tau immunohistochemistry. The core neuroanatomical regions affected include basal ganglia, subthalamic nucleus, and substantia nigra, with cortical involvement more pronounced in motor and premotor cortices (Dickson et al., 2011b). Neuropathological criteria for PSP are based on the distribution of tau pathology and the exclusion of other neurodegenerative disorders associated to parkinsonism and dementia (Hauw et al., 1994). However, these criteria did not take into account the atypical clinical PSP presentations that can present under the FTLD spectrum.

FTLD–TDP

In this group the pathological changes signature consists in the presence of immunoreactive TDP-43 neuronal cytoplasmatic inclusions (NCI), dystrophic neurites (DN), and in some cases neuronal intranuclear inclusions (NII) in the frontotemporal neocortex and dentate granule cells of the hippocampus (**Figure 5**; Neumann et al., 2006; Davidson et al., 2007). TDP-43 is a ubiquitously expressed, highly conserved nuclear protein that regulates RNA in a variety of ways. Converging lines of research suggest that TDP-43 is mechanistically linked to neurodegeneration, with many pathways probably involved, including gain of toxic functions and loss of normal functions (Lee et al., 2011a). Four subtypes of FTLD–TDP are currently recognized based on morphology and anatomical distribution of TDP-43 lesions (Mackenzie et al., 2011a). Type A is characterized by numerous short DN and crescentic or oval NCI, as well as moderate numbers of NII (**Figure 5**), type B consists of moderate numbers of NCI and minimal or absent DN and Type C have a predominance of elongated and minimal to absent NCI. Finally, type D refers to the

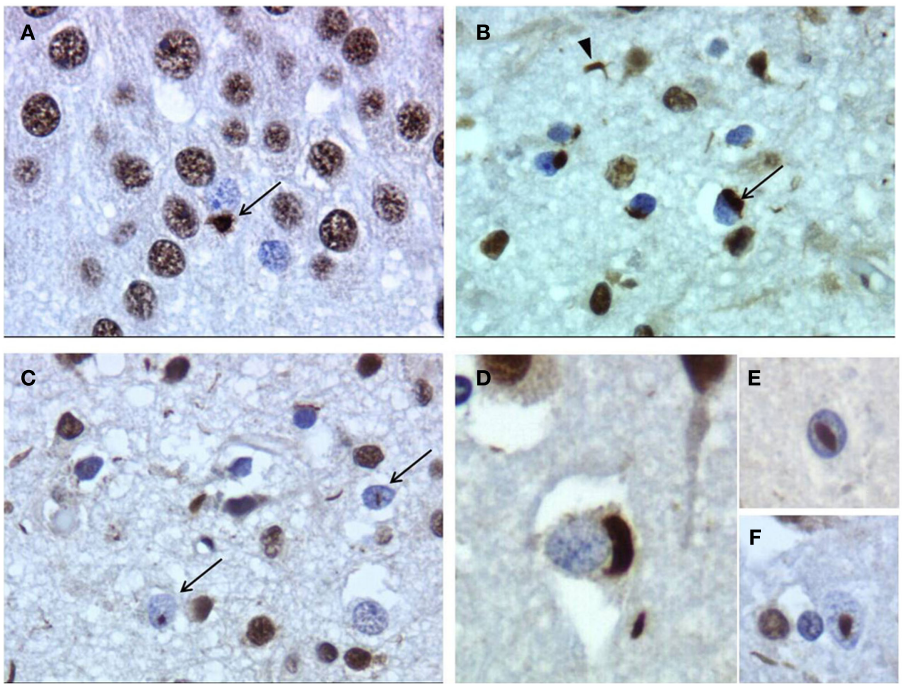

FIGURE 5 | Frontotemporal lobar degeneration–TDP neuropathology of patient with *progranulin* gene mutation. **(A)** Neuronal cytoplasmatic inclusion (NCI) in the hippocampus (*arrow*). **(B)** Superficial frontal neocortex showing NCIs (*arrow*) and dystrophic neurites (DN; *arrowhead*). **(C)** Superficial parietal neocortex showing NCIs, DN, and neuronal intranuclear inclusions (NII; *arrow*). **(D)** NCI in frontal cortex. **(E,F)** Lentiform and round NII in frontal cortex. Magnification, 400×.

pathology associated to inclusion body myopathy with Paget's disease of bone and frontotemporal dementia caused by CHMP2B *VCP* gene mutations, and is characterized by numerous short DN and frequent lentiform NII. There is good association between FTLD–TDP types and clinical syndromes (see below).

FTLD–FUS

Fused in sarcoma is a ubiquitously expressed protein that binds to RNA and DNA and is involved in diverse cellular processes (Neumann et al., 2009). Given the fact that Both TDP-43 and FUS are ubiquitously expressed DNA/RNA-binding proteins involved in multiple aspects of gene expression, transcription regulation, RNA splicing, transport and translation, although its precise function is poorly characterized. The understanding of the mechanisms underlying the pathophysiology of FUS accumulation and FUS-mediated neurodegeneration is still limited. As for TDP-43 proteinopathies, a toxic gain-of-function mechanism, a loss-of-function mechanism by depletion of physiological FUS and maybe co-sequestration of other vital factors, or both, is possible (Mackenzie et al., 2010b). This recently described FTLD category is pathological characterized by the presence of NCI and NII that are strongly immunoreactive for FUS protein and negative for the other proteins associated to neurodegenerative dementias (Neumann et al., 2009). Another consistent and striking feature of this group is the severe atrophy of the head of caudate nucleus (Roeber et al., 2008) that can be a useful clinical predictor of this pathology when detected by neuroimaging (Josephs et al., 2010). The true incidence and prevalence of FTLD–FUS is unknown. Based on brain bank studies has an estimate frequency of approximately 5% of all FTLD patients (Mackenzie et al., 2011b).

CLINICO-PATHOLOGICAL CORRELATIONS

The recent discoveries on FTLD pathologies and their classification according to the major protein deposited in brain allowed to established associations between the FTLD pathologies and the clinical syndromes. In this section we will described the most important clinico-pathological associations taking as starting point the clinical syndrome and genetic variability.

The syndrome bvFTD, the most common clinical syndrome in FTLD spectrum, is histopathologically heterogeneous (Josephs et al., 2011; Rohrer et al., 2011), with half of the patients having tau pathology and the other 50% have tau-negative FTLD with ubiquitin immunoreactive inclusions (FTLD-U), which in the majority of cases are TPD-43 positive (Hodges et al., 2004; Snowden et al., 2007). In the FTLD-tau group presenting with bvFTD, Pick's disease account for the majority of the cases (∼70%) followed by CBD and a minority of cases have PSP pathology (Wadia and Lang, 2007; Ling et al., 2010; Josephs et al., 2011). It should keep in mind that classical PSP clinical presentation, recently referred as Richardson syndrome, permit accurate ante-mortem diagnosis in most cases (Josephs and Dickson, 2003). The atypical clinical presentations, which can fall under the umbrella of FTLD, reflect varying anatomical distribution of tau pathology. In the FTLD–TDP group, bvFTD is not strongly associated to any TDP particular type (Josephs et al., 2011). A subtype of bvFTD characterized by

a very young onset patient (∼40 years), with a clinical syndrome dominated by hypersexual and hyperphagic behavior, prominent stereotypy, and obsessionality, together with striatal atrophy was tightly associated to FTLD–FUS (Roeber et al., 2008; Urwin et al., 2010; Snowden et al., 2011).

The phenotype FTD–MND is highly specific of FTLD–TDP pathology (Josephs et al., 2011; Rohrer et al., 2011), with type B being the most common (Mackenzie et al., 2011a). The associated neuropathology of patients with mutations on C9ORF72 gene is also a FTLD–TDP type B (Stewart et al., 2012). Interestingly, this subset of patients (MND/ALS and FTLD–TDP with C9ORF72 repeat expansion) have also p62 positive, TDP-43 negative, neuronal cytoplasmic, and intranuclear inclusions in the cerebellum and hippocampus that seems to be specific for this condition (Al-Sarraj et al., 2011).

Progressive non-fluent aphasia is associated predominantly with FTLD–tau (70%; Josephs et al., 2011) and no particular association with specific tau pathology can be made (i.e., PiD, CBD, or PSP).

Semantic dementia is predominantly associated to FTLD–TDP (83%), particularly type C (Josephs et al., 2011; Rohrer et al., 2011).

Although clinically heterogeneous, even among family members carrying the same mutation, certain characteristics have been linked more frequently to FTLD patients with progranulin mutations, such extrapyramidal features and parietal lobe deficits (Rohrer et al., 2008; van Swieten and Heutink, 2008; Taipa et al., 2012).

In summary, FTLD is the umbrella term for a heterogeneous group of clinical (bvFTD, PNFA, SD, FTD–MND) and pathological disorders (FTLD–tau, FTLD–TDP, and FTLD–FUS), with strong clinico-pathological associations in certain groups (i.e., FTD–MND/FTLD–TDP, SD/FTLD–TDP, PNFA–FTLD–tau, young onset bvFTD/FTLD–FUS).

CONCLUSION

The precise mechanisms involved in neurodegeneration remain largely unknown, but some proteins have emerged as important players in the mechanism of neurodegeneration. This suggests, at least partially and probably early in the process, specific pathophysiological characteristics in the different neurodegenerative dementias. Consequently, the rational use of disease modifying treatments will almost certainly imply a specific diagnosis at a molecular level. This brings an outstanding challenge to clinicians due to heterogeneous clinical presentations with the same molecular pathology. Clinico-pathological studies helped in refining diagnosis and continue to be essential in order to pursuit *in vivo* biomarkers to achieve higher diagnostic specificity. Adding to the clinical overlap of distinct neuropathological diagnosis, it must be taken into account that while evaluating post-mortem brains, pathologists have to assess numerous pathologies, keeping in mind the clinical presentation, but also to be aware of the frequent findings of comorbidity or unexpected pathologies which characterize the aging brain (Alafuzoff et al., 2009).

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Behavioral and psychological symptoms of dementia

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Behavioral and psychological symptoms of dementia (BPSD), also known as neuropsychiatric symptoms, represent a heterogeneous group of non-cognitive symptoms and behaviors occurring in subjects with dementia. BPSD constitute a major component of the dementia syndrome irrespective of its subtype. They are as clinically relevant as cognitive symptoms as they strongly correlate with the degree of functional and cognitive impairment. BPSD include agitation, aberrant motor behavior, anxiety, elation, irritability, depression, apathy, disinhibition, delusions, hallucinations, and sleep or appetite changes. It is estimated that BPSD affect up to 90% of all dementia subjects over the course of their illness, and is independently associated with poor outcomes, including distress among patients and caregivers, long-term hospitalization, misuse of medication, and increased health care costs. Although these symptoms can be present individually it is more common that various psychopathological features co-occur simultaneously in the same patient. Thus, categorization of BPSD in clusters taking into account their natural course, prognosis, and treatment response may be useful in the clinical practice. The pathogenesis of BPSD has not been clearly delineated but it is probably the result of a complex interplay of psychological, social, and biological factors. Recent studies have emphasized the role of neurochemical, neuropathological, and genetic factors underlying the clinical manifestations of BPSD. A high degree of clinical expertise is crucial to appropriately recognize and manage the neuropsychiatric symptoms in a patient with dementia. Combination of non-pharmacological and careful use of pharmacological interventions is the recommended therapeutic for managing BPSD. Given the modest efficacy of current strategies, there is an urgent need to identify novel pharmacological targets and develop new non-pharmacological approaches to improve the adverse outcomes associated with BPSD.

Keywords: behavioral and psychological symptoms, dementia, neuropsychiatric symptoms, Alzheimer's disease

INTRODUCTION

During the natural course of dementia a heterogeneous group of clinical phenomena is subjectively experienced by the patient and/or observable by an examiner (e.g., caregiver, physician) consisting in disturbed emotions, mood, perception, thought, motor activity, and altered personality traits. These "neuropsychiatric symptoms," according to the terminology most used in the United States, or "behavioral and psychological symptoms of dementia" (BPSD), as designated by the International Psychogeriatrics Association (Finkel et al., 1996), are very common and associated with high levels of distress both in dementia sufferers and their caregivers, as well as with adverse outcomes and increased use of health care resources. Thus, in addition to cognitive deterioration, BPSD are a relevant and meaningful clinical target for intervention (Katona et al., 2007).

BPSD: CONCEPTUAL OVERVIEW

BPSD IN THE CURRENT CLASSIFICATION SYSTEMS

Despite being almost universally present during the course of dementia, BPSD have not been included in the defining criteria of dementia in the current classification systems. The core features of dementia according to DSM-IV-TR and ICD-10 consist of gradual onset of multiple cognitive deficits (involving memory and at least one additional cognitive domain) not occurring exclusively during delirium and representing a decline from a previous level of functioning (American Psychiatric Association, 1994). In DSM-IV-TR the presence or absence of a clinically significant behavioral disturbance can be coded, but no guidance is provided about the diagnostic criteria of these symptoms. It is also possible to code dementia (e.g., Alzheimer disease, AD) in axis III and specific mental disorders (e.g., mood or psychotic disorder) in axis I with the advantage of better characterizing prominent clinical features related to dementia (American Psychiatric Association, 1994).

PSYCHOPATHOLOGICAL FEATURES

Neuropsychiatric symptoms in subjects with dementia are heterogeneous and largely unpredictable, affecting the emotional experience, thought content, perception, and motor function. While some symptoms can be more often recognized in a specific pathological sub-type, the clinical presentation has a wide variation within each sub-type and even within each dementia individual. The first step to better understand the psychiatric manifestations of dementia is to appropriately recognize and describe

the psychopathology and accurately distinguish between similar symptoms (e.g., depression vs. apathy). This can be challenging considering the overlap between symptoms and the lack of proper definitions and consensus criteria for their diagnosis. Secondly, it is useful to evaluate whether specific symptoms occur in association and to group them in syndromes with common clinical evolution, neurobiology, and management.

Disturbances in emotional experience

As the symptoms of depression are frequently masked by dementia, the patient rarely is able to express the typical pathological feelings of sadness, unhappiness, and preoccupation with depressing topics, hopeless (strongly associated with suicidal ideation) and loss of self-esteem (Prado-Jean et al., 2010). Instead, the prominent symptoms can be anhedonia (lost of interest in previous pleasurable stimuli), expression of somatic concerns and anxiety, a subjective unpleasant experience of fear manifested as apprehension, tension, panic, or worry associated with autonomic activation and observable physical and motor manifestations of tension. In the context of dementia, apathy has been defined as a disorder of motivation with additional loss or diminished goal-directed behaviors, cognitive activities and emotions (Robert et al., 2009). Apathy may be mistaken for depression because both symptoms can manifest themselves as diminished interest, slowing and lack of energy (Mulin et al., 2011). Although lack of motivation occurs both in apathy and depression, apathy denotes a lack of motivation without dysphoria. Elated mood, ranging from hypomania to severe mania, refers to a sustained and exaggerated feeling of well-being, cheerfulness, euphoria that is out of proportion to the circumstances often associated with a heightened emotional tone or emotional reactivity. Both depression and elated mood are commonly associated with irritability, a pervasive feeling of unease in response to a sense of threat with enhanced readiness to hostile attitudes or actions, which can be aggravated by hunger, sleepiness, and pain. Affective (or mood) lability is characterized by rapid emotional shifts, within seconds or minutes.

Delusions and abnormal thought content

Delusional ideas (false believes strongly held, enduring, and irrefutable) can vary widely in respect to complexity, systematization, conviction, and the extent to which patients take action in response to them. The delusions are typically less complex and organized than those observed in non-demented psychotic patients and the usual content of delusional thoughts involves suspiciousness, abandonment, and misidentification (Jeste et al., 2006). Common examples include the conviction that: people are coming into the home and hiding/stealing objects; the place in which one is residing is not one's home; conviction that spouse is an impostor (Capgras delusion); accusation of a conspiracy to abandon or institutionalize; conviction that spouse is unfaithful; believes that other persons have acted maliciously; or with discriminatory intent (Tariot et al., 1995). When associated with severe depression, delusional thoughts can involve guilt, worthless, reference, and persecution.

PERCEPTUAL DISTURBANCES

Perceptual disturbances in dementia can occur in every sensorial modality. In some instances, it is somewhat difficult to ascertain whether the perceptual disturbance is an illusion or whether the patient is having a perception in the absence of sensory stimuli (hallucination). Visual hallucinations are particularly common in subjects with dementia with Lewy bodies (DLB). They are recurrent, and typically consist of well formed images of animals or persons that the patient describes in detail (McKeith et al., 2005).

DISTURBANCES IN MOTOR FUNCTION

Unlike the prior psychopathological domains, disturbances in motor function can be directly observed and consist in reduced or increased motor activity, not necessarily associated with specific motor abnormalities. In *motor retardation* the patient presents with slowed movements and speech, reduced body tone, and decreased number of spontaneous body movements, whereas *motor hyperactivity* is characterized by an increased energy level with more frequent movements and/or rapid speech.

Agitation has been defined as "inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to result directly from the needs or confusion of the agitated individual" (Cohen-Mansfield et al., 2010). This term is used interchangeably with aberrant motor behavior and encompasses a range of activities such as wandering away from home; repetitive, purposeless behaviors; social inappropriate activities including those associated with disinhibition (tendency to disregard social and cultural norms and not restrain inner feelings, such as sexual drives). According to Cohen-Mansfield (1999) four distinct categories of agitation are: (1) physically non-aggressive behavior; (2) verbally non-aggressive behavior; (3) physically aggressive behavior; and (4) verbally aggressive behavior.

CIRCADIAN RHYTHMS

Sleep pattern changes may occur as a consequence of normal aging, but are particularly prevalent in individuals with dementia. These include hypersomnia, insomnia, sleep-wake cycle reversal, fragmented sleep, and rapid eye movement sleep behavior disorder. Patients with dementia often show daytime napping and nighttime awakenings associated with poor quality of sleep (Rongve et al., 2010). Several factors, e.g., pain, need to urinate during the night, medications (diuretics), as well as stimulants such as coffee and bronchodilators, may contribute to this problem.

APPETITE AND EATING BEHAVIOR

Appetite changes can be quantitative (anorexia or hyperphagia) or qualitative (preference for particular foods associated or not to changes in taste). The preference for sweets is particularly frequent in fronto-temporal dementia. Most dementia patients lose weight which can be due to hypermetabolism and inflammatory processes, in relation with hormonal disturbances.

BPSD ASSESSMENT

The assessment of neuropsychiatric symptoms requires a thorough examination to collect specific and detailed information about the clinical history, patient's subjective experiences, and objective behavior. Information from a reliable family member or caregiver is essential to obtain adequate characterization of neuropsychiatric disturbances from the patient's own ecological context as many abnormal symptoms cannot be elicited during the clinical interview. When determining whether the disturbances require medical

attention it is useful to promote early interventions instead of a crisis-based or reactionary approach.

INTERVIEW WITH THE PATIENT

Although subjects with dementia may be handicapped in their communication and social skills, it is essential to have an individual assessment with them. Whenever possible, it is desirable that patients are encouraged to express their own concerns in answer to open questions before proceeding to a more systematic approach to specific symptoms. Patient's free descriptions are least prone to be influenced by the interviewer and/or caregiver and can provide crucial information about emotional states underlying behaviors.

CAREGIVER INTERVIEW

The interview with caregivers is an opportunity to characterize the psychopathological features and to recognize which BPSD are of greatest concern to them as these may not necessarily coincide with the patient's own complaints or with the clinician's priorities.

Understanding the sources of these discrepancies is important to determine the usefulness and limitations of the information obtained from both patients and caregivers as caregiver's emotional state can influence assessment ratings (Logsdon et al., 1999; Snow et al., 2005; Karlawish et al., 2008). In some parts of the assessment, it is important to observe how caregivers interact with the patient and how symptoms are manifested in such interactions. Behavioral symptoms, particularly apathy, have a significant impact in the patient–caregiver relationship deterioration (de Vugt et al., 2003) and subjects with dementia are likely to be affected by dysfunctional interactions with their caregivers (de Vugt et al., 2004; Sink et al., 2006). Caregiver's characteristics, such as younger age, less education, depressive symptoms, and more hours per week providing care assistance, appear to contribute to the presence of or reported higher rates of BPSD (Sink et al., 2006). However, more research is needed to clarify how the patient–caregiver interpersonal interactions contribute to the presence of certain neuropsychiatric symptoms.

STANDARDIZED CLINICAL ASSESSMENT

Several validated instruments have been developed to quantify BPSD based on data collected from clinical assessment of dementia patients and caregivers' interviews with some scales assessing a wide range of neuropsychiatric symptoms and others focusing on specific symptoms (e.g., aggression and agitation). Self-administered questionnaires are also available for caregivers.

The first behavior rating scale for AD was the *BEHAVE-AD* (Reisberg et al., 1987), evaluating the presence and severity of 25 behavioral symptoms in 7 symptomatic categories (paranoid and delusional ideation, hallucination, activity disturbances, aggressiveness, sleep disturbances, affective symptoms, and anxieties and phobias), and providing a global rating of caregiver burden. Currently, one of the most extensively used instruments to assess BPSD is the *Neuropsychiatric Inventory* (NPI) whose validity and reliability has been well established in several languages (Cummings, 1997). It consists of a semi-structured interview retrospectively assessing 12 symptoms based on the caregiver information: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night time behavior disturbances, and eating behavior abnormalities. Important factors to take into account when selecting an instrument include the purpose of the assessment (e.g., comprehensive vs. specific symptom evaluation) and the setting (e.g. busy clinical practice vs. research). When possible, it is advisable to obtain information from different caregivers to cover behavior in different settings, and thus providing an overall picture of patient's functioning. Disagreements among informants should be regarded as a valuable cue to identify situational factors implicated in the genesis of symptoms. It is unlikely that new rating scales will completely solve the problems that are inherent in the assessment of BPSD. Yet, future challenges lie in the improvement of the construction and the use of the scales with an increasing need for more standardized assessment of BPSD and for evaluation of their treatment.

CLINICAL RELEVANCE OF BPSD

PREVALENCE AND SEVERITY OF INDIVIDUAL SYMPTOMS

There is an overall agreement that BPSD are very common regardless of the type of dementia and are present in virtually all patients during the course of their disease. Even in the early stages of cognitive impairment, neuropsychiatric symptoms are frequent with estimated rates of 35–85% in subjects with mild cognitive impairment (MCI; Monastero et al., 2009).

The reported frequency of BPSD largely depends on the type of sample and setting considered. In community-dwelling subjects with dementia, neuropsychiatric symptoms are generally less frequent (56–98%) and severe than in patients recruited in hospital or long-term care facilities (91–96%). When looking at individual symptoms in dementia patients, the most prevalent BPSD are apathy, depression, irritability, agitation and anxiety, while the rarest are euphoria, hallucinations, and disinhibition. The most clinically significant symptoms are depression, apathy, and anxiety. Importantly, 50% of patients have at least four neuropsychiatric symptoms simultaneously (Frisoni et al., 1999).

THE BURDEN OF BPSD

BPSD are a source of significant distress and poor quality of life (QoL) to both dementia patients and their caregivers (Ryu et al., 2011). In AD patients, depressive symptoms are associated with worse self-reported QoL scores (Karttunen et al., 2011) whereas mood and psychotic symptoms predict changes in the QoL 2 years later (Tatsumi et al., 2009). Moreover, increased number of BPSD correlates negatively with survival rates over a 3-year period (Tun et al., 2007) whereas presence of psychosis in AD has been found to be associated with increased mortality and acceleration of cognitive decline (Emanuel et al., 2011; Russ et al., 2011).

BPSD also have a profound physical and psychological impact on both formal and informal caregivers. A considerable part of caregivers' time and distress relate directly to the manifestation of BPSD (Ballard et al., 2000a), which is a major reason for earlier institutionalization of patients (Chan et al., 2003). Nursing home placement determines a significant increase in the overall cost of dementia care in addition to other direct and indirect costs associated with BPSD (Beeri et al., 2002; Herrmann et al., 2006). Psychotic symptoms (e.g., delusions) and disruptive behaviors (e.g., aggression, screaming) have been reported to be the most burdensome to caregivers (Miyamoto et al., 2010; Rocca et al.,

2010; Huang et al., 2011). In addition to BPSD, certain characteristics of caregivers are known to determine the risk of burden including overload, quality of the relationship with the patient, adverse life events, gender, level of neuroticism, role captivity, and levels of confidence (Campbell et al., 2008).

In MCI subjects, comorbid neuropsychiatric symptoms have been associated with worse cognitive performance, mild extrapyramidal signs, and functional disability (Monastero et al., 2009). Depressive symptoms in subjects with MCI have also been linked to progression to dementia (Modrego and Ferrández, 2004; Gabryelewicz et al., 2007) and increased brain atrophy over 2 years (Lee et al., 2012) suggesting that they may represent an early sign of a neurodegenerative disease.

SYMPTOMS INTERRELATION AND EVOLUTION

The unitary concept of BPSD encompassing the full range of emotional, psychological, and behavioral abnormalities occurring in dementia reflects the clinical heterogeneity and complexity of the symptoms and the difficulty in characterizing more specific subsyndromes or proprieties clusters co-varying during the course of the disease. Several studies have tried to identify neuropsychiatric sub-syndromes by grouping a number of individual symptoms which contingently co-occur during the course of dementia (**Table 1**). Ultimately, the recognition of discrete clinical entities is important to disclose underlying causal mechanisms and to develop etiological-based therapeutic interventions, even if the precise delineation of each syndrome remains elusive.

Although these studies differ in respect to study designs, assessment tools, and the size of samples, there is also a degree of concordance between the neuropsychiatric syndromes found (**Table 1**). Thus, delusions and hallucinations have been consistently grouped in a "*psychosis*" sub-syndrome in all factor analytical studies using the NPI. A distinct "*mood*" or "*affective*" cluster (depression and anxiety) has been reported by some studies (Aalten et al., 2007; Zuidema et al., 2007; Dechamps et al., 2008; Savva et al., 2009; Kang et al., 2010; Spalletta et al., 2010), while these symptoms have been included in different sub-syndromes by other authors (e.g., psychosis, agitation; Fuh et al., 2001; Mirakhur et al., 2004). A less reliable factor characterized by high levels of *agitation, aggression, and aberrant motor behavior* has emerged in several studies under various names (e.g., agitation, hyperactivity, frontal) (Frisoni et al., 1999; Aalten et al., 2003) presenting with heterogeneous psychopathological structure and suggesting that psychomotor features co-occur with psychotic and/or affective symptoms. There is evidence that "*psychosis,*" "*affective,*" *and* "*agitation/aggression*" factors remain stable across a 31-month period (Selbæk and Engedal, 2012).

The debate about the definition of the several psychiatric and behavioral symptoms in dementia continues as a number of symptoms (apathy, sleep, and eating disturbances) have not been grouped consistently across studies. Particularly, the relation between apathy (highly prevalent in dementia) and the "*mood*" sub-syndrome remains unclear. Studies conducted on outpatients (Aalten et al., 2008; Spalletta et al., 2010) and in nursing-homes (Zuidema et al., 2007; Dechamps et al., 2008; Selbæk and Engedal, 2012) support that apathy and depression are distinct phenomena and belong to different neuropsychiatric syndromes. However, other studies group both symptoms in the same factor (Frisoni et al., 1999; Aalten et al., 2003; Hollingworth et al., 2006).

These discrepancies may result from the fact that individual symptoms evolve differently over the course of dementia. For example, as shown by a large cross-sectional study involving 3404 subjects, while apathy increases linearly with cognitive decline, the relations between BPSD and level of cognitive impairment are non-linear with higher prevalence rates observed in the middle stages of dementia (Lövheim et al., 2008). Several other cross-sectional studies in both community and institutionalized populations reported that greater cognitive impairment or dementia severity is associated with higher rates of some BPSD (**Table 2**). Yet, other studies were in disagreement with these findings and a systematic review found a lack of association between the severity of dementia and the prevalence of depressive symptoms or diagnosed depression (Verkaik et al., 2007). Psychotic (Scarmeas et al., 2005; Emanuel et al., 2011) and depressive symptoms (Chan et al., 2011) were reported to predict a faster cognitive deterioration.

There is limited information about the natural history and course of neuropsychiatric symptoms in MCI. In this context, Ryu et al. (2011) have concluded that neuropsychiatric symptoms in MCI usually persist, with a significant percentage of patients having at least one persistent symptom. These symptoms were more severe at baseline (Ryu et al., 2011). On the other hand, the presence of specific symptoms can aggravate cognitive decline; patients who present with both amnestic-MCI and apathy, but not those with depression, had an almost seven-fold risk of AD progression compared to amnestic-MCI patients without apathy, after adjustment of variables (Palmer et al., 2010).

Longitudinal studies provided further insight into the evolution of BPDS during the course of the disease (**Table 3**). In the Maastricht Study of Behavior in Dementia (MAASBED) patients with mild dementia at baseline showed more neuropsychiatric symptoms, whereas patients with severe dementia showed fewer neuropsychiatric symptoms throughout 2 years (Aalten et al., 2005b). Overall, BPSD tend to be present chronically and most patients with baseline symptoms continue to show at least one symptom at subsequent assessments. In the population-based Cache County Study, 67% of dementia subjects with clinically significant symptoms presented at least one symptom both at baseline and at 18 months follow-up assessment, with delusions and depression being the most persistent (Steinberg et al., 2004). In the MAASBED study 65% of outpatients who had a clinically relevant NPI total score at baseline continued to experience problems during the 2-year study period, with the most persistent symptoms being apathy and aberrant motor behavior (Aalten et al., 2005a). Persistence rates over 16 months were highest for delusions, agitation, depression, disinhibition, irritability, and aberrant motor behavior in a study conducted in nursing homes (Bergh et al., 2011). Repeated assessments have clarified that individual symptoms have an intermittent course, with elevated resolution and incidence rates throughout the time. Thus, one-third of patients with delusions, hallucinations, disinhibition, and agitation were symptom-free in the following 4 months (Bergh et al., 2011). Although it appears that BPSD have a heterogeneous pattern during the course of dementia, it has been proposed, especially in

Table 1 | Neuropsychiatric sub-syndromes reported in patients with dementia.

Reference	Sample/methods	Clusters
Devanand et al. (1992)	106 AD patients (outpatient clinic) BSSD	*Disinhibition* *Apathy-indifference* *Dependency motor agitation* *Self-destructive behaviors*
Hope et al. (1997)	97 AD or VaD patients (community) PBE, PCA	*Overactivity*: walking more, aimless walking, trailing or checking *Aggressive behavior*: aggressive resistance, physical aggression, verbal aggression and hostility *Psychosis*: hallucinations, persecutory ideas, anxiety
Harwood et al. (1998)	151 AD patients (outpatient clinic) BEHAVE-AD, PCA	*Agitation/anxiety*: agitation, anxiety of upcoming events, other anxiety *Psychosis*: delusions of theft, suspiciousness/paranoia, visual hallucinations *Aggression*: verbal aggression, physical treats/violence, fear of being left alone, other delusions *Depression*: tearfulness, depressed mood *Activity disturbance*: wandering, delusion one's house is not one's home
Frisoni et al. (1999)	162 AD patients (hospital) NPI, PCA	*Mood syndrome* *Psychosis syndrome* *Frontal syndrome*
Fuh et al. (2001)	320 AD + 212 VaD patients (outpatient clinic) NPI, FA	*Mood and psychosis* *Psychomotor regulation* *Social engagement*
Lyketsos et al. (2001)	198 AD patients (community) NPI, LCA	*Minimally symptomatic* *Affective disturbance* (depression, irritability, anxiety euphoria) *Psychotic disturbance* (delusions, hallucinations)
Aalten et al. (2003)	199 dementia patients (outpatient clinic) NPI, PCA	*Hyperactivity*: agitation, euphoria, irritability, disinhibition, aberrant motor behavior *Mood/apathy*: depression, apathy, sleep, appetite *Psychosis*: delusions, hallucinations, anxiety
Mirakhur et al. (2004)	435 AD patients (outpatient clinic) NPI, PCA	*Affect*: depression/dysphoria; anxiety; irritability; agitation/aggression *Physical behavior*: apathy; aberrant motor behavior; sleep disturbance; appetite/eating disturbance *Psychosis*: delusions; hallucinations *Hypomania*: disinhibition; elation/euphoria
Schreinzer et al. (2005)	133 dementia patients (chronic care hospital) BEHAVE-AD, PCA	*Agitation* *Affective disturbance* *Altered circadian rhythms*
Matsui et al. (2006)	140 AD patients (outpatient clinic) NPI, FA	*Psychosis*: delusions, hallucinations, anxiety, agitation, disinhibition, irritability, aberrant motor activity *Mood*: apathy, depression/euphoria *Euphoria*: euphoria
Hollingworth et al. (2006)	1120 AD patients (community + nursing homes) NPI, PCA	*Behavioral dyscontrol:* euphoria, disinhibition, aberrant motor behavior, sleep, appetite *Psychosis:* delusions, hallucinations *Mood:* depression, anxiety, apathy *Agitation:* irritability, aggression
Aalten et al. (2007) Aalten et al. (2008)	2354/2808 AD patients (outpatient clinic) NPI, PCA	*Hyperactivity*: agitation; euphoria; disinhibition; irritability; aberrant motor behavior *Psychosis*: delusions; hallucinations; night time behavior disturbance *Affective symptoms*: depression; anxiety *Apathy*: apathy; appetite/eating abnormalities

(Continued)

Table 1 | Continued

Reference	Sample/methods	Clusters
Zuidema et al. (2007)	1437 dementia patients (nursing homes) NPI, FA	GDS 4/5: *Factor 1*: agitation, disinhibition, irritability, delusions *Factor 2*: depression, anxiety, delusions, hallucinations, aberrant motor behavior, night time behavior *Factor 3*: apathy, eating disorders *Factor 4*: euphoria GDS 6 *Factor 1*: agitation, disinhibition, irritability, euphoria *Factor 2*: depression, anxiety *Factor 3*: delusions, hallucinations *Factor 4*: aberrant motor behavior, night-time behavior *Factor 5*: apathy, eating disorders GDS 7: *Factor 1*: agitation, irritability *Factor 2*: delusions, hallucinations, disinhibition *Factor 3*: depression, anxiety *Factor 4*: apathy, aberrant motor behavior *Factor 5*: night-time behavior, eating disorders
Dechamps et al. (2008)	109 dementia patients (nursing homes) NPI, PCA	*Hyperactivity*: agitation, euphoria, disinhibition and irritability *Affective*: depression, anxiety, and eating change *Psychosis*: delusions, apathy and aberrant motor behavior *Hallucinations*: hallucination and sleeping disturbances
Savva et al. (2009)	587 AD patients (community) GMS, FA	*Factor 1*: psychosis, apathy and wandering *Factor 2*: anxiety and depression *Factor 3*: irritability, persecution, agitation *Factor 4*: elated mood, sleep disorder, hallucinations, agitation and wandering
Kang et al. (2010)	778 AD patients (hospital) NPI, FA (exploratory and confirmatory)	*Hyperactivity*: agitation/aggression; disinhibition; irritability *Affect*: depression; anxiety *Psychosis*: delusions; hallucinations *Apathy/vegetative symptoms*: apathy; sleep; appetite
Prado-Jean et al. (2010)	319 dementia patients (nursing homes) NPI, PCA	*Factor 1:* disinhibition, irritability, agitation, anxiety *Factor 2*: sleep disorder, aberrant motor behavior, apathy *Factor 3*: Euphoria, hallucinations, delusions *Factor 4*: Appetite and eating
Garre-Olmo et al. (2010b)	491 AD patients (outpatient clinic) NPI, FA (exploratory and confirmatory)	*Psychotic:* hallucinations, delusions *Affective*: depression, anxiety, irritability, agitation *Behavior*: euphoria, disinhibition, apathy, aberrant motor behavior
Spalletta et al. (2010)	1015 AD patients (outpatient clinic) NPI, PCA	*Psychomotor:* agitation, irritability, aberrant motor behavior. *Psychosis:* delusions, hallucinations *Affective:* anxiety, depression *Maniac:* euphoria, disinhibition *Apathetic:* apathy
Selbæk and Engedal (2012)	895 dementia patients (nursing homes) NPI, PCA	*Agitation:* agitation, euphoria, disinhibition, irritability, aberrant motor behavior, night-time behavior *Psychosis/affective:* delusions, hallucinations, depression, anxiety *Apathy/appetite:* apathy, appetite

AD, Alzheimer disease; BSSD, behavioral syndromes scale for dementia; GMS, geriatric mental state; LCA, latent class analysis; NPI, neuropsychiatric inventory; NPI-NH, neuropsychiatric inventory-nursing home version; PBE, present behavioral examination; PCA, principal component analysis; VaD, vascular dementia.

Table 2 | BPSD and dementia severity: cross-sectional studies.

Reference	Sample	Findings
Aalten et al. (2008)	2808 AD patients (outpatient clinic)	*Psychosis* and *hyperactivity* co-occurred more often in more severe stages of dementia.
Cheng et al. (2009)	138 (outpatient clinic) +173 (long-term care) AD patients	Severity of *delusion/paranoid ideation, hallucination, activity disturbances, aggressiveness, diurnal rhythm disturbance and behavioral problems* significantly associated with severity of dementia.
Craig et al. (2005)	435 AD patients (hospital)	*Depression*/dysphoria and *apathy*/indifference more frequent in less severe dementia; hallucinations, elation/euphoria, and aberrant motor behavior more frequent in severe dementia. *Apathy* was the most persistent symptom; psychotic symptoms, delusions, and hallucinations exhibited the most rapid disappearance over time.
Di Iulio et al. (2010)	119 AD + 68 multidomain-MCI + 58 amnestic-MCI + 107 controls	*Apathy* more prevalent with increasing severity of cognitive syndromes (amnestic-MCI to multidomain-MCI, to AD). *Depression* prevalence increased from amnestic-MCI to multidomain-MCI, but not with dementia. No association with *night-time disturbances*.
Fernández Martínez et al. (2008a)	37 AD + 28 VaD patients (hospital, outpatient clinic)	*Behavioral changes* without correlation with severity of dementia in AD. Severity of *delusions, hallucinations, aggression, irritability, aberrant motor behavior, night-time behavior and appetite changes* correlated to cognitive decline in VaD.
Fernández Martínez et al. (2008b)	81 AD + 14 VaD + 10 PLBD + 3FTD (community)	Prevalence of neuropsychiatric symptoms increased with dementia severity, but was not statistically significant.
Fernandez-Martinez et al. (2010)	344 AD + 91 MCI + 50 controls (hospital, outpatient clinic)	All behavioral disorders increased with cognitive impairment*, except for sleep and appetite disorders*.
Fuh et al. (2005)	320 AD + 212 VaD patients (hospital, outpatient clinic)	*Delusions, hallucinations, and aberrant motor activities* more common in later stages in both AD and subcortical VaD.
García-Alberca et al. (2010)	125 AD patients (outpatient clinic)	No predictive value for MMSE in BPSD.
Geda et al. (2004)	87 AD + 54 MCI + 514 controls	Total NPI scores significantly different among the 3 groups.
Lopez et al. (2003)	1155 AD patients	Psychiatric symptoms, *except major depression,* more frequent in more severe stages of the dementia.
Lövheim et al. (2008)	3040 residents in geriatric care centers	Higher prevalence rates of BPSD in the middle stages of dementia. *Passiveness* increased linearly with the severity of cognitive impairment.
Lyketsos et al. (2000)	329 dementia patients (community)	Severity of dementia associated with increased prevalence of *agitation/aggression* (13% in mild dementia, 24% in moderate dementia, and 29% in severe dementia) and *aberrant motor behavior* (9% in mild, 17% in moderate, and 19% in severe dementia).
Matsui et al. (2006)	140 AD patients (outpatient clinic)	*Psychosis* and *agitated behaviors* co-occurred with dementia progression.
Spalletta et al. (2010)	1015 AD patients (outpatient clinic)	Poor association between cognitive deficits and severity of BPSD symptoms.
Thompson et al. (2010)	377 AD + 74 VaD patients (outpatient clinic)	Association between severity of BPSD and severity of dementia

(Continued)

Table 2 | Continued

Reference	Sample	Findings
Youn et al. (2011)	216 AD patients (hospital, outpatient clinic)	Neuropsychiatric symptoms more frequent in moderate-to-severe stages of AD, except *loss of enjoyment* and *social withdrawal* (more frequent in mild stages). Frequencies of all neuropsychiatric syndromes significantly different in relation to the severity of disease, except for *vegetative symptom*. *Inertia* showed the highest frequency in mild stages.
Zuidema et al. (2010)	1289 dementia patients (nursing homes)	Dementia severity predicted *physically aggressive behavior* and *apathy*, with higher prevalence in more severe stages of dementia.

NPI, neuropsychiatric inventory; BPSD, behavior and psychological symptoms of dementia; MCI, mild cognitive impairment; AD, Alzheimer disease; VaD, vascular dementia; RAVLT, Rey auditory verbal learning test; TMT, trail-making test; MMSE, mini mental state examination; PLBD, Parkinson–Lewy body dementia.

AD, that distinct groups of patients can be identified based on progressive changes in the frequency and severity of their BPSD (Garre-Olmo et al., 2010c).

In conclusion, instead of being independent phenomena, BPSD occur in a psychopathological pattern partially resembling primary psychiatric disorders, supporting a syndrome approach to their study and management. However, the psychopathological profile of each sub-syndrome is highly variable across patients (Savva et al., 2009). Also, the co-occurrence of sub-syndromes is common reflecting the complex and multi-level interaction between each BPSD (Dechamps et al., 2008) and supporting a personalized approach to each patient.

ALZHEIMER'S DISEASE VS. OTHER DEMENTIA TYPES

Although the manifestations of BPSD may be influenced by a variety of factors, they are primarily the result of the ongoing pathophysiological brain changes. It would be reasonable to assume that, as with the clinical and neuropsychological features, different profiles of neuropsychiatric symptoms could emerge in each sub-type of dementia, even at early stages. Thus, a higher prevalence of hallucinations and sleep disorders has been reported in non-amnestic-MCI, more likely to progress to non-AD dementia, in comparison to amnestic-MCI (Rozzini et al., 2008). However, studies comparing the profile of BPSD in AD and non-Alzheimer dementia have not yielded entirely uniform results (**Tables 4** and **5**).

ALZHEIMER DISEASE VS. VASCULAR DEMENTIA

The most consistent finding from the studies comparing vascular dementia (VaD) with AD is a higher prevalence and severity of depression and anxiety, similar rates of psychotic symptoms, and less severe aberrant motor behavior among subjects with VaD, although a substantial overlap can exist between the two dementia syndromes (**Table 4**). Similarly, the type of underlying vascular disease seems to determine a different clinical profile in VaD as apathy, aberrant motor behavior, and hallucinations have been associated with small-vessel VaD, whereas euphoria and agitation/aggression were more severe among patients with large-vessel VaD (Staekenborg et al., 2010).

ALZHEIMER DISEASE VS. DEMENTIA WITH LEWY BODIES

Studies comparing the clinical profile of autopsy-confirmed cases of DLB and AD have consistently found a higher prevalence of delusions (misidentification, theft) and hallucinations (usually visual) in DLB patients independently of gender, ethnicity, and degree of cognitive impairment (Rockwell et al., 2000). These symptoms occur in up to 80 and 60% of patients respectively and tend to be more persistent over the course of the disease compared with AD patients (Ballard et al., 2001; Chiu et al., 2006; Stavitsky et al., 2006).

ALZHEIMER DISEASE VS. FRONTO-TEMPORAL LOBAR DEGENERATION

Fronto-temporal lobar degeneration (FTLD) is the prototype of a neurodegenerative disorder where changes in behavior, rather than in cognitive function, are the presenting feature and dominate the clinical picture throughout the disease course. The clinical spectrum of FTLD encompasses three distinct syndromes. The most common fronto-temporal dementia (also known as behavioral variant of fronto-temporal dementia) presents with a dramatic change in personal and social behavior. Early changes in language function are observed in semantic dementia and primary progressive non-fluent aphasia (Neary et al., 2005). Stereotypic behavior, appetite changes, and loss of social awareness are characteristic of FTLD with complex ritualized behaviors occurring more frequently in patients with fronto-temporal and semantic dementia than in AD (Bozeat et al., 2000; Ikeda et al., 2002). In contrast, simpler verbal stereotypes/perseveration or stimulus bound behavior, such as echolalia, seem to be equally common across the three groups (Nyatsanza et al., 2003). According to Bathgate et al. (2001) features that best discriminate FTLD from other dementias consist in loss of basic emotions, food cramming, pacing a fixed route, preserved capacity of locating objects, and impaired insight. Some behavioral features, such as lack of pain awareness, although not so common, provide diagnostic specificity as they are only rarely seen in other sub-types of dementia (Bathgate et al., 2001). Using the BEHAVE-AD scale, Chiu et al. (2006) found that AD outpatients presented with an increased incidence of anxiety and phobias (61.2%) whereas subjects with fronto-temporal dementia had higher levels of activity disturbances (92.3%).

OTHER FACTORS ASSOCIATED WITH BPSD

Besides the influence of dementia stage and subtype on the emergence of BPSD, other factors such as demographic variables and the use of medication have not been extensively explored. A number of associations, albeit not consistently replicated,

Table 3 | BPSD evolution: longitudinal studies.

Reference	Follow-up	Findings
Aalten et al. (2005a)	2 years (each 6 months)	No significant changes over time in the three sub-syndromes or in the NPI total score. *Depression* became less common, persistent and severe with disease progression. *Apathy* increased from the second visit (after six months), and persisted during the more advanced stages of dementia. *Psychosis* (delusions) was most common in the moderate stages, showing low persistence over time.
Aalten et al. (2005b)		Mild dementia at baseline predicted increasing prevalence of NPS with time, whereas the reverse was observed with severe dementia. Presence of NPI symptoms at baseline predicted the subsequent development of symptoms (especially mood/apathy). Hyperactivity predicted the development of psychosis but not vice-versa.
Bergh et al. (2011)	16 months (each 4 months)	Highest cumulative incidence *for irritability* (42.6%), *disinhibition* (37.8%) and *depression* (31.5%). High persistence for Delusions, agitation, depression, disinhibition, irritability and aberrant motor behavior. No significant change in the severity of the NPS during the follow-up period.
Garre-Olmo et al. (2010c)	24-months	Increase of psychotic and behavioral symptoms (18–26% and 63–72%, respectively). Affective symptoms remained stable over the follow-up.
Savva et al. (2009)	2 years	Presence of *apathy*, *elated mood* or *confabulation* at follow-up was not significantly linked to their presence at baseline. Conversely, *anxiety*, *depression*, and *wandering behavior* at baseline were strong indicators for their presence at follow-up. Anxiety, depression, and elation did not tend to persist. Symptoms of *psychosis* were more persistent.
Selbaek et al. (2008)	12-month	Symptoms were chronically present, although individual symptoms often showed an intermittent course with higher resolution for *depression (58%), delusions (56%), and agitation/aggression (47%).*
Selbæk and Engedal (2012)	31 months	The most stable co-occurring symptoms in one and the same factor were depression and anxiety (*affective*), agitation, irritability, and disinhibition (*agitation*), delusions and hallucinations (*psychosis*), and apathy and appetite disorder.
Serra et al. (2010b)	12 months	Frequency and severity of dysphoria/depression, apathy, agitation/aggression, and anxiety remained substantially the same at follow-up. Delusions and irritability/lability increased significantly.
Steinberg et al. (2004)	18 months	Delusions and depression were the most persistent, while disinhibition was the least.
Tschanz et al. (2011)	3.8 years Drop-out: 29%	Increasing occurrence, rate, and overall severity of NPS over time. Rate of change in NPS was weakly correlated with rate of change in cognition or function.
Wancata et al. (2003)	6 months Drop-out: 26.9%	While, at T1, 33.7% suffered from any marked or severe non-cognitive symptoms, 11.6% remitted from these symptoms within 6 months.
Weamer et al. (2009)	2 years	Greater global cognitive impairment was present at base line in subjects who developed psychosis at follow-up.
Wetzels et al. (2010)	2 years	Agitation, irritability, and aberrant motor behavior were the most prevalent over the 2 years. Affective symptoms decreased, apathy tended to increase. Agitation and aberrant motor behavior were the most persistent symptoms.

have been described between neuropsychiatric symptoms, and patient-related or environmental factors.

PATIENT-RELATED FACTORS

Demographic factors

Aggressiveness or aberrant motor behavior has been more frequently reported in men with dementia whereas female gender has been associated with depressive/anxious symptoms and verbally agitated help-seeking behavior (Lövheim et al., 2009; Zuidema et al., 2010; Karttunen et al., 2011). In one study, female elderly with VaD had more neuropsychiatric symptoms than male elderly (Hsieh et al., 2009). In other studies, age and gender did not influence the likelihood of BPSD manifestation in AD or VaD (Savva et al., 2009; Di Iulio et al., 2010; Staekenborg et al., 2010).

Table 4 | BPSD: Alzheimer's disease vs. vascular dementia.

Reference	Sample	Findings
Aharon-Peretz et al. (2000)	30 AD + 30 VaD	Aggression, depression, anxiety and apathy significantly more severe in VaD-WSI than in AD.
Ballard et al. (2000a)	92 AD + 92 VaD	Depression and anxiety more common in VaD than in AD. Psychotic symptoms similarly common in VaD and in AD.
Chiu et al. (2006)	85 AD + 32 VaD	VaD with higher incidence of paranoid and delusional ideation and affective disturbance.
Fernández Martínez et al. (2008a)	37 AD + 28 VaD	Sleep disturbances and appetite changes more prevalent in AD than in VaD. Aberrant motor activity more common in subcortical VaD.
Fernández Martínez et al. (2008b)	81 AD + 14 VaD	Similar prevalence of BPSD in AD and VaD.
Fuh et al. (2005)	320 AD + 212 VaD	Similar prevalence in AD, cortical VaD, sub-cortical VaD, and mixed VaD. More severe sleep disturbance in cortical VaD than in AD.
Hsieh et al. (2009)	77 AD + 77 VaD	Higher prevalence of night-time behavior (sleep disturbance) in AD; higher prevalence of depression in VaD. Similar prevalence of delusions, hallucinations, and agitation in AD and VaD
Ikeda et al. (2004)	21 AD + 28 VaD	Delusions and aberrant motor behavior more likely in AD.
Kim et al. (2003)	99 AD + 36 VaD	Depression and anxiety significantly more severe in VaD than in AD.
Lyketsos et al. (2000)	214 AD + 62 VaD	Delusions more likely in AD and depression more frequent in VaD.
Lyketsos et al. (2002)	258 AD + 104 non-AD	Similar prevalence in AD and non-AD dementia, except for more frequent aberrant motor behavior in AD.
Srikanth et al. (2005)	44 AD + 31 VaD	Similar symptom profile in AD and in VaD.
Thompson et al. (2010)	377 AD + 74 VaD	No significant difference in AD and VaD patients on the BPCL or on the RMBPCL.

AD, Alzheimer disease; VaD, vascular dementia; VaD-WSI, ischemic white matter subcortical changes and lacunar infarctions; BPCL, behavior problems check list; RMBPCL, revised memory and behavior problems check list.

Table 5 | BPSD: Alzheimer's disease vs. fronto-temporal lobar degeneration.

Reference	Sample	Findings
Bathgate et al. (2001)	30 FTD + 75 AD + 34 VaD	Loss of basic emotions, food cramming, pacing a fixed route, an absence of difficulty in locating objects, and an absence of insightfulness differentiated FTD from other dementias.
Bozeat et al. (2000)	13 FTD + 20 SD + 37 AD	Stereotypic and eating behavior and loss of social awareness more common in the FTD group. Mental rigidity and depression more frequent in SD than in FTD. Patients with FTD more disinhibited.
Chiu et al. (2006)	17 FTD + 85 AD + 32 VaD	Higher incidence of activity disturbances in FTD.
Fernández Martínez et al. (2008b)	3 FTD + 81 AD + 14 VaD	Higher aberrant motor activity prevalence in FTD.
Ikeda et al. (2002)	23 FTD + 25 SD + 43 AD	Changes in eating behaviors more common in both FTLD groups compared with AD.
Levy et al. (1996)	22 FTD + 30 AD	Higher scores for disinhibition, apathy, aberrant motor behavior, and euphoria in patients with FTD compared with AD.
Nyatsanza et al. (2003)	18 FTD + 13 SD + 28 AD	Complex ritualized behaviors were significantly more frequent in patients with fvFTD and semantic dementia than in AD.
Srikanth et al. (2005)	23 FTLD + 44 AD + 31 VaD	Disinhibition, aberrant motor behavior, and appetite/eating disturbances could reliably differentiate AD and VaD from FTLD.

AD, Alzheimer disease; FTLD, fronto-temporal lobar degeneration; FTD, fronto-temporal dementia; SD, semantic dementia.

Considering that most studies included white population from northern European descent it's difficult to make assumptions about whether different symptom profile may arise according to ethnicity as reported by a few studies (Chen et al., 2000; Chow et al., 2002). In the study by Kim et al. (2003), age of onset and duration of dementia did not show any significant correlation with BPSD in patients with AD or VaD. Toyota et al. (2007) found conversely that early onset AD patients showed fewer BPSD than their late onset counterparts, particularly delusions, hallucinations, agitation, disinhibition, and aberrant motor behavior although this was not confirmed by a recent study (Garre-Olmo et al., 2010a).

Psychotropic medication

Aggressiveness and psychotic symptoms in outpatients with dementia have been found to increase the likelihood of receiving psychotropic medications by at least two-fold and this was coupled with a higher caregiver burden (Chiu et al., 2006). However, conclusions regarding the effects of medication on the natural course of BPSD are unclear as most studies don't have available data concerning the usual treatment of patients or don't include sub-analysis regarding this variable. Aalten et al. (2008) reported that the use of cholinesterase inhibitors (ChEI) influenced the structure of the apathy factor. Although this finding could derive from a therapeutic effect the available evidence suggests a modest impact of these drugs on neuropsychiatric symptoms (Rodda et al., 2009).The same holds true for antipsychotics which have been found to have little effect on the sub-syndrome factor structure of BPSD (Aalten et al., 2008).

Psychopathological symptoms

Depression affects up to 43% of patients with dementia and it predicts an increased number of neuropsychiatric symptoms, particularly agitation, anxiety, and irritability (Prado-Jean et al., 2010). Lack of insight occurs in the majority of AD patients even in early stages and appears to be an important predictive factor for the occurrence of increased levels of neuropsychiatric symptoms including apathy, agitation, irritability, psychosis, or behavioral symptoms in general (Vogel et al., 2010).

Neuropsychological deficits

The presence of alterations in specific cognitive domains may have a predictive value for the occurrence of BPSD. Psychotic symptoms in AD patients have been found to correlate with impairments in verbal fluency (Tsai et al., 2010) and in verbal learning tasks (Starr and Lonie, 2007). Premorbid IQ has been proposed to mediate the relationship between BPSDs and cognition in AD as it significantly correlated with mood, frontal, and psychotic factors (Starr and Lonie, 2007). In a cross-sectional study, impairments in memory (episodic and semantic), executive function, and verbal fluency all correlated with the severity of neuropsychiatric symptoms (García-Alberca et al., 2010). The presence of specific neurocognitive deficits, such as executive dysfunction, was reported to predict greater BPSD symptom severity in patients with MCI, particularly of depression and anxiety (Rosenberg et al., 2011).

ENVIRONMENTAL FACTORS

Presence of neuropsychiatric symptoms may arise from the characteristics of psychosocial/physical environment, such as crowded housing conditions leading to sensory overstimulation (for which patients with dementia are more susceptible), attitudes of care staff toward challenging behaviors and/or the size of the units in which patients reside throughout the day (Zuidema et al., 2010). Similarly, patients being restrained, or subjected to multiple moves and procedures, may also contribute to a range of BPSD symptoms, especially wandering and aggression (Kunik et al., 2010).

PATHOPHYSIOLOGY AND NEUROBIOLOGY OF BPSD

The behavioral or psychological disturbances occurring in dementia can be understood as ineffective attempts of the patient to cope with environmental or physiological stress factors. Indeed, BPSD are also common in non-demented older adults with rates of 5.6% for anxiety, 4.5% for irritability and 2.8% for agitation/aggression (Lyketsos et al., 2000) while psychotic symptoms are present in up to 10.5% of Swedish 85 years-old people (Ostling et al., 2009). It is important, therefore, to trace back these symptoms to premorbid psychosocial functioning which is determined by constitutional factors (e.g., personality traits, cognitive styles, and emotional reactivity), past experiences and level of education. Abnormalities in the intensity, magnitude, duration, timing, and modifiability of internal conditions and/or observable behaviors are expected to emerge beyond the limits of normal variability as the ongoing neuropathological changes of dementia undermine the individual's usual psychological capacities to adequately respond to everyday demands. Defining these neuroanatomical and neurochemical correlates of BPSD has been an area of active research with a hope that clarification of the underlying neurobiology will lead to more effective treatments (**Tables 6–8**).

PSYCHOSIS

Not many studies have examined the neuropathological correlates of psychosis in AD. Two studies found an association of psychosis with increased severity of beta-amyloid senile plaques (SP) in the presubiculum (Zubenko et al., 1991) and across cortical regions (Mukaetova-Ladinska et al., 1995). Förstl et al. (1994) reported changes in neuronal counts in the CA1 hippocampus and parahippocampal gyrus, while Zubenko et al. (1991) described increased density of neurofibrillary tangles (NFT) in the middle frontal cortex. Furthermore, Farber et al. (2000) reported that AD patients with psychosis had a 2.3-fold greater density of neocortical NFTs than AD subjects devoid of psychotic symptomatology. However, no similar relation was observed in non-neocortical areas or with SP burden. On the other hand, no significant differences were found between AD patients with ($n = 24$) and without ($n = 24$) psychosis in respect to SP and NFT densities in the study by Sweet et al. (2000). Consistently with the neocortical role underlying psychotic symptomatology, AD subjects with psychosis demonstrated significant elevations of glycerophosphoethanolamine and significant reductions of *N*-acetyl-L-aspartate in temporal, frontal, and parietal cortices (Sweet et al., 2002).

Neuroimaging studies have similarly confirmed severe abnormalities in grey matter volume, cerebral blood flow, and metabolism in the above cortical regions of AD subjects with psychotic symptoms (reviewed in Casanova et al., 2011). Anatomically, these changes partially coincide with cholinergic and dopaminergic pathways supporting, together with neurochemical and

Table 6 | BPSD and structural changes in neuroimaging exams.

Symptoms	Findings	References	Sample
	Computerized tomography		
Delusional misidentification	Right frontal and temporal atrophy	Förstl et al. (1994)	56 AD patients
	Magnetic resonance imaging		
Depression	Decreased gray matter volume in right hippocampus and amygdala	Egger et al. (2008)	14 AD patients
Apathy	Anterior cingulated gyrus, orbitofrontal, and frontosubcortical areas atrophy	Tunnard et al. (2011)	111 AD patients
		Bruen et al. (2008)	31 mild AD patients
		Massimo et al. (2009)	40 FTLD patients
Delusions	Decreased GM volume in frontal, temporal, and limbic regions	Bruen et al. (2008)	31 mild AD patients
		Massimo et al. (2009)	40 FTLD patients
Visual hallucinations	Lesions on visual cortex and association areas detected in MRI	Holroyd et al. (2000)	14 AD patients
Agitation	Anterior cingulated cortex and left insula atrophy	Bruen et al. (2008)	31 mild AD patients
Aggressive behavior	Amygdala atrophy	Poulin et al. (2011)	264 AD patients
Disinhibition	Cingulate frontal cortex atrophy and medial orbital frontal cortex atrophy	Serra et al. (2010a)	54 AD patients
		Massimo et al. (2009)	40 FTLD patients
Anxiety, sleep disorders, and aberrant motor behavior	Increased WMH volume	Berlow et al. (2010)	37 AD patients

AD, Alzheimer disease; FTLD, fronto-temporal lobar degeneration; GM, gray matter; MRI, magnetic resonance imaging; WMH, white matter hyperintensities.

Table 7 | BPSD and functional changes in neuroimaging exams (PET and SPECT studies).

Symptoms	Findings	References	Sample
Depression	Hypoperfusion and hypometabolism in some areas of temporal, frontal, and parietal lobes	Hirono et al. (1998)	53 AD patients
		Staffen et al. (2009)	149 MCI +131 DA + 127 DCI patients
Apathy	Decreased perfusion and hypometabolism in anterior cingulated gyrus, orbitofrontal, and frontosubcortical areas	Lanctôt et al. (2007b)	51 AD patients
		Benoit et al. (1999)	63 AD patients
		Marshall et al. (2007)	41 AD patients
		Craig et al. (1996)	31 AD patients
Psychosis	Hypometabolism in frontal lobe	Sultzer et al. (1995)	21 AD patients
Hallucinations	Hypoperfusion in parietal lobe	Kotrla et al. (1995)	30 AD patients
Delusions	Hypometabolism of prefrontal, anterior cingulate, right temporal, and parietal cortex	Staff et al. (2000)	45 AD patients
		Sultzer et al. (2003)	25 AD patients
	Increased metabolism in the inferior temporal gyrus and decreased metabolism in the occipital lobe	Hirono et al. (1998)	65 AD patients
Agitation	Changes in metabolism in frontal and temporal cortices	Sultzer et al. (1995)	21 AD patients
Aggressive behavior	Hypoperfusion in the temporal cortex (right middle and left anterior)	Lanctôt et al. (2004)	49 AD patients
		Hirono et al. (2000)	10 dementia patients

AD, Alzheimer disease; MCI, mild cognitive impairment; FTLD, fronto-temporal dementia; DCI, depression with cognitive impairment (DCI).

Table 8 | Associations between BPSD and genes.

References	Gene	Sample	Pathway	Clinical correlates
Borroni et al. (2006)	COMT	232 AD patients	Dopamine	Higher risk for "psychosis" (ORs = 3.05, 2.38, and 1.80 for delusions, hallucinations, and sleep disturbance symptoms, respectively) $p < 0.05$ Lower risk for "frontal" endophenotype (ORs = 0.25 and 0.25 for disinhibition and euphoria, respectively). $P < 0.05$
	5-HTTLPR		Serotonin	Lower risk for "psychosis" (ORs = 0.32, 0.41, and 0.54 for disinhibition and euphoria, respectively)
	APOE4			No correlation with any endophenotype
Angelucci et al. (2009)	5-HT2A receptor polymorphism (102T/C)	80 AD patients	Serotonin	Delusions associated with T allele ($p < 0.05$)
Di Maria et al. (2009)	G72 gene (locus DAO)	185 AD patients	Glutamate	Delusions and hallucination ($p < 0.05$)
Proitsi et al. (2012)	SERT STin2 12R	1008 AD patients	Serotonin	Less "psychosis" ($p = 0.025$) and less apathy ($p = 0.007$)
	DAT 10R		Dopamine	Increased agitation ($p = 0.003$) increased aberrant motor behavior ($p = 0.009$)
	DRD4 2R			Increased "moods" levels ($p = 0.004$); increased sleep abnormalities ($p = 0.032$)
	DRD1 G			Higher irritability ($p = 0.01$); lower aberrant motor behavior ($p = 0.023$)
	DRD3 *Ball* C			Lower depression ($p = 0.007$)

COMT, catechol-O-methyl transferase; 5-HTTLPR, serotonin gene-linked polymorphic region; APOE, apolipoprotein E; 5-HT2A, serotonin 2A receptor; DAO, D-amino acid oxidase; SERT STin2, serotonin transporter gene polymorphism STin2; DAT, dopamine transporter gene; DRD4, dopamine receptor 4; DRD1, dopamine receptor 1; DRD3, dopamine receptor 3 Ball polymorphism.

pharmacological evidence, the role of acetylcholine and dopamine imbalance in the pathogenesis of AD psychosis (reviewed in Pinto et al., 2011). Psychosis has also been associated with the relative preservation of norepinephrine in the substantia nigra and a significant serotonin reduction in the presubiculum (Ismail et al., 2011). A strong hereditability has been reported for psychosis in AD, suggesting an important role for APOE4 (Ismail et al., 2011). Other genes have also been associated with higher risk of psychosis [(COMT, G72 gene (locus DAO); 5-HT2A receptor polymorphism (102T)] while others may be "protective" (5-HTTLPR, SERT STin2 12R; **Table 8**). In DLB, visual hallucinations have been linked to higher Lewy Body density in the temporal cortex and amygdala (Harding et al., 2002; Tsuang et al., 2009) and with less severe density of neocortical tangles (Ballard et al., 2004). Cholinergic deficits have been described for hallucinations and delusions in both AD (Tsang et al., 2008) and DLB (Ballard et al., 2000b; Teaktong et al., 2005), thus providing a rationale for the therapeutic use of cholinergic drugs to treat these symptoms.

DEPRESSION

Several lines of evidence suggest that depression shares complex pathophysiological routes with dementia. It has been hypothesized that chronic depression may accelerate neurodegenerative changes of AD as a result of the neurotoxic effects of elevated cortisol levels in the hippocampus (Korczyn and Halperin, 2009). Moreover, the observation that the late-life depressive disorders are commonly associated with increased number of white matter hyperdensities in subcortical areas supported the so-called "vascular hypothesis" of depression (Alexopoulos, 2005). Reversely, neurodegenerative and vascular changes may act as a risk factor for depression.

Depressed non-demented patients present with chronic elevation of inflammatory mediators, known to play a central role in AD pathogenesis, together with altered serotonin metabolism and reduced neurotrophic activity (Caraci et al., 2010). So, in addition to being merely an emotional reaction to early memory deficits depression can be a prodromal symptom of dementia, a risk factor for neurodegeneration or co-occur with cognitive impairment. Post-mortem studies in AD subjects found higher burden of neuropathological lesions in those with a lifetime history of depression (Rapp et al., 2006) or presenting with concurrent depression (Rapp et al., 2008). Functional imaging studies revealed decreased perfusion and hypometabolism in the temporal, frontal, and parietal cortex, as well as in thalamus and lentiform nucleus of depressed compared to non-depressed AD patients (Hirono et al., 1998; Staffen et al., 2009). However, in other post-mortem studies in AD subjects with depressive symptoms were not related to the level of pathology (Wilson et al., 2003; Sweet et al., 2004).

The only prospective study assessing brain tissue from dementia-free subjects ($n = 153$) did not find increased AD or cerebrovascular pathology in those with late-life depression (Tsopelas et al., 2011), suggesting that depression *per se* may be linked to additional, more subtle neuropathological and/or neurobiochemical changes, such as those involving the neurotransmitter systems. Indeed, a disturbed serotoninergic system has been associated with depressive symptoms in AD as several areas of the brain exhibit decreased serotonin concentration, with a significant

reduction in 5-HT1 and 5-HT2 receptors throughout the cerebral cortex (Lanari et al., 2006). Similarly, loss of noradrenergic cells in consequence of degeneration of the locus coeruleus is also seen in individuals with dementia who manifest depressive symptoms (Lanari et al., 2006). Changes of GABAergic plasma levels observed in final stages of AD have also been associated with depression, apathy, and aggressive behaviors (Lanctôt et al., 2007a). Association between genetic factors and depression are summarized in **Table 8**.

APATHY

Post-mortem and *in vivo* studies suggest that AD is associated with a dysfunctional dopaminergic system, since reduced levels of dopamine (DA) and homovanilic acid, as well as altered DA receptor density, have been described in discrete brain regions coinciding with the mesocorticolimbic pathway (Mitchell et al., 2011). On the other hand, neuroimaging studies in AD have been consistently showing a significant association between apathy and changes in the brain reward system including atrophy (Apostolova et al., 2007; Bruen et al., 2008; Tunnard et al., 2011), hypoperfusion and hypometabolism (Craig et al., 1996; Benoit et al., 1999; Lanctôt et al., 2007b; Marshall et al., 2007) in the anterior cingulated gyrus and orbitofrontal areas (**Tables 6**, **7**). It is also possible that dysfunction in these areas underlies the reported relation between increased frontal white matter changes and apathy (Starkstein et al., 2009) together with disruption of deep white matter afferents and efferents to the basal ganglia and/or by decrement of metabolic activity in frontal subcortical regions. In FTD subjects, apathy has been associated with atrophy in the anterior cingulated cortex, right dorso-lateral prefrontal cortex (Massimo et al., 2009), and adjacent medial frontal cortex (Rosen et al., 2005). This suggests that dysfunction in the frontosubcortical cingulate pathways is implicated in apathy regardless of the sub-type of dementia.

OTHER SYMPTOMS

Increased burden of NFT in the orbitofrontal cortex has been linked to agitation (Tekin et al., 2001), while aggressive behaviors have been associated with neuronal loss in locus ceruleus (Matthews et al., 2002). Deterioration of brainstem regions and in the suprachiasmatic nucleus of the hypothalamus has been reported in patients with sleep disorders (Yesavage et al., 2003).

MANAGEMENT OF BPSD

Management of BPSD is a key component of a comprehensive approach to the treatment of dementia requiring the judicious combination of pharmacological and non-pharmacological interventions. Treatment of these symptoms remains problematical, with an increased risk of psychotropic medication misuse, and, thus, represents an important challenge for clinicians. Current guidelines recommend non-pharmacological interventions as first-line treatment followed by the least harmful medication for the shortest time possible (Gauthier et al., 2010; Azermai et al., 2011).

NON-PHARMACOLOGICAL INTERVENTIONS

Non-pharmacological interventions have been classified into the following categories (O'Neil et al., 2011): (i) cognitive/emotion-oriented interventions (reminiscence therapy, simulated presence therapy, validation therapy); (ii) sensory stimulation interventions (acupuncture, aromatherapy, light therapy, massage/touch, music therapy, Snoezelen multisensory stimulation, transcutaneous electrical nerve stimulation); (iii) behavior management techniques; and (iv) other psychosocial interventions such as animal-assisted therapy and exercise. Unfortunately, despite efforts in investigating these interventions, consistent evidence about the efficacy of the various psychosocial therapies is lacking (Kong et al., 2009). Benefits from psycho-educational interventions for caregivers were documented to be long-lasting, especially when delivered individually (Livingston et al., 2005). Special care units have been developed since the 1980s and are commonly situated in nursing homes. They include the features of trained staffing, a modified physical environment, and family involvement (Lai et al., 2009).

Specific therapeutic interventions for different symptoms of BPSD have also been investigated. In relation to agitation and aggressive behavior, and before opting for any intervention, it is important to carefully analyze the causes for the disruptive behavior: such causes may include pain, medical illness, fatigue, depression, loneliness, understimulation, or overstimulation; and social and environmental stressors (Iwata et al., 1993; Salzman et al., 2008). Strategies reported to be useful to reduce agitation include sensory interventions, particularly music therapy (Choi et al., 2009), aromatherapy (Ballard et al., 2009), and environmental modification (Weitzel et al., 2011). Regarding depression, recent studies support the effectiveness of home-based exercise programs for people with dementia and their caregivers to reduce depressive symptoms (Prick et al., 2011). Recently animal-assisted activities were suggested to be associated with a decrease in anxiety and sadness and an increase in positive emotions and motor activity (Mossello et al., 2011).

PHARMACOLOGICAL INTERVENTIONS

A variety of medications have been used to treat BPSD including typical and atypical antipsychotics, antidepressants, anticonvulsant mood stabilizers, ChEI, benzodiazepines, and other drugs, such as memantine. These drugs have variable efficacy and effectiveness in treating BPSD, depending on the target symptom and class of medication. The pharmacological treatment of BPSD should consider the presence of additional comorbidities and associated medications, which increase significantly the risk of both medical complications and drug interactions. Current guidelines recommend careful consideration of both benefits and limitations of each drug class with the use of the least harmful medication for the shortest time possible (Gauthier et al., 2010).

Antipsychotics

The use of antipsychotics, particularly since the introduction of atypical antipsychotics, has increased over time (Briesacher et al., 2005). They have shown efficacy in treating specific symptoms, such as aggression, psychosis, and agitation (Ballard et al., 2008; Gauthier et al., 2010). However the evidence regarding other BPSD symptoms is not convincing (Ballard et al., 2008). Despite serious side effects, including extrapyramidal symptoms, sedation, tardive dyskinesia, gait disturbances, falls, anticholinergic side effects, cerebrovascular events, and increased mortality, antipsychotic are

still widely used off-label (Azermai et al., 2011). Risperidone, olanzapine, and haloperidol appear to be more effective for managing BPSD (Azermai et al., 2011). A recent study on dementia patients reported a 1.5-fold increase in mortality associated with the use of haloperidol, compared to risperidone, olanzapine or quetiapine. The mortality risk with haloperidol was highest during the first 30 days and decreased significantly over time (Kales et al., 2012). The use of an antipsychotic for severe symptoms such as agitation, aggression, and psychotic symptoms should be time-limited and a careful individual evaluation is recommended due to increased risk of stroke and mortality. In the UK, risperidone is licensed for up to 6 weeks treatment of persistent aggression in subjects with moderate-to-severe AD, and the recommendations are to be used as a last resort for aggression, when all other methods have failed to alleviate the most distressing symptoms of dementia, and only when it is in the best interests of the person (https://www.alzheimers.org.uk/antipsychotics). It is prudent to initiate with a low dose and regularly review the prescription in function of the patient's response and presence of adverse events.

Antidepressants

Antidepressants can be an effective and well-tolerated alternative to antipsychotics in vulnerable elderly individuals for treatment of BPSD (Henry et al., 2011). This class of drugs has been used primarily for depression, with efficacy especially for the selective serotonin reuptake inhibitors (SSRIs; Gauthier et al., 2010). Some authors found that citalopram and sertraline could improve symptoms of agitation and psychosis in subjects with dementia with similar efficacy, but better tolerability and safety, than haloperidol and risperidone (Gauthier et al., 2010; Seitz et al., 2011). Citalopram was effective in treating disinhibition, irritability and depression and also behaviors specific to FTD (Herrmann et al., 2011). However, the evidence so far does not support the use of these medications for BPSD other than depression (Azermai et al., 2011).

Cholinergic inhibitors

Current guidelines support the use of ChEI for BPSD although different recommendations exist to each specific drug (Gauthier et al., 2010). Donepezil, galantamine, or rivastigmine have all shown a modest effect on the broad spectrum of neuropsychiatric symptoms in AD (Rodda et al., 2009). They should be initiated prior to the use of other psychotropic agents since ChEIs reduce behavioral changes and improve or delay cognitive and functional decline (Gauthier et al., 2010). The behavioral symptoms most likely to improve with ChEIs treatment appear to be apathy, depression, and aberrant motor behavior (Cummings, 2004; Holmes et al., 2004; Feldman et al., 2005).

Memantine

Memantine, an NMDA receptor antagonist, can also have beneficial effects on behavior, as well as on cognition and function; however there is insufficient evidence to recommend its use (Azermai et al., 2011). The use of memantine appears to improve specific behaviors, such as agitation and irritability, which differ from those affected by ChEIs (mood symptoms, apathy, and aberrant motor behavior). Combination therapy may have advantages in patients with multiple BPSD (Gauthier et al., 2010). The latest report on combined memantine and ChEIs (donepezil) treatment did not show any major advantages on cognitive and behavioral changes in subjects with moderate-to-severe AD, compared to those treated with either memantine or donepezil, with only negligible improvement on the NPI scores in the subjects treated with the combination of the two antidementia drugs (Howard et al., 2012).

Anticonvulsants

Anticonvulsant mood stabilizers such as carbamazepine, valproic acid, gabapentin, lamotrigine, topiramate are widely used in clinical practice. Treatment regimens with anticonvulsant mood stabilizers have shown promising results and seem to be beneficial for some dementia patients (Konovalov et al., 2008). Anticonvulsants may allow dose reduction of antipsychotics; however, investigation regarding benefits, safety, and tolerability of these drugs has produced mixed results, so they are not recommended for routine use. In particular sodium valproate has been shown to be ineffective in the treatment of agitation in AD, and has been associated with increased adverse effects, including falls, infection, and gastrointestinal disorders (Lonergan and Luxenberg, 2009).

Benzodiazepines

Benzodiazepines may be used at short-term for acute agitation or agitation associated with anxiety (Azermai et al., 2011).

CONCLUSION

Neuropsychiatric symptoms are frequent in dementia and contribute significantly for burden caregiver and illness costs. Correct identification and evaluation of these symptoms is a crucial part of the clinical approach to dementia. Despite the tentative efforts to group different symptoms into clusters (to facilitate clinical/diagnostic investigations), there is not yet an established model. The pathogenesis of these symptoms is not well understood, and the current knowledge supports multifactorial causes. Development and use of new specific investigation techniques may be helpful to better understand the underlying etiological mechanisms of various neuropsychiatric symptoms. At present, combination of non-pharmacological and appropriate pharmacological strategies represents the best treatment of BPSD. However, there is no consistent evidence about specific strategies for individual symptoms. It is necessary to encourage application of novel non-pharmacological interventions, which are safer than pharmacological therapies. Further investigation is similarly needed to find more effective, safe, and well-tolerated pharmacological therapies. This will help to devise novel, more symptom targeted, and specific interventions that will improve significantly the management of BPSD symptoms in subjects with dementia.

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Delirium in elderly people: a review

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The present review aims to highlight this intricate syndrome, regarding diagnosis, pathophysiology, etiology, prevention, and management in elderly people. The diagnosis of delirium is based on clinical observations, cognitive assessment, physical, and neurological examination. Clinically, delirium occurs in hyperactive, hypoactive, or mixed forms, based on psychomotor behavior. As an acute confusional state, it is characterized by a rapid onset of symptoms, fluctuating course and an altered level of consciousness, global disturbance of cognition or perceptual abnormalities, and evidence of a physical cause. Although pathophysiological mechanisms of delirium remain unclear, current evidence suggests that disruption of neurotransmission, inflammation, or acute stress responses might all contribute to the development of this ailment. It usually occurs as a result of a complex interaction of multiple risk factors, such as cognitive impairment/dementia and current medical or surgical disorder. Despite all of the above, delirium is frequently under-recognized and often misdiagnosed by health professionals. In particular, this happens due to its fluctuating nature, its overlap with dementia and the scarcity of routine formal cognitive assessment in general hospitals. It is also associated with multiple adverse outcomes that have been well documented, such as increased hospital stay, function/cognitive decline, institutionalization and mortality. In this context, the early identification of delirium is essential. Timely and optimal management of people with delirium should be performed with identification of any possible underlying causes, dealing with a suitable care environment and improving education of health professionals. All these can be important factors, which contribute to a decrease in adverse outcomes associated with delirium.

Keywords: delirium, aged, diagnosis, etiology, prevention and control

INTRODUCTION

The word delirium is derived from the Latin term *delirare*, meaning to become "crazy or to rave" (Saxena and Lawley, 2009). It has been documented in medical literature for more than 2000 years, with a fairly consistent clinical description (Adamis et al., 2007). It was reported during the time of Hippocrates, who used the words *phrenitis* (frenzy) and *lethargus* (lethargy) to describe the hyperactive and hypoactive subtypes of delirium. As a medical term, delirium was first used by Celsus in the first century A. D. to describe mental disorders associated with fever or head trauma (Khan et al., 2009).

A variety of terms have been used in the literature to describe delirium, including "acute confusional state," "acute brain syndrome," "acute cerebral insufficiency," and "toxic-metabolic encephalopathy" (Morandi et al., 2008). However, delirium is now the preferred term (Gill and Mayou, 2000) and it has been suggested that acute confusional state should be the only accepted synonym for this syndrome (Lipowski, 1992).

Delirium was standardized for the first time as a clinical entity in the Diagnostic and Statistical Manual of Mental Disorders, third edition/DSM-III (APA, 1980). The more recent version of this manual is now considered to be the gold standard for delirium diagnosis (CCSMH, 2006; NICE, 2010). Furthermore, this classification has been designed to be simple and sensitive enough to detect the presence of delirium in different settings, in particular among acutely ill and hospitalized elderly patients (Laurila et al., 2004).

According to the current DSM criteria (APA, 2000), delirium is characterized by the rapid onset of symptoms that tend to fluctuate even during the same day with an altered level of consciousness, global disturbance of cognition or perceptual abnormalities and evidence of a physical cause, substance intoxication/withdrawal, or multiple etiologies.

Delirium is a common and serious problem, mainly in hospitalized elderly patients (Saxena and Lawley, 2009). Its diagnosis is based on clinical history, key features observation, and physical and cognitive assessment (Fearing and Inouye, 2009; Fong et al., 2009a).

The etiology of delirium is usually multifactorial, resulting commonly from a combination of predisposing and precipitating factors (Rolfson, 2002; CCSMH, 2006). Its pathophysiological mechanisms remain poorly understood, with some evidence for the contribution of neurotransmission disruption, inflammation, or acute stress responses (Saxena and Lawley, 2009).

Delirium has also been associated with multiple adverse outcomes (Siddiqi et al., 2006; Cole et al., 2009). It is often poorly diagnosed, in particular due to its fluctuating nature, its overlap with dementia and lack of formal cognitive

assessment in general hospitals (Cole, 2005; CCSMH, 2006; Inouye, 2006).

In the management of delirium, non-pharmacological interventions have been considered the first-line strategy (Fong et al., 2009a), which includes, initially, the identification of underlying causes, supportive care (with involvement of family), and manipulation of the environment. In spite of that, prevention strategies emerge as the most important and cost-effective approaches for delirium, contributing to the decrease in its frequency, and associated poor outcomes (Inouye, 2006; NICE, 2010), namely in patients with Alzheimer's disease (Fick et al., 2002), given the evidence that delirium accelerates disease progression, even in cases where the etiology does not involve any cerebral structural insult.

EPIDEMIOLOGY

Delirium is a common and serious condition among the elderly, particularly in hospitalized patients, affecting up to 30% of this patient population (Saxena and Lawley, 2009). Most recent studies report a prevalence of delirium of 10–31% on admission and an incidence of 3–29% during hospitalization (Siddiqi et al., 2006).

This risk increases exponentially in intensive care units, with prevalence rates of up to 80% (Morandi and Jackson, 2011) and in palliative care units, where it is reported to be as high as 85% (Casarett and Inouye, 2001). Higher rates are also noted in surgical settings (Young and Inouye, 2007), with an incidence reported to range from 10 to 70% after surgery (Guenther and Radtke, 2011), especially in patients undergoing cardiothoracic surgery, emergency orthopedic procedures (repair of a hip fracture), vascular surgery, or cataract removal (Saxena and Lawley, 2009). Studies among elderly people presenting in emergency departments have reported prevalence rates of 5–30% (Lewis et al., 1995; Elie et al., 2000; Inouye, 2006).

In spite of long-term care, nursing home residents represent a vulnerable group, but only a few studies have been carried out (CCSMH, 2006). In a recent study (McCusker et al., 2011) the prevalence of delirium has been estimated between 3.4 and 33.3%. In the community, as expected, the prevalence is lower, ranging from 1 to 2% (Popeo, 2011).

CLINICAL FEATURES

Based on DSM-IV-TR criteria, delirium is characterized by the rapid onset of symptoms (usually hours or days) and tends to fluctuate, with an altered level of consciousness, with an inability to focus, sustain or shift attention, and a change in cognition (such as memory impairment, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by dementia. Moreover, there is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition, or substance intoxication/withdrawal, or due to multiple etiologies (APA, 2000).

This definition has the advantage of covering a broad clinical spectrum, but it also implies great complexity. The areas of neurological function identified are indeed wide and can hardly be attributed to the activity of discrete cerebral structures. Also controversial is the interpretation that the syndrome is caused by the ability of different etiological factors to impact on a final common pathway producing stereotyped clinical consequences (Caraceni and Grassi, 2011).

Sudden and acute onset and fluctuating course are the central features of delirium. Therefore, it is important to establish the patient's level of baseline cognitive functioning and the course of cognitive change (Fearing and Inouye, 2009). Symptom fluctuation is unpredictable. They may be intermittent, and are often worse at night (Cole, 2004).

Consciousness as a brain function allows the awareness of oneself and of the environment (Fish, 1967) and is characterized by two main aspects: the level of consciousness and the content of consciousness (Plum and Posner, 1972). The level of consciousness reflects arousal and vigilance: being awake, asleep, or comatose. The content of consciousness, or part of it, is experienced by the subject as awareness of him or herself and of the environment when awake and normally alert. The content of consciousness and cognition can be examined only if at least a certain degree of wakefulness and alertness are preserved (Caraceni and Grassi, 2011).

Consciousness should also be considered as a continuum from full alertness and awareness to coma and its impairment appears as the primary change in acute organic disorders. In this sense, it places an important role in the detection of acute disturbances of brain function, as well as, in the assessment of its severity (Lishman, 1997).

In delirium, the disturbance of consciousness is one of the earliest manifestations, which often fluctuates, mainly in the evening when environmental stimulation is at its lowest (Burns et al., 2004). The level of consciousness may fluctuate between extremes in the same patient, or alternatively may present with more subtle signs, such as mild drowsiness, or an impaired level of attention (Saxena and Lawley, 2009). In fact, the patient may appear obviously drowsy, lethargic, or even semi-comatose in more advanced cases. The opposite extreme, hyper-vigilance, may also occur, especially in cases of alcohol or sedative drug withdrawal (less common in elderly people; Francis and Young, 2011).

Attention is the process that enables one to select relevant stimuli from the environment, to focus and sustain behavioral responses to such stimuli, and to switch mental activity toward new stimuli, reorienting the individual behavior, according to the relevance of the stimulus (Caraceni and Grassi, 2011). Attention is a different function from consciousness, but it is dependent on it. Thus, variable degrees of attention are possible with full consciousness, but complete attention and concentration are impossible with diminished consciousness. In fact, attention may be pathologically decreased in organic states, usually with lowering of consciousness (Oyebode, 2008).

In delirium, inattention occurs and it is also considered one of the important cardinal features (Cole, 2005). Usually these patients are easily distractible by irrelevant stimuli, or have difficulty keeping track of what was being said during the clinical interview. Moreover, most of the time, the questions must be repeated because the individual's attention wanders (APA, 2000).

Typically there are global or multiple deficits in cognition, including memory impairment and disorientation. In fact, due to this inattentiveness, the registration of new information can be impaired, affecting memory, and orientation functions (Cole, 2004).

In the first case, the short-term memory is the most commonly affected (APA, 2000; Longo et al., 2011), but retrieval of stored information can also be disturbed (Saxena and Lawley, 2009). For instance, patients can have an inability to remember events in the hospital or difficulty in remembering instructions (Inouye, 2003).

Disorientation is usually common, first in reference to time and then to place (Burns et al., 2004). However, it may be considered not abnormal for an inpatient that has been seriously ill for a long time, without references of days or months.

The functions of thinking and speaking overlap and cannot be readily separated from each other, but they are clearly different. Both can be impaired in delirium (Oyebode, 2008).

Language difficulties and its impoverishment in delirium patients are probably more related to the disorder of arousal and attention levels, than a specific cause, or still they may reveal a thought process alteration. In severe cases of global impairment, frank confabulation can dominate, leaving little opportunity to assess language, memory, and thought content. Often language and speech, including reading, are less affected than writing, especially in mild or early stages. Few specific observations on language disturbances found in the course of delirium are available. In one study, misnaming has been commonly found, as frequent as observed in demented patients, but they differed in being more often of the types of word intrusion and unrelated misnaming (Wallesch and Hundsaltz, 1994). Word intrusion is in part explained by perseveration. The patient repeats a previously uttered word (therefore perseverating) rather than the expected word that he/she is unable to find or pronounce. Unrelated misnaming is the use of word that wildly differs in meaning from the intended word and therefore has no relationship with the word appropriate for the context, unlike paraphasia (Caraceni and Grassi, 2011).

Another clinical feature is disorganized thinking, manifested by incoherent speech and rambling or irrelevant conversation, or unclear or illogical flow of ideas (Inouye, 2006). The patient may be unable to make appropriate decisions, or execute simple tasks. Their judgment and insight may be poor and delusions can also occur in around 30% of the cases (Meagher et al., 2007), particularly of a paranoid or persecutory nature (Cole, 2004).

Perceptual disturbances have also been described in people with delirium. These may include illusions and misinterpretations, which arise from a false impression of an actual stimulus. For example, a patient may become agitated and fearful, believing that a shadow in a dark room is actually an attacker. The perceptual disturbance can also include hallucinations, where no object is actually present (Oyebode, 2008). Visual hallucinations are the most frequent, often occurring at night (Cole, 2004), and in some cases they can appear during the day as soon as the patient closes his eyes. The content of the hallucinations tends to be simple, at times just colors, lines, or shapes (Caraceni and Grassi, 2011). However, it can include, for instance, dangerous animals or bizarre images (Saxena and Lawley, 2009).

There are other clinical features commonly associated with delirium that are not included in the diagnostic criteria (Fearing and Inouye, 2009). One of them is sleep-wake cycle disturbance, characterized by an excessive daytime sleepiness with insomnia at night, fragmentation, and reduction of sleep or complete sleep-cycle reversal (Inouye, 2006).

Some studies have observed the potential role of these disturbances, in particular disordered circadian rhythm (Bachman and Rabins, 2006) and sleep fragmentation (Kim et al., 2005) as an important contributing factor to the sundowning syndrome. This phenomenon has been seen in patients with delirium and is characterized by worsening of disruptive behavior in the late afternoon or evening. This syndrome may also be due to fatigue and reduced sensory input toward the evening (Bachman and Rabins, 2006; Saxena and Lawley, 2009).

Disturbed psychomotor behavior is another clinical feature of delirium, with unusually increased or decreased motor activity. In the first case, patients may have restlessness or frequent sudden changes of position. On the other hand, the patient may also show sluggishness or lethargy, approaching stupor (APA, 2000).

In these patients, emotional disturbances, such as anxiety, fear, irritability, anger, depression, and euphoria, may also be seen. These symptoms are often influenced by factors, such as medical or surgical conditions, personality characteristics, premorbid psychiatric disorders, or recent life events (Cole, 2004).

According to some authors (Meagher et al., 2008) some caveats should be taken into account in the discussion of delirium classification and criteria currently used.

For instance, despite the tendency to make the criteria explicit according to the specificity of the symptoms of delirium, it must be remembered that certain clinical situations, hospitalization, or physical symptoms, such as pain or breathing difficulty, can give rise to pseudo-delirious symptoms, such as sleep disturbance (Caraceni and Grassi, 2011).

Moreover, a poor correlation has been shown between the different sets of diagnostic criteria (DSM-IV, ICD-10). In particular, a study (Laurila et al., 2003) reported different delirium prevalence rates in elderly people admitted to hospital or nursing homes, according to the criteria used (24.9% by DSM-IV and 10.1% by ICD-10). These results clearly indicate that too inclusive or too restrictive criteria can cause marked differences in estimated prevalence rates of delirium (Caraceni and Grassi, 2011).

Bearing this controversy in mind, some authors (Watt et al., 2012) go beyond this criticism of delirium in the DSM-IV criteria. These authors have questioned the notion of delirium as reflecting an "altered level of consciousness." As an alternative, these authors have suggested that delirium reflects the collapse of cognitive operations (attention, working memory, and executive functions), in direct proportion to the severity of any confusional state, and given that these processes are basilar for every other cognitive process, their breakdown compromises the entire cognitive apparatus (Watt et al., 2012). These processes define a base for the cognitive pyramid and are functionally deeply interdigitating, and difficult to neatly separate (Watt and Pincus, 2004). This perspective is not present in the current DSM criteria.

Another limitation is related to the severity of delirium, which is inadequately represented in this classification, as the complete clinical spectrum ranges from very severe deliriums where patients are minimally conscious, to low-grade encephalopathic states in a broad continuum, frequently missed by clinicians (Watt et al., 2012).

So, according to these authors (Watt et al., 2012), delirium might belong to a broader category of diseases of consciousness. They have suggested the following as a rough heuristic, with disorders of consciousness ranging from the most severe to the least severe: Coma; Persistent Vegetative State; Stupor; Akinetic Mutism; Minimally Conscious State; Delirium/Confusional States (Watt and Pincus, 2004). Such taxonomy would provide a continuum, with "gray zones," or transitional regions demarcating one disorder from the next. This approach would further allow for a continuum of severity in relation to delirium itself, which is currently disregarded in DSM-IV (Watt et al., 2012).

In spite of this, clinical evaluation according to the symptom phenomenology and the nosographic criteria appears as a reference standard for the diagnosis of delirium. In addition, the correct examination of delirious symptoms for epidemiological reasons, research, and clinical purposes is essential and has been reported by many authors (Casarett and Inouye, 2001; Breitbart et al., 2009).

SUBSYNDROMAL DELIRIUM

Since the publication of well-established sets of diagnostic criteria, such as the DSM-IV, there has recently emerged a new concept known as subsyndromal delirium (Voyer et al., 2009).

This condition has been defined as the presence of one or more core diagnostic symptoms that do not meet the full criteria for delirium, and where progression to delirium does not occur. The core symptoms were: inattention, altered level of consciousness, disorientation, and perceptual disturbances (Levkoff et al., 1996; Cole et al., 2003).

From a clinical perspective, some authors have suggested an alternative term: "low-grade confusional state." This emphasizes the need to rate the severity of confusional states – mild, moderate, severe – in opposition to the strict concept of DSM-IV (Watt et al., 2012). As suggested by Voyer et al. (2009), these criteria, when applied very literally, produce underestimation of delirium.

Subsyndromal delirium occurs in 21–76% of hospitalized elderly people (Cole et al., 2008). Prevalence rates of 30–50% have been reported in intensive care units (Ouimet et al., 2007). In long-term care elderly residents, with dementia, the occurrence was 48.4 or 50.3%, depending on the criteria used (Voyer et al., 2009). A recent cohort study has found that 68 of the 104 residents had incident subsyndromal delirium during 6 months of observation. The incidence rate was 5.2 per 100 person-weeks of follow-up (Cole et al., 2011).

The risk factors for subsyndromal delirium are similar to those for classical overt delirium: advanced age, dementia, and severe illness. Moreover, this condition has been associated with poor outcomes, such as a lower cognitive and functional level, increased length of acute care hospital stay, and decreased post-discharge survival at 12 months (Cole et al., 2003).

Thus, patients with subsyndromal delirium require identification and clinical attention in line with management of delirium in order to attain the best outcome (Levkoff et al., 1996).

CLINICAL SUBTYPES

Lipowski (1980) was the first author to suggest that delirium can occur in three clinical forms: hyperactive, hypoactive, and mixed, based on psychomotor behavior. This classification is not recognized by DSM-IV or ICD-10 (International Classification of Diseases; WHO, 1992) diagnostic criteria (Lindsay et al., 2002). However several studies have confirmed the existence of this clinical classification (Camus et al., 2000; de Rooij et al., 2005).

In the hyperactive subtype, there is increased psychomotor activity. Patients show features such as hyper-vigilance, restlessness, agitation, aggression, mood lability, and in some cases, hallucinations and delusions (Lipowski, 1980). Behaviors are frequently disruptive (e.g., shouting or resisting, pulling out the IV tubing) or potentially harmful (e.g., pulling out catheters). Because of this, this subtype is the most easily identified (Saxena and Lawley, 2009). Moreover, patients with this form are more likely to be medicated, in particular with benzodiazepines and neuroleptics (Caraceni and Grassi, 2011).

In contrast, the hypoactive form is characterized by decreased psychomotor activity, with the presence of lethargy and drowsiness, apathy, and confusion. Patients become withdrawn, answering slowly to questions and without spontaneity. Sometimes patients can also appear to be sedated (NICE, 2010). This is the most common subtype of delirium in elderly people (Meagher et al., 2011). In a recent study (Khurana et al., 2011) with hospitalized elderly delirious patients, a high prevalence of hypoactive delirium was found (65%), when compared to the other forms. However, due to the absence of disruptive and injurious behaviors, this subtype can be more difficult to recognize by clinicians (NICE, 2010; Mittal et al., 2011).

In mixed delirium, patients have symptoms of both the subtypes mentioned above (Liptzin and Levkoff, 1992). It has been reported to be the most common type.

Different patterns have been suggested for these three different forms of delirium. Dissimilar underlying pathogenetic pathways will determine different management, course, prognosis, and outcomes (Meagher et al., 2000; de Rooij et al., 2005; Fong et al., 2009a).

Unfortunately, the literature is inconsistent about which subtype has the worse prognosis. However, some authors have suggested there is evidence that the hypoactive form is associated with a relatively poorer prognosis (Yang et al., 2009) and in a recent longitudinal study (Meagher et al., 2011), the patients with this subtype have been significantly more likely to die within 1 month of study entry.

DIAGNOSIS

Delirium is frequently under-recognized and often misdiagnosed by health professionals. Between a third and two-thirds of delirium cases go unrecognized (Siddiqi et al., 2006). A recent study (Han et al., 2009) in an emergency department concluded that the emergency physicians missed delirium in 76% of the cases.

This under-recognition has been associated with factors such as the fluctuating nature of delirium, its overlap with dementia and depression, the scarcity of formal cognitive assessment in general hospitals by routine, under-appreciation of its clinical consequences, and failure to consider the diagnostic importance (CCSMH, 2006; Inouye, 2006; Philpot, 2011). Non-detection of delirium has been also associated with the high prevalence of the hypoactive form of delirium (Armstrong et al., 1997). Four independent risk factors for the under-recognition of delirium by

nurses have been identified: hypoactive delirium, advanced age, vision impairment, and dementia (Inouye et al., 2001).

A recent survey of trainee physicians in the UK revealed a lack of basic knowledge about the diagnosis and management of delirium, although they appeared to be aware of its high prevalence in hospitals as well as its potential clinical significance (David and MacLullich, 2009).

The diagnosis of delirium remains primarily clinical, without specific diagnostic tests (Young and Inouye, 2007). In this way, it is made on the basis of clinical history, behavioral observation of key features, and comprehensive physical and cognitive assessment (Fearing and Inouye, 2009; Fong et al., 2009a). In this context, understanding and considering its clinical features is crucial for a correct diagnosis (Inouye, 2006).

Taking into account the acute onset and fluctuating course of delirium, it is important to establish the patient's level of baseline cognitive functioning and the course of cognitive change. In this way, the diagnosis is made more easily if there has been a prior assessment of cognitive abilities. In other instances it is necessary, in a clinical interview, to obtain information from the family members/caregivers and/or medical and nursing staff (Cole, 2005; Fearing and Inouye, 2009). Moreover, patients should be assessed more than once during the day, in order to detect a possible fluctuating path of symptoms.

Inattention is another central feature of delirium. The cognitive assessment should include not only global cognitive screening tools (e.g., Mini-Mental State Examination – MMSE; Folstein et al., 1975), but also a measurement of attention (Fearing and Inouye, 2009). There are quick screening instruments for inattention that are commonly used: Digit Span Test (Wechsler, 1997) and Trail Making Test A (Reitan, 1958). In this context, it is also important to note that changes in arousal can affect performance in attention tests as can other conditions, such as fatigue. Moreover, depending on the severity of delirium, cognitive tasks can be affected proportionally to attention demands required by the task (Oyebode, 2008).

The level of consciousness is another important aspect of this evaluation that has to be determined. The Glasgow Coma Scale (Teasdale and Jennett, 1974) has been classically used to quantify this level of consciousness.

According to the most recent international guidelines (NICE, 2010), all elderly people admitted to hospital or in long-term care units should be screened for risk factors of developing delirium and cognitive impairment, using a brief cognitive test (e.g., MMSE). If recent changes or fluctuations in cognitive function, perception, physical function, or in social behavior are identified in people at risk, a clinical assessment should be carried out based on the DSM-IV criteria or short Confusion Assessment Method – CAM (Inouye et al., 1990), CAM (algorithm) to confirm the diagnosis. This evaluation should also be carried out by a trained healthcare professional.

The CAM is a widely used delirium screening instrument, based on DSM-III-R criteria (APA, 1987). It can be readily used in routine clinical settings by non-psychiatric medical or nursing staff with some previous training (Wei et al., 2008). The short version includes a diagnostic algorithm, based on four cardinal features of delirium: (1) acute onset and fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. A diagnosis of delirium according to the CAM requires the presence of features 1, 2, and either 3 or 4. In critical care or in the recovery room after surgery, in particular in patients who are not able to communicate verbally, CAM-ICU (Ely et al., 2001), an adaptation derived from CAM, should be used (Luetz et al., 2010; NICE, 2010). Recent review studies (Adamis et al., 2010; Wong et al., 2010) corroborated this recommendation, citing evidence to support the use of CAM as a diagnostic instrument. The use of the Delirium Rating Scale-R-98 – DRS-R-98 (Trzepacz et al., 2001) has also been suggested as a measure of delirium symptom severity in effective assessment. This scale includes three diagnostic items (onset, fluctuation of symptoms, physical disorder) and 13 severity items (sleep-wake cycle, perceptual disturbances/hallucinations, delusions, lability of affect, language, thought process abnormalities, motor agitation, motor retardation, orientation, attention, short-term memory, long-term memory, visuospatial ability). A high score is indicative of greater severity.

The identification of underlying causes is crucial in delirium diagnosis (Marcantonio, 2011). Because of that, physical and neurological examinations are extremely important, helping to rule out infectious, metabolic, endocrine, cardiovascular, and cerebrovascular diseases (Fong et al., 2009a).

The diagnostic approach should include the following tests: complete blood count, blood urea and creatinine levels, electrolytes, blood sugar, C-reactive protein, liver function, and thyroid function (Cole, 2004; Saxena and Lawley, 2009).

It is also important to identify medication and substance usage, namely alcohol or benzodiazepines use, which can contribute to this ailment (Inouye, 2006).

The physical examination should also include the evaluation of vital signs, with oxygen saturation. The general examination should focus on cardiac and pulmonary function. Beyond this, a neurological examination should incorporate the mental status, as well as focal findings (Marcantonio, 2011).

No laboratory test, brain imaging or other tests are more accurate than clinical assessment (Inouye, 2006). However, they can be useful to identify possible causes of delirium and correctable contributing factors. In some situations, brain imaging and electroencephalography (EEG) can be useful, when there is strong evidence of an intracranial cause, based on clinical assessment (e.g., change in mental status after a blow to the head) or if focal neurological signs or seizure activity is detected during physical examination (Hirano et al., 2006; Saxena and Lawley, 2009).

DIFFERENTIAL DIAGNOSIS

Delirium is frequently confused with dementia (**Table 1**). Globally, dementia is characterized by cognitive and functional impairment and usually follows a chronic deteriorating course, whereas delirium is characterized primarily by inattention and has an acute onset with a fluctuating course (Meagher et al., 2006). Also, an abnormal level of consciousness is highly suggestive of delirium, while in dementia attention and the level of consciousness tend to remain intact (Fearing and Inouye, 2009; Marcantonio, 2011), at least until late stages, or in the case of Dementia with Lewy Bodies (DLB; McKeith et al., 2005).

Table 1 | Differential diagnoses of delirium and dementia.

	Delirium	Dementia
Onset	Acute	Insidious
Duration	Hours, days, months	Months to years
Course	Fluctuating (often worse at night)	Chronic, progressive (but stable over the course of the day, except for DLB)
Consciousness	Altered (hyperalert, alert, or hypoalert)	Alert
Attention	Impaired	Normal (except in late stages)
Memory	Impaired (registration, recent, and remote)	Impaired (recent and remote)
Orientation	Usually impaired	Often impaired
Speech	Often incoherent, slow, or rapid	Coherent (with mild errors) until the late stage
Thinking	Disorganized or incoherent	Impoverished and vague
Perception	Altered	Altered or normal
	Hallucinations are frequent (mainly visual)	Hallucinations often absent (except in advanced stages or DLB)

Additionally, physical illness or drug toxicity can alone or together be present in delirium, whereas it is often absent in Alzheimer's disease (Saxena and Lawley, 2009).

Although delirium and dementia are often separated clinically and methodologically, these conditions often occur together, with prevalence ranges from 22 to 89% in both hospital and community settings. These clinical situations are also probably highly interrelated, specifically because both share many pathophysiological features (Fick et al., 2002, 2009).

Delirium complicates 24–89% of inpatient stays for elderly patients with dementia (Sampson et al., 2009). Inversely, the available evidence strongly suggests that delirium increases the risk of new-onset dementia in the long-term, as much as sixfold at 3 year follow-up (MacLullich et al., 2009). Also, people with pre-existing dementia suffer from an acceleration of cognitive decline following an episode of delirium (Fong et al., 2009b).

However, distinguishing delirium and dementia becomes crucial because the diagnosis of delirium is urgent, as it can be the first indicator of a serious medical problem (Wahlund and Bjorlin, 1999), which can be treatable, and because it has been associated with poor outcomes (Siddiqi et al., 2006).

Differential diagnosis with DLB can also be difficult. In both clinical situations, there is a fluctuating course, altered level of consciousness, as well as visual hallucinations. However, this type of dementia has a longer duration (months or years) and parkinsonian symptoms are common (McKeith et al., 2005). Besides, visual hallucinations are more complex and persistent in DLB than in delirium (Cole, 2005).

Depression may also be mistaken for the hypoactive form of delirium, due to the presence of symptoms such as slowed thinking, decreased concentration, and memory impairment. However, the presentation of depression tends to be insidious, without fluctuations and the level of consciousness remains unaffected. Moreover, there is usually a history of previous episodes, and a predominance of mood symptoms (Cole, 2005; Saxena and Lawley, 2009).

Other less common situations should also be considered, such as mania and schizophrenia (Saxena and Lawley, 2009). In the first case, it can be confused with the hyperactive form of delirium, with reduced attention, agitation, and rapid fluctuations. However, in this situation there are usually previous episodes of euphoria/mania (Cole, 2005).

In the second case, disturbance of thought can be also present in both. However, in delirium, these alterations fluctuate and are often fragmentary and less complex. Thought insertion, very common in schizophrenia, is unusual in delirium. On the other hand, schizophrenic delusions are very systematized, bizarre, and not influenced by the environment, which contrasts with the poor systematization and environmental influence observed in delirium (Cole, 2005).

Perception is also affected in schizophrenia, with hallucinations. They are persistent, consistent, and usually auditory, as opposed to those occurring in delirium, which are predominantly visual (Saxena and Lawley, 2009).

PATHOPHYSIOLOGY

The pathophysiological mechanisms of delirium remain unclear (Gofton, 2011). However, current evidence suggests that disruption of neurotransmission can contribute to the development of this disorder (Saxena and Lawley, 2009).

The neurotransmitter hypothesis suggests that cholinergic deficits and dopaminergic excess could be involved in the development of delirium (Trzepacz, 2000; Gaudreau and Gagnon, 2005). Indeed, the cholinergic system has an important role in cognition and attention (Hshieh et al., 2008), so its impact in the development of delirium is not surprising. Moreover, drugs with anticholinergic properties may precipitate delirium, in susceptible individuals (Trzepacz, 1996). There is also strong evidence supporting the importance of the role of cholinergic deficits in the development of this condition (Gofton, 2011).

Another important neurotransmitter that could be involved in delirium is dopamine, since delirium can be a common side effect of the dopaminergic drugs used in the treatment of Parkinson's disease (Trzepacz and van der Mast, 2002). This neurotransmitter has been related to psychotic symptoms (Ramirez-Bermudez et al., 2008), which can reinforce the function of these symptoms in delirium, if not the whole syndrome (Hall et al., 2011). Furthermore, dopamine also has an important role in motor activity, as well as, cognitive functions, such as attention, thought, and perception (Trzepacz, 2000), which are affected in this clinical condition.

Inflammation or acute stress responses are less supported pathophysiological mechanisms (Fong et al., 2009a). The first has been inferred from basic and clinical research literature evidence, supporting the hypothesis that trauma and infection or surgery can lead to increased production of cytokines (Rudolph et al., 2008; Cerejeira et al., 2010). This mechanism may induce delirium in susceptible patients (Maclullich et al., 2008). Furthermore, a recent review concluded that this increase in cytokines plays a crucial role, specifically in the development of cognitive dysfunction, observed in delirium (van Munster et al., 2008; Simone and Tan, 2011).

On the other hand, a recent prospective study (Cerejeira et al., 2011) stated that elective hip-replacement surgery induced a reduction of plasma activity of cholinesterases (acetylcholinesterase – AChE and butyrylcholinesterases – BuChE) and found lower preoperative activity levels of plasma cholinesterases in subjects who developed delirium postoperatively.

Another hypothesis is related to cortisol, a hormone of the hypothalamic-pituitary-adrenal axis, which is part of the body's major response to stressful or traumatic insults (Olsson, 1999). Aging and dementia have been connected with an increase and duration of cortisol response to stress (MacLullich et al., 2008). This could explain why high levels of this hormone associated with acute stress have been hypothesized to precipitate and/or sustain delirium (Trzepacz and van der Mast, 2002).

Some authors (Watt et al., 2012) have suggested a simple heuristic that all etiologies for delirium emerge due to the deleterious effect of insults on neural networks supporting large-scale and highly integrative global cognitive processes involved in attention, working memory, and executive functions, which depend on the functional integrity of cortical prefrontal and parietal networks, as well as specific subcortical structures, such as the basal ganglia, cerebellum, thalamic nuclei, and the reticular activating system.

According to these authors, "a true understanding of delirium cannot emerge through simply focusing on single molecules, however important those particular transmitter systems may be, but can only come from focusing on the large-scale networks that underlie organized behavior and thought" (Watt et al., 2012).

RISK FACTORS

The etiology of delirium is usually multifactorial. However, it can be caused by a single factor, such as alcohol withdrawal or substance abuse (Burns et al., 2004; Fearing and Inouye, 2009).

Research has identified several consistent risk factors for delirium, which are classified into two groups: predisposing and precipitating factors. The first one makes the elderly person more vulnerable to the development of delirium and the second comprises acute factors for triggering delirium (CCSMH, 2006). A combination of these predisposing and precipitating factors appears to be the rule rather than an exception in delirious elderly people (Inouye, 1999; Rolfson, 2002).

The most common predisposing factors are: advanced age, male gender, pre-existing dementia and depression, visual and hearing impairment, functional dependence, dehydration and malnutrition, polymedication (mainly psychoactive drugs), alcohol abuse and coexistence of multiple, and severe medical conditions (Saxena and Lawley, 2009).

Next to increasing age, dementia appears as the second most frequent risk factor for delirium (Burns et al., 2004; Cole, 2004; CCSMH, 2006; Inouye, 2006). According to Inouye (2006), the underlying vulnerability of the brain in patients with dementia may predispose them to the development of delirium, as a consequence of insults related to the acute medical disease, medication, as well as environmental factors.

According to Saxena and Lawley (2009), the most common precipitating factors are: intercurrent illnesses (e.g., infections), iatrogenic complications, metabolic derangements, primary neurological conditions (e.g., acute stroke), surgery, drugs (particularly benzodiazepines, narcotic analgesics, and drugs with anticholinergic effects (Han et al., 2001). Uncontrolled pain has also been associated with the development of delirium.

Environmental factors, such as admission to an ICU, use of physical restraints or bladder catheterization have also been implicated (Brauer et al., 2000; Rolfson, 2002; Cole, 2004; Fong et al., 2009a; Saxena and Lawley, 2009).

In this context, Inouye and Charpentier (1996) present a model to predict the development of delirium in elderly hospitalized patients, with a greater number of or more severe predisposing factors (use of physical restraints, malnutrition, more than three medications in the previous day, use of a bladder catheter, and any iatrogenic event), in association to few precipitating factors. This model has been considered an excellent framework for identification of various etiologies of delirium in old age (Rolfson, 2002).

More recently, the guidelines (NICE, 2010) recommend the identification, in elderly people admitted to hospital or in long-term care, of the following risk factors: age 65 years old or over, cognitive impairment (past or present), dementia or both, current hip fracture, and presence of a severe illness. This identification brings the opportunity to change the risk factors for the development of delirium.

PROGNOSIS

Delirium in both medical and surgical elderly hospitalized patients has been associated with multiple adverse outcomes that have been well documented (NICE, 2010).

Overall, delirium has been associated with the increase of hospital stay (Cole and Primeau, 1993; Dubois et al., 2001; McCusker et al., 2003; Koster et al., 2011; van den Boogaard et al., 2011; Shi et al., 2012), cognitive decline (Inouye et al., 1998; McCusker et al., 2001; Jackson et al., 2004; Fong et al., 2009b; Witlox et al., 2010), functional decline (Inouye et al., 1998; Marcantonio et al., 2000; McCusker et al., 2001, 2002a), institutionalization (Cole and Primeau, 1993; Inouye et al., 1998; Witlox et al., 2010), and mortality (Cole and Primeau, 1993; Cole et al., 2008; Inouye et al., 1998; McCusker et al., 2002b; Witlox et al., 2010; Koster et al., 2011; Shi et al., 2012).

In intensive care units, delirium has been shown to be associated with prolonged duration of mechanical ventilation (van den Boogaard et al., 2011), longer stay in hospital, and in the ICU (Dubois et al., 2001; van den Boogaard et al., 2011) as well as mortality during hospitalization (van den Boogaard et al., 2011).

A systematic review (Siddiqi et al., 2006), with medical elderly in patients, concluded that this condition had been related to an

increase of mortality (discharge/12 months), length of hospital stay, and institutionalization.

More recently, a meta-analysis (Witlox et al., 2010) confirms that delirium is associated with the increased risk of dementia, institutionalization, and mortality, independently of important confounder factors (age, gender, comorbidity, severity of illness, and baseline dementia).

Fong et al. (2009b) demonstrate that incident delirium accelerates the trajectory of cognitive decline in hospitalized elderly patients with Alzheimer's disease.

Although traditionally viewing delirium as a transient and reversible condition, some studies have found evidence that a significant proportion of patients do not recover from delirium, presenting persistent symptoms at time of discharge, or beyond (Levkoff et al., 1992; Murray et al., 1993; McCusker et al., 2002b; Siddiqi et al., 2006; Cole et al., 2009). According to Cole et al. (2009), this situation, called persistent delirium, may contribute to the poor prognosis of delirium. These patients have worse outcomes (mortality, nursing home placement, function, and cognition), when compared with patients who have recovered from delirium (Cole et al., 2009; Cole, 2010). In a recent systematic review (Dasgupta and Hillier, 2010) persistent delirium was associated with dementia, medical conditions, severity of delirium, hypoactive symptoms, and hypoxic illness.

PREVENTION

Due to the adverse outcomes and increased health care costs that accompany delirium, the interventions to prevent this condition become crucial for reducing its frequency and complications (Inouye, 2006). In fact, one-third of delirium episodes could be prevented (Inouye, 2006; Marcantonio, 2011). Beyond that, the most recent guidelines (NICE, 2010) have considered delirium prevention as a cost-effective strategy. These provide a quick reference guide for preventing delirium in elderly people at risk, based on a multicomponent and non-pharmacological intervention that addresses a number of modifiable risk factors. First of all, people at risk of developing delirium (advanced age, suffering from cognitive impairment/dementia, hip fracture, or severe illness) should be assessed within 24 h of admission. In this case, the following 10 precipitating factor groups should be taken into consideration: cognitive impairment and disorientation, dehydration, and constipation, hypoxia, immobility/limited mobility, infection, polymedication, pain, poor nutrition, sensory impairment, and sleep disturbance. Based on this assessment, a trained and multidisciplinary team should provide a multicomponent intervention, taking into account the needs of the person, as well as the clinical care setting.

The success of a multidisciplinary and multicomponent approach in prevention of delirium springs from the many causes in the origin of this condition (Inouye, 2006; Fearing and Inouye, 2009; Salawu et al., 2009).

One of the most important examples of this kind of intervention was the Hospital Elder Life Program – HELP (Inouye et al., 1999, 2006), which was widely implemented (Marcantonio, 2011).

This intervention was carried out by a skilled interdisciplinary team and trained volunteers with standardized protocols for a personalized management of six risk factors (cognitive impairment, sleep deprivation, immobility, visual and hearing impairment, and dehydration). The effectiveness of this intervention decreased the incidence of delirium in 40% of cases and resulted in significantly fewer days and episodes of delirium.

On the other hand, educational programs targeting health professionals have been used alone or as part of multicomponent interventions, which seems to be crucial for a more appropriate management of patients with delirium (CCSMH, 2006), from the primary care level.

In regard to this, Naughton et al. (2005) have studied the effectiveness of multifactorial intervention designed to reduce delirium and hospital stay in elderly patients, carried out among a group of physicians and nurses from an emergency department and an acute geriatric unit. This intervention was shown to contribute to a decrease in psychotropic medication prescription (benzodiazepine and antihistamine), delirium prevalence, and hospital stay.

In another study (Tabet et al., 2005), an educational program for medical and nursing staff on an acute medical ward also contributed to a reduction in delirium prevalence in an intervention group, compared with a control group. Staff members were also more likely to correctly recognize this clinical condition.

In this context, a recent review (Teodorczuk et al., 2010) concluded that the majority of educational interventions focused on delirium prevention and management were shown to be effective in various healthcare settings. Moreover, this study also recognized that these programs should be carried out by a Liaison Old Age Psychiatry team, in particular in a hospital setting. This has been shown to be effective, with an improvement in key outcomes (Slaets et al., 1997).

MANAGEMENT

Once delirium occurs, non-pharmacological interventions should be considered as the first-line of delirium management (Cole, 2004; Fong et al., 2009a; Aguirre, 2010). This approach should address all evident causes, providing supportive care and preventing complications and treating behavioral problems (Inouye, 2006).

As delirium is a medical emergency and requires urgent intervention, the management of this condition must focus initially on identification and monitoring of underlying causes (CCSMH, 2006; NICE, 2010).

Supportive care remains as another important non-pharmacological strategy (Young and Inouye, 2007). This includes close and continuing observation and care from nursing staff, which should include vital sign monitoring, protecting the patient's airway, ensuring nutrition, correction and prevention of dehydration, attention to oral intake, prevention of aspiration, encouragement of mobility, and ensuring a good sleep pattern. In this context, it is also essential to support the patient's daily care and encourage self-care (Meagher et al., 1996; Cole, 2005; BGS, 2006; Inouye, 2006; Young and Inouye, 2007; Fearing and Inouye, 2009). The use of physical restraint is always questionable, but may be necessary to control violent behavior or to prevent the removal of important devices, such as endotracheal tubes (Marcantonio, 2011). However, it should be avoided, because it has been associated with worsening agitation and injury, prolonged delirium, and increased complications (Inouye, 2006; Young and Inouye, 2007).

Another important factor for the effective management of delirium is the involvement of the family and caregivers by health professionals. They can help re-orientate, calm, assist, protect, and support older people. Furthermore, they can also facilitate effective communication (CCSMH, 2006; NICE, 2010; Marcantonio, 2011). Medical and nursing staff, as well as families, should know the importance of effective communication in these situations. This can include strategies such as frequent verbal reorientation, clear instructions, and eye contact (Fearing and Inouye, 2009).

Delirium can be a psychologically traumatic experience, not only for the patients, but also for their family or caregivers (Breitbart et al., 2002). In this way, providing support and information can help throughout this process, as well as encouraging people to share their experiences (Inouye, 2006).

The education of families and caregivers by health professionals about delirium, in particular about its symptoms (especially disinhibition, agitation, hallucinations, and delusions) becomes crucial (CCSMH, 2006). It is also important to explain the fluctuating course, explaining that the transitory phases of awareness do not necessarily mean a recovery, because symptoms can recur. The possible causes of delirium, a possible relation with Alzheimer's disease or dementia, as well as treatment options should also be clearly explained. In fact, this specific intervention can be extremely important to the family, contributing not only to an improvement of their involvement in the management of delirium, but also to alleviate the profound sense of helplessness, incredulity, and anxiety that these members can feel during an episode of delirium (Gagnon et al., 2002).

Environmental manipulation is also recommended as an integral part of delirium management (NICE, 2010). It may include the following strategies: ensuring that there is a clock and a calendar in the room; giving the older person frequent verbal reminders of the time, day, and place; avoiding medical/nursing staff changes; transferring the patient to an isolated room, if possible; obtaining familiar possessions from home (e.g., family picture); avoiding sensory deprivation (e.g., windowless room) or sensory overload (e.g., too much noise); minimizing sensory impairment (including vision and hearing loss) by the use of corrective devices.

Pharmacological interventions in delirium should be considered only in the management of behavioral symptoms, but not for the basic treatment of this condition (Flaherty et al., 2011). They can be useful in situations of severe agitation, which interfere with medical procedures or when the patient puts himself or others, at risk and when non-pharmacological interventions fail (Inouye, 2006; NICE, 2010; Rathier and Baker, 2011).

In this context, the most recent guidelines (NICE, 2010) recommend the administration of haloperidol or olanzapine, only for a short period of time (for a maximum of 1 week or less), starting with low doses and titrating carefully, according to symptom severity.

In spite of this, the U.S. Food and Drug Administration has not yet approved any of these agents for the treatment of delirium (Flaherty et al., 2011).

With the use of antipsychotics one always has to take into consideration one of the most adverse effects of this high-potency medication: akathisia (motor restlessness), which can be confused with worsening of delirium (Marcantonio, 2011), or even being worse it in reality (Francis, 1992; Inouye et al., 2011). Recent evidence indicates that the use of antipsychotics is not safe in elderly patients, especially in those with dementia. Concerns include the development of adverse vascular events and death (Mittal et al., 2011).

On the other hand, the administration of antipsychotics should be avoided in Parkinson's disease or DLB (NICE, 2010).

Benzodiazepines have also been recommended, but only in delirium due to alcohol and benzodiazepine withdrawal, or neuroleptic malignant syndrome (Lonergan et al., 2009).

The introduction of cholinesterase inhibitors for the treatment of dementia suggested their potential usefulness to improve symptoms of delirium (Caraceni and Grassi, 2011). However, there is no specific evidence from controlled trials that donepezil or rivastigmine are effective in the treatment of this medical condition (Overshott et al., 2008; Gamberini et al., 2009).

The plan of discharge from hospital should be handled carefully, involving the team of health professionals and the patient, as well as the family (Saxena and Lawley, 2009). In addition, as symptoms of delirium can persist (Cole, 2010), a close clinical follow-up after discharge is crucial, especially due to the poor outcomes associated with this situation (BGS, 2006; Inouye, 2006). This could help identify residual cognitive, social, or functional problems, modify risk factors and help to reduce the recurrence of an episode of delirium (Saxena and Lawley, 2009).

CONCLUSION

Delirium is a common neuropsychiatric syndrome, mainly in elderly hospitalized patients. Despite this, it is frequently underrecognized by health professionals, due to its fluctuating nature, its overlap with dementia and the scarcity of formal cognitive assessment in general hospitals by routine. Once manifested, delirium is associated with increased morbidity and mortality. For that reason, prevention based on risk factor identification, early recognition, as well as an effective management, particularly if based on non-pharmacological strategies, is essential, because of the prevalence and the adverse outcomes associated with this disorder.

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Cognitive dysfunction in Multiple Sclerosis

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In Multiple Sclerosis (MS) prevalence studies of community and clinical samples, indicate that 45–60% of patients are cognitively impaired. These cognitive dysfunctions have been traditionally described as heterogeneous, but more recent studies suggest that there is a specific pattern of MS-related cognitive dysfunctions. With the advent of disease-modifying medications for MS and emphasis on early intervention and treatment, detection of cognitive impairment at its earliest stage becomes particularly important. In this review the authors address: the cognitive domains most commonly impaired in MS (memory, attention, executive functions, speed of information processing, and visual–spatial abilities); the pathophysiological mechanism implied in MS cognitive dysfunction and correlated brain MRI features; the importance of neuropsychological assessment of MS patients in different stages of the disease and the influence of its course on cognitive performance; the most used tests and batteries for neuropsychological assessment; therapeutic strategies to improve cognitive abilities.

Keywords: multiple sclerosis, cognition, neuropsychological batteries

INTRODUCTION

Multiple Sclerosis (MS) is a chronic demyelinating, inflammatory neurological disease, classically considered the most physically disabling non-traumatic neurological disease in young adults. In the last years many studies have described cognitive dysfunction is MS patients that contributes significantly to their disability status (Peyser et al., 1990; Rao et al., 1991a; Benedict et al., 2006). Prevalence studies of community and clinical samples, indicate that 45–60% of MS patients are cognitively impaired. Yet, severe dementia in accordance with the criteria of the ICD-10 is relatively uncommon, and is observed in 20–30% of cognitively impaired MS patients, mainly in the final stages of the disease (Rao et al., 1993). The measurement of these neuropsychological abnormalities in the clinical setting, unlike motor and sensory deficits, can be difficult; and also this difficult exists because MS-related cognitive dysfunctions were traditionally described as heterogeneous in nature. However, recent studies suggest a more specific pattern of MS-related cognitive dysfunction (Chiaravalloti and DeLuca, 2008).

The factors associated with cognitive dysfunction in this disease have not been fully elucidated yet, but several findings suggest that cognitive dysfunction could appear in the earliest stages of the disease as the first symptoms of MS (Schulz et al., 2006). Based on the recent studies appointing for the importance of MS cognitive dysfunction, the authors review the literature and describe: the cognitive domains most commonly impaired in MS, the nature of this cognitive MS-related impairments, lesion distribution in MRI or changes in brain structure and correlated cognitive dysfunctions, the influence of the course of the disease on cognitive performance, the importance of neuropsychological assessment of MS patients, which batteries and tests in neuropsychological assessment are actually recommended and the influence of disease-modifying therapeutics in cognition.

COGNITIVE DOMAINS IMPAIRED IN MS

The cognitive domains impaired in MS seem to have an inter-patient variability, but a characteristic pattern may be defined: memory, information processing efficiency, executive functioning, attention, processing speed, are the most commonly compromised functions (Rao et al., 1991a).

Impaired *memory* is one of the most consistently impaired cognitive functions in MS and is seen in 40–65% of patients; besides, MS-related memory dysfunctions most typically affect long-term and working memory (Rao et al., 1993). The nature of the MS-related memory impairments is a topic of debate in the literature, some studies suggest that memory dysfunctions in MS result primarily from impaired retrieval from long-term memory, whereas encoding and storage capacity seems to remain intact (Thornton et al., 2002). Recent research on the nature of memory dysfunction in MS shows that MS patients have difficulty with acquisition of new knowledge as opposed to retrieval from long-term storage (Chiaravalloti and DeLuca, 2008). Initially, based on the work of Rao and colleagues it was thought that memory difficulty was due to impaired retrieval, but more recent explanations are based in inadequate acquisition secondary to information processing insufficiency.

Impaired *speed of information processing* has been identified as a key deficit in MS (Bergendal et al., 2007) and is seen in 20–30% of patients. Information processing efficiency refers to the ability to maintain and manipulate information in the brain for short time period and to the speed with which one can process that information. Processing speed deficits are observed on even the most

basic tasks in MS patients and are related with decreased neuronal conduction speed secondary to demyelinating. This slowed information processing may impact an individual's ability to complete tasks and to cope in demanding work (Archibald and Fisk, 2000).

Executive functions concern to the cognitive abilities necessary to behavior directed to objectives and to the adaptation to environment demands and changes; examples are planning, organization, reasoning, and abstract conceptualization. Deficits in executive functions in MS patients (detected in 19% of the patients) occur less frequently than memory or processing speed disability. But MS patients have specific impairment deficits in some executive functions, especially in generating strategies, divergent thinking, problem solving and estimation (Rao et al., 1991a). So, abstract reasoning, verbal fluency, planning, or problem solving capabilities, have been shown to be frequently reduced in MS patients.

Attention is also a complex cognitive function and comprehends different aspects like alertness, vigilance, selective or focused and divided attention. Up to 25% of MS patients have deficits in attention, especially in complex functions like selective and divided attention (Nebel et al., 2007).

NEUROPSYCHOLOGICAL ASSESSMENT

The assessment of cognitive functions is undoubtedly important in MS patients, however it is not wise to rely on the routine neurological consultation. Cognitive symptoms are usually hidden by more visible deficits (e.g., motor, sensory, cerebellar), may be masqueraded by emotional complains, as depression, by fatigue or pain and most times are not thoroughly recognized by the patients. Besides, the predominant subcortical nature of cognitive impairment in MS is not suited to the current tests employed more often by neurologists in the clinical setting, as, for instance the Mini-Mental State Examination (MMSE) in dementia syndromes; yet, MMSE might be useful for quick screening of cognitive impairment before the application of more specific batteries in selected cases (Rao, 1986).

Since the pioneering reports of Rao and co-workers in the nineties (Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990; Rao et al., 1991a,b), the characteristics of cognitive dysfunction in MS and the appropriate tests for its detection have been extensively addressed in the literature (Benedict et al., 2002; Montalban and Rio, 2006; Benedict and Zivadinov, 2007; Strober et al., 2009; Comi, 2010; Ferreira, 2010; Kinsinger et al., 2010; Lyros et al., 2010; Messinis et al., 2010; Arnett and Strober, 2011; Langdon, 2011). In general, cognition in MS may be assessed by two separate, yet complementary, modes: the self-reported evaluation of MS patients and relatives and the neurocognitive batteries adapted to the disease. As elsewhere stated, the self-reported cognitive impairment is prone to depend more on the emotional status, depressive and fatigue complains rather than on real cognitive test performance; on the contrary, the evaluation of relatives and caregivers is usual more reliable (Kinsinger et al., 2010). Even so, the self-perceived cognitive dysfunction is important for the patients to be aware of its impact in daily life activities and to overcome items related with the disease itself, as treatment adherence or scheduled appointments.

The neuropsychological tests and batteries indicated for measuring the cognitive domains which are compromised in MS patients require expertise and are still matter of debate in the literature. Ideally, the neuropsychological tests and batteries should be sensitive, reproducible, reliable easy to administer and last few time, taking into account the patient's comfort, the human resources of MS clinics and the implied costs. These batteries need to have good normative data, corrected for age, and education level. In parallel, tests to evaluate depression and fatigue must be performed, since those symptoms have a recognized impact in cognitive abilities (Kinsinger et al., 2010). In a recent systematic review, the use of 23 batteries and 74 neuropsychological tests was identified in the literature, which means a lack of homogeneity in this issue despite the recognized consensus on the characteristics of cognitive impairment in MS patients (Ferreira, 2010).

Two cognitive batteries are particularly relevant and validated in MS, being widely used in clinical practice and also for research purposes: the Brief Repeatable Battery of Neuropsychological tests (BRBN; Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990) and the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2002). The BRNB is composed by tests that were found to be most sensitive to the cognitive impairment in MS, after a previous application of a comprehensive neuropsychological battery (Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990), as follows: the selective reminding test (SRT), the 7/24 (later substituted by the 10/36) spatial recall test, the controlled oral word association test (COWAT), and the paced auditory serial addition test (PASAT). These measures achieved 71% sensitivity and 94% specificity when compared with the more comprehensive neuropsychological battery. Later the authors revised the battery to include the symbol digit modality test (SDMT) that evaluates the speed of information processing. In 2002 a group of experts on neuropsychological functioning in MS from different countries created by consensus the MACFIMS battery (Benedict et al., 2002), choosing tests according to their sensitivity to the disease, reliability, validity, ease of administration and the presence of alternate types to make the repeat testing feasible. This battery is composed of seven neuropsychological tests, covering five cognitive domains commonly impaired in MS (processing speed/working memory, learning and memory, executive function, visual–spatial processing, and word retrieval) and takes around 90 min to administer. Specifically, the battery includes the PASAT and the SDMT for Processing speed/Working memory, the California Verbal Learning Test-II and the Brief Visuospatial Memory Test – Revised (BVMTR) for Learning and Memory, the D-KEFS Sorting Test for Executive Functions, the Judgment of Line Orientation Test for Visual perception/Spatial processing and the COWAT for Language. Besides, additional tests are recommended in the MACFIMS, such as measures of premorbid ability with word recognition tests which are not affected in MS, visual screening to evaluate the impact of visual symptoms on neuropsychological tests based in visual tasks, screening of motor problems with the 9-Hole Peg Test, screening of oral motor speed deficits since some tests require rapid answers, and also fatigue evaluation with the Fatigue Impact Scale (Benedict et al., 2002).

Briefly, the BRNB and the MACFIMS batteries are quite similar, only differing in the tests that assess the specific auditory–verbal

and visual–spatial memory: whereas the former employs the SRT and the 10/36 Spatial Recall Test (10/36), the latter uses the California Verbal Learning Test, Second Edition (CVLT2) and BVMTR. Nevertheless, both batteries were found to have identical sensitivity in a comparative study (Strober et al., 2009), being the SDMT the most sensitive measure.

Despite the consortium recommendation for the use of MACFIMS (Benedict et al., 2002) in MS, the BRNB (Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990) remains, up to now, the most widely used neuropsychological battery for assessing cognitive functions in the disease. The longer experience in applying the BRNB, and the fact that it has been traduced and validated in some populations might explain its traditional use. The BRBN is also routinely since several years in our MS Clinic, where the neuropsychologists have acquired expertise in the performance of the tests and interpretation of the results (Rio et al., 2004; Barbosa et al., 2011a). Nonetheless, it must be highlighted that the MACFIMS presents some advantages regarding the BRBN, as it is easy to administer and the included measures demonstrate good psychometrics. Besides the MACFIMS battery is suited to repeated assessments which, ideally, should be periodically conducted in the follow-up of the disease progression (Benedict et al., 2002).

NATURE OF COGNITIVE MS-RELATED IMPAIRMENTS

The mechanism underlying cognitive impairment in MS has not been fully elucidated. Cognitive decline in MS patients has been correlated with both macro- and microscopic changes in brain anatomy; and this has been demonstrated by using structural and functional brain imaging. Recent studies have shown that both gray and white-matter lesions contribute to mental dysfunction in MS (Morgen et al., 2006; Dineen et al., 2009). Initially, some studies correlate white-matter lesions localizations with specific cognitive impairments (Rao et al., 1989). For example a white mater lesion in frontal lobe lesions has been shown to affect performance in tests of frontal lobe function (Rovaris et al., 1998). Also it was demonstrated that there is a significant association between executive deficits and damage in the prefrontal cortex (Foong et al., 1997) and frontal and parietal lesion burden has been shown to correlate with performance on tests of complex attention and verbal working memory (Sperling et al., 2001). This relationship between specific white lesion location and cognitive performance was also demonstrated in early stage of MS. For example Ranjeva (2006) studied patients with clinically isolated syndromes and cognition impairment and conclude that poorer performance in processing speed and working memory was associated with abnormalities in the splenium of the corpus callosum and in the right superior longitudinal fasciculus.

More recent investigation, discussed the contribution of ultrastructural tissue injury in normal-appearing white-matter and the correlation between cognitive dysfunction and gray–white-matter lesions (Kidd et al., 1999; Geurts et al., 2005; Sanfilipo et al., 2006). The correlation between multifocal white-matter and gray-matter lesions in cognitive dysfunction pathology has geared the disconnection theory. This model is based in the predilective topology of MS-associated lesions, predominantly involving subcortical periventricular fiber systems, which hinders distal flow of cortical cholinergic pathways. Disconnection occurs between cortical and subcortical regions interactions (Amato et al., 2004; Morgen et al., 2006). Cortical involvement related to MS is heterogeneous since it may arise from local demyelinating lesions, meningeal inflammation, neuronal injury, and Wallerian or transsynaptic degeneration (Nelson et al., 2011). As well, selective decrease of the cortical volume was found in patients with relapsing–remitting (RR) MS and mild cognitive deficits; this was associated with poorer performance on tests of verbal and spatial memory, attention and concentration, and verbal fluency (Piras et al., 2003). MS patients with cognitive deficits showed more cortical lesions and more severe cortical atrophy than patients who were cognitively preserved (Calabrese et al., 2009). But this cortical involvement is better understand by subcortico-cortical involvement with the multiple disconnection syndrome, in which a more than one cognitive domain can be interrupted in its afferent or efferent loop, producing a variety of neuropsychological defects (Calabrese and Penner, 2007). Also in recent study, Dineen et al. (2009) confirm that MS-related cognitive dysfunction results from a series of domain-specific disconnection phenomena. As such, disruption of critical white-matter tracts will lead to reduced functional connectivity between cortico-cortical and cortico-subcortical cognitive processing regions, resulting in impairment to specific cognitive domains.

MAGNETIC RESONANCE IMAGING AND COGNITIVE IMPAIRMENT

Conventional and non-conventional magnetic resonance imaging (MRI) measures have been correlated with cognitive impairment in MS. Initially Rao et al., 1991a) examined by a conventional way a number of MRI variables including total lesion area, ventricular-brain ratio and size of the corpus callosum. In the past few years, a large effort has been devoted to the development of MRI techniques with the ability to characterize *in vivo* the different substrates of gray-matter and white-matter damage to improve the understanding of its clinical consequences in MS patients (Rinaldi et al., 2010).

Measures of brain atrophy are particularly sensitive in elucidating the relation between brain integrity and cognitive status (Calabrese et al., 2009). Longitudinal imaging studies have shown a strong correlation between changes in cognitive functioning, suggesting that a progression of brain atrophy early in the disease can predict cognitive impairment 5 years later (Summers et al., 2008). Recent MRI studies, which assessed the extent of brain tissue loss on a regional basis, have suggested that cortical volume loss is more closely associated with cognition than whole-brain atrophy. More recently, the application of double inversion recovery (DIR) sequences has convincingly demonstrated that cortical lesions are a frequent finding in patients with MS, even at the earliest clinical stages (Calabrese et al., 2009).

Quantitative imaging techniques, such as diffusion tensor imaging (DTI) are a powerful non-invasive technique for exploring cerebral ultrastructure. Fractional anisotropy (FA), a parameter derived from DTI data provides a quantification of ultrastructural fiber organization (Basser and Pierpaoli, 1996). DTI examination of MS patients has revealed reduced FA in plaques,

adjacent to plaques and to varying degrees in normal-appearing white-matter (Kealey et al., 2005). Measures derived from magnetization transfer ratio have also consistently been shown to be associated with cognition, as documented with many types of brain tissue, including cortical and subcortical regions and normal-appearing white-matter tissue on conventional imaging. Magnetic resonance spectroscopy, which provides a measure of metabolic changes in the cerebral cortex and white-matter, is also a sensitive indicator of cognitive functioning in MS, particularly in normal-appearing white-matter (Staffen et al., 2002).

Functional MRI (fMRI) has brought new insight into a better understanding of cognitive impairment at the very early stage of MS (Audoin et al., 2006). Brain connectivity assessed by fMRI have provided new data about the real influence of diffuse white-matter damage on connectivity efficiency. fMRI has evidenced how the brain accommodates to diffuse white-matter injury during controlled information processing task. Brain activation observed by fMRI permits the understanding of cortical reorganization processes and the disturbance in brain connectivity (Ranjeva et al., 2005).

COURSE OF THE DISEASE AND COGNITIVE PERFORMANCE

Some studies suggest an influence of the course of the disease on cognitive performance. Although some studies indicate that cognitive dysfunction is more frequent and severe in the progressive forms of MS (Beatty et al., 1989), cognitive impairment can be present since the early clinical stages of the disease. Moreover, another study pointed out that different courses of the disease are associated with different cognitive profiles (Huijbregts et al., 2004). It was shown that chronic progressive MS patients were more likely than RRMS patients to suffer from attention deficits, in particular reduced speed of information processing, executive dysfunctions, verbal intelligence and abstraction deficits. Also a recent study (Schulz et al., 2006) investigated patterns of cognitive decline in MS patients in the early stage of the disease and neuropsychological assessment revealed cognitive impairments of MS patients in the early stage of their disease. Between 10 and 38% of the MS patients displayed significantly lengthened reaction times and deficient attention. Reduced speed of information processing may be a fundamental neuropsychological deficit in the earliest stages of the disease.

Throughout the course of the disease, some other clinical problems can intensify or simulate cognitive deficits. Specifically, depression or fatigue must be discriminated from cognitive dysfunctions. Up to 90% of MS patients suffer from fatigue, a subjective lack of energy, which can reduce cognitive performance; on the other hand, cognitive deficits can produce exhaustion (Engel et al., 2007). Fatigue might affect performance over time in tasks that require sustained mental effort, specially in cognitive tasks of working memory and visual vigilance (Krupp and Elkins, 2000). Psychiatric symptoms of MS, like anxiety and depression, which can appear in up to 50% of the patients, have a significant effect on subjective perceived performance (Landro et al., 2004). Depression affects many aspects of cognitive functioning in MS, including working memory, processing speed, learning and memory functions, abstract reasoning, and executive functioning (Chiaravalloti and DeLuca, 2008). In addition, an anamnesis of medication is necessary, because many therapeutic agents like antidepressants, anticonvulsants, antispastics, glucocorticosteroids, or neuroleptics can produce cognitive impairment, especially in attention (Engel et al., 2007).

TREATMENT OF COGNITIVE DYSFUNCTION

The treatment of cognitive symptoms in MS patients begins with the patient education about the possibility of their occurrence and with an open relation with the MS team, to favor the earliest recognition as possible. As soon as the patients become aware of cognitive impairment the better, because they may be quickly submitted to neuropsychological assessment and request someone's help, if needed, for daily life activities.

At first, some general advices may be provided, as simple tools to improve cognitive abilities: strategies to organize the information (use of scheduled agendas and elaboration of lists of tasks), offer more time to perform usual tasks and process information, taking into account that the impairment of information processing speed is characteristic of cognitive dysfunction in MS. As elsewhere described, paring down information to the essentials and avoiding unnecessary or unrelated details are advantageous (Langdon, 2010).

Most important, the treatment of MS with disease-modifying drugs (DMD) is naturally expected to bring some benefits in cognitive functioning, in parallel with the improvement in clinical outcomes (reduction of the annualized relapse rate, disability progression) and MRI parameters (new T2 lesions, gadolinium-enhancing lesions), in as much as DMD act by controlling inflammation, reduce the accumulation of lesions and somewhat might have a neuroprotective role (Mendes and Sá, 2011; Sá et al., 2011). However, as repeatedly emphasized in the literature (for review see Comi, 2010), the results of DMD in cognition must be cautiously interpreted because they generally have considerable drawback. In effect, the largest clinical trials (pivotal phase III studies, extension phases) of DMD do not include cognitive parameters in the primary outcomes and when those assessments were done the psychometric measures vary with different studies, use different samples sizes, MS populations, and statistic analyses, which altogether prevents their comparability (Montalban and Rio, 2006; Comi, 2010; Lyros et al., 2010). Focusing only on randomized double-blind, placebo-controlled studies, some positive results in cognition were seen with interferon beta-1a in RR forms (Fischer et al., 2000), with interferon beta-1b in RR (Pliskin et al., 1996), secondary progressive forms (European Study Group, 1998), and clinically isolated syndromes (Kappos et al., 2009); on the contrary, glatiramer acetate showed no cognitive benefit in RR patients (Weinstein et al., 1999). In addition, clinical trials specifically designed to evaluate cognition are scarce. In the IMPACT trial, designed to assess whether weekly intramuscular IFN b-1a reduces disability progression in SPMS, the MS functional composite (MSFC) that includes PASAT was used as primary endpoint, a modest effect 2 years after the baseline evaluation was detected (Cohen et al., 2002). In the CogniMS study, performed to evaluate cognition, fatigue, depression, and quality of life in patients with early MS treated with interferon beta-1b, cognitive scores improved over time, which seemed to

be due to practice effects (Langdon et al., 2010); however data have not yet been published so far. With respect to natalizumab, an improvement was noticed in the PASAT tests performed during the MSFC evaluations, and in the mental component of SF-36 in both pivotal trials (Polman et al., 2006; Rudick et al., 2006).

Another pharmacological attempt to ameliorate cognitive dysfunction in MS has been the use of licensed drugs for dementia diseases, despite the existence of substantive differences between the nature of cognitive deficits in both situations and their respective underlying pathogenetic processes in the CNS. Even so, some authors have tried acetylcholinesterase inhibitors, as donepezil, rivastigmine, and galantamine, as well as memantine, an antagonist of NMDA receptors (Doraiswamy and Rao, 2004). Donepezil (10 mg/day) showed an improvement in learning and memory in a randomized placebo-controlled trial enrolling 69 MS patients (Krupp et al., 2004), further showing clinical benefit to patients and physicians (Christodoulou et al., 2006); however negative results were recently reported by other groups which found that donepezil 10 mg daily for 24 weeks is not superior to placebo in improving MS-related cognitive dysfunction, in randomized control trials (Krupp et al., 2011; O'Carroll et al., 2012). Rivastigmine has also been tested in MS patients with neurocognitive dysfunction, where no benefit in a general score memory in comparison to placebo (Shaygannejad et al., 2008) or a trend to an improvement in cognitive processing speed by enhancing compensatory brain activation (Huolman et al., 2011) have been found so far; positive effects were detected in imaging studies, since MS patients treated with rivastigmine displayed increased brain activity during cognitive tasks in fMRI studies (Parry et al., 2003). The effect of memantine given 10 mg twice a day in MS patients with cognitive impairment has been evaluated in a randomized placebo-controlled trial, which failed to show any positive result (Lovera et al., 2010). Based on the assumption that these drugs might have positive effects in cognitive impairment of MS, they are sometimes used off label in the clinical setting, especially in cases with overt dementia symptoms, mimicking primary degenerative dementias. However, up to now there is insufficient evidence of the efficiency of these drugs in MS and their role in the cognitive decline of MS patients is still controversial (Christodoulou et al., 2008), awaiting specifically designed trials allowing longitudinal assessments. As stated in a recent Cochrane review of this subject, until the results of ongoing studies are available, there is no convincing evidence to support pharmacologic intervention as an effective treatment for memory disorder in MS patients (He et al., 2011).

Finally, the importance of cognitive rehabilitation must be stressed, which is a field that needs to be better explored, bearing in mind that it still lacks a consistent evidence base. The concept of submitting cognitively impaired MS patients to techniques of cognitive rehabilitation was based in the knowledge obtained in other CNS pathologies, as stroke. As cognitive dysfunction was more and more studied in MS, the need for the development of cognitive rehabilitation increased, originating an extensive literature that is rather difficult to appreciate because methods and technologies vary with the study. The rationale for cognitive rehabilitation relies upon the stimulation of the natural restorative phenomena taking place in CNS in response to some kind of injury, as inflammation and demyelination, which is commonly called neuroplasticity. Recent fMRI studies showed that brain activity in the cerebellum of cognitively impaired MS patients increased with a cognitive rehabilitation program (Sastre-Garriga et al., 2011).

Briefly, two types of strategies have been pointed out: compensatory and restorative. Compensatory approaches are easier for patients and caregivers to carry out and include all measures that favor learning and memory, as above-mentioned organizers of information and memory aids in general. Restorative strategies are based in the plastic properties of the nervous system (e.g., cortical reorganization), and are more ambitious because they identify specific impaired cognitive functions in each patient and then introduce techniques that aim to increase the performance in those tasks, ideally to provide a successful recover or remediation (Messinis et al., 2010). As part of restorative strategies, several computerized programs have been developed and applied to MS patients with cognitive impairment targeting different cognitive domains. In general, most studies suggest that memory is the cognitive domain with major improvement, namely spatial memory (Barbosa et al., 2011b) and episodic memory (Brissart et al., 2011). The studies of memory training suggest that specific patient-individualized computerized schemas are more effective (Langdon, 2011); conversely, programs focusing working memory, attention and executive functions are less developed so far. With respect to executive skills, the direct training by a therapist seems to be more successful (Langdon, 2010). The effects of neuropsychological rehabilitation in MS has been recently addressed in an extensive systematic review that only included randomized controlled trials and quasi-randomized trials in comparison with other interventions or any kind of intervention; the authors stress methodological limitations and heterogeneity in the interventions included in the review, the low level evidence for the positive effects of neuropsychological rehabilitation in MS, and give recommendations to improve the quality of futures studies about this issue (Rosti-Otajärvi and Hämäläinen, 2011).

CONCLUSION

Neuropsychological assessment is not required to diagnose MS (Polman et al., 2005) and cognitive deficits may not be evident during a follow-up consultation in clinical practice. But with the advent of DMD for MS and emphasis on early intervention and treatment, detection of cognitive impairment at its earliest stage becomes particularly important, in as much as the patients may also benefit of symptomatic and rehabilitation interventions.

Thus, with this revision the authors are able to conclude that: it is important to include cognitive evaluation of MS patients in clinical routine, since these cognitive deficits may be present in early phases of disease; the standardization of cognitive profile evaluation seems to be mandatory in MS patients; MRI is crucial in the understanding and follow-up of MS cognitive impairment; the therapeutic strategies to improve cognitive abilities need to be better evaluated with appropriately designed randomized controlled trials.

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