U.PORTO

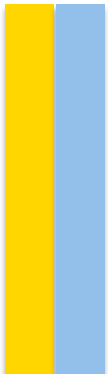
MESTRADO INTEGRADO EM MEDICINA
NEUROLOGIA

Neuropsychiatric symptoms in dementia patients: a comparative study between Alzheimer's Disease, Dementia with Lewy Bodies and Frontotemporal Dementia in a hospital cohort

Beatriz Loureiro Marques

M

2025



Neuropsychiatric Symptoms in Dementia Patients: A Comparative Study Between Alzheimer's Disease, Dementia with Lewy Bodies and Frontotemporal Dementia in a Hospital Cohort

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Beatriz Loureiro Marques
Estudante do 6º ano do Mestrado Integrado em Medicina
Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto
Endereço Eletrónico: bia.marques9@hotmail.com

Orientador: Professor Doutor Ricardo Jorge Ferreira Taipa
Grau académico: Doutorado
Diretor do Serviço de Neuropatologia / Banco Português de Cérebros
Assistente Graduado de Neurologia e Neuropatologia do Centro Hospital Universitário do Porto
Professor Associado Convidado no Instituo de Ciências Biomédicas Abel Salazar – Universidade do Porto

Porto, junho de 2025

DECLARAÇÃO DE INTEGRIDADE CIENTÍFICA

Este estudo foi autorizado pela Comissão de Ética da Unidade Local de Saúde de Santo António | ICBAS, pelo Gabinete de Projetos de Investigação do Centro Académico Clínico ICBAS-CHP, pela Direção do Centro Académico Clínico, pelo Presidente do Conselho de Administração e pelo Conselho de Administração da ULS de Santo António.

Ref.ª: 2024.277(214-CAC/248-CE)

Beatriz Loureiro Marques

Orientador: Prof. Dr. Ricardo Taipa

AGRADECIMENTOS

Ao Professor Doutor Ricardo Taipa, pela sua orientação e disponibilidade constante. Agradeço profundamente todo o seu tempo e atenção generosa.

À Dra. Claúdia, à Dra. Alexandra e a toda a equipa de Neuropsicologia que me acolheram sempre com gentileza e paciência.

Não podia também deixar de agradecer também a várias pessoas que, não tendo contribuído diretamente para a realização desta tese, foram absolutamente determinantes em tantas etapas. Este é o primeiro e último momento formal que posso escrever os seus nomes e faço o com todo o coração:

Aos amigos com quem partilhei estes 6 anos, aprendi, ri e cresci convosco. Obrigada por fazerem parte do caminho.

Às minhas amizades que são refúgio e alegria, em vós encontro sempre o que preciso, seja o que isso for.

À Bárbara, que torna tudo mais leve e mais bonito. Obrigada por seres certeza.

Aos meus pais, que sempre foram força tranquila e abrigo sereno. Devo-vos tudo. A minha sorte começa em vós.

Aos meus avós, que vivem em mim de tantas formas. Reúno em mim bocadinhos de cada um.

Muito obrigada.

RESUMO

Introdução: A demência é uma condição neurodegenerativa progressiva associada não apenas ao declínio cognitivo, mas também a uma ampla variedade de sintomas neuropsiquiátricos (NPS). Esses sintomas variam entre os diferentes subtipos de demência e são frequentemente subestimados, apesar de sua relevância clínica.

Objetivo: Avaliar a prevalência e o perfil dos sintomas neuropsiquiátricos numa coorte hospitalar composta por doentes com diagnóstico de Doença de Alzheimer (DA), Demência Frontotemporal (FTD) e Demência com Corpos de Lewy (DLB), explorando também a sua relação com o desempenho cognitivo.

Métodos: Foi realizado um estudo retrospetivo baseado em dados clínicos e neuropsicológicos de doentes seguidos em consulta de doenças neurodegenerativas no Centro Hospitalar Universitário de Santo António. Os sintomas neuropsiquiátricos foram avaliados através do Inventário Neuropsiquiátrico e da Escala Hospitalar de Ansiedade e Depressão e o desempenho cognitivo através da Dementia Rating Scale-2 (DRS-2). Realizaram-se comparações entre grupos diagnósticos, análises de correlação e análises estratificadas por diagnóstico.

Resultados: Os sintomas neuropsiquiátricos estão sistematicamente presentes na nossa amostra, sendo a apatia, a ansiedade e a depressão os mais frequentes. A apatia e a desinibição foram significativamente mais comuns na FTD, enquanto os doentes com DLB apresentaram níveis mais elevados de sintomas depressivos. Na amostra total, observaram-se poucas associações globais entre os sintomas neuropsiquiátricos e o desempenho cognitivo, no entanto, destacam-se os delírios, que se correlacionaram positivamente com alguns domínios cognitivos e com o score global do DRS-2. Não foi encontrada nenhuma associação entre os scores totais de NPI e HADS com a performance cognitiva global. Quando os dados foram analisados por diagnóstico, foram encontrados padrões mais específicos: na AD, a depressão avaliada pelo NPI esteve associada a pior desempenho nos domínios executivo e construtivo, enquanto os delírios e a euforia surgiram associados a uma preservação relativa do funcionamento executivo. Na FTD, a apatia e a depressão associaram-se a défices de atenção e de memória, respetivamente.

Conclusão: Este estudo confirma a elevada prevalência dos sintomas neuropsiquiátricos nas demências, reforçando a importância da sua caracterização para fins diagnósticos, para uma melhor compreensão da relação entre estes sintomas e a cognição, e para determinar o seu impacto clínico e social. A ausência de correlação entre medidas globais de cognição e escalas

neuropsiquiátricas, sugere que os sintomas comportamentais e de humor podem constituir uma dimensão independente da expressão da doença.

Apesar das limitações relacionadas com o tamanho da amostra, os dados obtidos contribuem para um melhor reconhecimento dos perfis clínicos nas demências neurodegenerativas particularmente na DA, FTD e DLB.

ABSTRACT

Introduction: Dementia is a progressive neurodegenerative condition associated not only with cognitive deterioration but also with a wide range of neuropsychiatric symptoms (NPS). These symptoms vary between dementia subtypes and are often under-recognised despite their clinical relevance.

Objective: This study aimed to compare the prevalence and severity of NPS across patients with Alzheimer's Disease (AD), Frontotemporal Dementia (FTD), and Dementia with Lewy Bodies (DLB) and to explore how these symptoms relate to cognitive performance.

Methods: A retrospective study including 124 patients with a clinical diagnosis of AD, FTD, or DLB followed at Centro Hospitalar Universitário de Santo António. Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory and the Hospital Anxiety and Depression Scale. Cognitive performance was evaluated with the Dementia Rating Scale-2. Statistical analyses included non-parametric comparisons and correlations. The significance level was set at $p < 0.05$.

Results: NPS were highly prevalent in all dementia groups, with apathy, anxiety, and depression being the most frequent. Apathy and disinhibition were significantly more common in FTD, while DLB patients showed higher depressive symptoms compared to AD. In the total sample, only a few global associations were observed between NPS and cognition, however, delusions positively correlated with certain DRS-2 subdomains and global scores. In the total sample, no significant associations were found between NPI or HADS scores and global cognitive performance. Nonetheless, stratified analyses revealed specific patterns: in AD, caregiver-rated depression was associated with poorer executive and constructional performance, while delusions and euphoria were linked to relatively preserved executive functioning. In FTD, apathy and depression were respectively associated with deficits in attention and memory.

Conclusion: This study confirms the high prevalence of neuropsychiatric symptoms in dementias, reinforcing the importance of their characterization for diagnostic purposes, for a better understanding of the relationship between these symptoms and cognition, and for assessing their clinical and social impact. The absence of correlation between global cognitive measures and neuropsychiatric scales suggests that behavioral and mood symptoms may represent an independent dimension of disease expression.

Despite limitations related to the sample size, the findings contribute to a better recognition of clinical neuropsychiatric profiles in neurodegenerative dementias, particularly in AD, FTD, and DLB.

LIST OF ABBREVIATIONS

AD – Alzheimer's Disease

APP – Amyloid Precursor Protein

bvFTD - Behavioral variant of Frontotemporal Dementia

CHUdSA – Centro Hospitalar Universitário de Santo António

CSF – Cerebrospinal-fluid

DLB – Dementia with Lewy Bodies

DRS-2 – Dementia Rating Scale-2

FTD – Frontotemporal Dementia

HADS – Hospital Anxiety and Depression Scale

LPA – Logopenic Progressive Aphasia

NIA – National Institute of Aging

NPI – Neuropsychiatric Inventory

NPS – Neuropsychiatric Symptoms

PCA – Posterior Cortical Atrophy

PNFA – Progressive Non-Fluent Aphasia

PPA – Primary Progressive Aphasia

PSEN1 – Presenilin-1

PSEN2 – Presenilin-2

REM – Rapid Eye Movement

SD – Semantic Dementia

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION

1. Dementia

Dementia is a clinical syndrome marked by the progressive, persistent decline of cognitive abilities acquired throughout life. Typically, multiple domains, like memory, comprehension, language, attention, reasoning and judgment, are affected, leading to pronounced functional deterioration that severely restricts an individual's capacity to perform everyday activities[1-3] (Table I shows the diagnostic criteria for dementia). Although the cognitive repercussions of dementia have been thoroughly documented, its neuropsychiatric symptoms remain under-recognized despite their clinical significance relevance[4].

Dementia ranks among the most prevalent disorders in older adults and represents a major public-health challenge in Portugal. Its impact reaches well beyond patients themselves, placing a substantial burden on families, primary caregivers, and health-care systems[1,5,6]. With demographic shifts towards an elderly society, the global prevalence of dementia is anticipated to increase dramatically over the coming decades[5,6]. According to data provided by the World Health Organization, dementia currently affects approximately 55 million individuals globally, with projections indicating a rise to roughly 139 million cases by 2050[7]. In Portugal alone, dementia cases reached an estimated 193.516 individuals in 2018 and this figure is projected to more than double by mid-century[8].

This dissertation focuses on three common degenerative dementias subtypes: Alzheimer's disease, Frontotemporal Dementia and Dementia with Lewy Bodies. While these conditions share certain clinical features, each exhibit distinct clinical and neuropsychological profiles, warranting a comparative analysis throughout the present work.

1.1 Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, accounting for at least two-thirds of cases in individuals aged 65 years and over[2]. This type of dementia is distinguished from other forms by its unique combination of neuropathological changes and a well-characterized set of clinical symptoms. Apart from neuronal loss, which is common to all degenerative dementias, the most prominent neuropathological features of AD are 1) the extracellular accumulation of beta-amyloid in the cerebral cortex in the form of amyloid plaques, and 2) the accumulation of phosphorylated tau in the form of intracellular neurofibrillary tangles, particularly in the hippocampus and entorhinal cortex[9-11].

The dementia syndrome typical of AD is mainly characterized by a marked impairment of episodic memory, almost invariably the earliest and most frequent clinical manifestation. Lexical

retrieval failures are likewise common, with patients often struggling to generate the appropriate word in spontaneous speech. Another common early symptom is visuospatial impairment, leading to disorientation and a tendency to become lost in previously familiar settings. As the disease progresses, difficulties in executive functions emerge, with alterations in abstract reasoning, poor concentration, impaired calculation skills and difficulty maintaining visual attention[12]. Inter-individual variability in the clinical expression of AD has been partly attributed to the concept of cognitive reserve, that reflects the brain's capacity to tolerate pathological changes without manifesting symptoms, and which is closely associated with educational level[1,13]. Although the typical clinical presentation of AD is amnesic, atypical variants involving predominant visual or language deficits may also occur, particularly in early-onset cases[14].

In terms of diagnosis, AD can be categorized into three main groups: 1) probable Alzheimer's dementia, 2) possible Alzheimer's dementia, and 3) probable or possible Alzheimer's dementia with evidence of the pathophysiological process. The first two categories are intended for general clinical use, while the third is more suitable for research purposes[3]. The diagnostic criteria for probable Alzheimer's disease were established in 2011 by the National Institute of Aging (NIA) and the simultaneous presence of the diagnostic criteria shown in Table I and Supplementary Table I is required. The diagnostic confidence for AD rises substantially when a pathogenic mutation, such as amyloid precursor protein (APP), presenilin-1 (PSEN1), or presenilin-2 (PSEN2), is identified. Likewise, the detection of specific AD biomarkers also increases the conviction that the pathophysiological processes responsible for AD are indeed responsible for the dementia in question. In fact, neurochemical biomarkers play a fundamental role in this context, because they markedly boost both the sensitivity and specificity of the diagnosis[15]. Among the most widely adopted measures are cerebrospinal-fluid (CSF) concentrations of β-amyloid and tau proteins, which provide a biochemical signature of AD pathology: Aβ42 levels typically fall by roughly 50 %, reflecting its extracellular deposition in brain parenchyma, whereas total tau rises sharply, and phosphorylated tau increases further still, the latter serving as a direct indicator of neuronal damage[15-17].

In addition to its neuropathological and clinical distinctiveness, Alzheimer’s disease displays notable epidemiological patterns: there seems to be higher incidence of AD among women; particularly this sex difference becomes especially pronounced after the age of 85, where incidence continues to rise in women but plateaus in men, contributing to the marked predominance of AD in older female populations, which may reflect not only increased female

longevity, but also biological and hormonal factors that affect susceptibility to neurodegeneration[2,18,19].

1.2 Frontotemporal Dementia

Frontotemporal Dementia (FTD) refers to a set of clinical syndromes resulting from the degeneration of specific brain regions, including the frontal and anterior temporal lobes, the insular cortex and subcortical structures, leading to a spectrum of behavioral and language disorders that set it apart from both AD and DLB[20]. The various pathological processes underlying FTD are classified under a histopathological term known as frontotemporal lobar degeneration, characterized by selective atrophy of the frontal and temporal cortex[10]. These clinical syndromes primarily show changes in behavior, language and executive functions[21,22].

Frontotemporal dementia is a common cause of early-onset dementia, accounting for approximately 10% of diagnoses in individuals under the age of 65[23]. When considering all age groups, FTD is the third most common form of neurodegenerative dementia, following AD and DLB. In comparison to AD, FTD is characterized by a faster progression of cognitive decline and a shorter life expectancy[22]. Approximately 40% of patients with FTD have a first-degree relative with dementia, and 15% of cases suggest autosomal dominant transmission[20,22,24]. The typical age of diagnosis is 56, but it can manifest as early as the second decade of life[20]. However, in younger individuals, FTD is often mistaken for psychiatric disorders such as schizophrenia or major depression[22,25]. In all suspected cases of FTD, it is essential to use imaging, particularly magnetic resonance imaging, to rule out conditions that could mimic this dementia, such as brain tumors and to identify characteristic patterns of brain atrophy in the frontal and temporal lobes, which make the diagnosis more likely[22,26]. The most common variants of FTD include the behavioral variant and the progressive aphasia variant. Supplementary Table II presents an overview of the clinical presentations of the various FTD syndromes[21,27-30]. The behavioral variant is the most common form of FTD, accounting for about half of FTD cases[31]. It is characterized by a progressive decline in cognition along with at least three of the following features: behavioral disinhibition, apathy or inertia, early loss of sympathy or empathy, stereotyped or compulsive behavior, hyperorality or eating disorders and deficits in executive tasks[29]. The primary progressive aphasia variant, on the other hand, corresponds to a syndrome characterized by speech or language impairment[27]. This variant is diagnosed when all three of the following criteria are met: 1) the patient has an insidious onset and a gradual progression of aphasia, 2) the aphasia must initially be prominent and isolated, i.e. the aphasia is the main factor responsible for disrupting the patient's activities of daily living (the other cognitive functions remain relatively preserved), and 3) the diagnostic tests must point to a progressive

neurodegenerative process as the sole cause[27,32]. Although other cognitive functions may be affected in the later stages of the disease, language disorder remains the most affected domain throughout this variant[27,30].

1.3 Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) is recognized as the second most common form of neurodegenerative dementia, accounting for about 10% to 25% of dementia cases[33,34]. DLB is characterized by the abnormal buildup of alpha-synuclein in neurons, forming structures known as Lewy bodies, which are concentrated in various regions of the brain[10,35].

Unlike Alzheimer's disease and Frontotemporal dementia, DLB often appears sporadically, without a family history of the disease[35], which furthers complicates diagnostic certainty, especially in prodromal stages, because its heterogenous clinical presentation can be easily mistaken for Alzheimer's disease or other synucleinopathies, such as Parkinson's disease. Up to 20% of DLB patients are misdiagnosed, with many initially being diagnosed with AD[33,36]. Moreover, the median age of onset for DLB is 76.3 years, which may contribute to diagnostic delays, particularly when symptoms are attributed to nonspecific age-related changes[37]. Compared to AD, patients with DLB experience a less decline in memory and have better verbal memory in the early stages. However, they generally have a lower quality of life and shorter survival[12,38,39].

To diagnose DLB, dementia must be present (refer to Supplementary Table I) along with at least two of the following core characteristics[33,40-42]: 1) symptoms of parkinsonism, such as bradykinesia, rigidity, and rest tremor, which are present in approximately 85% of DLB patients; 2) visual hallucinations: recurrent, spontaneous, and typically complex, often involving people, children, or animals, found in 80% of cases and are one of the main clinical signs leading to the diagnosis of DLB; 3) Rapid Eye Movement (REM) sleep disturbance: manifested by loss of atonia and motor behaviors that mimic dream content, which can begin up to 15 years before diagnosing DLB, and 4) fluctuations in attention and wakefulness which include episodes of daytime sleepiness, lethargy, staring into space, and disorganized speech. Fluctuations in consciousness are a distinctive feature of DLB and are seldom observed as prominently and as early as in other neurodegenerative disorders[12,41]. Sometimes DLB can be foreshadowed by a cluster of supportive clinical features that appear decades before cognitive decline, most notably neuropsychiatric symptoms like apathy and anxiety, autonomic disturbances like orthostatic hypotension and constipation and even olfactory loss[33,43,44].

2. Neuropsychiatric symptoms in dementia

Neuropsychiatric symptoms (NPS) occur in 98% of individuals with dementia, at any time during the course of the disease[45,46]. These symptoms can be severe and ultimately lead to increased morbidity and mortality. These symptoms consist of apathy, anxiety, depression/dysphoria, appetite/eating changes, irritability/lability, agitation/aggression, sleep disturbances, aberrant motor behavior, disinhibition, hallucinations, delusions and euphoria/elation[45,47,48]. In addition to being practically universal in any type of dementia, NPS pose a significant problem, impacting not only the day-to-day of patients but also affecting family members and caregivers, increasing their suffering and stress. Additionally, they further contribute to the need for institutionalization and are responsible for a higher financial cost of care[49-51]. Several studies suggest a relationship between the presence and severity of NPS and overall cognitive decline; however, this association is complex and may vary depending on the symptom, cognitive domain, and dementia subtype[47,52,53].

The type of neuropsychiatric symptom can vary depending on the specific type of dementia, meaning that they can serve as an important guide for differential diagnosis[12,54,55]. In fact, some of the NPS listed are also among the core diagnostic criteria for both DLB (visual hallucinations) and bvFTD (disinhibition), as mentioned before[56].

In AD, NPS are quite common and varied. Up to 35% of AD patients may experience delusions, particularly of the paranoid, somatic, and theft types. Interestingly, patients with delusional symptoms tend to be older than those without psychotic symptoms, and they have a worse prognosis with a faster deterioration in cognitive function[42,48,57-59]. Nonetheless, the most frequent and persistent neuropsychiatric symptom in AD is apathy, followed by depression, aggression, anxiety, and sleep disturbances; these symptoms often become apparent before the clinical stage of dementia is recognized[48,57,60,61]. It's worth highlighting that the depression seen in AD patients is less severe than the one seen in DLB patients[10]. As the AD progresses, aggressiveness becomes increasingly more common and can affect up to 50% of institutionalized patients[60].

In FTD , NPS are also highly prevalent and often define the clinical presentation, with one of the most prevalent symptoms, throughout the course of the disease, being apathy, present in around 90% of patients[30,62,63], manifesting itself with a marked reduction in social involvement, self-care and activities of daily living, aspects which are specially distressing and debilitating for caregivers[30]. Compared to AD, apathy in FTD often appears in the early stages of the disease and is typically more severe[21,30]. Other neuropsychiatric symptoms such as agitation, disinhibition, and aberrant motor disturbances are also more common in FTD[64]. In fact, disinhibition is a

distinctive symptom of the behavioral variant of frontotemporal dementia and can manifest itself through socially inappropriate behaviors (hypersexuality, excessive play, impulsiveness), which explains why it's a key indicator for an early diagnosis[48,65,66]. Euphoria, although less frequent, is also described in FTD[67].

Regarding DLB, NPS are also prominent with psychotic features, such as visual hallucinations and delusions, occurring in 60%-80% of patients[34,68-70]. As previously stated, visual hallucinations are usually recurrent and complex, can involve seeing people, children, or animals, and may be accompanied by visual illusions and are much more common in DLB than in AD, making them one of the most distinctive characteristics between these two conditions[12,33,34,36,41]. As a result, they have a high positive predictive value for the diagnosis of DLB[35,56]. Another characteristic that sets DLB apart from other dementias, in terms of NPS, is the higher prevalence of REM sleep disturbances, which can appear as early as 15 years before diagnosis, indicating a prodromal state of disease, thereby being a very specific symptom of DLB when compared to AD and FTD[57]. At the beginning of the dementia, patients with DLB also show apathy, anxiety, and depression, with some studies describing aberrant motor behavior as a relatively frequent symptom[59,71]. However, it is noted that these patients have a lower probability of experiencing euphoria compared to other dementias[71].

It is worth emphasizing that the presence or absence of these symptoms in any dementia has a strong impact on the patient's prognosis and are in themselves early indicators of risk[45,72]: the presence of NPS such as agitation and apathy in AD, for example, is associated with faster cognitive decline and shorter survival[39,73]. In reality, the presence of any neuropsychiatric symptom in an apparently cognitively normal individual may be enough to justify greater clinical vigilance since these symptoms can be important precursors for the various neurodegenerative dementias. In a matter of fact, depression or apathy in a cognitively normal individual, can be indicative of an increased risk of developing AD or FTD. Similarly, around 70-90% of patients with REM sleep disturbance will eventually develop dementia or parkinsonism within 15 years[36,61,72,74,75].

Given the significant impact of neuropsychiatric symptoms, their study will not only guide differential diagnosis but also contribute to more effective management of dementias, as well as support earlier diagnosis, which will allow for a more targeted treatment[44,73,76]. A better understanding of these symptoms in each patient, regardless of cognitive stage, may help mitigate their impact on quality of life and caregiver burden, while also delivering more individualized care[77,78].

3. Instruments of Neuropsychological and Behavioral Assessment

Neuropsychological assessment plays a crucial role in understanding cognitive and behavioral deficits in patients with dementia, enabling a detailed analysis of the various cognitive areas[79-81]. In fact, through a neuropsychological assessment, it is possible to gain a deeper understanding of each patient, identifying which cognitive functions are preserved or which areas have been compromised[82,83]. In this study, only patients who had gone through a comprehensive neuropsychological assessment protocol, which included the application of validated scales such as the Dementia Rating Scale-2, the Neuropsychiatric Inventory and the Hospital Anxiety and Depression Scale, were selected. The analysis of the results obtained by this neuropsychological assessment served as the basis for the statistical analysis.

3.1 Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) is an assessment tool that was created to evaluate 10 neuropsychiatric symptoms in patients with dementia: delusions, hallucinations, agitation/aggressiveness, depression/dysphoria, anxiety, euphoria/elation, apathy, disinhibition, irritability/emotional lability and aberrant motor behavior[54]. The 10-item version was later expanded to include two more symptoms: sleep disturbances and appetite changes, resulting in a 12-item version[54,84]. The NPI is administered through a structured interview with an informed caregiver, ideally someone who lives with the patient. This interview is carried out in the absence of the patient in order to allow the caregiver to report the observed behaviors more openly and accurately, avoiding the potential difficulties that could arise otherwise[54].

The NPI measures both the frequency and severity of the symptoms that occurred over the past month: frequency is rated on a scale of 1 to 4, where 1 represents “occasionally” (less than once a week) and 4 “very often” (daily or almost constantly), and severity is assessed on a scale of 1 to 3, where 1 indicates “mild” (little discomfort for the patient) and 3 means “severe” (very disturbing symptoms). The total score for each symptom is obtained by multiplying the frequency values by the severity, and the total NPI score results from adding up each symptom's score. In addition, the NPI assesses the emotional impact on the caregiver for each symptom, with a distress scale ranging from 0 (no suffering) to 5 (extreme suffering). Although this value does not contribute to the total NPI score, it is particularly relevant to the holistic clinical approach of these patients[54,85,86].

The NPI is a widely recognized reference tool for assessing neuropsychiatric symptoms in patients with dementia, due to its validity and reliability, and is therefore considered a gold standard for measuring these symptoms[54,87,88]. It has already been validated in multiple

languages, including the Portuguese version, which showed results compatible with the international versions[50].

3.2 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a self-reporting tool developed to identify levels of anxiety and depression in patients attending an out-patient hospital/clinic visit[89]. The scale consists of 14 items, broken down equally into two subscales: HADS-A, which evaluates anxiety, and HADS-D, which evaluates depression[90,91]. Each item in each subscale is rated from 0 to 3, which makes the total score in each subscale go from 0 to 21: scores between 0 and 7 are considered normal, while scores from 8 to 10 indicate moderate symptoms and scores of 11 or higher suggest the presence of significant signs of anxiety or depression[90,92]. This tool is recognized for its quick application (usually takes 5 minutes), being easy for patients to understand, and is particularly effective in distinguishing between anxiety and depression, while avoiding to analyze common symptoms that may be present in other frequent illnesses other than these mood disorders[93-95]. The HADS stands out for its wide use in various languages and disease populations and is a versatile tool in both clinical contexts and research studies[93]. The Portuguese version of the HADS showed reliability and validity similar to the original versions[96].

Combining the HADS with the NPI enriches the assessment of neuropsychiatric symptoms, providing a more detailed analysis by integrating the patient's auto-perspective, captured by the HADS, with the caregiver's perception, reflected in the NPI.

3.3 Dementia Rating Scale-2

The Dementia Rating Scale-2 (DRS-2), also known as the Mattis Dementia Rating Scale, is widely used in the assessment of general cognitive status, as it stands out for its ability to assess five central cognitive domains: attention, initiation/perseveration, construction, conceptualization and memory, providing a robust and comprehensive cognitive profile[97,98].

The attention subdomain evaluates the individual's capacity to remain focused during specific tasks, such as repeating sequences of numbers backwards or performing basic actions upon request, for instance, opening their mouth. The initiation/perseveration subdomain examines the individual's ability to both initiate and maintain the performance of a certain task; examples include listing items available in a supermarket or performing alternating palm-up and palm-down movements, 5-times. In the construction subdomain, visuospatial skills are assessed by asking individuals to replicate simple drawings. The conceptualization subdomain measures conceptual understanding and problem-solving abilities, using tasks such as explaining similarities and differences between common objects, for example, describing how apples and

bananas are alike and how they may differ. Lastly, the memory subdomain assesses memory function, specifically targeting the individual's capacity to retain and recall newly learned information, such as repeating sentences previously stated by the interviewer after a brief interval.

A key element in interpreting the results of the DRS-2 is the use of normative comparison standards, making it possible to compare pathological changes between population groups with very different demographic and cultural characteristics that could influence the results, for example, education level. Thus, performances below -1 or -1.5 standard deviations in relation to what is expected for the normative group are indicative of cognitive impairment, while scores below -2 are generally considered suggestive of dementia in clinical practice[81,83]. The DRS-2 presents an efficient methodology for reducing assessment time in individuals without significant alterations. Within each subscale, the most complex tasks are presented first. If the individual performs adequately on the first tasks, competence is assumed for the rest, allowing them to move on to the next domain. As a result, in individuals without cognitive deficits, the total application time can be reduced to around 10 to 15 minutes, while in patients with dementia the application can last between up to 1 hour[81,99]. The validation and normative study of the DRS-2 for the Portuguese population was carried out by Dr. Sara Cavaco and Dr. Armando Teixeira-Pinto, ensuring that the normative data reflects the specific characteristics of the Portuguese population[100].

OBJECTIVE

The main goal of this dissertation was to investigate the prevalence, distribution and potential differences of neuropsychiatric symptoms in a hospital-based cohort of patients diagnosed with Alzheimer's Disease, Dementia with Lewy Bodies and Frontotemporal Dementia. As a secondary objective, the study also aimed to explore potential associations between neuropsychiatric and mood symptoms and cognitive performance.

METHODS

This retrospective observational study utilizes clinical and neuropsychological data of patients followed up at neurology outpatient clinic of Centro Hospitalar Universitário de Santo António (CHUdSA). Internal clinical database of the dementia group of the Neurology Department was used to identify the patients, being considered the patients actively followed in clinic in the year of 2024. Eligible participants were adults with a clinical diagnosis of AD (with positive CSF biomarkers for AD), DLB and FTD who had undergone a formal neuropsychological assessment, including Dementia Rating Scale-2, Neuropsychiatric Inventory and the Hospital Anxiety and Depression Scale. Because DLB cases were initially under-represented, historical records were re-examined by Dr. Ricardo Taipa, enabling the inclusion of additional suitable cases and yielding a final sample of 124 patients (64 AD, 14 DLB and 46 FTD).

For all participants, demographic data included sex, years of education, age at the time of neuropsychological evaluation and age at symptom onset were collected. The time interval between symptom onset and cognitive assessment was also calculated for all patients, based on the recorded age at symptom onset and the date of the neuropsychological evaluation.

Cognitive performance was assessed using DRS-2 with analysis based on standardized z-scores for each subdomain (Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory) and the Total Adjusted Score, corrected for demographic factors.

Neuropsychiatric symptoms were assessed using the 12-item version of the NPI: for each symptom, an individual severity score was calculated by multiplying the frequency (1-4) by the severity (1-3), as per standard methodology. A total NPI score was also computed by summing all individual symptom scores.

Mood symptoms were evaluated using the Hospital Anxiety and Depression Scale, yielding separate scores for anxiety (HADS-A) and depression (HADS-D), each ranging from 0 to 21 and only the subscales scores were used in this analysis.

The information was first structured in Microsoft Excel and subsequently exported to IBM SPSS Statistics (version 30.0) for comprehensive statistical analyses. Descriptive statistics were calculated for all variables. For continuous variables, results were expressed as means, standard deviations, and observed ranges; categorical variables were reported as frequencies and percentages. The distribution of continuous variables was assessed using both the Shapiro-Wilk and Kolmogorov-Smirnov tests. Most continuous variables, including DRS-2 z-scores, years of education, age at symptom onset, HADS-D scores, and NPI symptom scores, were found to be non-normally distributed. Therefore, non-parametric statistical methods were adopted for these variables. Group comparisons for categorical variables (e.g., sex distribution, presence of NPI symptoms by diagnosis) were conducted using the Chi-square test. Comparisons between diagnostic groups for continuous variables were performed using the Kruskal-Wallis test for non-normally distributed variables (such as years of education, HADS-D scores, and DRS-2 z-scores), and one-way ANOVA was applied when the normality assumption was met (e.g., for HADS-A). When the Kruskal-Wallis test indicated statistically significant differences, post-hoc pairwise comparisons were conducted using the Mann-Whitney U test. Correlation analyses were conducted using Spearman's correlation coefficient.

The significance level was set at $p < 0.05$.

RESULTS

Sample Characteristics

As Table II shows, the total sample consisted of 124 patients, of whom 64 (51.6%) were diagnosed with AD, 14 (11.3%) with DLB and 46 (37.1%) with FTD. Among the 46 patients diagnosed with FTD, 17 (36.96%) had a confirmed genetic mutation, including 8 with *C9orf72* expansion, 7 with *GRN* mutations (progranulin), 1 with a *TARDBP* variant and 1 with a *SQSTM1* mutation.

In terms of sex distribution, 63 (50.8%) were men and 61 (49.2%) were female. Statistically significant differences were observed between diagnostic groups ($p = 0.003$), with the AD group presenting a lower proportion of male patients (35.9%) compared to DLB (64.3%) and FTD (67.4%).

As for education, the overall mean years were relatively similar across the three diagnostic groups, a Kruskal-Wallis test revealed a statistically significant difference in the distribution of years education ($p = 0.001$). Post-hoc pairwise comparisons indicated that the DLB group differed significantly from both AD and FTD ($p = 0.001$), while no significant difference was found between AD and FTD ($p = 1.000$).

Mean age at symptom onset was 60.69 ± 6.13 years in the AD group, 67.57 ± 7.40 years in the DLB group, and 59.28 ± 8.83 years in the FTD group (Table IV). A Kruskal-Wallis test indicated a statistically significant difference between groups ($p = 0.003$), with post hoc pairwise comparisons showing that DLB patients had a significantly later symptom onset than both AD and FTD patients ($p < 0.01$), while no significant difference was found between AD and FTD. The time interval between symptom onset and neuropsychological evaluation did not differ significantly between groups ($p = 0.310$); on average, this interval was 2.55 ± 2.07 years for AD, 3.57 ± 2.24 years for DLB, and 3.07 ± 3.48 years for FTD.

Descriptive and Comparative Analysis

DRS-2 Scores

The descriptive statistics for the DRS-2 subdomains are presented in Table V, which summarizes the mean scores, standard deviations and observed score ranges for each cognitive domain, stratified by dementia diagnosis. The DRS-2 evaluates multiple cognitive domains, each represented by a specific z-score: Attention (Z_1), Initiation/Perseveration (Z_2), Construction (Z_3), Conceptualization (Z_4), Memory (Z_5), and the Total Adjusted Score (Z_t), which provides a global measure of cognitive performance.

Patients with AD showed the lowest scores in the Memory domain (-4.72 ± 1.85), whereas individuals with DLB obtained comparatively higher scores in most domains, particularly in Attention (-0.56 ± 1.49), Initiation/Perseveration (-0.14 ± 0.94), and Construction (-0.43 ± 1.44). The FTD group demonstrated lower scores in Attention (-3.09 ± 4.54), Initiation/Perseveration (-3.48 ± 2.77), Memory (-3.48 ± 2.61), while scores in Construction (-1.64 ± 2.15) were comparatively higher.

DRS-2 subdomain scores Initiation/Perseveration (Z_2), Memory (Z_5), and the Total Adjusted Score (Z_t) were different between the clinical groups (Table VI). Post-hoc pairwise comparisons (Table VII) showed that in Initiation/Perseveration, the DLB group scored significantly higher than both AD and FTD ($p < 0.001$), while no significant difference was found between AD and FTD. In the Memory subdomain, all group comparisons were statistically significant: AD patients had lower scores (-4.72 ± 1.85) than both FTD (-3.48 ± 2.61) and DLB (-1.34 ± 1.70), and FTD patients also scored significantly lower than those with DLB. Regarding the Total Adjusted Score, AD (-5.01 ± 3.21) and FTD (-5.18 ± 4.10) groups had significantly lower scores than DLB (-1.60 ± 2.12), with no statistically significant difference observed between AD and FTD.

Within the FTD group, we further explored whether cognitive performance differed between patients with a known pathogenic mutation (genetic FTD) and those without (non-genetic FTD). No statistically significant differences were found across any of the DRS-2 domains or the Total Adjusted Score (all $p > 0.05$; Table VIII).

NPI Scores

Among the 64 patients with available NPI data (51.6% of the total sample), apathy was the most frequently reported symptom, present in 76.6% of cases. This was followed by Anxiety (62.5%) and Depression/Dysphoria (60.9%). Other commonly observed symptoms included Irritability/lability (46.9%), Appetite/Eating changes (48.4%), and Agitation/Aggression (43.8%). In contrast, symptoms such as Euphoria/Elation (20.3%), Hallucinations (15.6%), and Delusions (10.9%) were among the least frequently reported in the overall sample.

Table IX presents the prevalence of each neuropsychiatric symptom assessed using the NPI, stratified by dementia diagnosis and in the total sample. Apathy was reported in 100% of patients with FTD, compared to 67.6% in AD and 60.0% in DLB, with a statistically significant difference between groups ($X^2 = 9.157$; $p = 0.010$), with the largest difference observed between FTD and the other two groups. Disinhibition also varied significantly across diagnostic categories ($X^2 = 13.943$, $p < 0.001$), with clearly distinct prevalence patterns in each dementia: 50.0% in FTD, 30.0% in DLB, and only 5.9% in AD. No significant differences were found across groups for

the remaining symptoms, including Delusions, Agitation/Aggression, Anxiety, Aberrant Motor Behavior, Sleep Disturbances, Hallucinations, Depression/Dysphoria, Euphoria/Elation, Irritability/Lability and Appetite/Eating Changes (all p-values > 0.05).

No statistically significant differences were in NPI total score or prevalence of individual NPI symptoms between genetic and non-genetic FTD (all p-values > 0.05).

HADS Scores

Regarding the HADS results, as Table X shows, it was found that the mean score for the anxiety subscale (HADS-A) was 7.26 and the mean score for the depression subscale (HADS-D) was 6.88. When analyzing the results by diagnostic group, despite DLB presented higher mean scores for both anxiety and depression compared to participants with AD and FTD, in HADS-A, there was not a statistically difference ($p = 0.376$), between diagnostic groups.

In contrast, for the HADS-D, there were statistically significant differences between groups ($p = 0.036$). Post-hoc analysis showed that participants with DLB had significantly higher depression scores than those with AD ($p = 0.010$). No statistically significant differences were observed between AD and FTD ($p = 0.915$), nor between DLB and FTD ($p = 0.031$).

No statistically significant differences were observed in HADS-A and HADS-D total between genetic and non-genetic FTD (all p-values > 0.05).

Correlation Analysis Between NPI Scores, HADS and Cognitive Domains

In order to explore the relationship between neuropsychiatric and mood symptoms and cognitive performance, several correlation analyses were carried out, using Spearman's rho, since the data is non-normally distributed.

Firstly, correlations were examined between global symptom scores (NPI total score, HADS-A and HADS-D) and overall cognitive performance reflected in Total Adjusted Score (Z_t) (Table XI). None of these scores were significantly correlated with the DRS-2 total adjusted score (p-values > 0.05). A moderate positive correlation was observed between HADS-A and HADS-D themselves ($\rho = 0.491$, $p < 0.001$). To examine whether these associations varied across dementia subtypes, the same analyses were stratified by diagnostic group. Once again, at the global level, no significant correlations were found between NPI Total Score, HADS-A or HADS-D and the DRS-2 Total Adjusted Score in any of the three groups (Table XII).

Secondly, correlations were assessed between individual NPI symptom scores, HADS subscales and the DRS-2 cognitive subdomains across the total sample (Table XIII). Among all symptoms tested, Delusions were strongly and positively correlated with Initiation/Perseveration ($\rho =$

0.798), Memory (ρ = 0.729) and the Total Adjusted Score (ρ = 0.798), all with p-values < 0.05. Additionally, Hallucinations and Euphoria were positively associated with Conceptualization (ρ = 0.680 and ρ = 0.575, respectively; p < 0.05), while Apathy was weakly negative associated with Attention (ρ = -0.305, p < 0.05). No significant correlations were found regarding HADS-A and HADS-D scores in this analysis.

Finally, individual NPI symptoms scores and HADS subscales were analyzed in relation to specific DRS-2 cognitive subdomains within each diagnostic group. In this analysis several significant associations emerged (Table XIV). In the AD group, Sleep Disturbance and Hallucinations were negatively correlated with Memory (Z_5) (ρ = -0.632, p = 0.027; ρ = -0.949, p = 0.014, respectively), while Depression was associated with poorer performance in Construction (Z_3) (ρ = -0.594, p = 0.004), Initiation/Perseveration (Z_2) (ρ = -0.628, p = 0.002), and the Total Adjusted Score (Z_t) (ρ = -0.641, p = 0.001). Euphoria was positively associated with Initiation/Perseveration (Z_2) (ρ = 0.912, p = 0.011). In the FTD group, HADS-D correlated negatively with Memory (Z_5) (ρ = -0.369, p = 0.041), and Apathy was negatively associated with Attention (Z_1) (ρ = -0.468, p = 0.038). In the DLB group, Apathy correlated positively with Conceptualization (Z_4) (ρ = 0.912, p = 0.011) and Anxiety was significantly associated with Construction (Z_3) (ρ = 0.778, p = 0.039).

DISCUSSION

Neuropsychiatric and Mood Profiles – Insights from NPI and HADS

As highlighted in the introduction, NPS represent a core but often underrecognized component for dementia syndromes, contribution to functional impairment and disease burden. The analysis of NPI data confirmed what was anticipated: NPS are highly prevalent among patients with dementia, with Apathy (76.6%), Anxiety (62.5%) and Depression/Dysphoria (60.9%) being the most frequently reported symptoms. These findings are consistent with the existing literature, which highlights NPS as nearly universal across all types of dementia, and often among the first signs to emerge, even before formal cognitive diagnosis[45,46]. The analysis of HADS data showed that symptoms of anxiety and depression were present among patients with dementia, with mean scores in the normal range (0-7), but close to the clinical threshold for moderate symptoms (≥8)[90,92]. These findings are in line with previous studies that describe anxiety and depression as frequent symptoms in dementia patients[45,46].

Diagnostic Differences in Neuropsychiatric Profiles

The analysis by diagnostic group revealed distinct neuropsychiatric profiles that align with known clinical characteristics of each dementia subtype.

In AD, the predominant symptoms mirrored those of the total sample, ie., Apathy, Depression, and Anxiety were the most frequently reported, reflecting a pattern frequently described in the literature[48,57,60,61]. On the HADS scale, patients with AD showed intermediate levels of both anxiety and depression, higher than FTD but lower than DLB, with no statistically significant differences between groups for anxiety. However, AD patients scored significantly lower on the HADS-D than those with DLB, indicating relatively milder depressive symptoms. This aligns with literature suggesting that, while emotional symptoms are common in AD, their severity may be more variable[34,59,71].

In FTD patients, the neuropsychiatric profile was particularly distinctive: Apathy was present in 100% of cases, a significantly higher proportion compared to AD (67.6%) and DLB (60%). This finding reinforces apathy as a hallmark of FTD, particularly in the behavioral variant, where it often presents early and contributes heavily to functional decline and caregiver burden[30,62,63]. Disinhibition was also markedly more prevalent in FTD (50%) than in DLB (30%) or AD (5.9%), in line with classical descriptions of FTD as a syndrome marked by impulsivity and socially inappropriate behaviors[29,48,65,66]. This clear contrast reinforces the clinical utility of Disinhibition as a differential feature that helps distinguish FTD, particularly its behavioral variant, from Alzheimer's disease. In the literature, euphoria is another symptom classically associated with FTD although only present in a subset of patients[67,71]. In our sample, while it was more frequently observed in FTD (25%) than in AD (17.6%) or DLB (20%), there was no statistical significance. Interestingly, although FTD has been associated with changes in Appetite and Eating Behavior, such as hyperphagia or increased preference for sweets[71], no increased frequency of appetite/eating alterations was observed in the FTD group compared to AD or DLB (45.0% vs. 50.0% in both). The observation that 50.0% of AD patients also presented with Appetite or Eating Alterations is particularly noteworthy. Although these disturbances are often considered more typical of FTD, such symptoms are increasingly recognized in AD, particularly when detailed behavioural assessments like the NPI are used. This scale captures not only hyperphagic traits, but also anorexia, changes in food preference, stereotyped eating patterns and behavioural rigidity. Rather than differing in prevalence, the two syndromes may be better distinguished by the nature of their eating alterations: while bvFTD tends to present with disinhibited and compulsive behaviours, AD is more often marked by loss of appetite, diminished food-related motivation, and structured or avoidant behaviours. Kai, et al. [101] found that nearly half of the patients with mild AD already exhibited appetite changes, and that alterations in food preference peaked during the moderate stages of the disease. Cipriani, et al. [102] further described early manifestations in AD such as diminished motivation to eat, refusal of meals, and

stereotyped eating behaviours, which may reflect executive dysfunction. Similarly, Ikeda, et al. [103] reported that 58.1% of AD patients exhibited at least one eating-related disturbance, including altered appetite and food preference, indicating that these behavioural changes are not unique to FTD. It should be noted, however, that the NPI provides only a final score for each symptom, and narrative descriptions of the specific behaviors were not systematically collected in this study.

In terms of emotional symptoms, HADS scores revealed that FTD patients had lower mean levels of both anxiety and depression compared to DLB, but scores comparable to AD. This pattern is consistent with the behavioral findings from the NPI and suggests that affective symptoms may be less prominent, less recognized or less easily expressed in FTD[104].

To explore whether the presence of a known pathogenic mutation influenced the neuropsychiatric phenotype in FTD, we conducted a subgroup comparison between genetic and sporadic cases. No statistically significant differences were observed in HADS-A, HADS-D or NPI total score between the two groups (all p-values > 0.05). Similarly, the prevalence of individual NPI symptoms did not differ significantly between genetic and non-genetic FTD (all p-values > 0.05). These results suggest that, within this hospital-based sample, the expression of neuropsychiatric symptoms in FTD appears relatively independent of underlying genetic status.

DLB patients presented the highest means HADS scores for both anxiety and depression. Statistically significant differences were only found for HADS-D, with DLB patients showing higher depression scores compared to the other dementias. These results are consistent with what has been described, where depression is frequently observed in DLB and tends to be more severe than in AD[34,59,71]. Although the HADS-A scores were also higher in DLB, no statistically significant differences were found between the groups. Nevertheless, in the literature the prevalence of anxiety in DLB patients tends to be superior compared to FTD patients[105]. Although several NPI symptoms traditionally associated with DLB, such as Hallucinations and Sleep Disturbances, did not reach statistical significance in the analysis, they were still more frequent in DLB patients compared to the other groups. Specifically, Hallucinations were present in 30.0% of DLB patients versus 14.7% in AD and 10.0% in FTD, and Sleep Disturbances affected 60.0% of DLB patients, compared to 38.2% in AD and 35.0% in FTD. These trends are consistent with what was outlined in the introduction, where both visual Hallucinations and Sleep Disturbances are considered core/hallmark clinical features of DLB, helping distinguish this condition from AD and FTD[33,35,56,57]. The lack of statistical significance may be explained by the small number of DLB patients with NPI data (n = 10), which limits the ability of statistical tests to detect real differences.

Cognitive Profiles Across Dementia Subtypes – Insights from the DRS-2

As expected, the analysis of DRS-2 performance across diagnostic groups revealed distinct cognitive patterns.

Patients with AD exhibited marked deficits predominantly in the Memory subdomain. This finding corroborates the extensive body of literature highlighting memory impairment as the central cognitive feature of AD, particularly the early deterioration of episodic memory frequently described as characteristic of the disease pathology[12]. Additionally, the significant lower scores observed in AD patients compared to both DLB and FTD further reinforce the notion of severe amnestic impairment as a key distinguishing clinical feature of the most common AD amnesic presentation[3].

Regarding the FTD group, prominent impairments were observed in the Initiation/Perseveration subdomain, underscoring substantial executive dysfunction, an observation particularly relevant for bvFTD[29]. Pairwise comparisons revealed significantly worse performance in this domain compared to DLB, but not significantly different from AD, suggesting that while executive dysfunction is a hallmark of FTD, some degree of impairment may also emerge in AD, leading to partially overlapping profiles. This is particularly relevant considering that the average interval between symptom onset and neuropsychological evaluation in our cohort was 2.85 years, suggesting that these results reflect early to intermediate stages of disease progression. The presence of dysexecutive features in AD at this stage aligns with previous studies showing that frontal dysfunction can arise early in the disease course, particularly in complex tasks requiring initiative and cognitive flexibility[106,107]. Still, the overall cognitive profiles remained distinct: FTD patients exhibited more severe impairments in executive function, while AD patients showed significantly worse performance in the Memory domain, a double association supported by neuropathologically confirmed studies[107]. In contrast, FTD patients showed intermediate levels of impairment in the Memory subdomain compared to AD and DLB, reinforcing the notion that memory deficits, though present, are generally less pronounced when compared to AD[108]. Additionally, the relative preservation of Construction abilities in the FTD group is consistent with the notion that these functions tend to be less affected in the early stages of this dementia[109].

On the other hand, individuals diagnosed with DLB exhibited mean scores in Initiation/Perseveration and Construction that fell within the normal or borderline range, suggesting relative preservation in these domains. This pattern contrasts with the more pronounced deficits observed in the AD and FTD groups and aligns with previous literature, which define DLB as a condition characterized primarily by fluctuations in cognitive function and

domain-specific impairments rather than generalized cognitive decline[33,40-42]. Indeed, as confirmed by pairwise comparisons, this relative preservation is significantly different from both AD and FTD groups.

When considering the global cognitive performance as reflected by the DRS-2 total adjusted score (Z_t), both the AD and FTD groups performed significantly worse than DLB, with no significant difference between AD and FTD. This suggests that, although the nature of cognitive impairment differs between these two conditions, the overall level of dysfunction is comparable.

Associations Between Neuropsychiatric Symptoms and Cognitive Function

Findings in the Total Sample

Concordant to our study, it's established that NPS are highly prevalent across all dementia types, yet the specific ways in which individual neuropsychiatric and mood symptoms relate to cognitive domains hasn't been well explored. In our study, the exploration of these associations in the total sample revealed a small but clinically relevant number of significant correlations. Among the symptoms assessed, Delusions showed the strongest positive correlations with cognitive performance, including the DRS-2 Initiation/Perseveration domain, Memory and the total adjusted DRS-2 score, suggesting that patients who exhibited delusional symptoms tended to perform better on these domains. Although this may initially seem counterintuitive, several studies suggest that the presence of Delusions may depend on the preservation of certain cognitive abilities. In other words, patients may require a minimum degree of cognitive organization to generate and sustain false beliefs. For instance, Bylsma, et al. [110] found that AD patients with delusions symptoms demonstrated relatively preserved attention. Similarly, Lee, et al. [111] observed that delusional patients were more likely to produce confabulations particularly in response to questions about recent personal experiences. These patients did not have preserved memory in the strict sense but instead attempted to compensate for memory gaps by generating plausible, yet false, narratives. This leads to the idea that Delusions in dementia are not necessarily a marker of more advanced global impairment but may instead arise when certain cognitive functions remain sufficiently active to construct distorted, interpretations of reality. Interestingly, additional associations emerged between Hallucinations and Euphoria and the Conceptualization subdomain (Table XIII), suggesting that other psychotic symptoms may also be linked to specific cognitive patterns. Nonetheless, it is important to recognize that Delusions have also been associated with more rapid cognitive decline in longitudinal studies. For example, Scarmeas, et al. [112] found that Delusions present at baseline in patients with AD predicted a faster rate of global cognitive deterioration over time.

Consequently, it may be that patients who currently maintain sufficient cognitive function to generate psychotic symptoms are nonetheless at higher risk for accelerated decline, underscoring the clinical importance of identifying and monitoring such features even in patients who still perform well on cognitive assessments.

Apathy, conversely, was the most prevalent symptom across the entire cohort (more than ¾) and the only one to show a significant negative correlation with the Attention domain (Table XIII), indicating that more apathetic individuals performed worse on attention-related tasks. This result is consistent with prior evidence highlighting Apathy as a core feature of executive and attentional dysfunction in dementia[113,114]. Its impact on attention aligns with the low attentional scores observed in FTD patients (Table V) and in the correlation analysis within FTD group where apathy was significantly associated with attentional deficits.

Interestingly, no significant associations were found between global cognitive performance, as measured by DRS-2 total adjusted score, and the overall burden of neuropsychiatric or mood symptoms, as captured by the NPI total scores and HADS-A or HADS-D scales. This finding reinforces the idea that neuropsychiatric scores, when examined in aggregate, may have limited sensitivity as markers of cognitive function in diagnostically heterogeneous cohorts and that they may constitute a relatively independent dimension of disease burden, with limited overlap with measurable cognitive decline[47,115]. This interpretation is supported by prior research showing that, in what regards caregiver burden, it is often more closely linked to the nature and severity of NPS than to the cognitive impairment of the patient per se. In a recent study comparing patients with DLB and AD, Yuuki, et al. [116] found that caregiver distress was significantly associated with symptoms such as Anxiety, Disinhibition, Apathy and Agitation, rather than with global cognitive scores. Similarly, Chen, et al. [117] showed that in patients with AD, NPS like Agitation, Delusions and Disinhibition, were the strongest predictors of caregiver burden. Therefore, even in the absence of measurably cognitive deterioration, the clinical significance of NPS remains paramount. A patient presenting with prominent NPS such as Agitation, Disinhibition or Psychosis may be considerably more challenging to manage than one with equivalent cognitive deficits but minimal neuropsychiatric disturbance. In this context, the high prevalence of such symptoms, just like we observed in our cohort reinforces the need for their routine assessment. Even in the absence of a clear association with cognitive scores, the presence and profile of NPS should remain a key element in the comprehensive and holistic assessment of patients with dementia, to provide individualized care and targeted support for caregivers, since they are essential to fully capture the clinical complexity of neurodegenerative dementias.

However, the apparent lack of global correlation may obscure more nuanced relationships that emerge when individual diagnostic subgroups are considered. As discussed in the following section, stratified analyses revealed that in specific subgroups such as FTD and AD, mood and behavioral symptoms did show meaningful associations with cognitive performance, indicating that these effects may be diagnosis-specific and domain-selective.

Diagnostic-Specific Associations

While global analyses revealed only a few significant associations between neuropsychiatric symptoms and cognitive performance, stratification by diagnostic group (Table XIII and Table XIV) uncovered a richer and more nuanced landscape of symptom-cognition interactions.

In the AD group, the strongest associations between neuropsychiatric symptoms and cognitive performance were observed for Depression, as rated by caregivers using the NPI, not HADS-D. Higher Depression scores were significantly associated with worse performance in the Construction and Initiation/Perseveration subdomains, as well as with lower global cognitive performance. These findings reinforce the potential cognitive impact of affective symptoms in AD, aligning with previous studies that have linked depression to executive dysfunction and accelerated functional decline in this population[118]. It is particularly noteworthy that these associations emerged only with the NPI depression score, not with the HADS-D scale, suggesting that caregiver observations may capture aspects of behavioral dysfunction with stronger cognitive correlates than patient self-report. This distinction is supported by previous findings showing only moderate concordance between self-reported and informant-rated depressive symptoms in dementia populations, with larger discrepancies between sources being associated with worse cognitive outcomes and greater functional impairment[119]. Additional associations were found between Sleep Disturbance and Hallucinations, and the Memory subdomain. These results may point to the vulnerability of memory systems in the presence of sleep and perceptual dysregulation. Winer, et al. [120] found that short self-reported sleep duration was associated not only with poorer performance on cognitive tasks, but also with increased β-amyloid burden (reduced sleep may impair Aβ clearance). Moreover, the authors observed that both short and long sleep durations were associated with worse subjective cognitive function and higher depressive symptoms. Surprisingly, Euphoria was positively correlated with Initiation/Perseveration within the AD group. This finding, although based on a very small number of patients, may suggest that the presence of Euphoria in AD could be related to the preservation of specific executive functions, particularly those involved in initiation and goal-directed behavior. In line with what was previously discussed for Delusions, this supports the idea that certain neuropsychiatric symptoms may require a minimum degree of cognitive

organization to emerge. It is therefore plausible to speculate that the circuits underlying this cognitive domain, when relatively spared in the context of overall decline, may contribute to the manifestation of euphoric states, potentially as a result of neurotransmitter imbalance and neuroanatomical changes associated with the disease. Although Euphoria is infrequent in AD, previous studies have shown that it does not necessarily increase with the severity of cognitive impairment and that, in other forms of dementia, it may be more commonly associated with frontal dysfunction, particularly in conditions such as FTD[121,122]. While the mechanisms may differ, this parallel reinforces the broader observation that symptoms such as Delusions and Euphoria may arise not from a more advanced stage of deterioration, but rather from specific patterns of disruption occurring in patients who still retain some degree of functional cognitive organization. Nonetheless, given the rarity of Euphoria in our sample, these interpretations must remain cautious.

In the FTD group, apathy once again stood out as a clinically relevant marker, displaying a significant negative correlation with the Attention domain. This reinforces previous findings and supports the conceptualization of FTD as a syndrome characterized by prominent frontal lobe dysfunction, with Apathy serving as a behavioural proxy for executive and attentional deficits[113,114]. Additionally, depressive symptoms (HADS-D) were negatively associated with memory performance, suggesting that mood symptoms may, nonetheless, exert a measurable cognitive toll.

In contrast, the DLB group revealed a unique pattern. Apathy was positively correlated with the Conceptualization domain, a counterintuitive result that contrasts with the negative association observed in FTD. Additionally, Anxiety was significantly associated with Construction. One possible explanation lies in the very small sample size for DLB patients with NPI data (n = 10), therefore these findings should be interpreted with caution. However, it is also plausible that these symptoms, particularly Anxiety, may be reactive in nature rather than directly driven by underlying neurodegeneration. This reactive phenomenon may arise in patients who retain greater insight into their cognitive impairments. DLB is known for relatively preserved cognitive functioning in certain domains, particularly early in the disease course, and for the fluctuating nature of deficits, which may allow patients to intermittently recognize their decline. In this context, higher conceptual and construction abilities may be associated with increased awareness and, consequently, greater emotional distress, such as anxiety or demoralization. Rather than indicating neuropathology, these associations may reflect the psychological burden of insight, especially in individuals who remain cognitively engaged and

aware of their limitations. In fact, in our sample, patients with DLB demonstrated the most preserved cognitive abilities, further supporting this interpretation.

Sociodemographic Factors

Our sample revealed significant differences in sex distribution, educational attainment and age at symptom onset between diagnostic groups. The proportion of male patients was significantly lower in the AD group compared to DLB and FTD, a finding consistent with the higher prevalence of Alzheimer's disease among women[18,19]. The small number of DLB cases in this cohort may partially reflect a referral bias, particularly given that DLB often presents later in life and may be underrepresented in hospital settings that focus on early-onset dementias.

Statistically significant differences were found in the age at symptom onset across diagnostic groups. Patients with DLB presented with a later onset of symptoms compared to those with AD and FTD, with no significant difference between the latter two. This finding aligns with previous literature suggesting that DLB tends to manifest later in life than other major neurodegenerative dementias[37]. Nonetheless, the relatively young age of onset observed in the AD group, is younger than typically reported in epidemiological studies, which reflect a selection bias in this hospital-based sample, where younger or atypical cases are more likely to be referred for specialized evaluation[2]. This highlights the importance of interpreting absolute age values in the context of the clinical setting, especially when generalizing findings beyond the studied population.

Educational attainment, by contrast, emerged as a more informative and robust variable. As shown in Table II and Table III, while the mean years of education were similar across groups, distributional differences were evident. The AD group displayed a highly skewed pattern with a substantial proportion of patients having minimal formal education, while FTD patients had a higher median and more centrally distributed educational profile. These differences were statistically significant and likely reflect the combined effect of generational, regional and socioeconomic factors shaping educational access across decades. However, as previously noted, these results may also be influenced by referral bias and should not be extrapolated to the general population.

Limitations of the study

This study presents several limitations that should be acknowledged. Firstly, the overall sample size was relatively small, particularly within the DLB group, which limited statistical power and may have constrained the detection of differences between diagnostic groups. Secondly, the sample was derived from a hospital-based population, which may not be representative of broader community-based cohorts and introduces potential referral bias, particularly towards younger and complex cases. Thirdly, the average level of education was low, especially in the AD group, which may limit the generalizability of the cognitive findings to contemporary populations with higher educational attainment. Finally, although the NPI and HADS provided structured information on neuropsychiatric and mood symptoms, we did not collect narrative descriptions or conduct a systematic review of neuropsychological reports, therefore, we were unable to explore the qualitative nature of certain behaviours, such as appetite or eating changes, beyond the scores recorded in the structured instruments. Moreover, not all patients had complete data for behavioural and mood assessments, particularly the NPI, which may have reduced the ability to detect certain associations and introduced potential selection bias: these assessments were possibly more likely to be completed in patients who were more functional or had caregivers who were more available, which could have introduced a bias in the sample.

CONCLUSION

This study sought to examine the prevalence and diagnostic differences of neuropsychiatric symptoms in a hospital-based cohort of patients diagnosed with Alzheimer's disease, Frontotemporal Dementia and Dementia with Lewy Bodies to explore how these symptoms relate to cognitive performance across and within diagnostic groups.

Consistent with prior literature, neuropsychiatric symptoms were highly prevalent across all dementia types, with apathy, anxiety, and depression emerging as the most frequently reported. Marked diagnostic differences were identified: apathy and disinhibition were significantly more common in FTD, while DLB patients showed higher depression scores compared to AD.

Regarding the relationship between neuropsychiatric symptoms and cognitive performance, only a few global associations were observed in the total sample, with delusions showing a positive correlation with specific cognitive subdomains and the global cognitive score. When stratified by diagnosis, more specific and clinically relevant patterns emerged. In AD, caregiver-rated depression was associated with poorer performance in executive and construction domains, while delusions and euphoria were linked to relatively preserved executive functioning. In FTD, apathy and depressive symptoms were respectively associated with deficits in attention and memory.

Importantly, however, no significant correlations were found between global cognitive performance and the overall burden of neuropsychiatric or mood symptoms, as measured by the NPI and HADS total scores. These findings support the notion that behavioral and emotional symptoms may constitute a relatively independent dimension of disease expression, often unrelated to the degree of cognitive impairment.

Overall, the findings highlight the value of integrating neuropsychological and behavioral assessments in dementia care and underline the importance of using both patient- and caregiver-reported measures in clinical evaluation. Although the sample was limited in size and drawn from a hospital setting, the results offer relevant insights into how specific neuropsychiatric symptoms relate to cognitive functioning in different dementia syndromes.

TABLES

Table I - Diagnostic criteria for Dementia

Criteria	Explanation
Interference with Activities of Daily Living	Cognitive or behavioral symptoms significantly interfere with the ability to perform tasks at work or in usual activities.
Decline from the previous level of functioning	Clear evidence of a decline in cognitive or behavioral capabilities compared to previous functioning.
Exclusion of other conditions	The symptoms are not explained by delirium, major psychiatric disorders or other medical conditions.
Identification of cognitive impairment	The deficit is identified through: – clinical history supported by information from a knowledgeable family member or caregiver; – objective mental state examination.
Minimum of 2 affected cognitive domains	The cognitive or behavioral impairment involves at least two of the following domains: – Memory – Reasoning and Judgment – Visuospatial abilities – Language – Behavior and Personality

Table II - Sociodemographic Variables – Total Sample

Variable	Total sample (n=124)	Alzheimer's Disease (n=64)	Dementia with Lewy Bodies (n=14)	Frontotemporal Dementia (n=46)	p-value*
Sex (n, % male)	63 (50.8%)	23 (35.9%)	9 (64.3%)	31 (67.4%)	0.003
Education (years), mean ± SD	6.8 ± 4.3	6.7 ± 4.5	6.9 ± 4.2	7.0 ± 4.1	0.001

*p-values refer to comparisons across diagnostic groups, based on Chi-square test for sex and Kruskal-Wallis test for years of education.

Table III - Descriptive Distribution of Years of Education Across Diagnostic Groups

Diagnostic Group	Mean (years)	Standard deviation	Median	Minimum	Maximum	Skewness
Alzheimer's Disease	6.7	4.5	4.0	3	21	+ 1.67
Dementia with Lewy Bodies	6.9	4.2	4.0	3	16	+ 1.18
Frontotemporal Dementia	7.0	4.1	5.5	3	17	+ 1.22

Table IV – Comparison of Age at Symptom Onset, Age at Time of Neuropsychiatric Assessment, and Time Elapsed Between the Two Events

Clinical Variable	Alzheimer's Disease	Dementia with Lewy Bodies	Frontotemporal Dementia	p-value
Age at symptom onset (years), mean ± SD	60.69 ± 6.13	67.57 ± 7.40	59.28 ± 8.83	0.003
Age at time of neuropsychiatric evaluation (years), mean ± SD	63.23 ± 6.36	71.14 ± 6.94	62.24 ± 8.44	0.001
Time elapsed between symptom onset and age at evaluation (years), mean ± SD	2.55 ± 2.07	3.57 ± 2.24	3.07 ± 3.48	0.310

*All variables in this table refer to the full sample of 124 patients with available data on age at symptom onset and neuropsychological assessment. Time elapsed was computed as the difference between the two timepoints.

Table V - DRS-2 Descriptive Statistics (Z-scores by Cognitive Domain and Diagnosis)

Diagnosis	Attention (Z_1)	Initiation/Perseveration (Z_2)	Construction (Z_3)	Conceptualization (Z_4)	Memory (Z_5)	Total Adjusted Score (Z_t)
Alzheimer's Disease	-2.25 ± 2.72	-3.06 ± 2.35	-2.19 ± 2.68	-2.55 ± 5.33	-4.72 ± 1.85	-5.01 ± 3.21
Dementia with Lewy Bodies	-0.56 ± 1.49	-0.14 ± 0.94	-0.43 ± 1.44	-1.08 ± 1.34	-1.34 ± 1.70	-1.60 ± 2.12
Frontotemporal Dementia	-3.09 ± 4.54	-3.48 ± 2.77	-1.64 ± 2.15	-2.66 ± 2.71	-3.48 ± 2.61	-5.18 ± 4.10
Total	-2.35 ± 3.45	-2.86 ± 2.59	-1.78 ± 2.43	-2.42 ± 4.22	-3.88 ± 2.39	-4.69 ± 3.63

Z-scores correspond to each DRS-2 subdomain (Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory). The Total Adjusted Score corresponds to the global DRS-2 performance adjusted for demographic variables. Values are expressed as mean ± standard deviation.

Table VI - Kruskal-Wallis Test Results for DRS-2 Subdomains Across Dementia Groups

DRS-2 subdomain	p-value*
Attention (Z_1)	0.066
Initiation/Perseveration (Z_2)	< 0.001
Conceptualization (Z_3)	0.051
Construction (Z_4)	0.164
Memory (Z_5)	< 0.001
Total Adjusted Score (Z_t)	< 0.001

*p-value refers to the significance level of the Kruskal–Wallis test, which evaluates whether the distribution of scores are the same across diagnostic groups (null hypothesis). A p-value < 0.05 indicates that the null hypothesis can be rejected, suggesting significant difference in score distributions between at least 2 diagnostic groups.

Table VII - Pairwise comparisons between diagnostic groups in DRS-2 subdomains with significant overall differences

DRS-2 Subdomain	Group Comparison	p-value
Initiation/Perseveration (Z_2)	AD vs. FTD	1.000
	AD vs. DLB	< 0.001
	FTD vs. DLB	< 0.001
Memory (Z_5)	AD vs. FTD	0.003
	AD vs. DLB	< 0.001
	FTD vs. DLB	0.005
Total Adjusted Score (Z_t)	AD vs. FTD	1.000
	AD vs. DLB	< 0.001
	FTD vs. DLB	< 0.001

*Significant difference was defined as a p-value < 0.05.

Table VIII - Comparison of DRS-2 subdomain scores between genetic and non-genetic FTD patients

DRS-2 Subdomain	Genetic FTD Mean ± SD	Non-genetic FTD Mean ± SD	p-value
Attention (Z_1)	-4.10 ± 5.49	-2.64 ± 4.09	0.425
Initiation/Perseveration (Z_2)	-3.80 ± 2.82	-3.34 ± 2.79	0.620
Conceptualization (Z_3)	-1.99 ± 2.21	-1.48 ± 2.14	0.425
Construction (Z_4)	-3.01 ± 3.50	-2.50 ± 2.33	0.988
Memory (Z_5)	-3.79 ± 3.09	-3.35 ± 2.42	0.964
Total Adjusted Score (Z_t)	-5.72 ± 5.13	-4.71 ± 3.71	0.918

Descriptive statistics (mean ± standard deviation) and Mann-Whitney U test results for each DRS-2 subdomain and the Total Adjusted Score, comparing patients with genetically confirmed FTD and those without a known genetic mutation. No statistically significant differences were found across any domain.

Table IX - Frequency of Neuropsychiatric Symptoms by Diagnosis in Patients with Available NPI data

Symptom	Total Sample (%)	Alzheimer's disease (%)	Dementia with Lewy Bodies (%)	Frontotemporal dementia (%)	p-value
Apathy	76.6	67.6	60.0	100.0	**0.01**
Anxiety	62.5	58.8	70.0	65.0	783
Depression/Dysphoria	60.9	67.6	60.0	50.0	0.438
Appetite/Eating Changes	48.4	50.0	50.0	45.0	0.933
Irritability/Lability	46.9	47.1	40.0	50.0	0.874
Agitation/Aggression	43.8	35.3	40.0	60.0	0.203
Sleep Disturbances	40.6	38.2	60.0	35.0	0.387
Aberrant Motor Behavior	31.3	23.5	30.0	45.0	0.258
Disinhibition	23.4	5.9	30.0	50.0	**< 0.001**
Euphoria/Elation	20.3	17.6	20.0	25.0	0.81
Hallucinations	15.6	14.7	30.0	10.0	0.355
Delusions	10.9	8.8	10.0	15.0	0.777

Percentages reflect symptom presence among patients with available NPI data (n = 64; AD = 34, FTD = 20, DLB = 10).

Table X - Mean HADS-A and HADS-D Scores by Diagnosis in Patients with Available HADS Data (n = 108)

Diagnostic Group	HADS-A (Mean ± SD)	HADS-D (Mean ± SD)
Alzheimer's disease	6.87 ± 4.23	6.35 ± 3.99
Dementia with Lewy Bodies	8.71 ± 4.53	9.57 ± 4.18
Frontotemporal dementia	7.35 ± 4.81	6.71 ± 4.85
Total Sample	7.26 ± 4.46	6.88 ± 4.39

Table XI - Spearman's correlation coefficients between NPI Total Score and HADS subscale scores and DRS-2 total adjusted score – Total Sample

Variables	Spearman's rho	p-value
NPI Total Score vs Total Adjusted Score (Z_t)	-0.042	0.741
HADS-A vs Total Adjusted Score (Z_t)	0.088	0.365
HADS-D vs Total Adjusted Score (Z_t)	-0.028	0.772
HADS-A vs HADS-D	0.491	**< 0.001**

Table XII - Spearman's Correlation Coefficients Between NPS and HADS and Global Cognitive Performance - Stratified by Diagnostic Group

Diagnostic Group	Symptom Score	Cognitive Variable	Spearman's ρ	p-value	Number of cases
Alzheimer's Disease	NPI Total Score	DRS-2 Total Adjusted Score	-0.16	0.373	33
	HADS-A		0.157	0.232	60
	HADS-D		-0.128	0.332	60
Frontotemporal Dementia	NPI Total Score		0.009	0.97	20
	HADS-A		-0.086	0.630	31
	HADS-D		-0.176	0.319	31
Dementia with Lewy Bodies	HADS-A		0.134	0.713	10
	HADS-D		-0.148	0.613	14
	HADS-D		-0.109	0.71	14

All correlations computed using Spearman's rho. Analyses stratified by diagnostic group.

Table XIII - Spearman's correlations between individual NPI symptom scores, HADS and cognitive domains assessed by the DRS-2 – Total Sample

		Attention (z_1)	Initiation/ Perseveration (z_2)	Conceptualization (z_3)	Construction (z_4)	Memory (z_5)	Total Adjusted Score (Z_t)
NPI Symptom Score	Delusions	0.061	**0.798***	0.110	0.454	**0.729***	**0.798***
	Agitation	0.117	-0.089	0.221	-0.244	0.129	-0.087
	Anxiety	-0.015	0.018	0.105	0.173	0.088	0.09
	Apathy	**-0.305***	-0.037	-0.059	-0.145	-0.157	-0.089
	Hallucinations	0.095	0.343	**0.680***	-0.489	-0.574	-0.165
	Disinhibition	0.189	0.143	0.362	0.141	0.353	0.314
	Irritability	0.024	0.188	0.228	-0.134	0.325	0.152
	Appetite disturbance	-0.001	-0.153	0.321	-0.057	0.030	0.095
	Sleep disturbance	0.058	-0.098	0.147	-0.027	-0.118	-0.044
	Depression	-0.026	-0.185	0.164	-0.093	-0.005	-0.116
	Euphoria	0.156	0.491	**0.575***	-0.020	0.073	0.405
	Aberrant Motor Behavior	0.002	-0.133	0.020	-0.352	-0.079	-0.143
HADS	HADS-A	0.035	0.075	0.040	0.150	-0.067	0.088
	HADS-D	-0.010	0.011	0.028	0.76	0.03	-0.028

*Statistically significant correlation at the $p < 0.05$ level. Values represent Spearman's correlation coefficients (ρ) between the individual NPI symptom scores (frequency × severity), HADS subscales and DRS-2 cognitive subdomains.

Table XIV - Statistically Significant Spearman's Correlations Between Individual NPI Symptom Scores, HADS and DRS-2 Cognitive Domains – Stratified by Diagnostic Group

Diagnostic Group	Symptom Score	Cognitive Domain – DRS-2 subdomains	Spearman's ρ	p-value
Alzheimer's Disease	Sleep Disturbance	Memory (Z_5)	-0.632	0.027
	Hallucinations	Memory (Z_5)	-0.949	0.014
	Depression	Construction (Z_3)	-0.594	0.004
	Depression	Initiation/Perseveration (Z_2)	-0.628	0.002
	Depression	Total Adjusted Score (Z_t)	-0.641	0.001
	Euphoria	Initiation/Perseveration (Z_2)	0.912	0.011
Frontotemporal Dementia	HADS-D	Memory (Z_5)	-0.369	0.041
	Apathy	Attention (Z_1)	-0.468	0.038
Dementia with Lewy Bodies	Apathy	Conceptualization (Z_4)	0.912	0.011
	Anxiety	Construction (Z_3)	0.778	0.039

Only statistically significant correlations ($p < 0.05$) are presented. Spearman's rho (ρ) was used to assess the association between individual NPI symptom scores and domain-specific z-scores of the DRS-2 within each diagnostic group.

APPENDIX

Supplementary Tables

Supplementary Table I - Diagnostic Criteria of Probable Alzheimer's Dementia according to NIA

Criteria	Explanation	Essential vs. Complementary
Insidious start	Symptoms start gradually, developing over months or years, without a sudden onset.	Essential
History of cognitive deterioration	Clinical history or observation of a continuous decline in cognitive function, confirmed by reports from the patient and/or informants.	Essential
Main syndromic presentation is necessarily amnesic or non-amnesic	Amnesic presentation: the most common (75% of cases[20]), with deficits in learning and recollection of recent information, together with impairment in another cognitive area. Non-amnesic presentation: – Language: major deficits in word recall; – Visuospatial: visual cognitive deficits; – Executive Impairment: prominent compromise of reasoning, judgment and/or problem solving.	Essential
Presence of Biomarkers	The presence of biomarkers that indicate AD pathology	Complementary
Genetic Mutation (APP, PSEN1, PSEN2)	The presence of a known genetic mutation that causes AD.	Complementary

Supplementary Table II - Overview of the most frequent clinical presentations of Frontotemporal Dementia

<table>
<tr><th colspan="4">Frontotemporal Dementia</th></tr>
<tr><th>Behavioural-variant frontotemporal dementia</th><th colspan="3">Primary Progressive Aphasia</th></tr>
<tr><td rowspan="2">¬ Disinhibition
¬ Apathy/inertia
¬ Loss of sympathy/empathy
¬ Perseverative/compulsive behaviors
¬ Hyperorality
¬ Dysexecutive neuropsychological profile</td><td>Semantic dementia</td><td>Progressive nonfluent aphasia</td><td>Lopogenic aphasia</td></tr>
<tr><td>¬ Loss of semantic knowledge
¬ Impaired word comprehension and naming objects
¬ Spared repetition
¬ Spared speech production</td><td>¬ Apraxia of speech
¬ Involuntary, effortful manner of speech production
¬ The individual is able to retain object knowledge and comprehend words.</td><td>¬ Hesitant yet grammatically correct speech
¬ Impaired single-word retrieval in spontaneous speech and naming
¬ Impaired repetition of sentences and phrases</td></tr>
</table>

REFERENCES

1 Sobral, M. I. R. d. L. *A pessoa com demência e a sua reserva cognitiva* PhD thesis, Instituto de Ciências Biomédicas de Abel Salazar e Universidade de Aveiro, (2015).

2 Kumar, A. S., J. Lui, F. Tsao, J. W. in *StatPearls* (StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC., 2024).

3 McKhann, G. M. *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269 (2011). https://doi.org/10.1016/j.jalz.2011.03.005

4 Eikelboom, W. S. *et al.* Neuropsychiatric and Cognitive Symptoms Across the Alzheimer Disease Clinical Spectrum: Cross-sectional and Longitudinal Associations. *Neurology* **97**, e1276-e1287 (2021). https://doi.org/10.1212/wnl.0000000000012598

5 Alves, S., Duarte, N. & Gomes, B. Forecasted Dementia Prevalence in Portugal (2020-2080). *J Geriatr Psychiatry Neurol*, 8919887241237220 (2024). https://doi.org/10.1177/08919887241237220

6 Qiu, C., Kivipelto, M. & von Strauss, E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci* **11**, 111-128 (2009). https://doi.org/10.31887/DCNS.2009.11.2/cqiu

7 Organization, W. H. *Global status report on the public health response to dementia*. (2021).

8 Europe, A. *Dementia in Europe Yearbook 2019 "Estimating the prevalence of dementia in Europe"*. (2019).

9 Madnani, R. S. Alzheimer's disease: a mini-review for the clinician. *Front Neurol* **14**, 1178588 (2023). https://doi.org/10.3389/fneur.2023.1178588

10 Taipa, R., Pinho, J. & Melo-Pires, M. Clinico-Pathological Correlations of the Most Common Neurodegenerative Dementias. *Frontiers in Neurology* **3** (2012). https://doi.org/10.3389/fneur.2012.00068

11 Tiwari, S., Atluri, V., Kaushik, A., Yndart, A. & Nair, M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *Int J Nanomedicine* **14**, 5541-5554 (2019). https://doi.org/10.2147/ijn.S200490

12 Karantzoulis, S. & Galvin, J. E. Distinguishing Alzheimer's disease from other major forms of dementia. *Expert Rev Neurother* **11**, 1579-1591 (2011). https://doi.org/10.1586/ern.11.155

13 Meng, X. & D'Arcy, C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One* **7**, e38268 (2012). https://doi.org/10.1371/journal.pone.0038268

14 Graff-Radford, J. *et al.* New insights into atypical Alzheimer's disease in the era of biomarkers. *The Lancet Neurology* **20**, 222-234 (2021). https://doi.org/https://doi.org/10.1016/S1474-4422(20)30440-3

15 Tapiola, T. *et al.* Cerebrospinal Fluid β-Amyloid 42 and Tau Proteins as Biomarkers of Alzheimer-Type Pathologic Changes in the Brain. *Archives of Neurology* **66**, 382-389 (2009). https://doi.org/10.1001/archneurol.2008.596

16 Hampel, H. *et al.* Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. *Alzheimers Dement* **4**, 38-48 (2008). https://doi.org/10.1016/j.jalz.2007.08.006

17 Huynh, R. A. & Mohan, C. Alzheimer's Disease: Biomarkers in the Genome, Blood, and Cerebrospinal Fluid. *Front Neurol* **8**, 102 (2017). https://doi.org/10.3389/fneur.2017.00102

18 Fratiglioni, L. *et al.* Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* **54**, S10-15 (2000).

19 Aggarwal, N. T. & Mielke, M. M. Sex Differences in Alzheimer's Disease. *Neurol Clin* **41**, 343-358 (2023). https://doi.org/10.1016/j.ncl.2023.01.001

20 Erkkinen, M. G., Kim, M. O. & Geschwind, M. D. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases. *Cold Spring Harb Perspect Biol* **10** (2018). https://doi.org/10.1101/cshperspect.a033118

21 Olney, N. T., Spina, S. & Miller, B. L. Frontotemporal Dementia. *Neurol Clin* **35**, 339-374 (2017). https://doi.org/10.1016/j.ncl.2017.01.008

22 Antonioni, A. *et al.* Frontotemporal Dementia, Where Do We Stand? A Narrative Review. *International Journal of Molecular Sciences* **24**, 11732 (2023).

23 Hogan, D. B. *et al.* The Prevalence and Incidence of Frontotemporal Dementia: a Systematic Review. *Can J Neurol Sci* **43 Suppl 1**, S96-s109 (2016). https://doi.org/10.1017/cjn.2016.25

24 Goldman, J. S. *et al.* Comparison of family histories in FTLD subtypes and related tauopathies. *Neurology* **65**, 1817-1819 (2005). https://doi.org/10.1212/01.wnl.0000187068.92184.63

25 Warren, J. D., Rohrer, J. D. & Rossor, M. N. Frontotemporal dementia. *BMJ : British Medical Journal* **347**, f4827 (2013). https://doi.org/10.1136/bmj.f4827

26 Landin-Romero, R. *et al.* Disease-specific patterns of cortical and subcortical degeneration in a longitudinal study of Alzheimer's disease and behavioural-variant frontotemporal dementia. *NeuroImage* **151**, 72-80 (2017). https://doi.org/https://doi.org/10.1016/j.neuroimage.2016.03.032

27 Gorno-Tempini, M. L. *et al.* Classification of primary progressive aphasia and its variants. *Neurology* **76**, 1006-1014 (2011). https://doi.org/10.1212/WNL.0b013e31821103e6

28 Watanabe, H. *et al.* Primary Progressive Aphasia Lacking Core Features of Nonfluent and Semantic Variants: Clinical, Neuroimaging, and Neuropathologic Features. *Neurology* **103**, e209924 (2024). https://doi.org/10.1212/wnl.0000000000209924

29 Rascovsky, K. *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**, 2456-2477 (2011). https://doi.org/10.1093/brain/awr179

30 Johnson, E. & Kumfor, F. Overcoming apathy in frontotemporal dementia: challenges and future directions. *Current Opinion in Behavioral Sciences* **22**, 82-89 (2018). https://doi.org/https://doi.org/10.1016/j.cobeha.2018.01.022

31 Schönecker, S. *et al.* Frequency and Longitudinal Course of Behavioral and Neuropsychiatric Symptoms in Participants With Genetic Frontotemporal Dementia. *Neurology* **103**, e209569 (2024). https://doi.org/doi:10.1212/WNL.0000000000209569

32 Mesulam, M.-M. Primary progressive aphasia and the language network. *Neurology* **81**, 456-462 (2013). https://doi.org/doi:10.1212/WNL.0b013e31829d87df

33 Monteiro, A. *et al.* [Portuguese Consensus on the Diagnosis and Management of Lewy Body Dementia (PORTUCALE)]. *Acta Med Port* **33**, 844-854 (2020). https://doi.org/10.20344/amp.13696

34 Ballard, C. *et al.* Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatry* **156**, 1039-1045 (1999). https://doi.org/10.1176/ajp.156.7.1039

35 Capouch, S. D., Farlow, M. R. & Brosch, J. R. A Review of Dementia with Lewy Bodies' Impact, Diagnostic Criteria and Treatment. *Neurol Ther* **7**, 249-263 (2018). https://doi.org/10.1007/s40120-018-0104-1

36 Walker, Z., Possin, K. L., Boeve, B. F. & Aarsland, D. Lewy body dementias. *Lancet* **386**, 1683-1697 (2015). https://doi.org/10.1016/s0140-6736(15)00462-6

37 Hershey, L. A. & Coleman-Jackson, R. Pharmacological Management of Dementia with Lewy Bodies. *Drugs Aging* **36**, 309-319 (2019). https://doi.org/10.1007/s40266-018-00636-7

38 Oliveira, F. F. Assessing Independence in Activities of Daily Living and Quality of Life in Patients with Dementia with Lewy Bodies. *J Alzheimers Dis* **101**, 441-443 (2024). https://doi.org/10.3233/jad-240676

39 Breitve, M. H. *et al.* Apathy is associated with faster global cognitive decline and early nursing home admission in dementia with Lewy bodies. *Alzheimers Res Ther* **10**, 83 (2018). https://doi.org/10.1186/s13195-018-0416-5

40 Outeiro, T. F. *et al.* Dementia with Lewy bodies: an update and outlook. *Mol Neurodegener* **14**, 5 (2019). https://doi.org/10.1186/s13024-019-0306-8

41 McKeith, I. G. *et al.* Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* **89**, 88-100 (2017). https://doi.org/10.1212/wnl.0000000000004058

42 Naasan, G. *et al.* Psychosis in neurodegenerative disease: differential patterns of hallucination and delusion symptoms. *Brain* **144**, 999-1012 (2021). https://doi.org/10.1093/brain/awaa413

43 Jellinger, K. A. Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J Neural Transm (Vienna)* **125**, 615-650 (2018). https://doi.org/10.1007/s00702-017-1821-9

44 McKeith, I., Taylor, J. P., Thomas, A., Donaghy, P. & Kane, J. Revisiting DLB Diagnosis: A Consideration of Prodromal DLB and of the Diagnostic Overlap With Alzheimer Disease. *J Geriatr Psychiatry Neurol* **29**, 249-253 (2016). https://doi.org/10.1177/0891988716656083

45 Phan, S. V., Osae, S., Morgan, J. C., Inyang, M. & Fagan, S. C. Neuropsychiatric Symptoms in Dementia: Considerations for Pharmacotherapy in the USA. *Drugs in R&D* **19**, 93-115 (2019). https://doi.org/10.1007/s40268-019-0272-1

46 Kales, H. C., Gitlin, L. N. & Lyketsos, C. G. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc* **62**, 762-769 (2014). https://doi.org/10.1111/jgs.12730

47 Sabates, J. *et al.* The Associations Between Neuropsychiatric Symptoms and Cognition in People with Dementia: A Systematic Review and Meta-Analysis. *Neuropsychology Review* **34**, 581-597 (2024). https://doi.org/10.1007/s11065-023-09608-0

48 Argyriou, S. *et al.* Beyond memory impairment: the complex phenotypic landscape of Alzheimer's disease. *Trends Mol Med* **30**, 713-722 (2024). https://doi.org/10.1016/j.molmed.2024.04.016

49 Aalten, P., de Vugt, M. E., Jaspers, N., Jolles, J. & Verhey, F. R. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* **20**, 523-530 (2005). https://doi.org/10.1002/gps.1316

50 Ferreira, A. R., Martins, S., Ribeiro, O. & Fernandes, L. Validity and reliability of the European portuguese version of neuropsychiatric inventory in an institutionalized sample. *J Clin Med Res* **7**, 21-28 (2015). https://doi.org/10.14740/jocmr1959w

51 Kálmán, J., Kálmán, S. & Pákáski, M. [Recognition and treatment of behavioral and psychological symptoms of dementias: lessons from the CATIE-AD study]. *Neuropsychopharmacol Hung* **10**, 233-249 (2008).

52 Gallo, J. L., Schmidt, K. S. & Libon, D. J. Behavioral and psychological symptoms, neurocognitive performance, and functional independence in mild dementia. *Dementia* **7**, 397-413 (2008). https://doi.org/10.1177/1471301208093291

53 Giil, L. M., Aarsland, D. & Vik-Mo, A. O. Differentiating traits and states identifies the importance of chronic neuropsychiatric symptoms for cognitive prognosis in mild dementia. *Alzheimers Dement (Amst)* **13**, e12152 (2021). https://doi.org/10.1002/dad2.12152

54 Cummings, J. L. *et al.* The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **44**, 2308-2314 (1994). https://doi.org/10.1212/wnl.44.12.2308

55 Silvestri, C. *et al.* Sex Differences in the Severity and Progression of Neuropsychiatric Symptoms Across Different Dementia Types. *Neurol Clin Pract* **14**, e200299 (2024). https://doi.org/10.1212/cpj.0000000000200299

56 Devanand, D. P., Lee, S., Huey, E. D. & Goldberg, T. E. Associations Between Neuropsychiatric Symptoms and Neuropathological Diagnoses of Alzheimer Disease and Related Dementias. *JAMA Psychiatry* **79**, 359-367 (2022). https://doi.org/10.1001/jamapsychiatry.2021.4363

57 Zhao, Q. F. *et al.* The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord* **190**, 264-271 (2016). https://doi.org/10.1016/j.jad.2015.09.069

58 Cressot, C. *et al.* Psychosis in Neurodegenerative Dementias: A Systematic Comparative Review. *J Alzheimers Dis* **99**, 85-99 (2024). https://doi.org/10.3233/jad-231363

59 Simard, M., Reekum, R. v. & Cohen, T. A Review of the Cognitive and Behavioral Symptoms in Dementia With Lewy Bodies. *The Journal of Neuropsychiatry and Clinical Neurosciences* **12**, 425-450 (2000). https://doi.org/10.1176/jnp.12.4.425

60 Lyketsos, C. G. *et al.* Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *Jama* **288**, 1475-1483 (2002). https://doi.org/10.1001/jama.288.12.1475

61 Eratne, D. *et al.* Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. *Australas Psychiatry* **26**, 347-357 (2018). https://doi.org/10.1177/1039856218762308

62 Diehl-Schmid, J., Pohl, C., Perneczky, R., Förstl, H. & Kurz, A. Behavioral Disturbances in the Course of Frontotemporal Dementia. *Dementia and Geriatric Cognitive Disorders* **22**, 352-357 (2006). https://doi.org/10.1159/000095625

63 Husain, M. Mechanisms underlying apathy in frontotemporal dementia. *Brain* **146**, 416-417 (2022). https://doi.org/10.1093/brain/awac494

64 de Vugt, M. E. *et al.* Impact of Behavioural Problems on Spousal Caregivers: A Comparison between Alzheimer's Disease and Frontotemporal Dementia. *Dementia and Geriatric Cognitive Disorders* **22**, 35-41 (2006). https://doi.org/10.1159/000093102

65 Rankin, K. P. *et al.* Detecting sarcasm from paralinguistic cues: anatomic and cognitive correlates in neurodegenerative disease. *Neuroimage* **47**, 2005-2015 (2009). https://doi.org/10.1016/j.neuroimage.2009.05.077

66 Lee, S. E. Frontotemporal dementia: Clinical features and diagnosis. (2024). <https://www.uptodate.com/contents/frontotemporal-dementia-clinical-features-and-diagnosis?source=mostViewed_widget>.

67 Hirono, N. *et al.* Distinctive Neurobehavioral Features Among Neurodegenerative Dementias. *The Journal of neuropsychiatry and clinical neurosciences* **11**, 498-503 (1999). https://doi.org/10.1176/jnp.11.4.498

68 Bjoerke-Bertheussen, J., Ehrt, U., Rongve, A., Ballard, C. & Aarsland, D. Neuropsychiatric symptoms in mild dementia with lewy bodies and Alzheimer's disease. *Dement Geriatr Cogn Disord* **34**, 1-6 (2012). https://doi.org/10.1159/000339590

69 Aarsland, D., Ballard, C. G. & Halliday, G. Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? *J Geriatr Psychiatry Neurol* **17**, 137-145 (2004). https://doi.org/10.1177/0891988704267470

70 Morrow, C. B. & Pontone, G. M. Exploring Psychosis in Neurodegenerative Dementia: Connecting Symptoms to Neurobiology. *J Alzheimers Dis* **99**, 101-103 (2024). https://doi.org/10.3233/jad-240328

71 Schwertner, E. *et al.* Behavioral and Psychological Symptoms of Dementia in Different Dementia Disorders: A Large-Scale Study of 10,000 Individuals. *J Alzheimers Dis* **87**, 1307-1318 (2022). https://doi.org/10.3233/jad-215198

72 Jang, J. Y., Ho, J. K., Blanken, A. E., Dutt, S. & Nation, D. A. Affective Neuropsychiatric Symptoms as Early Signs of Dementia Risk in Older Adults. *J Alzheimers Dis* **77**, 1195-1207 (2020). https://doi.org/10.3233/jad-200190

73 Liew, T. M. Neuropsychiatric symptoms in cognitively normal older persons, and the association with Alzheimer's and non-Alzheimer's dementia. *Alzheimer's Research & Therapy* **12**, 35 (2020). https://doi.org/10.1186/s13195-020-00604-7

74 Rapp, M. A. *et al.* Cognitive decline in patients with dementia as a function of depression. *Am J Geriatr Psychiatry* **19**, 357-363 (2011). https://doi.org/10.1097/JGP.0b013e3181e898d0

75 Ismail, Z. *et al.* Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement* **12**, 195-202 (2016). https://doi.org/10.1016/j.jalz.2015.05.017

76 Geda, Y. E. *et al.* Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. *Alzheimers Dement* **9**, 602-608 (2013). https://doi.org/10.1016/j.jalz.2012.12.001

77 Borsje, P., Wetzels, R. B., Lucassen, P. L., Pot, A. M. & Koopmans, R. T. The course of neuropsychiatric symptoms in community-dwelling patients with dementia: a systematic review. *Int Psychogeriatr* **27**, 385-405 (2015). https://doi.org/10.1017/s1041610214002282

78 Devanand, D. P. Management of neuropsychiatric symptoms in dementia. *Curr Opin Neurol* **36**, 498-503 (2023). https://doi.org/10.1097/wco.0000000000001199

79 Braaten, A. J., Parsons, T. D., McCue, R., Sellers, A. & Burns, W. J. Neurocognitive differential diagnosis of dementing diseases: Alzheimer's Dementia, Vascular Dementia, Frontotemporal Dementia, and Major Depressive Disorder. *Int J Neurosci* **116**, 1271-1293 (2006). https://doi.org/10.1080/00207450600920928

80 Possin, K. L. Visual spatial cognition in neurodegenerative disease. *Neurocase* **16**, 466-487 (2010). https://doi.org/10.1080/13554791003730600

81 Lezak, M. D. *Neuropsychological assessment*. (Oxford University Press, USA, 2004).

82 Saúde, D.-G. d. Norma nº 053/2011 de 29/12/2011: Abordagem diagnóstica e terapêutica do doente (versão de abril de 2023). Report No. Norma nº 053/2011, (Lisboa, 2023).

83 Duarte, A. J. M. *Relatório de Estágio na Unidade de Neuropsicologia*, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, (2019).

84 Cummings, J. L. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* **48**, S10-16 (1997). https://doi.org/10.1212/wnl.48.5_suppl_6.10s

85 Steinberg, M. *et al.* Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry* **23**, 170-177 (2008). https://doi.org/10.1002/gps.1858

86 Kaufer, D. I. *et al.* Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* **12**, 233-239 (2000). https://doi.org/10.1176/jnp.12.2.233

87 Cummings, J. The Neuropsychiatric Inventory: Development and Applications. *J Geriatr Psychiatry Neurol* **33**, 73-84 (2020). https://doi.org/10.1177/0891988719882102

88 Massimo, L. *et al.* Neuroanatomy of Apathy and Disinhibition in Frontotemporal Lobar Degeneration. *Dementia and Geriatric Cognitive Disorders* **27**, 96-104 (2009). https://doi.org/10.1159/000194658

89 Zigmond, A. S. & Snaith, R. P. The hospital anxiety and depression scale. *Acta Psychiatr Scand* **67**, 361-370 (1983). https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

90 Bocéréan, C. & Dupret, E. A validation study of the Hospital Anxiety and Depression Scale (HADS) in a large sample of French employees. *BMC Psychiatry* **14**, 354 (2014). https://doi.org/10.1186/s12888-014-0354-0

91 Cosco, T. D., Doyle, F., Ward, M. & McGee, H. Latent structure of the Hospital Anxiety And Depression Scale: A 10-year systematic review. *Journal of Psychosomatic Research* **72**, 180-184 (2012). https://doi.org/https://doi.org/10.1016/j.jpsychores.2011.06.008

92 Teles, S. *et al.* Profiling early adopters of 'iSupport-Portugal': a country-specific version of a worldwide adapted digital support program for informal caregivers of people with dementia. *Front Psychol* **15**, 1359695 (2024). https://doi.org/10.3389/fpsyg.2024.1359695

93 Herrmann, C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res* **42**, 17-41 (1997). https://doi.org/10.1016/s0022-3999(96)00216-4

94 Botega, N. J., Bio, M. R., Zomignani, M. A., Garcia, C., Jr. & Pereira, W. A. [Mood disorders among inpatients in ambulatory and validation of the anxiety and depression scale HAD]. *Rev Saude Publica* **29**, 355-363 (1995). https://doi.org/10.1590/s0034-89101995000500004

95 Meneses, R., Pais-Ribeiro, J., Silva, A. & Giovagnoli, A. R. Portuguese Hospital Anxiety and Depression Scale (HADS): Usefulness in Focal Epilepsy. *The Internet Journal of Mental Health* **5** (2008). https://doi.org/10.5580/19e1

96 Pais-Ribeiro, J. *et al.* Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. *Psychol Health Med* **12**, 225-235; quiz 235-227 (2007). https://doi.org/10.1080/13548500500524088

97 Mattis, S. Dementia Rating Scale (DRS): Professional Manual. *Psychological Assemssment Resources* (1988).

98 Monsch, A. U. *et al.* Clinical validity of the Mattis Dementia Rating Scale in detecting Dementia of the Alzheimer type. A double cross-validation and application to a community-dwelling sample. *Arch Neurol* **52**, 899-904 (1995). https://doi.org/10.1001/archneur.1995.00540330081018

99 Matteau, E. *et al.* Mattis Dementia Rating Scale 2: screening for MCI and dementia. *Am J Alzheimers Dis Other Demen* **26**, 389-398 (2011). https://doi.org/10.1177/1533317511412046

100 Group, H. P. *DRS-2 Escala de Avaliação da Demência - 2*, <https://www.hogrefe.com/pt/shop/media/downloads/sample-reports/9NCPNP0031A_Flyer.pdf> (2011).

101 Kai, K. *et al.* Relationship between eating disturbance and dementia severity in patients with Alzheimer's disease. *PLoS One* **10**, e0133666 (2015). https://doi.org/10.1371/journal.pone.0133666

102 Cipriani, G., Carlesi, C., Lucetti, C., Danti, S. & Nuti, A. Eating Behaviors and Dietary Changes in Patients With Dementia. *American Journal of Alzheimer's Disease & Other Dementias®* **31**, 706-716 (2016). https://doi.org/10.1177/1533317516673155

103 Ikeda, M., Brown, J., Holland, A. J., Fukuhara, R. & Hodges, J. R. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **73**, 371-376 (2002). https://doi.org/10.1136/jnnp.73.4.371

104 Hirono, N. *et al.* Distinctive neurobehavioral features among neurodegenerative dementias. *J Neuropsychiatry Clin Neurosci* **11**, 498-503 (1999). https://doi.org/10.1176/jnp.11.4.498

105 Breitve, M. H. *et al.* A longitudinal study of anxiety and cognitive decline in dementia with Lewy bodies and Alzheimer's disease. *Alzheimer's Research & Therapy* **8**, 3 (2016). https://doi.org/10.1186/s13195-016-0171-4

106 Porto, C. S. *A escala de avaliação de demência (DRS) no diagnóstico de comprometimento cognitivo leve e doença de Alzheimer* Doutoramento thesis, Faculdade de Medicina, Universidade de São Paulo, (2006).
107 Rascovsky, K. *et al.* Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. *Neurology* **58**, 1801-1808 (2002). https://doi.org/10.1212/wnl.58.12.1801
108 Rascovsky, K., Salmon, D. P., Hansen, L. A. & Galasko, D. Distinct cognitive profiles and rates of decline on the Mattis Dementia Rating Scale in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. *J Int Neuropsychol Soc* **14**, 373-383 (2008). https://doi.org/10.1017/s135561770808051x
109 Walker, A. J., Meares, S., Sachdev, P. S. & Brodaty, H. The differentiation of mild frontotemporal dementia from Alzheimer's disease and healthy aging by neuropsychological tests. *Int Psychogeriatr* **17**, 57-68 (2005). https://doi.org/10.1017/s1041610204000778
110 Bylsma, F. W. *et al.* Delusions and Patterns of Cognitive Impairment in Alzheimer's Disease. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* **7**, 98–103 (1994).
111 Lee, E. *et al.* Confabulations in Episodic Memory Are Associated With Delusions in Alzheimer's Disease. *Journal of Geriatric Psychiatry and Neurology* **20**, 34-40 (2007). https://doi.org/10.1177/0891988706292760
112 Scarmeas, N. *et al.* Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol* **62**, 1601-1608 (2005). https://doi.org/10.1001/archneur.62.10.1601
113 Kuzis, G., Sabe, L., Tiberti, C., Dorrego, F. & Starkstein, S. Neuropsychological correlates of apathy and depression in patients with dementia. *Neurology* **52**, 1403-1403 (1999).
114 McPherson, S., Fairbanks, L., Tiken, S., Cummings, J. L. & Back-Madruga, C. Apathy and executive function in Alzheimer's disease. *Journal of the International Neuropsychological Society* **8**, 373-381 (2002). https://doi.org/10.1017/S1355617702813182
115 Fuller, J. T., Choudhury, T. K., Lowe, D. A. & Balsis, S. Hallucinations and Delusions Signal Alzheimer's Associated Cognitive Dysfunction More Strongly Compared to Other Neuropsychiatric Symptoms. *J Gerontol B Psychol Sci Soc Sci* **75**, 1894-1904 (2020). https://doi.org/10.1093/geronb/gbz032
116 Yuuki, S. *et al.* Comparison of caregiver burden between dementia with Lewy bodies and Alzheimer's disease. *Psychogeriatrics* **23**, 682-689 (2023). https://doi.org/https://doi.org/10.1111/psyg.12978
117 Chen, P. *et al.* Neuropsychiatric Symptoms and Caregiver Burden in Individuals With Alzheimer's Disease: The TEAM-AD VA Cooperative Study. *Journal of Geriatric Psychiatry and Neurology* **31**, 177-185 (2018). https://doi.org/10.1177/0891988718783897
118 Rashidi-Ranjbar, N., Miranda, D., Butters, M. A., Mulsant, B. H. & Voineskos, A. N. Evidence for Structural and Functional Alterations of Frontal-Executive and Corticolimbic Circuits in Late-Life Depression and Relationship to Mild Cognitive Impairment and Dementia: A Systematic Review. *Front Neurosci* **14**, 253 (2020). https://doi.org/10.3389/fnins.2020.00253
119 Calamia, M. & Bernstein, J. P. K. Comparison of self-reported and informant-reported depressive symptoms in an outpatient neuropsychology clinic sample. *J Clin Exp Neuropsychol* **39**, 525-533 (2017). https://doi.org/10.1080/13803395.2016.1240759
120 Winer, J. R. *et al.* Association of Short and Long Sleep Duration With Amyloid-β Burden and Cognition in Aging. *JAMA Neurol* **78**, 1187-1196 (2021). https://doi.org/10.1001/jamaneurol.2021.2876

121 Mega, M. S., Cummings, J. L., Fiorello, T. & Gornbein, J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology* **46**, 130-135 (1996). https://doi.org/10.1212/wnl.46.1.130

122 Perri, R., Monaco, M., Fadda, L., Caltagirone, C. & Carlesimo, G. A. Neuropsychological correlates of behavioral symptoms in Alzheimer's disease, frontal variant of frontotemporal, subcortical vascular, and lewy body dementias: a comparative study. *J Alzheimers Dis* **39**, 669-677 (2014). https://doi.org/10.3233/jad-131337

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**