Universitat Autònoma de Barcelona

Early detection of distinctive features of Alzheimer's Disease and other dementias in population with Mild Cognitive Impairment and associated Neuropsychiatric Symptoms

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— Natalia Roberto Herrero

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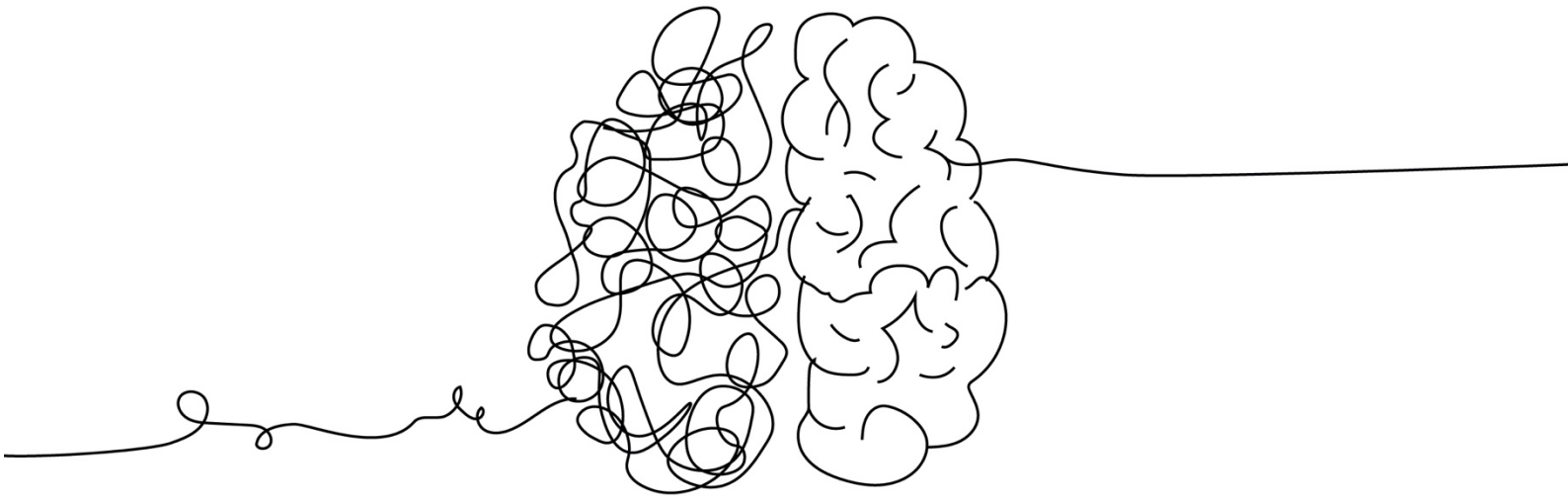

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To my family,

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Hereby, they assert that this thesis meets all the requirements to be defended for the Degree of Doctor.

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“Tell me and I forget,

teach me and I remember,

involve me and I learn”.

-Benjamin Franklin.

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Table and figure index

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Abbreviations

MCI: Mild Cognitive Impairment.

NC: Normal cognition.

IADL: Instrumental Activities of Daily Living.

AAMI: Age-associated memory impairment.

LLF: Late-life forgetfulness.

ARCD: Age-related cognitive decline.

AD: Alzheimer's disease.

aMCI-sd: Amnestic MCI single domain.

aMCI-md: Amnestic MCI multiple domains.

naMCI-sd: Non-amnestic MCI single domain.

naMCI-md: Non-amnestic MCI multiple domains.

CSF: Cerebrospinal fluid.

MMSE: Mini-Mental State Examination.

MoCA: Montreal Cognitive Assessment.

WMS: Weschler Memory Scale.

CVLT: California Verbal Learning Test.

RAVLT: Rey Auditory Verbal Learning test.

FCSRT: Free and Cue Selective Reminding Test.

ADAS-COG: Alzheimer's Disease Assessment Scale- Cognitive Subscale.

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

WMS-III: WMS-third edition.

EAIA: *Equipo de Atención Integral Ambulatoria*.

WHO: World Health Organization.

NPS: Neuropsychiatric symptoms.

VD: Vascular Dementia.

FTD: Fronto-Temporal Dementia.

LBD: Dementia caused by Lewy Bodies.

HIV: Human immunodeficiency virus.

DMTs: Disease-modifying therapies.

CR: Cognitive reserve.

Aβ: Amyloid-β.

AGES: Advanced glycation end products.

MRI: Magnetic resonance imaging.

CT: Computed tomography scan.

MBI: Mild Behavioural Impairment.

CDR: Clinical Dementia Rating Scale.

GDS: Global Deterioration Scale.

ICD-10: International Statistical Classification of Diseases and Related Health Problems.

DSM-V: Diagnostic and Statistical Manual of Mental Disorders.

MDR: Mattis Dementia Rating scale.

PD-CRS: Parkinson's Disease Cognitive Rating Scale.

NBACE: Neuropsychological Battery of ACE.

NPI: Neuropsychiatric Interview.

NPI-Q: NPI-Questionnaire.

Tau-t: Total tau protein.

Tau-p: Hyperphosphorylated tau.

PET: Positron Emission Tomography.

MTL: Medial temporal lobe.

DPD: Dementia caused by a psychiatric disorder.

LCA: Latent Class Analysis.

LMMs: Linear Mixed Models.

Summaries

Spanish summary

El envejecimiento produce cambios biológicos en el cerebro que afectan a la memoria, la atención y otras funciones cognitivas, las cuales pueden repercutir en el funcionamiento del día a día. El proceso normal de envejecimiento comporta cambios en la cognición, aunque una parte de la población sufre alteraciones que implican un deterioro cognitivo superior al esperable respecto a la población de referencia. Denominamos Deterioro Cognitivo Leve (DCL) a la alteración leve de estas funciones cognitivas, que no cumple criterios de demencia, pero sí que se asocia a mayor riesgo de un diagnóstico futuro. Por otro lado, los síntomas afectivos y/o conductuales (o síntomas neuropsiquiátricos) también se han asociado a mayor riesgo de conversión a demencia. La presente tesis doctoral pretende, desde una perspectiva integradora de la cognición, la afectividad y la conducta, abordar los siguientes objetivos: 1) determinar agrupaciones de pacientes con diagnóstico de DCL basadas en la predominancia de síntomas neuropsiquiátricos y explorar el valor predictivo de estas agrupaciones de cara a la conversión a tipos específicos de demencia según su etiología; y 2) analizar las posibles trayectorias de deterioro cognitivo en diferentes dominios (orientación, velocidad de procesamiento de la información, atención, memoria, gnosias, praxias, capacidad visuoespacial y funciones ejecutivas). Para la presente tesis doctoral incluimos un total de 2137 pacientes diagnosticados de DCL seguidos en una unidad de memoria. En el primer estudio se detectaron cuatro grupos de pacientes diferenciados por los síntomas neuropsiquiátricos predominantes: pacientes con Irritabilidad, con Apatía, con Ansiedad/Depresión y Asintomáticos. Formar parte del grupo con predominio de irritabilidad y el grupo con predominio de apatía resultaron ser los mejores predictores de conversión a demencia (en comparación con el grupo en que predominaba la clínica ansioso-depresiva y el grupo asintomático). El grupo que discriminaba mejor la demencia de diferente etiología que la causada por enfermedad de Alzheimer fue el grupo con predominio de irritabilidad. En el segundo estudio se hizo un seguimiento longitudinal a 3 años y se observó que los grupos con predominio de irritabilidad y de apatía sufrían un mayor declive en dominios de memoria verbal, concretamente en la capacidad de aprendizaje y el reconocimiento. En conclusión, síntomas neuropsiquiátricos poco prevalentes como la apatía y la irritabilidad resultan útiles para diagnosticar de forma específica y precoz la demencia, a la vez que pueden actuar como marcadores del pronóstico futuro de la evolución cognitiva a tres años vista.

Catalan summary

L'envelliment produeix canvis biològics al cervell que afecten la memòria, l'atenció i altres funcions cognitives, les quals poden repercutir en el funcionament del dia a dia. El procés normal d'envelliment comporta canvis en la cognició, però una part de la població pateix alteracions que impliquen un deteriorament cognitiu superior a l'esperable respecte la població de referència. Anomenem Deteriorament Cognitiu Lleu (DCL) a l'alteració lleu d'aquestes funcions, que no compleix criteris de demència però sí que s'associa a major risc d'un diagnòstic futur. D'altra banda, els símptomes afectius i/o conductuals (o símptomes neuropsiquiàtrics) també s'han associat a un major risc de conversió a demència. La present tesi doctoral pretén, des d'una perspectiva integradora de la cognició, l'afectivitat i la conducta, abordar els següents objectius: 1) determinar agrupacions de pacients amb diagnòstic de DCL basades en la predominança de símptomes neuropsiquiàtrics i explorar el valor predictiu d'aquestes agrupacions de cara a la conversió als tipus específics de demència segons la seua etiologia; i 2) analitzar les possibles trajectòries de deteriorament cognitiu en diferents dominis (orientació, velocitat de processament de la informació, atenció, memòria, gnòsies, pràxies, capacitat visuoespaial i funcions executives). Per a la present tesi doctoral vam incloure un total de 2137 pacients amb DCL seguits en una unitat de memòria. En el primer estudi es van detectar quatre grups de pacients diferenciats pels símptomes neuropsiquiàtrics predominants: pacients amb Irritabilitat, amb Apatia, amb Ansietat/Depressió i Asimptomàtics. Formar part del grup amb predomini d'irritabilitat i d'apatia van resultar ser els millors predictors de conversió a demència (en comparació amb el grup on predominava la clínica ansioso-depressiva i el grup asimptomàtic). El grup que discriminava millor la demència d'una altra etiologia diferent a la causada per la malaltia d'Alzheimer va ser el grup amb predomini d'irritabilitat. En el segon estudi es va fer un seguiment longitudinal a 3 anys i es va observar que els grups amb predomini d'irritabilitat i el d'apatia patien un declivi de dominis de memòria verbal significatius, concretament en la capacitat d'aprenentatge i el reconeixement. En conclusió, símptomes neuropsiquiàtrics poc prevalents com l'apatia i la irritabilitat resulten útils per a diagnosticar de forma específica i precoç la demència, a la vegada que poden actuar com a marcadors del pronòstic futur de l'evolució cognitiva a tres anys.

English summary

Aging produces biological changes in the brain that affect memory, attention and other cognitive functions, which can have an impact on day-to-day functioning. The normal aging process involves changes in cognition, but part of the population suffers alterations that imply a cognitive deterioration higher than expected with respect to the reference population. Mild Cognitive Impairment (MCI) refers to a mild alteration of these functions that does not meet dementia criteria but is associated with a higher risk of a future diagnosis. On the other hand, affective and/or behavioural symptoms (or neuropsychiatric symptoms) have also been associated with an increased risk of conversion to dementia. The present doctoral thesis aims, from an integrative perspective of cognition, affection and behaviour, to address the following objectives: 1) to determine groups of patients with a diagnosis of MCI based on the predominance of neuropsychiatric symptoms and explore the predictive value of these clusters for conversion to specific types of dementia according to their aetiology; and 2) to analyse the possible trajectories of cognitive impairment in different domains (orientation, speed of information processing, attention, memory, gnosias, praxias, visuospatial ability and executive functions). For the present dissertation we included a total of 2137 patients diagnosed with MCI and followed in a memory unit. In the first study obtained four groups of patients differentiated by predominant neuropsychiatric symptoms were detected: patients with Irritability, with Apathy, with Anxiety/Depression and Asymptomatic. Being part of the group with predominant irritability and the group with predominant apathy proved to be the best predictors of conversion to dementia (compared to the group with predominant anxious-depressive symptoms and the asymptomatic group). The group that discriminated best in identifying dementia of an aetiology other than Alzheimer's disease was the group with predominant irritability. In the second study, a 3-year longitudinal follow-up was performed, and it was observed that patients of the irritability-predominant and apathy-predominant clusters suffered a significant decline in verbal memory domains, specifically in verbal learning and cued-recall. In conclusion, low prevalent neuropsychiatric symptoms such as apathy and irritability are useful for specific and early diagnosis of dementia and may act as markers of future prognosis of cognitive evolution at a period of three-year’s time.

Preface

This doctoral thesis is the result of five years of work at *ACE* Alzheimer Centre Barcelona. During this period, I have learnt much more than merely academic knowledge that made me grow in many different facets.

Since the beginning, this ambitious project was created with the aim of helping patients who year after year passed through *ACE* with the intention of finding out what happened in the brain of individuals when they reached old age, and something was not properly working. This was possible due to the countless help of two important figures in my life in terms of academics and work, Dra. Maria J. Portella and Dra. Montserrat Alegret, who always believed in the potential of this project.

As a neuropsychologist, my main interests have always been around cognition in different pathologies. Yet in the early stages of my specialized MSc training, conducted at Hospital de la Santa Creu i Sant Pau in the Psychiatry Department, and in collaboration with the Human Neuropsychopharmacology team, I combined clinical tasks with my first research-driven projects. On one hand, I explored cognitive aspects of patients diagnosed with bipolar disease and major depression (among others), and I was in turn engaged in helping with different undertakings related to how drugs could affect cognition. Meanwhile, I was also involved in studying pharmacokinetics and pharmacodynamics of given substances. After a few projects collaborating with Dra. Marta Valle and Dr. Jordi Riba, I learnt about neuroimaging techniques acquisition process, pharmacological aspects of main components, antinociception and other topics related to drugs. On the other hand, I was deeply involved in clinical assessment and follow-up of cognitive performance in neurologic and psychiatric illnesses.

After my training I got my first professional position as a neuropsychologist at *ACE*, which is a pioneer centre in the diagnosis and evaluation of cognitive disorders. My role was devoted to helping people and their families in the diagnostic process of neurodegenerative disorders. Patients attended the centre with a variety of cognitive, behavioural and/or emotional problems and complaints that may probably lead to a diagnosis of Alzheimer or any other dementia. But also, these difficulties were mirroring other aspects of their lives, and then I realized that something had to be done to gather and interpret how these could represent risk factors or mediators of the progression of their possible disease. Overall, I found myself motivated towards patient-based research and I decided to explore this venue. Together with Maria J. Portella and Montserrat Alegret, the contents of this dissertation were set up. The main objective was to deepen into the processes and circumstances of brain functioning along the steps of dementia diagnosis. At this point, the project was presented as a doctorate thesis under the supervision of Dra. Portella and Dr. Valero.

By then, I was aware that the manifestation of most of brain-related pathologies are entangled symptoms, ranging from cognitive to emotional and behavioural alterations that cannot be mutually dissociated. In this regard, the current work was born (mainly) from my personal interest of joining two specialties that were present during my training as a neuropsychologist: the inner need to marry neurology and psychiatry to explore their influence on the diagnosis of mild cognitive impairment, and the progression to dementia from a multifaceted perspective.

Therefore, this dissertation is a compendium of two published articles that capture the interrelation of cognition and psychopathology in patients to be diagnosed of dementia. In addition, during these years I have collaborated in other works that have been published (see below).

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Dissemination has also been carried out through an oral presentation in Milan (Italy) by September 2019 at the *"7th Meeting of the Federation of the European Societies of Neuropsychology (FESN)",* as an oral communication under the title: **"Neuropsychiatric status as a predictor of cognitive decline in MCI".**

In addition, the results of this thesis have also been published as articles in national newspapers. Under the title **"*Un estudi identifica els símptomes psicològics que prediuen millor l'aparició de la demència*"**, and with a total audience of 1 80.338.716, as well as a total value of by 7 61.751 (values for disclosures obtained between the dates 23/03/2021-29/03/2021). Some that posted that press release were 'El Confidencial', 'News 3ª Edad', etc.

Additionally, during this professional stage of my life I took part of different projects in the discipline of mild cognitive impairment, early detection and engagement of patients

not assisted (*Models of Patient Engagement for Alzheimer's Disease, MOPEAD);* but also in an European pilot trial which aimed to help assisting patients at home, in terms of activities of daily living, when diagnosis was done in early stages of a dementia (*Robotic Assistant for MCI Patients at home).* All this brought me to present different posters in European congress in the field of Alzheimer's disease.

Index

Introduction.

1. Introduction

As humans age, biological changes are shown in our brain and some are intimately bonded to impairment of cognitive functions.[1] In the elderly, some cognitive skills such as attention, memory, executive functions or processing speed suffer from subtle changes associated with a normal aging process as it has already been demonstrated;[2,3] and some individuals are affected in cognition beyond expected. Nevertheless, not all decrement in cognitive functioning in this population is a precursor of disease, therefore it is important to distinguish between normal and pathological cognitive decline. Ergo, following the principle of evidence-based medicine, a term to include population with suspicion of a state of cognitive impairment (which could be a precursor of certain pathologies), was defined by the medical community.

1.1. Mild Cognitive Impairment (MCI)

Mild Cognitive Impairment (MCI) is a diagnostic entity defined as an objective performance below expected for age and education-corrected range (i.e. performance below 1.5 SD) in a standard neuropsychological measure; or by an objective decline in comparison with a premorbid state, that do not interfere with Instrumental Activities of Daily Living (IADL).[4]

1.1.1. History and concept of MCI

MCI condition has undergone through many changes in its nomenclature and specifications over the short period of time when it emerged. Initially, in 1962 a distinction between benign and malignant forgetfulness was suggested, coining the term '*Senescent Forgetfulness*' to refer to a part of the elderly population that had mild memory forgetfulness. It was based on a study performed in a clinical sample from a nursing home, although this concept was never validated.[5] Years later, in 1986 Crook et al published criteria for what was renamed as "age-associated memory impairment" (AAMI).[6] Both

terms were referring to a normal aging condition, but these were not the only ones; there were a few more attempts to coin a term for identifying subjects whose cognitive performance worsened below values established for that age group but not enough to believe there were neuropathological changes underlying, such as age-associated memory impairment (AAMI), age-consistent memory impairment (ACMI), late-life forgetfulness (LLF), and age-related cognitive decline (ARCD).

As opposed, in 1988 Reisberg and colleagues proposed that pathological changes were shown at a clear-cut stage (using an specific clinical scale) for this first AAMI but due to Alzheimer's disease (AD), which seem to derive into an MCI concept similar to what is known for today.[7] From then until 1999 there was a transitional time when 'questionable dementia' or 'minimal dementia' were terms used to refer to non-demented patients but AD was suspected.[8] A great amount of literature was growing by that time to classify individuals and to clarify terminology in regards to a worsening in cognition compatible with the actual MCI diagnostic. For example, *"F06.7 Mild Cognitive Disorder"* was provisionally included in the ICD-10 Classification of Mental and Behavioral Disorders, in the "Other mental disorders due to brain damage and dysfunction and to physical disease" section.[9] It was clearly noted that the status of the construct was being examined. So it was not until 1999 when the Mayo Clinic researchers described a community cohort and established the first and original criteria for an MCI diagnostic due to AD.[10] Since then, it is noteworthy to highlight that MCI has been progressively gaining relevance in research given the absence of pharmacological treatment options available for AD dementia.[11]

Even memory decline was postulated to be the prelude to dementia (excluding factors such as age-related as the main criteria) but not just focusing on memory as the sole cognitive domain affected, in 2003 a conference of international experts on MCI was carried out with the ulterior goal of combining and defining the core clinical criteria of MCI as it is known today. These criteria were divided into clinical phenotypes and cognitive performance. Even though memory was one of the core symptoms, MCI could be classified into four groups based on cognitive domains mainly affected (see next section *"1.1.2. MCI classification and diagnostic instruments"* for a proper classification and description). It was in 2004 when Petersen came with what is known as the formal diagnostic criteria for this 'new' entity, the so-called MCI. The cognitive domains that

may be affected include attention, executive functions, memory, language, praxis, visuoperception and visuospatial skills.[12,13]

1.1.2. MCI classification and diagnostic instruments

Depending on the number of affected cognitive domains, MCI can be classified into four possible groups (see *Fig. 1* flow diagram for MCI specific subtypes): predominantly amnestic single domain (aMCI-sd), multiple domain (aMCI-md), non-amnestic single domain (naMCI-sd) or non-amnestic multiple domains (naMCI-md).[14] When the term MCI was coined the subtype aMCI-sd received much more attention than the rest because it was postulated as a prodromal condition of AD.[15,16] Recently, research studies have confirmed that aMCI entails a higher risk of conversion to dementia due to AD. [17] Despite the weight of aMCI in AD, other forms of MCI may also be associated with a significant risk of an AD diagnosis, although these are mainly correlated with a higher risk of other neurodegenerative dementias. Therefore, MCI diagnosis was basically a theoretical construct, initially created with predictive purposes. Over the years, however, it has evolved to a diagnostic entity.

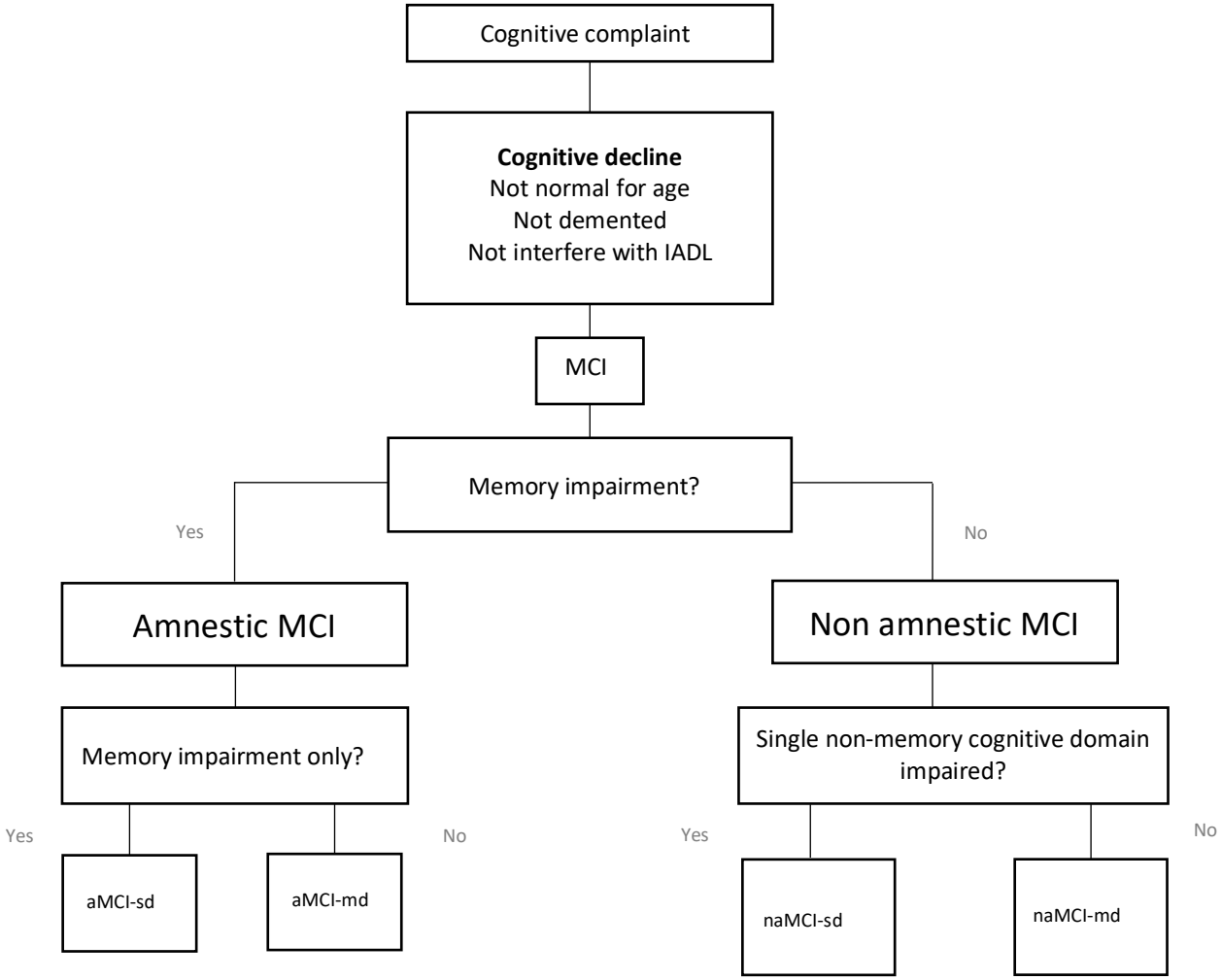

Figure 1. Flow diagram for diagnosis decision of MCI subtypes. Adapted from Petersen [4].

Comorbidities such as previous history of psychiatric disorders or presence of a cerebrovascular disease (among others) may contribute to the development of MCI. When this condition is due to comorbid causes, it does not have the same prognostic value as purer forms of MCI due to AD, thus, MCI is to be classified as possible or probable. Possible MCI refers to a condition in which is not clear to what extent comorbidity contributes to the pathology; whereas probable MCI suggests that a neurodegenerative cause is the main contributor to the pathology signs presented.[12,13] In this sense, in the absence of comorbidities that explain it, AD pathology represents the most probable cause of MCI, and therefore MCI is considered a prognostic marker of AD, while patients diagnosed with possible MCI should present psychiatric illnesses (e.g., depression), systemic neurological diseases (e.g., stroke, head injury, infectious diseases, or developmental disabilities), or insufficient information to refine their diagnosis (e.g., lack of neuroimaging -NI- evidence, lack of informant). The most common form of probable

MCI is the aMCI, which implies the deterioration of episodic memory as the core symptom (see *Fig. 2).* The increased risk of conversion to AD-type dementia in patients with MCI has led to consider this condition as a transitional stage between cognitive normality and dementia. Hence, independently of the MCI type, it is important to highlight that MCI diagnosis does not meet criteria for dementia, i.e. the cognitive impairment is insufficient to interfere with patient's independence, but sometimes compensatory strategies or greater efforts are needed to maintain autonomy.

Criteria for Amnestic MCI

Memory complaint, preferably corroborated by an informant
Impaired memory function for age and education
Preserved general cognitive function
Intact activities of daily living
Not demented

Figure 2. Criteria for aMCI. Adapted from Petersen[18]

Generally, the current diagnostic criteria in the clinical practice include:

- Subjective complaints about worsening cognition (compared to previous level) reported by the patient, a reliable informant, or a clinician.
- Impairment in the performance of one or more cognitive functions, objectively assessed by a formal cognitive examination, using age- and schooling-adjusted scales of the target population.
- Performance on global cognitive tests (screening tests) are within the normal range.
- Preserved autonomy in IADL.

In addition to Petersen's criteria for MCI subtypes, there exists the classification by Lopez and collaborators[12] that takes into account possible or probable association of MCI to develop a neurodegenerative disorder. Therefore, subjects with MCI can be classified into amnestic or non-amnestic;[14] affecting single or multiple domains; and also into probable or possible MCI:

- **Probable aMCI:** subjects with impaired verbal episodic memory on any of the memory tests used according to NBACE cut-off scores and being the potential impact in long-term retention; or in verbal learning and recognition processes. Always in the absence of psychiatric symptoms, vascular pathology or other factors that may explain their deficits.
    - **Single domain (aMCI-**sd): only a cognitive domain is affected.
    - **Multiple domain (aMCI-**md): more than one affected cognitive domain.
- **Probable naMCI:** subjects with preserved verbal episodic memory on any of the memory tests used and being the potential impact in long-term retention; or in verbal learning and recognition processes. Always in the absence of psychiatric symptoms, vascular pathology or other factors that may explain their deficits.
    - **Single domain (aMCI-**sd): only a cognitive domain is affected.
    - **Multiple domain (aMCI-**md): more than one affected cognitive domain.
- **Possible aMCI:** subjects with impaired verbal episodic memory on any of the memory tests used according to NBACE cut-off scores and being the potential impact in long-term retention; or in verbal learning and recognition processes. In the presence of psychiatric symptoms; or vascular pathology; or any other factors that may explain their deficits.
    - **Single domain (aMCI-**sd): only a cognitive domain is affected.
    - **Multiple domain (aMCI-**md): more than one affected cognitive domain.
- **Possible naMCI:** subjects with preserved verbal episodic memory on any of the memory tests used and being the potential impact in long-term retention; or in verbal learning and recognition processes. In the presence of psychiatric symptoms; or vascular pathology; or any other factors that may explain their deficits.
    - **Single domain (aMCI-**sd): only a cognitive domain is affected.
    - **Multiple domain (aMCI-**md): more than one affected cognitive domain.

In recent years, research has advanced basically on neurobiological models, which include data from biomarkers (such as cerebrospinal fluid -CSF-, neuroimaging and

genetics). This information has been used to define a new classification of MCI with an increased level of certainty (see "*1.2.5.4. Biological markers"* for more details). The implementation of such information would improve the detection and may help in the prediction of conversion to dementia in future clinical settings.

Meanwhile, since MCI was determined as a diagnostic entity, cognitive criteria remain as the core symptoms for its diagnose.[16] Therefore a set of neuropsychological instruments have been developed or adapted in order to assess cognition in this specific population (provided that impairment of cognitive functioning is the core symptom). The most common tools are validated and interview-administered,[19,20] although to date there is no consensus upon guidelines for routine **screening** of MCI. [21] The following scales are the most used worldwide and have the most suitable characteristics for clinical practice:

- Mini-Mental State Examination (MMSE)[22,23]

This screening tool evaluates mental state and allows to follow up on the progression of cognitive state. It is composed of the following domains: spatial and temporal orientation, immediate memory, attention and calculation, delayed memory, different language sub-domains, praxis and visual construction. For its correction, number of correct answers is counted, thus the higher the score, the better cognitive state. It ranges from 0-30. It is recommended by the American Geriatric Society as a choice instrument for cognitive assessment in the geriatric population mainly because it is brief and easy to administer, both useful characteristics for daily clinical practice. This tool has demonstrated enough validity and reliability in psychiatric, neurological, geriatric and other clinical populations.

- Montreal Cognitive Assessment (MoCA)[24]

It was originally designed to assess mild cognitive dysfunction. It includes the following cognitive skills exploration: attention, concentration, executive functions, memory, language, visuoconstructive abilities, calculation and orientation. The minimum score is 0. Final score is obtained by adding all correct answers, where each correct answer scores 1. Maximum score is 30. It is corrected by educational level attained by adding one point if the individual has 12 years or less of schooling. This tool can be used to compare measures over time to assess cognitive stability of patients. MoCA has good psychometric

properties as a screening tool for daily clinical practice. It is an effortless and brief assessment tool generally used by health practitioners.

In addition, when assessing cognition in depth, several **neuropsychological batteries and tests** exploring different domains have been widely used for this purpose. More emphasis has been placed in memory being the most highlighted domain given all the above mentioned about the typologies of existing MCI. Most frequently and widely tools used in this regard are:

- Weschler Memory Scale (WMS)[25]

This tool assesses immediate memory, delayed memory and working memory. Each of these types of memory is evaluated in two modalities (verbal and visual), all including two types of tasks (recall and recognition) except for working memory tasks. Last edition of WMS IV includes batteries for adults and seniors (ranging from 16-89 years old). It has wide clinical applications for exploring memory impairments and preserved aspects of it. The WMS has excellent psychometric properties and samples for correction scales are stratified by age, gender, race/ethnicity and educational level.

- California Verbal Learning Test (CVLT)[26]

It assesses learning and memory functions in adults. This tool consists of three-word lists that are presented as "shopping lists": a learning list (list A), an interference list (list B) and a recognition list. The structure of list A and B are identical, both contain words from certain semantic categories. Each list has 16 words belonging to four different semantic categories (four words from each category). The recognition list consists of 44 words. Final scores for each subdomain are obtained from the scale tables divided by 7 different age groups, ranging from 16 to more than 74 years old.

- Rey Auditory Verbal Learning test (RAVLT)[27]

RAVLT test evaluates verbal learning, immediate recall and retention memory. It consists of a verbal presentation of a 15-word list being read out loud by the rater. A total of five verbal presentations of the series are made. Each of the presentations is followed by its immediate evocation by the subject. Subsequently, a sixth evocation of the memory is requested after a non-mnestic interference task and a delayed period of 20-30 minutes. It is used to evaluate the nature and severity of memory dysfunction and to track changes

in memory function over time. It can be used to children and adults. Normative data has been published for population ranging from 7 to 89 years old.

- Free and Cue Selective Reminding Test (FCSRT)[28]

It is a test of episodic verbal memory that was designed to dissociate different processes involved in the formation of new memories and learning processes. It is a multi-trial memory test that uses a 'selective reminding' paradigm by presenting only the words not recalled, instead of all the to-be-remembered words. This paradigm is intended to facilitate learning by directing the subject's attention to the words not recalled previously. Individuals have to identify words included in different semantic categories. There are three recall trials and a delayed recall is done after 30-minutes interval of performing non-verbal tasks as distractors. Age-adjusted norms have been validated for population ranging from 56-98 years old. It has adequate psychometric properties.

- Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-cog)[29]

It was initially developed to assess the level of cognitive dysfunction associated with AD. It can be used to assess cognition in other population than AD, but it mainly focuses on cognitive deficits and behavioural disturbances commonly found in AD. It is a subscale included in the ADAS original battery, and it assesses 11 different cognitive sub-domains. ADAS-cog includes both self-administered tasks and observer-based assessments of different cognitive domains such as memory, language, and praxis. The maximum score in ADAS-cog is 70. There exists normative data for individuals ranging from 55 to 89 years old, with 10 to 21 years of education.

- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[30]

The RBANS assesses immediate memory (including delayed recall), spatial skills, language and attention. It is possible to obtain cognitive profiles upon cognitive performance. It was primarily developed for geriatric patients in suspicion of dementia, as a cognitive screening, but nowadays it is widely used in other neurological and psychiatric conditions. It is a tool appropriate when longitudinal measures of the same individual have to be obtained thanks to the psychometrically equivalent forms of administration. The original normative sample age range was 12 to 89 years. It included norms corrected by age, education, gender and race in the elderly.

Although different memory test are used depending on the type of visit and the professional applying it, the WMS-third edition (WMS-III) word list subtest,[31] included in the neuropsychological battery used in the studies of this thesis, is among the most frequently worldwide diagnostic tools used by neuropsychologists. It includes an assessment of the different memory processes, like the vast majority of tools, such as verbal learning word list (4 trials are included); long-term retention; and cued recall. Psychometric properties are excellent.

Besides memory, other cognitive domains must be explored to diagnose MCI. In general terms, a proper cognitive assessment should look for performance in all cognitive domains including sensitive tests for different domains (see *table 1* for more information about cognitive domains and functions recommended to be explored).

Cognitive domain	**Function**
Orientation	Temporal, spatial and personal orientation.
Attention and working memory	Attentional and short-term manipulation of information skills.
Visual memory	Copy, delayed recall and recognition.
Language	Comprehension, repetition, writing and naming
Gnosis	Perceptual integration of 2D objects.
Praxis	Ideomotor, imitational and constructional.
Visuospatial skills	Spatial relationship among objects.
Executive function	Automatic inhibition; verbal fluencies; abstract reasoning; cognitive flexibility.
Processing speed	Time to process visual information.

Table 1. Summary of cognitive domains and specific tasks recommended for a comprehensive cognitive assessment for MCI.

There are different tests or cognitive batteries used according to what the clinician is searching for. There is not a gold standard, instrument's choice will depend on the suspected pathology because there are cognitive profiles according to diverse affectations. As with memory subtests, there are multiple options for assessing the rest of cognitive domains which will be chosen at the discretion of the evaluating clinician. Sensitivity and specificity will always be a matter of interest when considering the best instruments to get the optimal results for the purpose.

1.1.3. Pathophysiology of MCI

The pathophysiology of MCI depends on the possible emerging disease that it will convert to, thus it is not expectable to have a specific and common etiological pathway for all cases of MCI. Different pathological mechanisms have been described in MCI. Strikingly, such mechanisms are closely related to the evolution of the condition. In other words, cognition deficits due to vascular alterations may lead to subcortical dementia, while other cortical abnormalities would probably be associated to AD. Among the pathophysiological factors the vascular and/or neurological diseases are the most well established and linked to conversion to specific types of dementia, while other factors such as psychiatric conditions or symptoms are not yet specifically associated with determined types of dementia.

Most studies have investigated MCI that converts to AD, suggesting that the gross morphologic features are a widening of sulci in different areas of the temporal pole, particularly in aMCI. However, MCI can be diagnosed in the absence of typical AD pathological features. Other mechanisms beyond those related to AD such as amyloid-β accumulation, synaptic dysfunction and tau-mediated neuronal injuries, are to be sought after. Emerging data has suggested that MCI pathology may initially be mediated by a trans-synaptic disconnection syndrome that could affect the central nervous system at different levels.[32] In those cases, the underlying pathological mechanism generally starts years before the onset of cognitive impairment.[33] Conversely, head trauma or brain injury in other cases, may also be pathological pathways underlying a diagnose of MCI. Even, compensatory neuroplastic responses could mask such etiological factors misleading an accurate diagnosis. It has been suggested that brain changes in MCI require more investigation, under a differential etiologic prism.

In summary, MCI can be a static syndrome (e.g., due to a brain injury or head trauma) or a progressive stage for which the pathophysiology of the end-product is causing it (e.g., vascular disease or AD). Therefore, the pathophysiology of MCI is heterogeneous and need more research. Apart of the presence of different MCI subtypes, there also exist different pathophysiological mechanisms contributing to its clinical manifestation.

1.1.4. Diagnostic process of MCI: *Patients' Journey*

Early intervention is increasingly sought when dementia is suspected to prevent and to mitigate possible effects caused in the individual's health. Dementia diagnostic one of the most feared medical conditions among general population. Therefore, early detection and risk factors are receiving more attention in this field of research. Most of them are focused on predicting models so as to start preventive strategies and treatments.

The MCI patient's journey starts with cognitive complaints of patients themselves or referred by their relatives who look for medical help. MCI diagnosis is a step-by-step process.[34] Early signs or symptoms are detected mainly by the general health practitioner or a family member. Sometimes even the patient complains about cognitive impairment. Routine work-up typically includes blood tests and neuroimaging measures. At this point, initial screening tests are carried out to assess cognitive mental state. As mentioned before, MMSE, MEC and MoCA are among the most used screening tests worldwide.[35] Nowadays, it can be said that none of them is superior to another in terms of diagnostic accuracy mainly because those instruments are usually calibrated to be sensitive rather than specific to a ultimate diagnosis. Indeed, individuals who obtain a suspected score of MCI (it cannot be said a 'confirmatory score' as these tools cannot be used to make a final diagnosis) should have further assessment to confirm initial diagnostic hypothesis. Final diagnosis of MCI is based on cognitive and functional assessment (this latter is commonly performed by social workers).

After detecting objectively impairment in cognition, the next step is to discern the causes (reversible versus non-reversible). If cognitive symptoms are caused by reversible factors (e.g., deficit in enzymatic functioning or urinary tract infection), the patient receives specific treatment. If these are caused by non-reversible factors (a probable neurodegenerative disease), the patient is referred to a comprehensive outpatient care team (in Spanish *'Equipo de Atención Integral Ambulatoria'*, EAIA),[36] specialized on cognitive and behavioural disturbances. This clinical resource offers an extensive and specific assessment to discern if there are cognitive, affective and/or behavioural

alterations that could be the prelude to a neurodegenerative disease, or to discern more about the cause of the alterations presented by the patient.

1.1.5. Outcomes of MCI

MCI is usually referred as a spectrum which ranges from NC to dementia (most commonly AD). But MCI trajectories are not unidirectional as it generally is a prelude of different medical conditions.[37] Thus there are three possible scenarios when talking about its outcomes: 1) reversion to NC or subjective cognitive decline (SCD); 2) stability of MCI; or 3) worsening of MCI and therefore conversion to dementia. Wide variety on data relative to prevalence on cases of reversion, stability or worsening of MCI depend on multiple variables, among them different population settings or disparity in diagnostic criteria, for example.

Differential MCI outcomes could be justified by the nature of this research entity, thus MCI population under study is one of the main characteristics that would determine the path towards MCI outcomes are heading.[38] Another important factor of differences found in stability versus reversion or conversion is the time-frame of related studies. In general terms, longer follow-ups tent to produce lower reversion rates because the instability of MCI might worsen by converting to dementia.[37]

In relation to MCI due to AD, Jack and collaborators described a hypothetical model of dynamic biomarkers of the pathological cascade in AD.[39] Different processes during the disease spectrum (*Fig. 3*) were postulated, including abnormal accumulation of proteins, synaptic dysfunction and neuronal injuries (among others) as being part of aggregated conditions that occur or co-occur along time. All these biological stages of these brain alterations are bonded to the different clinical stages. This is a model based on AD and not all MCI diagnosis are linked to this ulterior pathology, but other clinical manifestations could be the origin of this cognitive misfunctioning. Thus, a reversion to normal cognition, when reversible causes of cognitive impairment are found is also possible[40] based on this perspective of MCI like an spectrum.

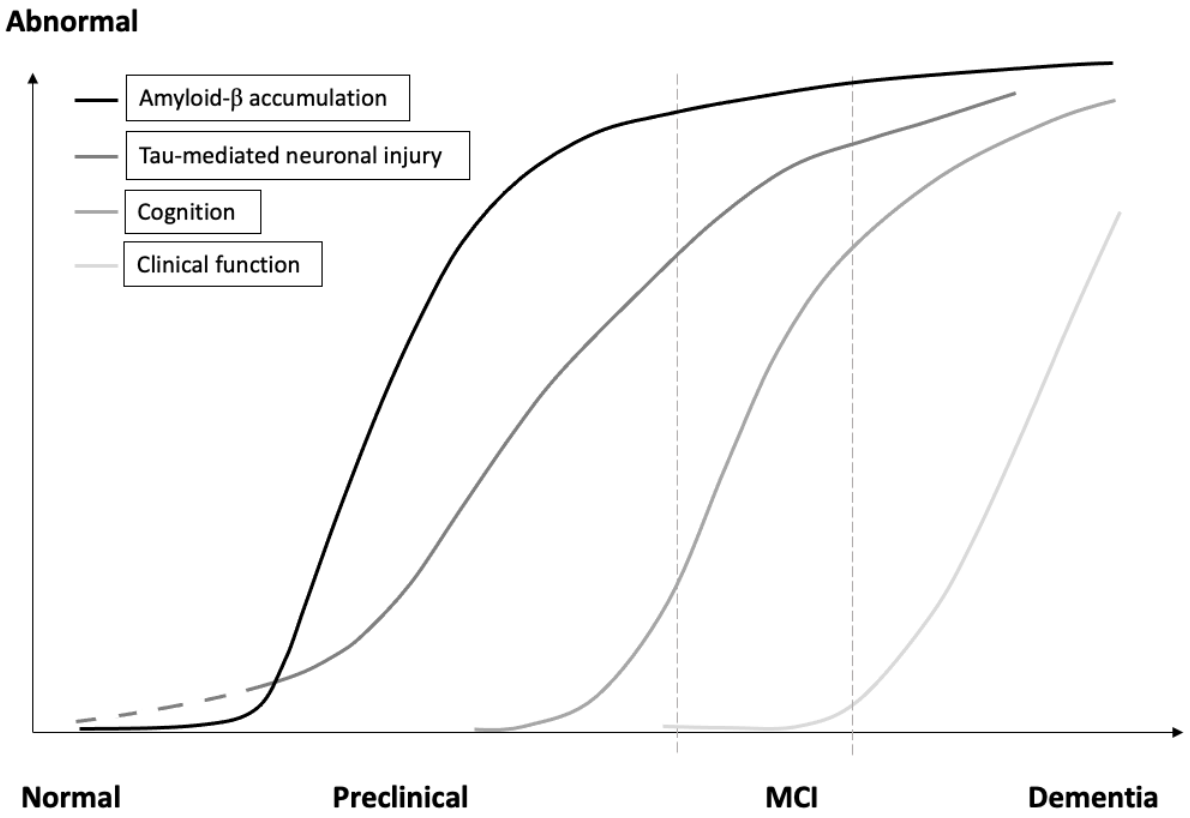

Figure 3. Dynamic markers of AD pathological cascade. Adapted from Jack[39].

- *Reversion to normal cognition (NC)*

Reversion rates of MCI to NC vary substantially depending on different variables, from 2.2-3% to 15.8% at 1-year period of time.[41] Whereas with a longer follow-up (>2 years) it was found an overall 18% reversion rate, being an 8% in clinical-based studies and a 25% in population-based studies. Reversion rates increased up to 26% when just studies of better quality were considered.[38] Among factors focus of dissidence in those rates, the classification criteria is one of the most important ones, followed by an accurate MCI diagnosis. Another important bias factor is the study design applied when exploring prevalence on reversion, which comprises clinical setting versus community dwelling, or general population studies.

Female gender, younger samples, engagement of cognitively stimulating activities, and an absence of APOE-ε4 allele are among the factors most related to reversion, and with more robust results among studies. Another predictor of reversion was single domain

impairment in terms of MCI type.[42] Cognitive impairment in these cases does not seem to be justified by an underlying AD, but instead other causes have to be sought. Some other factors favouring reversion from MCI to NC are less self-reported depressive symptoms; and less informant-reported mood and anxiety symptoms. Affective and behavioural symptoms are still controversial in this regards because results differ between studies.[43,44]

- *Stability of MCI*

MCI baseline diagnosis shows a stability rate of around 67-83.8% after one year.[41] As previously mentioned, classification criteria have a strong influence in terms of accurately seek for rates of reversion, stability or worsening of MCI.

Stable MCI was commonly associated with switching MCI subtypes.[37] In addition, better performance at baseline in some domain-specific neuropsychological testing (such as retention in verbal memory, and non-verbal abstraction) could predict a stability yield period of 10 years.[45] Main causes influencing stability are the presence of trauma, static injuries, or psychiatric diseases mainly, broadly any cause that excludes a neurodegenerative origin. Although in many cases one year is not enough time to evaluate stability since AD is a slowly progressive disease. Therefore, patients suffering from MCI due to AD could manifest relative stability for a period before converting, which could yield to misleading results about conversion rates.

- *Worsening of MCI*

After 1 year of follow-up, rates of MCI converting to dementia have been established at around 1.2-13.1%. Similar reasons stated above could justify such disparity in prevalence.[41]

Older age and lower educational level in MCI population are considered main predictive variables for conversion to dementia.[45] Also, more severe mood and hyperactivity symptoms in MCI patients (informed by a relative or caregiver) have demonstrated to be linked with a worsening of the clinical and cognitive condition of this population.[43] This

could be explained by two alternatives: 1) mood affection could adversely impact on cognitive function with the consequent functional aggravation of the patient; 2) these symptoms could be the core clinical presentation of a neurodegenerative disease such as AD. Also, less self-reported mood symptoms (mainly depressive) have been associated with conversion to dementia. One of the main reasons that could explain this biased self-perception of mood would be patient's anosognosia, which increases as the disease progresses.[46]

1.2. Dementia

The average life years have risen substantially given the increase in life expectancy and the decrease in mortality. This widening of the aging barrier implies that older people constitute a population group that is progressively growing. Nowadays, there is an estimation of over 55 million people worldwide diagnosed with dementia. By 2050, the number of people affected is set at 139 million. Figures have increased substantially and a new case of dementia is diagnosed every 3 seconds somewhere in the world.[47] Age is one of the main risk factors for the development of neurodegenerative diseases, but there is a misunderstood about expectations in aging. Nowadays, 62% of healthcare practitioners see symptoms of an underlying dementia as an age-related process. Also, the overall impact on caregivers suffering from its role is set at 50%. Finally, a significant number of people remain undiagnosed and go temporarily unnoticed even when first symptoms are manifested, with the consequences for the individual and their immediate circle. Currently, AD contributes to 60-70% of cases, being the most common form worldwide, even though different aetiologies may lead to dementia. According to these data, the World Health Organization (WHO) considers dementia treatment and research as a priority objective for global public health, which urges governments to take measures to reduce the socio-health impact of this pathology.[48]

Dementia is currently defined as an acquired syndrome of an organic nature. It is characterized by an impairment on different spheres, being cognition the central element. But it also involves affective and behavioural disturbances (also called neuropsychiatric symptoms, NPS), and worsening in functionality (initially in IADL). The severity of dementia is determined based on the latter, being the diagnosis made when patients'

autonomy is compromised. Chronic course and irreversibility are the most expected outcomes.

Dementia is not a disease *per se* but an amalgam of symptoms that primarily and initially affect the brain. It causes a number of changes that include the loss of the ability to think, remember, learn and make decisions, although symptoms also include disturbances in previous personality, affection and behaviour. The loss of complete autonomy and subsequent degree of dependence are the final consequences of the pathological process. Therefore, dementia is among the most disabling health conditions worldwide and a burdensome pathology that entails an impact not only on the patient but also on their relatives, caregivers and the society at large.

1.2.1. Conversion to dementia

Dementia is diagnosed by clinical criteria. It is recommended to count on an informant (relative or caregiver) for an accurate anamnesis to verify information provided by patients. Nowadays, clinical criteria for all causes of dementia includes the following patients' disturbances[49]:

1. Interfere with ability to function in work or social customs and activities

2. Represent a decline from previous levels of functioning and task performance

3. No delirium or psychiatric disorder justifies impairment

4. Cognitive impairment is detected and properly diagnosed*

5. Cognitive or behavioural impairment involves a minimum of two of the following:

- Impaired ability to acquire and recall new information.
- Impairment in reasoning and management of complex tasks, judgment.
- Impairment of visuospatial abilities.
- Functional language impairment (spoken, read, written).
- Personality, behavioral or behavioral changes.

*Combination of history-taking from patient and a reliable informant; and an objective cognitive assessment.

1.2.2. Types and aetiology of dementia

Once a dementia diagnosis is done, it is important to classify it according to its aetiology, since specific treatments will be determined by the characteristics of the underlying pathology. So it would be possible to target more precise neuropathological mechanisms in each case.[50]

According to family subtype of dementia, there are different aetiologies for each case (see *table 2* for a more detailed information on this topic). Probable cases mean that no other reason could justify patient's deterioration other than the pathology itself (mainly neurodegenerative causes); whereas possible cases are related to those where other possible causes should be considered.[12]

Depending on the aetiology, very diverse patterns of cognitive impairment have been described. Some concern mainly memory-related tasks (AD), meanwhile others affect processing speed of information (more related to Vascular Dementia, VD), or tasks involving an erratic functioning of executive functions (typical of Fronto-Temporal Dementia, FTD), for example.[51]

Worldwide prevalence rates place pure AD as the most common form of dementia, followed by VD, dementia caused by Lewy Bodies (LBD) and FTD (ordered highest to lowest).[48] Different forms of dementia could co-exist in some cases. One of the most common scenarios is the so-called mixed dementia, which is generally attributable to AD co-occurring with VD. Presenting a mixed dementia diagnosis usually has an additive value in terms of global patients' deterioration.

Family	Aetiology
Alzheimer's Disease (AD)	AD (probable or possible) Logopenic aphasia Frontal variant AD Cerebral amyloidosis
Frontotemporal dementia (FTD)	DFT-behavioural variant Progressive Non-Fluent Aphasia Semantic Dementia Corticobasal Dementia Progressive Supranuclear Palsy
Vascular Disease (VD)	Cortical VD (probable or possible) Subcortical VD (probable or possible) VD by strategic infarction
Lewy Body Disease (LBD)	LBD (probable or possible) Parkinson disease (with/without dementia)
Psychiatric diseases	Anxiety Depression Bipolar disease Schizophrenia Obsessive-compulsive disorder Borderline personality disorder Others
Other degenerative	Posterior Cortical Atrophy Primary Progressive Apraxia Multiple System Atrophy Huntington Hallervorden-Spatz Amyotrophic Lateral Sclerosis Prion Diseases
Other types of secondary cognitive impairment	Craniocerebral Trauma Hydrocephalus Tumour Multiple Sclerosis Drugs / Pharmaceuticals Epilepsy Cerebral Hypoxia
Infectious diseases	Human immunodeficiency virus (HIV) Syphilis Herpes Others
Metabolic-nutritional	Vitamin B12 deficiency Thyroid Hypo/Hyperthyroidism Anaemia Chronic renal insufficiency Alcoholism Hepatic insufficiency
Fibromyalgia	Fibromyalgia Chronic fatigue
Developmental disorder	Down syndrome Others

Table 2. Dementia family subtypes and etiologies.

1.2.3. Factors associated to conversion

A risk factor is a variable associated with an increased risk of developing any specific type of disease. There are two main groups of risk factors that could promote the development of a dementia in the future: potentially modifiable and non-modifiable risk factors. So far, the latter do not have reversibility. To date, studies attempting to control reversibility have not found robust conclusions. For example, some clinical trials had attempted to find disease-modifying therapies (DMTs) without positive results.

Among the **modifiable risk factors**, the most common studied ones are:

- *Cardiovascular risk factors*

There are several studies that postulate hypertension and diabetes (primary examples of cardiovascular risk factors), as having an increased risk of conversion to dementia.[52–55] For instance, a large study found that hypertension predicted significantly conversion from aMCI to AD, while patients who were treated with antihypertensive agents had a lower risk than the non-treated.[55] Large and high-quality studies exploring diabetes found that patients diagnosed with aMCI and concomitant diabetes were more likely to progress to AD, whereas those with treated diabetes were less likely to progress to AD.[52,55] Even though it is not fully elucidated yet if those factors could predict conversion to dementia in all MCI subtypes, neither how these are affecting a future dementia diagnosis.[56] Also, some authors have recently postulated both AD and VD as part of a spectrum rather than the possibility of both pathologies being developed in parallel aggravating cognitive consequences in the individual.[57,58]

- *Cognitive reserve (CR)*

One protective factor that has been given special emphasis is CR since it can act as a moderator between AD-related pathology and clinical symptoms. Recent work showed that there is an inversely proportional relationship, since the higher the CR in early stages, the later the onset of dementia. Whereas, once AD emerges, those with higher CR show a more rapid decline.[59] Therefore, higher CR seems to better cope with brain damage, independently of brain size. It has been hypothesized that CR could subserve as a compensatory mechanism for early deficits shown by patients. So cognitive maintenance,

i.e. brain stimulating activities, should be a priority in terms of protection against dementia and other pathologies that concur with cognitive impairment.[60,61]

- *Diet*

Antioxidants, vitamins and polyphenols haven shown to decrease the risk of AD. Whereas other dietary compounds such as saturated fatty acids, high-calorie intake and malnutrition are associated with an increased risk of suffering AD. Studies in this regard have pointed out that folate, vitamin B12 and vitamin D deficiencies are associated as well with a decrease in cognitive function. Other factors associated with cognitive decline are the advanced glycation end products (AGEs), which are harmful compounds formed through diet. Those have the ability to induce cell oxidative stress and inflammation.[62]

- *Physical activity*

A healthy lifestyle can protect against different pathologies and diseases. The exact biological mechanism underlying the protective effect of physical activity in relation to cognitive impairment is not well established. But performing these activities seems to promote angiogenesis, neurogenesis and synaptogenesis contributing on the brain ability to tolerate age-related changes and disease-related pathologies. Several studies have reported benefits of exercise by an associated reduced risk of dementia in MCI population.[50,63,64]

Other possible protective factors have been postulated and are currently under study, such as social contact and sleep quality, but to date no robust conclusions have been reported.

Beyond those, **non-modifiable risk factors** to date, some of which are, in turn markers of disease progression, include:

- *Pathophysiology.*

As standard, pathological landmarks such as amyloid-β (Aβ) accumulation, synaptic dysfunction, glial activation, tangle formation, and neuronal death are among the proposed biomarkers for AD.[62] All these biological events occur during AD spectrum, nevertheless some also happen in the context of simple brain aging.[50] This is the main reason why those can be considered risk factors and markers of disease progression simultaneously. Likewise, each etiological subtype of dementia has its own pathological

characteristics that might function as markers of the disease as well as non-modifiable risk factors.

- *Genetic factors*

Since the discovery of APOE-ε4 allele, it has been demonstrated to be the major genetic risk factor known so far for developing AD dementia. Carriers of this allele have been found to have more than twice likelihood to progress to AD-dementia type. Likewise, homozygotes had a 4-fold higher risk of progressing to AD.[65,66] There have been multiple attempts of finding other major genetic risk factors associated with AD (and other dementia-related pathologies) under different approaches,[67] mainly because genetic heritability is a robust reliable non-modifiable risk factor.

- *Imagining*

In relation to structural brain abnormalities found in dementia, brain imaging with either magnetic resonance imaging (MRI) or computed tomography scan (CT) is required to discern between treatable causes (by reversible factors) and non-treatable causes (by irreversible factors).[68] Major findings in main causes of dementia vary from clinical subtypes. Typical atrophy patterns of hippocampal and cortical atrophy in temporal and lateral parietal lobes are consistent with AD findings.[69] neuroimaging characterization of VD includes decreased blood flow and common radiologic findings are, among others, white matter lesions, lacunar infarcts, and brain atrophy, being small vessel disease the most common damage even no general criteria has been established for VD due to its cause heterogeneity.[70] Grey matter changes in parietal lobe, loss of dopaminergic nigral neurons and widespread occurrence of alpha-synuclein accumulation in the brain are specifically detected in LBD; but due to the nature of the disease (by a synaptic dysfunction), more complex neuroimaging techniques are required for a differential diagnosis.[71] FTD neuroimaging hallmarks include primarily frontal and anterior temporal lobe atrophy, predominantly in the right lobe.[72]

- *Affective and behavioural symptoms*

Mental health-related symptoms, so-called neuropsychiatric symptoms (NPS), have been addressed in the field of dementia since long ago. Some authors place these symptoms as

risk factors for pathologies involving cognitive impairment because they represent an added risk.[73] Others include them within prodromal signs[74] or potentially modifiable predictors of dementia (as a manifestation that something is starting to malfunction in an individual's brain).[56,75] Whereas some others see them as part of a reaction (conscious or unconscious) of the individual to their perceived cognitive state.[76] It is unclear if those symptoms precede cognitive decline,[77] or on the contrary if altered cognition is the prelude of NPS.[78] What is clear is that these symptoms are part of the disease, while the *how* is still a controversial issue. In terms of specific 30-day prevalence of suffering any of these symptoms when a formal diagnosis of MCI is being done, the paucity of studies points to report that the most frequently presented NPS in early stages -such as MCI- are apathy, depression, irritability and sleep difficulties.[79,80] (See *Fig 4a and Fig 4b* for detailed information about studies exploring prevalence of NPS over a 30-day period of time, and within a 10-year inter-studies range).

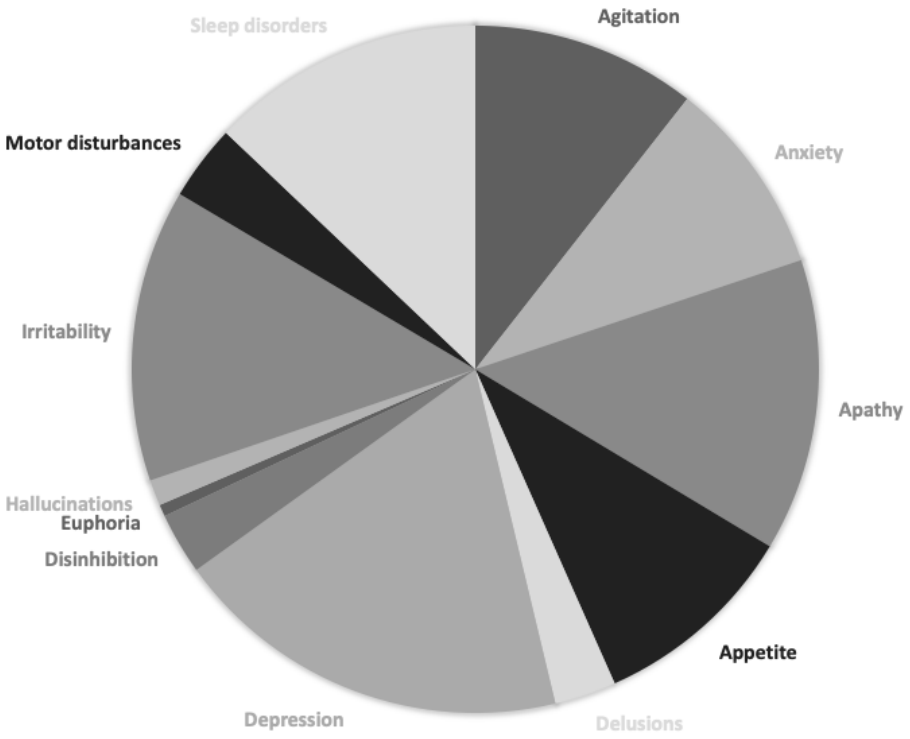

Figure 4. 30-Day prevalence of NPS by domain in MCI. Adapted from Lyketsos[81].

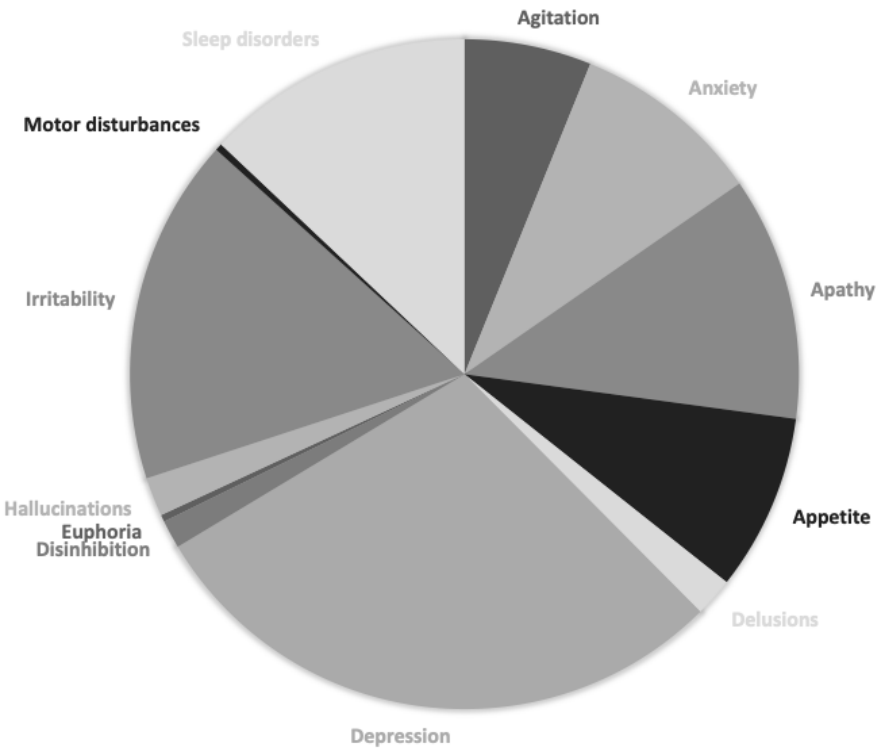

Figure 5. 30-Day prevalence of NPS by domain in MCI. Adapted from Peters[80].

Clinicians and researchers have tried to elucidate the relationship between cognitive decline and NPS, ever since the first case of AD was originally diagnosed by the psychiatrist Alois Alzheimer.[82] In this regards, it is also important to take into account that this symptoms rarely appear on isolation, these NPS are often (and mainly) presented by patients comorbidly.[83] Indeed it is not just about AD but to all dementia types,[84] that is why recently emphasis has been placed on studying this amalgam of symptoms and some theoretical proposals have emerged in order to establish an independent, but related, diagnosis of Mild Behavioural Impairment (MBI).[85]

1.2.4. Classification systems of dementia

Main classification systems depend on a wide variety of variables. There is a historically nomenclature used in daily clinical practice based on brain location. It is applied in order to understand the main impairment of higher functions in patients according to compromised regions. Nowadays this nomenclature is not a clinical classification tool itself, except for vascular dementia which gives the clinician topographical information

of interest for symptoms management. Currently, there are three main groups according to the purpose of the classification:

i) *Clinical* (based on clinical tools):
This is the most common used classification system. It classifies patient's actual mental state according to different clinical tools. It is useful to treat each case according to the deterioration degree or severity of symptoms. Main instruments for this purpose are Clinical Dementia Rating Scale (CDR) and Global Deterioration Scale (GDS).

ii) *Research-driven* (based on biomarkers):
This has been addressed as the main research classification for patients in order to take part in clinical trials. but it has recently arisen interest as complementary to neurological exploration in the clinical practice. It comprises *in vivo* techniques.

iii) *Confirmatory* (based on histopathological changes):
This is the definitive classification post-mortem. It allows final confirmation of the diagnosis due to proteinopathies or any other brain tissue changes favouring dementia.

There are certain dementia symptoms that are partially or totally attributable to a specific brain region, so historically a dissociation that could distinguish those profiles was proposed. In the early 90s, substantial bibliography appeared in an effort of studying topographical associated symptoms, thus cortical and subcortical dementias were commonly used terms. Different work groups focused their research in elucidating the hallmarks of both entities.[86–93] But nowadays, this nomenclature is not used in the daily clinical practice for a formal diagnosis, rather it has been replaced by an etiological classification. It provides the clinician useful information when starting a therapeutic plan and addressing accurately the needs patients.

Recently, different diagnostic criteria have been defined based on final utility, being clinical practice vs. research-driven the two predominant approaches at present. To

illustrate it, commonly used AD terminology refers to two different entities, being the first related to clinical manifestations of the disease, and being the latter referring to histopathological changes associated, which comes from a research perspective. Over time, distinction between clinical manifestations and neuropathological changes became blurred.[94] Specifically, AD classification is moving towards a more biological perspective of the disease. Currently diagnostic approaches based on *in vivo* detection of Aβ deposits, pathologic tau, and neurodegeneration is gaining attention bringing together all the knowledge achieved from clinical-based studies and research driven findings.

Neurodegenerative diseases are mostly due to an abnormal deposit of proteins that induce a cascade of neuropathological events ultimately leading to cell death. In turn, misfolded protein aggregation leads to a progressive decrease in the neuronal population, from selectively vulnerable ones to the entire brain. Distinguishing type or cause of dementia sometimes can be difficult; definitive diagnosis often requires *postmortem* pathologic examination of brain tissue mainly because there are comorbid possible causes rather than isolated, and this could mislead a diagnosis. Thus, clinical diagnosis focuses on distinguishing main causes of dementia; but also, it is important to identify cerebral areas affected and potentially reversible causes in order to make an accurate final diagnosis.

1.2.5. Procedures to identify conversion to dementia

The vast number of instruments for assessing dementia makes it difficult to choose the most adequate. An important question a clinician faces when exploring the patient's different spheres (cognition, behaviour, functionality) is what strategy would be the most appropriate. The aim of using scales is to increase the precision of decisions made while an accurate diagnosis is sought by rising objectivity about given information by patients, relatives or caregivers. Ideal properties of those instruments should include face validity, construct validity, concurrent validity, inter-rater and test-retest reliability (for a detailed overview see [95]). Also, it is of concern to be not time-consuming and well-accepted by patients. Diagnostic instruments should always be focused on assessing clinical, cognitive and behavioural aspects manifested by a given patient. Thus, categorizing patients'

current state will offer possible therapeutic options as well as assist in symptom management to both, patients and family members.

- *Clinical instruments*

Nowadays, in the daily clinical practice there are two main diagnostic tools for a formal diagnostic of dementia, i.e. International Statistical Classification of Diseases and Related Health Problems (ICD-11), and Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Both include dementia into "Mental and behavioural disorders" category, and the diagnostic categories are presented according to family-belonging, organized similarly. (See *Table 3* and *Table 4* including information about ICD-11 and DSM V for more information).

F00 **Dementia in Alzheimer disease**	Alzheimer disease is a primary degenerative cerebral disease of unknown aetiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years. Includes: AD with early onset; AD with late onset; AD atypical or mixed; unspecified.
F01 **Vascular dementia**	Vascular dementia is the result of infarction of the brain due to vascular disease, including hypertensive cerebrovascular disease. The infarcts are usually small but cumulative in their effect. Onset is usually in later life. Includes: VD of acute onset; multi-infarct dementia; subcortical VD; mixed cortical and subcortical VD; other VD; unspecified.

F02 **Dementia in other diseases** **(classified elsewhere)**	Cases of dementia due, or presumed to be due, to causes other than Alzheimer disease or cerebrovascular disease. Onset may be at any time in life, though rarely in old age. Includes: Pick disease; Creutzfeldt-Jakob disease; Huntington disease; Parkinson disease; in HIV disease; in other specified diseases classified elsewhere.
F03 **Unspecified dementia**	Others. Not previously classified.

Table 3. Dementia classification extracted from the original ICD-11.

F01-F99 Mental and behavioural disorders	AD dementia (early-onset, late-onset, atypical, etc.) Vascular dementia (acute onset, multi-infarct dementia, subcortical, mixed, etc.) Other diseases dementia (Pick, Creutzfeldt-Jakob, Huntington, Parkinson, VIH, etc.) Not specified dementia Delirium Other mental disorders due to cerebral disfunction (anxiety, catatonia, affective disorders)

Table 4. Dementia classification extracted from the original DSM 5.

To make an accurate diagnosis of dementia is necessary to classify persons' impairment degree, which involves evaluating functionality, cognition and behavioural state. Main clinical scales used to do so on a day-to-day basis are the two previously mentioned CDR and GDS. According to these, clinicians can make a comprehensive diagnosis including classification of the patient according to the stage of the disease at a given moment.

- CDR scale includes different domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care items. It measures limitations of the patient in every domain in a global 5-point scale. It ranges from normal (CDR= 0), MCI (CDR=0.5); mild dementia (CDR=1); moderate dementia (CDR=2); to severe dementia (CDR=3). For each specific

domain patient receives a concrete score according to individual assessment and caregiver or relative information gathered in a clinical-based interview. Final score is calculated based on an algorithm based on typical combination of deficits that characterize dementing illnesses.

	None *0*	*Questionable* *0.5*	*Mild* *1*	*Moderate* *2*	*Severe* *3*
Memory	No memory loss	Slight forgetfulness	Moderate memory loss	Severe memory loss	Only fragments remain
Orientation	Fully oriented	Oriented except for slight time difficulties	Moderate difficulty with time relationships	Severe difficulty with time, often disoriented to place	Oriented to person only
Judgment and problem solving	Solves everyday problems well	Slight impairment	Moderate difficulty in handling problems, similarities/ differences	Severely impaired (social judgment usually impaired)	Unable to make judgment or solve problems
Community affairs	Independent function in job and social groups	Slight impairment in these activities	Unable to function independently at these (although engaged in some)	No pretence of independent function outside home (appears well at 2; appears too ill at 3)	
Home and hobbies	Life at home and hobbies, well maintained	Life at home, and hobbies slightly impaired	Mild impairment at home; difficulties/abandoned chores and interests	Only simple chores preserved; very restricted interests,	No significant function in home
Personal care	Fully capable of self-care (dressing, hygiene, keeping of personal effects)		Needs prompting	Requires assistance in personal care	Requires much help with personal care; frequent incontinence

Table 5. Stages of dementia spectrum extracted from the original CDR.

- GDS includes 7 stages: normal cognitive performance (GDS 1), subjective cognitive decline (GDS 2), MCI (GDS 3); confirmed dementia diagnosis (GDS 4); moderate dementia (GDS 5), moderately severe dementia (GDS 6); and finally severe dementia (GDS 7). It is a semi-structured interview. Caregivers can get a global overview about where an individual is at in the disease progression by observed measures of behavioural characteristics presented by the patient.

	Stages	**Symptoms**
From normality to early signs of cognitive impairment.	**GDS 1** Normality	No impairment in cognition is detected.
	GDS 2 Subjective Cognitive Decline	Subtle memory difficulties, typical of aging.
	GDS 3 Mild Cognitive Impairment	Disorientation, loss of objects, difficulty in recalling words or names.
Diagnosis of dementia. *Early stages.*	**GDS 4** Mild dementia	Difficulty in planning and managing personal aspects (e.g., financial). Difficulty in remembering recent events. Confusion in details of personal history.
Moderate dementia. *Need of constant care.*	**GDS 5** Moderate dementia	Difficulty in performing daily tasks, inability to remember simple data, difficulties in temporal and spatial orientation. Still recognizes relatives and identifies family members.
	GDS 6 Moderately severe dementia	Impossibility to get dressed without help. Difficulties in maintaining proper personal hygiene. Beginning of sphincter control problems. Forgetting the names of close people. Marked changes in behaviour and previous personality.
Severe phase. *End of the process.*	**GDS 7** Severe dementia	Progressive loss of ability to speak and communicate. Need for help with basic activities (e.g. eating, walking, etc.)

Table 6. Stages of dementia extracted from the original GDS.

- *Cognitive batteries*

Cognition has been one of the most explored and studied aspects of dementia so far. The core symptom ever since dementia started to be diagnosed in the clinical practice is cognitive impairment, particularly memory complaints. There are several batteries for assessing patients' cognition, some of them were previously mentioned in section *1.1.2. MCI classification and diagnostic instrument.* Among the most common ones for dementia are the ADAS-cog and RBANS. Although the existence of these neuropsychological batteries, specific tests can also be used, upon clinician's decision. Some classic instruments initially developed for dementia have been validated for MCI population, as for instance the Mattis Dementia Rating scale (MDR).[96] Some other specific tools such as the Parkinson's Disease Cognitive Rating Scale (PD-CRS),[97] were mainly developed for movement disorders with associated cognitive impairment, including MCI population.

Among the cognitive batteries for dementia and other pathologies affecting cognition, the Neuropsychological Battery of *ACE* (NBACE)[31,98] was developed as an easy-to-administer and time-affordable (duration of 50 minutes approximately) instrument for day-to-day clinical practice. It is a compendium of subtests sensitive for neurodegenerative disorders, mainly focused on measuring verbal learning and memory. It also includes items exploring information processing speed, orientation, attention and working memory, visuoperception, praxis and executive functions. It was initially designed for the elderly when a diagnosis of dementia is suspected. It is complementary to the neurological exam done by neurologists, and the psychosocial interview done by social workers (see section Material and methods, in *4.2. Neuropsychiatric profile as a predictor of cognitive decline in Mild Cognitive Impairment* for detailed information about cognitive domains and sub-tests used).

- *Behavioural scales*

It is of utmost importance to properly assess NPS in a clinical context of patients at-risk, being those an essential piece for a future dementia diagnosis. In this regard, several tools have been designed with this purpose.[99,100] One of the most worldwide used tools to

evaluate NPS is the Neuropsychiatric Interview (NPI),[101] which was originally designed for population with a diagnosis of dementia. The original form NPI has been translated and validated into more than 30 different languages.

The NPI-Questionnaire (NPI-Q) is an adapted form, which is an informant-based brief interview that assess NPS over the previous month. It rates the most common symptoms in 12 domains for population with cognitive disorders such as: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, motor disturbances/aberrant motor behaviour, sleep/nigh-time behaviour, and appetite/eating.[102,103] It is adequate for routine clinical practice.

- *Biological markers*

Current diagnostic criteria of dementia include all the above (clinical, cognitive and behavioural parameters). Biomarkers are emerging tools that provide a higher degree of certainty by identifying disease's aetiology.[104,105] Also, those help clinicians to predict progression thanks to reaching a better knowledge of the neurodegenerative process.

The use of biomarkers may help clinicians to give patients and relatives or caregivers better information for understanding the disease. Also, those markers are useful for offering recommendations on specific treatments available, participation in clinical trials, and about comorbidities and the possibility of managing of them.[40]

Currently, most interesting applications of biomarkers are:

a) Pre-symptomatic diagnosis
b) Evidence for therapies' effectiveness
c) Differentiation of subtypes

Biomarkers may be divided into different classes. The three main groups in relation to dementia are peripheral and central biomarkers such as CSF, neuroimaging techniques, and genetics.

Most studies have taken place in relation to AD pathological findings. In those cases, results from CSF reflect an accumulation of key proteins deposited in patients' brains

during the course of the disease. Aβ protein acts as a marker of amyloidosis whereas total tau protein (tau-t) and hyperphosphorylated tau (tau-p), as markers of neuronal damage.[106,107] Aβ, tau-t and tau-p are generally obtained by a lumbar punction analysing CSF, but both can also be assessed via Positron Emission Tomography (PET). Depending on the alteration of CSF biomarkers, subjects with MCI have different probabilities of AD being the main cause of their cognitive symptoms.[108] In this regard, CSF is a valuable tool for predictive purposes, because it reports an absolute value reflecting the degree of abnormality for different brain alterations, even it does not allocate the lesion. When a different aetiology rather than AD is suspected, there are other biomarker candidates that help in the differential diagnosis. For instance, when DFT is suspected other protein aggregates related to fronto-temporal lobar degeneration such as Tau-positive aggregates, TAR-DNA-binding protein of 43 kDa, and FUS are obtained.[104]

Also, the recent knowledge acquired in neuroimaging techniques offers valuable information about the state of the brain, both anatomically and functionally. Structural brain atrophy is nowadays an accurate indicator of disease status in neurodegenerative pathologies.[109,110] Again, imaging markers of neuronal injury in AD have been the most studied ones. Anatomically, medial temporal lobe (MTL) atrophy is the most characteristic imaging feature of AD, in conjunction with hippocampal and entorhinal cortex atrophy.[111] Those findings have been extensively studied and replicated since they were first identified. Similar findings have been reported in terms of functional NI showing a decreased uptake of radiotracer in temporo-parietal and posterior cingulate areas of the brain, signs of brain hypometabolism detected even in early stages of the AD spectrum.[112]

Genetics assign a specific probability of suffering a disease. It does not mean that it provides with a final or completely reliable diagnosis, but rather it is considered a risk factor.[113] In relation to AD, genetic factors account for up to 80% of the attributable risk in common AD forms. This affirmation implies that genetic factors are highly likely to be present in most of the pathophysiological pathways of the disease. In the early 1990s, genetic studies emerged in the field of dementia. Nowadays, it is well established that among the three major allele variants of APOE (APOE ε2, APOE ε3 and APOE ε4), APOE ε4 allele, was identified to be highly associated with the susceptibility of late-onset

AD. Since then, it has been considered to be the main genetic risk factor for AD.[114,115] As previously mentioned, this allele increases substantially the likelihood of developing AD. But it estimates only a small proportion of patients, leaving most of AD heritability unexplained. Recently, using the so-called genome-wide association study (GWAS), there has been an increased number of identified genetic risk loci in relation to late-onset AD forms. The ulterior goal of these findings is to have applicability in the clinical practice to move towards a more individualised medicine so as to improve patients' and their families' quality of life.

Therefore, steps are moving towards an integrated model including biomarkers to obtain accurate and complete diagnosis of dementia and its previous stages. Unfortunately, it is not yet applied in the clinical context on a day-to-day basis. Biomarkers are not exempt from criticism upon its applicability in the clinical practice. There exist some problems such as lack of standardisation of calibrating materials, relatively large inter-centre variability and uncertainty about how to interpret untypical patterns. Moreover, there is still not enough evidence that biomarkers alone can distinguish one type of dementia from another.

1.3. Justification of the present thesis

Lately, in the field of aging and dementia, the focus has been placed in the early markers and predictors of the future development of a neurodegenerative disease. Therefore, and according to previous rationale, this doctoral thesis is devoted at clarifying possible early risk factors, in terms of affective or behavioural symptoms, that may predict the future outcome of an aging disease once a robust diagnosis of mild cognitive impairment has been established.

Hypotheses and Objectives.

2. Hypotheses and Objectives

2.1. General aims

The aims of this study were: 1) to determine comorbidly presented NPS as early markers of conversion to specific dementia subtypes in MCI diagnosed patients; and 2) to explore the prognostic capacity of those NPS in the future cognitive worsening.

NPS were explored from a comorbidity perspective, analysing the possibility of the existence of symptomatic profiles. The ultimate goal is to obtain specific diagnostic and prognostic markers, with high applicability to the clinic.

2.2. Specific objectives and hypotheses

2.2.1. Study 1

For the first retrospective study we hypothesized that **progression from MCI to specific types of dementia would be determined by NPS**. Therefore, the objectives of this study are:

(1) to explore consistent classes of NPS among patients with MCI using Latent Class Analysis (LCA).

(2) to determine the effect of the resulting NPS classes on progression to dementia by means of a survival analysis

(3) to investigate conversion to different types of dementia based on NPS classes accounting also for factors such as age, gender, level of education and/or APOE-Ɛ4.

2.2.2. Study 2

For the second longitudinal study, and based on results prom the first study, we hypothesized that **trajectories of cognitive decline would be different according NPS-clusters**. The main objective was to explore possible trajectories of cognitive decline based on previously obtained NPS clusters in a clinical MCI sample. Always accounting for the different comorbid symptoms collected at baseline visit and taking into consideration a perspective of isolated cognitive functions explored.

Methods.

3. Methods

This thesis comprises a compendium of two scientific publications both integrated into an observational, single-centred and retrospective study. The first article was published in March 2021 in Scientific Reports, and the second one was published in December 2021 in Frontiers in Aging Neuroscience.

A final sample of 2,137 MCI patients was used in both studies. Patients were diagnosed according to Petersen's criteria[14] and using the cut-off points for the NBACE neuropsychological battery[98] to test main hypothesis of the present work. Recruitment was carried out at the Diagnostic Unit of *ACE* - Alzheimer Centre Barcelona and data were collected from January 2006 to June 2017.

General inclusion criteria for both studies were:

- Schooling: primary education (minimum 6 years of formal education).
- No toxic habits (alcohol and drug disorder abuse).
- No psychiatric disorder diagnosed according to CIE-10 or DSM V.
- No personal history of Huntington's Disease or Multiple Sclerosis.
- No severe sensorial impairment compromising neuropsychological testing.

Specifically, from the pool of patients diagnosed with MCI at *ACE* (N=7,118) we selected those with at least one follow-up (n=4,645); we then filtered patients from 2006 onwards (n=3,431), since the implementation of the neurology protocol where the version currently used in the diagnostic unit of the NPI-Q was included dates from that date; we then applied the aforementioned criteria of age (n=3, 417) and MMSE score (n=2,793); a 6-month window was set as the conversion time frame (n=2,470), to avoid including patients very close to the conversion; and finally, those subjects who had correctly administered the NPI-Q were selected (n=2,137), for which the presence of an informant was mandatory. See flowchart (*Fig 5*. Flowchart of patients' inclusion).

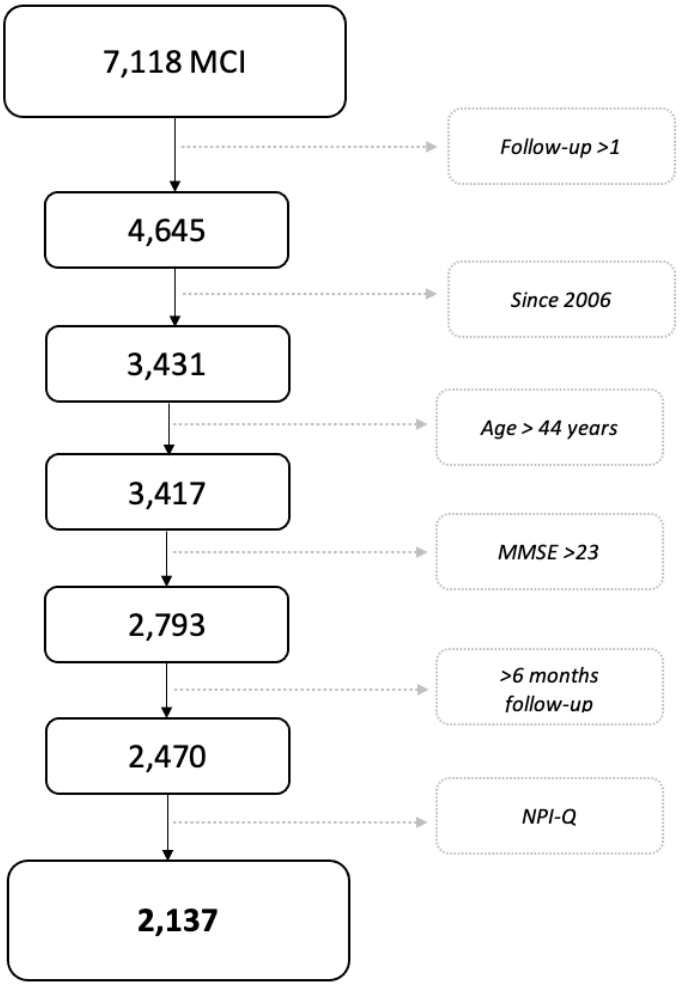

Figure 6. Flowchart of patients' inclusion.

MCI diagnosis was done during the initial visit after being referred to the Memory Clinic. Cognitive deficits (or subjective complaints) were mainly detected by their General Health practitioner or by their own decision of being evaluated in the Open House Initiative of *ACE*. Then, assessment was made by a multidisciplinary team of professionals (neurologists, neuropsychologists and social workers), exploring clinical cognitive and psychosocial variables for each case. Finally, diagnoses were set via consensus in a daily clinical committee by the same experts. At baseline, the sample had the following characteristics:

- a CDR of 0.5
- a GDS of 3 at maximum.

All MCI diagnosis were based on the modified Petersen's criteria for aMCI and naMCI, MCI-sd and MCI-md, and Lopez's criteria for possible or probable MCI due to AD.

Subsequent diagnosis of conversion to dementia depending on the aetiology were made following current established criteria as it follows:

Diagnostic	**Criteria**
Alzheimer's Disease	NIA-AA criteria[49]
Behavioural variant of frontotemporal dementia	Consortium criteria[116,117]
Vascular Dementia	NINDS-AIREN report[118]
Dementia due to Parkinson's disease	Last published criteria by the Movement Disorders Society[119]
Dementia with Lewy bodies	Fourth report of the Dementia by Lewy Body Consortium[120]

Table 7. Dementia criteria according to aetiology.

When a previous psychiatric disorder was diagnosed by a field-professional and when no criterion for a neurodegenerative disease was met, dementias were considered to be caused by a psychiatric disorder (DPD).

Baseline assessment and subsequent follow-ups were conducted with the same structure and always keeping the same procedure at each visit. All participants were evaluated for subsequent follow-ups by the same professionals. Each case was assessed individually using collected information about current state in order to validate the appropriate diagnosis. Any changes occurred in relation to reversion to NC or SCD; stability of MCI or worsening of conditions and conversion to dementia were reported. In the event of any doubt, the case was discussed in the daily clinical committee for the reassessment of the diagnosis among all professionals from the memory unit. Follow-ups were approximately done annually.

3.1. Study 1

To accomplishing the objectives of the first study, a subset of structural equation modelling was performed with available data, called Latent Class Analysis (LCA). It is

an analytic technique that has become popular among studies involving human research. The main goal of this approach is to identify latent or unobserved groups (coined as classes) based on responses to a set of observed indicators.[121] LCA is a person-centred approach focused on similarities and differences among people instead of relations among common variables.[122] Based in shared and intercorrelated characteristics between similar individuals, participants are assembled into distinct profiles.[123] Patterns of responses on dichotomous variables are used to estimate two different parameters, called *latent class probabilities* and *conditional probabilities*. The former become prevalence of each class and the latter are rates of each analysed variable given membership in each latent class. Once these estimations are done, it is possible to have an individual probability of affiliation in every latent class (or belonging group), according to their pattern of symptoms and their modal class membership. Finally, these classes can be applied to explore different trajectories according to shared characteristics of the resulted sub-samples or groups.

3.2. Study 2

Based on previous results based on LCA for clustering participants, linear mixed models (LMMs) were executed to explore relationships longitudinally to fulfil objectives of the second study. A mixed model is a statistical tool that allows researchers to explore the relationship among different variables always controlling by fixed and/or random effects that could affect main relationship sought. Fixed effects are constant across individuals, whereas random effects vary. This analytical approach is appropriate when longitudinal studies are performed.[124] Recently, this technique has received special attention due to its high applicability in clinical contexts of evaluation and re-evaluation of conditions presented by patients over time. It is also a tool that allows dealing with missing data, making it very useful with large samples and repeated measurements.[125–127]

(For more information about the procedure, treatment of variables and application in relation to the present thesis objectives see section *4. Results and publications*)

Results and publications.

4. Results and publications

4.1. Neuropsychiatric profiles and conversion to dementia in MCI, a latent class analysis.

Roberto N, Portella MJ, Marquié M, Alegret M, Hernández I, Mauleón A, Rosende-Roca M, Abdelnour C, de Antonio EE, Gil S, Tartari JP, Vargas L, Espinosa A, Ortega G, Pérez-Cordón A, Sanabria Á, Orellana A, de Rojas I, Moreno-Grau S, Montrreal L, Alarcón-Martín E, Ruíz A, Tárraga L, Boada M, Valero S. Neuropsychiatric profiles and conversion to dementia in mild cognitive impairment, a latent class analysis. *Scientific Reports*. 2021 Mar 19;11(1):6448.

ABSTRACT

Neuropsychiatric symptoms (NPS) have been recently addressed as risk factors of conversion to Alzheimer's disease (AD) and other dementia types in patients diagnosed with Mild Cognitive Impairment (MCI). Our aim was to determine profiles based on the prominent NPS in MCI patients and to explore the predictive value of these profiles on conversion to specific types of dementia. A total of 2137 MCI patients monitored in a memory clinic were included in the study. Four NPS profiles emerged (classes), which were defined by preeminent symptoms: Irritability, Apathy, Anxiety/Depression and Asymptomatic. Irritability and Apathy were predictors of conversion to dementia (HR = 1.43 and 1.56, respectively). Anxiety/depression class showed no risk effect of conversion when compared to Asymptomatic class. Irritability class appeared as the most discriminant neuropsychiatric condition to identify non-AD converters (i.e., frontotemporal dementia, vascular dementia, Parkinson's disease and dementia with Lewy Bodies). The findings revealed that consistent subgroups of MCI patients could be identified among comorbid basal NPS. The preeminent NPS showed to behave differentially on conversion to dementia, beyond AD. Therefore, NPS should be used as early diagnosis facilitators, and should also guide clinicians to detect

patients with different illness trajectories in the progression of MCI.

Key words: mild cognitive impairment, dementia, Alzheimer's disease, neuropsychiatric symptoms, latent class analysis.

INTRODUCTION

Mild Cognitive Impairment (MCI) is a transitional stage between cognitively healthy aging and dementia, mainly Alzheimer's Disease (AD).[1,2] Since it is a heterogeneous nosological entity, several clinical subtypes of MCI have been described. According to cognitive performance, MCI can be classified into four groups: amnestic single (aMCI-sd) and multiple domains (aMCI-md), and non-amnestic single (naMCI-sd) and multiple domains (naMCI-md)[1]. The cognitive domains that may be affected include attention, memory, language, praxis, visuoperception, executive functions and visuospatial skills.[3,4]

Conversion rate to dementia for patients diagnosed with MCI is a controversial topic given that estimations of prevalence and incidence of dementia depend on multiple factors.[5,6] Among them, neuropsychiatric symptoms (NPS) have been postulated to be related to conversion. Indeed, NPS are highly prevalent in the majority of patients with dementia over the course of the disease.[7] In this context, some authors have pointed out NPS as being specific risk factors of conversion to dementia.[8,9] A recent update emphasized the importance of NPS as diagnostic and prognostic markers.[10] The relevance of such studies relies on the fact that NPS may be present even before the appearance of a significant cognitive decline or even before alterations of patients daily functioning.[11] Two studies have already analysed in different population settings (from volunteers to MCI patients) the differential conversion rates to dementia depending on the presence of NPS. The study by Leoutsakos and colleagues identified four groups based on NPS (1: irritable; 2: depressed; 3: complex; and 4: asymptomatic) finding that the complex group had the higher hazard ratio of conversion (3.20, 95% CI: 2.24-4.58) in comparison with the asymptomatic group. The other study by Forrester and collaborators found three groups of patients classified according to NPS (1: severe cluster; 2: affective cluster; and 3: asymptomatic). In comparison to asymptomatic patients, individuals in the severe cluster showed more than twice the hazard of progression to dementia

(2.69, CI: 1.12-2.70), whereas the affective cluster had one and a half times the hazard of conversion (1.79, CI: 1.12-2.70).[12,13] Another recent study addressed the impact of NPS in patients diagnosed with MCI, and concluded that the coexistence of certain psychopathological symptoms, i.e., hyperactivity, affect disturbances and psychosis, embedded conversion to dementia.[14] These findings point out the need to establish NPS profiles rather than exploring individual symptoms that may account for conversion outcomes.

However, the mere existence of NPS alone should not be considered the unique factor to determine the conversion from MCI to specific types of dementia. Age, gender or even, level of education may also account for the progression of MCI towards dementia.[15,16] In terms of neurobiological factors, apolipoprotein E epsilon4 (*APOE-ε4*) has been found to be the main genetic risk factor for Alzheimer's disease (AD), specifically with sporadic and late-onset forms.[17–19] Interestingly, a synergistic interaction between some NPS (depression or apathy) and *APOE-ε4* has been found to increase the risk of dementia.[20,21] However, the possible influence of the *APOE-ε4* on the relation between comorbid NPS and conversion to dementia in MCI patients has never been explored.

In light of the above arguments, it can be postulated that NPS may determine the progression from MCI to specific types of dementia. Therefore, the objectives of this study are 1) to explore consistent classes of NPS among patients with MCI using Latent Class Analysis (LCA); 2) to determine the effect of the resulting NPS classes on progression to dementia by means of a survival analysis; and 3) to investigate conversion to different types of dementia based on NPS classes accounting also for factors such as age, gender, level of education and/or *APOE-ε4*.

RESULTS

Table 1 shows demographic and clinical characteristics of the final sample. As can be observed, the most prevalent neuropsychiatric symptoms (measured with the NPI-Q) were depression (n=1298, 60.7%) and anxiety (n=1286, 60.2%), closely followed by apathy (n=990, 46.3%), irritability (n=832, 38.9%) and sleep disorders (n=686, 32%). The least prevalent symptoms were appetite disorders (n=188, 8.8%),

disinhibition (n=75, 3.5%) and agitation (n=73, 3.4%).

Table 1. Demographic and clinical characteristics of the study participants (n= 2,137). SD= standard deviation; MMSE= Mini-Mental State Examination; NPI-Q= Neuropsychiatric Inventory Questionnaire.

	Mean (SD)
Age (yrs)	74.6 (8.2)
Gender (% of females)	58.5
Education (yrs)	7.3 (3.9)
MMSE (total score)	26.9 (1.7)
NPI-Q (mean of total symptoms)	4.19 (1.9)
Years of follow-up mean/median (range)	2.24/1.79 (0.5-9.38)

The final LCA solution was determined according to parameters included in Table 2: Bayesian Information Criteria (BIC), entropy and Vuong-Lo-Mendell-Rubin ratio test (LRT) non-adjusted and adjusted LRT. Based on these criteria, the 4-class model was considered to fit best. In detail, although BIC value of the 3-class model was the lowest, entropy value was higher in the 4-class model, starting to decrease for the 5-class model, this latter not being statistically significant in terms of the adjusted LRT. See Table 2 for all measures of tested models.

Table 2. Summarized model statistics for two- to five-class solutions of the Latent Class Analysis.

	Number of latent classes			
	2	**3**	**4**	**5**
BIC	15940.1	15833.9	15847.8	15838.1
Entropy	.66	.7	.77	.67
Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (LRT) p-value	<.001	<.001	<.001	.182
Lo-Mendell-Rubin Adjusted LRT p-value	<.001	<.001	<.001	.186

The results revealed a structure in which each class was determined by specific symptomatology, and the most preeminent symptom was used to name every particular class (see Figure 1). Class 1 (n=134; 6.3%) was constituted by patients with high probability of irritability (.93), followed by far by anxiety (.64) and apathy (.63); Class 2 (n=272; 12.7%) was strongly represented by apathy (1); Class 3 (n=1056; 49.4%) showed high probability of depression (.95), anxiety (.93) and, by far, apathy (.61); and Class 4 included the rest of patients (n=675; 31.6%) and was characterized by having low probabilities in all domains (<.3). Therefore, Class 1 was referred as 'Irritability', Class 2 as 'Apathy', Class 3 as 'Anxiety/Depression', and Class 4 as 'Asymptomatic'.

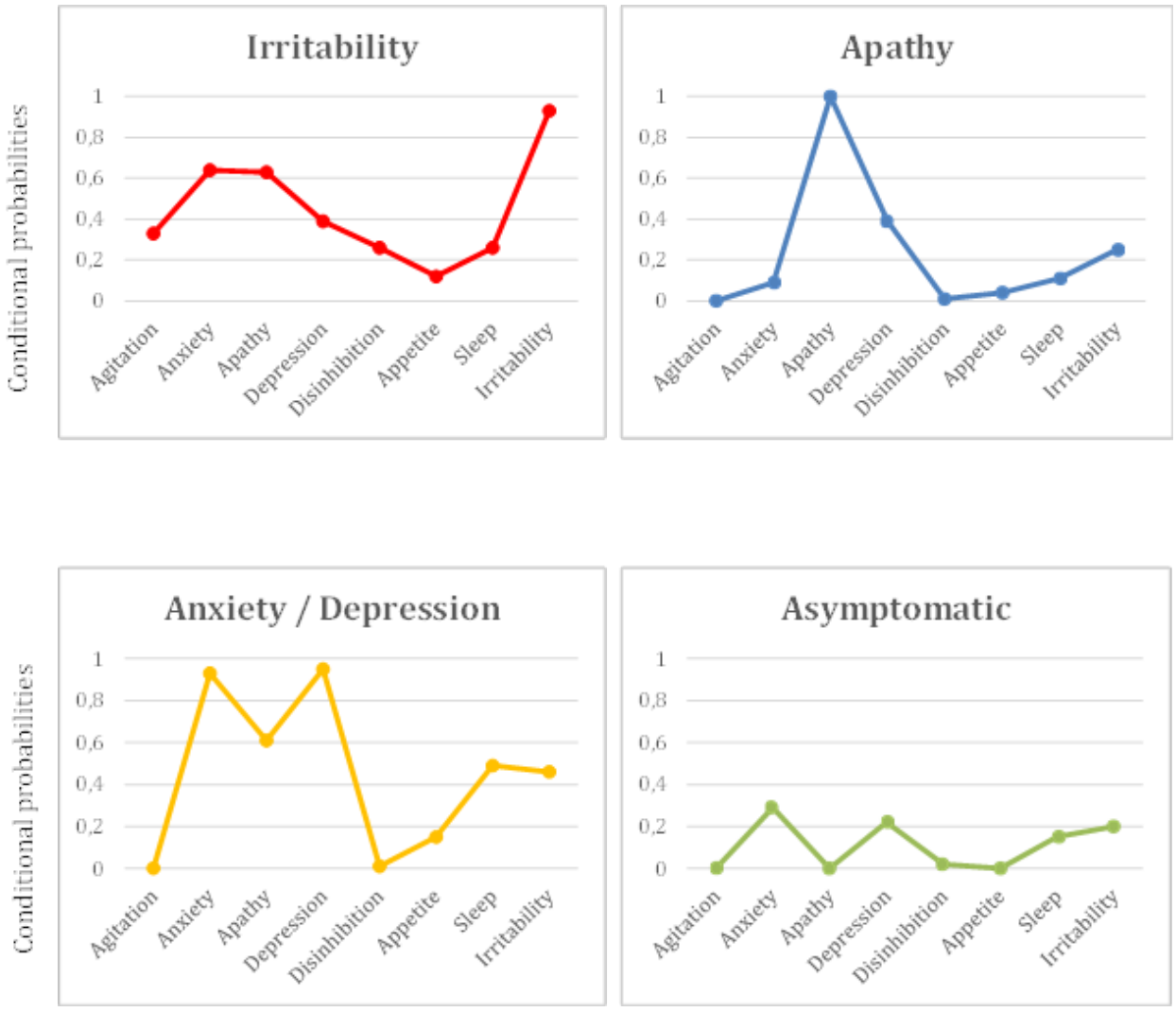

Figure 1. Profile plots represent estimated conditional probabilities (y-axis) observed in the latent class analysis (LCA) for the domains of the Neuropsychiatric Inventory-Questionnaire (NPI-Q; x-axis), displaying the 4-class solution: Irritability, Apathy, Anxiety/Depression and Asymptomatic.

Demographic and clinical variables stratified by clusters (4-class solution) are described in Table 3. There were significant differences among the four classes in most of the variables, with the exception of GDS. Regarding age, *Apathy* class was composed by the oldest patients, whereas *Anxiety/Depression* class was the youngest group. In relation to gender, *Irritability* class was predominantly composed by males, while patients classified in the *Anxiety/Depression* and *Asymptomatic* classes were mostly females. *Apathy* class showed the highest level of education, whereas the other 3 groups had similarly less years of education. In relation to general cognitive status, highest scores were found in the *Anxiety/Depression* class, followed by *Irritability* class. As for the NPS symptomatology (presence/absence), taking into account the 12 domains present in the NPI-Q, *Anxiety/Depression* class had the highest mean score in the number of symptoms suffered. The average length of follow-up was very similar among groups (over two years), with the exception of the *Apathy* class that showed the shortest length.

Table 3. Demographic characteristics of the study participants (n= 2,137) stratified by the 4-class LCA model. Values represent mean (SD) or otherwise specified. MMSE= Mini-Mental State Examination; NPI-Q= Neuropsychiatric Inventory Questionnaire.

	Irritability class (n=134)	***Apathy class (n=272)***	***Anxiety/ Depression class (n=1056)***	***Asymptomatic class (n=675)***	**F/χ^2**	***p***
Age (yrs)	75.17 (7.99)	76.20 (7.32)	73.82 (8.31)	75.23 (8.15)	8.30	**<.001**
Gender (% of females)	39 (29.1%)	112 (41.2 %)	688 (65.2%)	411 (60.9%)	102.14	**<.001**
Education (yrs)	7.38 (3.80)	8.04 (4.23)	7.1 (3.79)	7.25 (4.08)	4.14	**.006**
MMSE	27 (1.72)	26.65 (1.74)	27.02 (1.69)	26.97 (1.76)	3.46	**.016**
GDS	3	3	3	3	0.60	.600
NPI-Q (sum)	1.46 (1.35)	0.58 (0.79)	1.58 (1.27)	0.35 (0.63)	213.1	**<.001**
Years of follow-up mean/median (range)	2.31/1.79 (0.52-8.62)	1.92/1.48 (0.52-8.39)	2.27/1.78 (0.50-9.38)	2.30/1.92 (0.50-8.80)	4.02	**.007**
Conversion to dementia (%)	72 (53.7%)	149 (54.8%)	394 (37.3%)	264 (39.1%)	37.21	**<.001**
Time of conversion (median of years)*	2.69	2.09	3.30	3.55	21.01	**<.001**

*Kaplan Meier survival analysis.

Cox proportional hazard ratios were calculated to test three survival models of conversion to dementia. The first model only explored the effect of latent classes on conversion; the second model was adjusted by age, Mini-Mental State Examination (MMSE), gender and years of education; and the third model included dichotomic *APOE-Ɛ4* status (0=Non-carriers of 4 allele; 1=Carriers of allele 4, either having one or two alleles) together with the factors of the second model. This latter model was executed in a subsample of patients, since not all patients had been genotyped for *APOE-Ɛ4* (n=1,106, 51.7% of the total sample). Probability of conversion to dementia in the subsample was 1.7 times more frequent between *APOE-Ɛ4* carriers than in non-carriers (χ^2= 15.4, p<.001), but the distribution of *APOE-Ɛ4* carriers was homogeneous between the 4 class groups (χ^2= .14, p=.99). Results from the three models are summarized in Table 4.

Table 4. Risk of conversion to dementia by 4 classes of preeminent neuropsychiatric symptoms applying three different models (Cox proportional hazards). Values are hazard ratios (CI 95%); *p<.05; **p<.001; Model 1= Adjusted by class group. Model 2= Adjusted by class group, age, gender, MMSE score, and years of education. Model 3= Adjusted by class group, age, gender, MMSE score, years of education and APOE-Ɛ4.

	Model 1 (n=2,137)	**Model 2 (n=2,137)**	**Model 3 (n=1,106)**
Irritability class	1.35 (1.04-1.75)*	1.43 (1.09-1.86)*	1.5 (1.07-2.08)*
Apathy class	1.70 (1.38-2.07)**	1.56 (1.28-1.92)**	1.43 (1.1-1.85)**
Anxiety/Depression class	.96 (.82-1.12)	1.14 (.97-1.33)	1.08 (.89-1.31)
Asymptomatic class	*reference class*	*reference class*	*reference class*

Irritability and *Apathy* classes showed a higher risk of conversion when compared to the *Asymptomatic* class (reference class). Moreover, this effect appeared to be independent of adjustment variables (age, education, MMSE and *APOE-Ɛ4)*. By contrast, pertinence to the *Anxiety/Depression* class did not seem to add an extra risk of conversion compared to the *Asymptomatic* class. Figure 2 shows survival curves for the 4-class groups in the adjusted model.

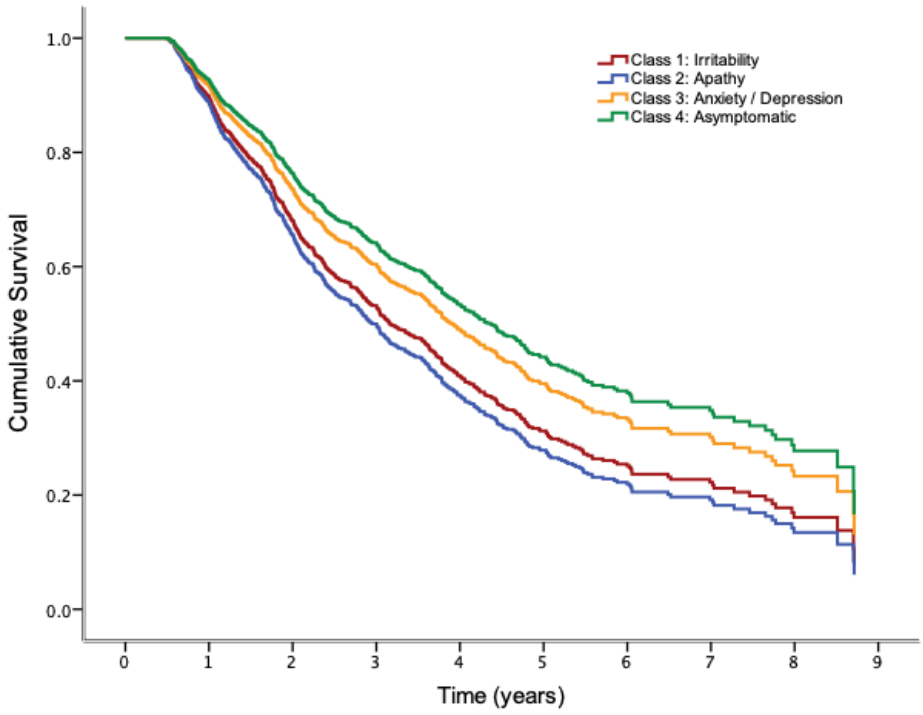

Figure 2. Survival curves of model 2 (adjusted by age, gender, mini-mental state examination and years of education) of the 4-class model obtained with LCA. Irritability and apathy classes showed significant increased hazard risks to convert to dementia compared to asymptomatic class.

The total percentage of converters was 45% (see Table 5 for specific class conversion to dementia). Percentages of conversion to dementia by class were 58.2% of patients in the *Irritability* class (n=78); 58.8% in the *Apathy* class (n=160); 41.2% in the *Depression/Anxiety* class (n=435); and 42.7% in the *Asymptomatic* class (n=288). Patients classified into the irritable group had lower percentages of conversion to AD and higher for BvFTD than the rest of classes. For the total sample of converters, grouping AD *vs*. other dementias revealed a significant association with neuropsychiatric classes (χ^2= 47.4; p<.005). When taking the *Asymptomatic* class as the reference condition, the hazard ratio of conversion to non-AD dementia was 5.6 times higher (p<.005) in the *Irritability* class, while in the *Apathy* and *Anxiety/Depression* classes this hazard was 2.6 and 1.99, respectively (p<.005). The risk of conversion to non-AD dementias was similar between *Apathy* and *Anxiety/Depression* classes (p=.173), but patients belonging to the *Irritability* class presented a higher probability of conversion to non-AD dementias compared to individuals in the *Apathy* class (OR=2.16, p<.015).

Table 5. Specific conversion type of dementia for 4 classes of preeminent neuropsychiatric symptoms. AD= Alzheimer Disease; BvFTD= Behavioral variant of Fronto-Temporal Dementia; VD= Vascular Dementia; Parkinson's disease; DLB: Dementia with Lewy Bodies; DPD= Dementia by Psychiatric Disorder; Non-degenerative= Dementia by non-degenerative disorders; other= Dementia by Others. Only converters are included here.

	AD	***BvFTD***	***VD***	***PD***	***DLB***	***DPD***	***Non-degenerative***	***Others***
Irritability class (n= 72)	23 (31.9%)	13 (18.1%)	21 (29.2%)	6 (8.3%)	0 NA	4 (5.6%)	5 (6.9%)	0 NA
Apathy class (n=149)	75 (50.3%)	12 (8.1%)	41 (27.5%)	11 (7.4%)	4 (2.7%)	3 (2.0%)	3 (2.0%)	0 NA
Anxiety / Depression class (n=394)	224 (56.9%)	24 (6.1%)	91 (23.1%)	19 (4.8%)	6 (1.5%)	22 (5.6%)	7 (1.8%)	1 (0.3%)
Asymptomatic class (n=265)	192 (72.5%)	12 (4.5%)	40 (15.1%)	5 (1.9%)	6 (2.3%)	9 (3.4%)	1 (0.4%)	0 NA
Total	514 (58.4%)	61 (6.9%)	193 (21.9%)	41 (4.7%)	16 (1.8%)	38 (4.3%)	16 (1.8%)	1 (0.1%)

DISCUSSION

Our study investigated the impact of NPS in the conversion to different types of dementia in a large cohort of MCI patients from a Memory Unit. The results of the LCA gave rise to four well characterized groups of MCI patients based on their NPS, i.e., *Irritability*, *Apathy, Anxiety/Depression* and *Asymptomatic* classes, which yielded different risk rates of conversion to dementia.

Those patients with MCI classified as 'irritable' (Class 1) tended to convert mainly to AD, but also to other different types of dementia (BvFTD and VD in similar percentages). Particularly, when analysing conversion to non-AD dementia, the *Irritability* class showed higher risk of conversion than the rest of symptomatic classes. By contrast, MCI patients belonging to the other NPS classes (*Apathy, Anxiety/Depression and Asymptomatic*) converted mainly to AD and, to a lesser extent, to VD, being both the most frequent types of dementia observed in our sample.

The survival curves of conversion to dementia showed on one hand a similar pattern for *Anxiety/Depression* and *Asymptomatic* classes, and on the other hand, *Apathy* and *Irritability* classes posed a risk factor of conversion to dementia contrary to the accepted fact of anxious and depressive symptoms being

classically described to be associated with dementia in the long term.[8,22,23] These findings may suggest that early detection and an adequate classification of NPS could lead to better the management of MCI progression. It is true that some studies have also related clinical features associated with AD to be present in adults with no diagnostic of dementia but depression. [24] In this regard, it has been postulated that successful treatment of this low-mood related symptoms could ameliorate cognitive impairment, thus increasing the probability of reversion from MCI to normal cognition. Going further, some researchers have proposed to investigate whether maintained antidepressant treatment could improve performance on neuropsychological testing, even though the causes of the instability that characterizes MCI are not well defined yet.[25]

The most frequent MCI trajectory was conversion to AD dementia, followed by VD, mirroring epidemiological studies of AD prevalence.[4] Interestingly, percentages of conversion to different types of dementia significantly varied across NPS-defined classes. In particular, less than a third of MCI patients classified as 'irritable' converted to AD, while those with no NPS (*Asymptomatic* class) showed up to 75% conversion to AD. This finding sheds light on the importance of exploring NPS in the very early stages of dementia as it reveals a differential impact on the prediction to specific types of dementia, at least at a group level.

Irritability and, to a lesser extent, *Apathy* classes appeared to be the determining factors in the conversion to dementia in our MCI sample, and this has scarcely been described in the literature. Previous works already found that irritability was a relevant behavioural disturbance,[11] as well as apathy and agitation, with high rates of prevalence among MCI patients.[26] The unadjusted model indicated that *Apathy* class was the best predictor, while once adjusted (including *APOE-Ɛ4* and the rest of variables), *Irritability* emerged as the most relevant neuropsychiatric condition when predicting conversion to dementia. Previous works reported other neuropsychiatric symptoms and were carried out in different sample of individuals (healthy volunteers) where MCI could be incident rather than prevalent.[12,13] In any case, our results suggest that the pre-eminence of irritability should be taken into consideration provided that it may confer

differential susceptibility to quicker decline and conversion to a variety of dementia types,[27] and highlight that a good characterization of MCI individuals is required, given the heterogenic nature of this diagnostic entity.

Most of the studies addressing the presence of NPS in aging and dementia have been mainly focused on anxious and depressive symptoms. For instance, Tau Ming Liew and colleagues have recently published a community-based study where these two symptoms were evaluated in order to analyse whether concurrence of both, associated with cognitive deficits, improved the specificity to identify subjects at high-risk for neurocognitive disorders. Their findings showed that the subtype with the highest risk of conversion to neurocognitive disorders was the group with both, NPS (Anxiety/Depression) and cognitive deficits.[28] Our findings show that, although anxiety and depression have been the most widely explored NPS in relation to MCI and dementia, other NPS are present in both stages and their nature can determine the prognosis of MCI. A possible explanation is that anxious and depressive symptoms may be more reactive, temporary and linked to the self-awareness of being cognitively and/or functionally affected. However, in light of our findings this is merely speculative, and could also be explained by the characteristics of the setting of the present study. According to our results, Sugarman and colleagues reported more mood symptoms and hyperactivity (such as irritability, agitation, etc.) to be associated with progression to AD, whereas treating depression was related to a higher probability of cognition improvement.[25]

Indeed, our findings may not be fully generalized to the MCI population, as prevalence and incidence differences between community samples and clinical settings have been described.[29,30] However, the present results highlight the existence of NPS and their undoubtable impact on MCI trajectories at a group level; yet the effect of NPS in the daily clinical practice remains to be clarified. A recent review has also shown that NPS predicted conversion to dementia, in which NPI-Q scores were higher in converters.[31] This represents an opportunity to think about potential interventions for the early stages of the different forms of dementia.

Our study has limitations that need to be acknowledged. The main weakness is

that despite the fairly large sample, patients were followed up only for 2.2 years on average, which may not be sufficient time to determine full conversion rates. Longer longitudinal designs would allow observing whether the impact of NPS on conversion profiles is stable or evolves along time. Patients were evaluated through the NPI-Q to determine NPS, which may not capture other psychopathological symptoms reported in previous studies. In any case, the NPI-Q is one of the most commonly used scales in neurology units. Also, pharmacological treatment was not well characterized which could also flaw our results.

CONCLUSIONS

The main finding of the present study is that patients diagnosed with MCI can also display NPS and such symptoms may lead to different MCI trajectories of conversion to dementia. In particular, 'irritable' patients tended to convert to non-AD dementia, while 'apathic', 'anxious/depressed' and asymptomatic individuals converted mainly to AD, even though these results cannot be generalized to each and every individual case, but it may provide valuable information to clinicians about the probability of conversion to specific types of dementia in order to be aware. These results open a new venue in which an accurate assessment of NPS at the time of MCI diagnosis is to be considered mandatory, as the presence or absence of such symptoms may define the long-term outcomes. Finally, assessment of NPS may provide an invaluable information to establish treatment strategies aiming at slowing down the progression to dementia or at least to improve the quality of life of MCI patients along illness trajectory in the context of a Memory Unit.

METHODS

Participants

To carry out the present study, a sample of patients with a baseline diagnosis of MCI was selected from the pool of patients at the Memory Clinic of *Fundació* ACE, Barcelona, Spain (see Sample Selection section for details of selection).[32] Data was collected from January 2006 to June 2017.

Diagnosis and Procedure

Participants were referred to the Memory Clinic by their General Health practitioner due to cognitive problems (or subjective complaints) or by their own decision of being evaluated in the

Open House Initiative of *Fundació ACE*.

After recruitment, neurologists, neuropsychologists and social workers assessed all participants. Diagnoses were made via consensus in a daily clinical committee by those professionals. At baseline, our sample had the following characteristics: a Clinical Dementia Rating Scale (CDR) of 0.5; and a Global Deterioration Scale (GDS) of 3 at maximum. The diagnosis of MCI was based on the modified Petersen's criteria for aMCI and naMCI, MCI-sd and MCI-md, and Lopez's citeria for possible or probable MCI due to AD;[33] whereas for dementia diagnoses depending on the aetiology were made as it follows: AD diagnosis was based on NIA-AA criteria, diagnoses of the behavioural variant of frontotemporal dementia (BvFTD) were made using consortium criteria, Vascular Dementia (VD) was diagnosed following the NINDS-AIREN report, for dementia due to Parkinson's disease (PD) the last published criteria by the Movement Disorders Society was used, for dementia with Lewy bodies (DLB) the fourth report of the DLB Consortium was followed, and dementia caused by a psychiatric disorder was diagnosed when there was a previous psychiatric disorder diagnosed by a professional and when no criterion for a neurodegenerative disease was met.

Baseline assessment and subsequent follow-ups were conducted following the same procedure at each visit. All participants were evaluated at baseline as indicated above, and each subsequent follow-up was carried out by the same professionals, who evaluated each case individually using collected information about current state in order to validate the appropriate diagnosis or to explore if any changes occurred in relation to conversion to dementia. In the event of any doubt, the case was discussed in the daily clinical committee for the reassessment of the diagnosis. Follow-ups were approximately done annually.

Ethical considerations

Informed written consent was obtained from all participants. The referral center ethics committee (Hospital Clínic i Provincial of Barcelona) approved the patient recruitment and collection protocols, which were in accordance with ethical standards of the World Medical Association and the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.

Measures

The Neuropsychiatric Inventory-Questionnaire (NPI-Q) is a simplified clinical scale used to assess dementia-related behavioural disturbances in 12 domains (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep and nighttime behaviours, and appetite and eating disorders).[34] In our study, NPI-Q was administered by trained physicians and the information about the patient was provided by a reliable informant (familiar or close others). For each of the 12 domains, a change during the last month was measured as present or absent (dichotomous variable). Psychometric properties of the NPI-Q are satisfactory, being the tests-retest correlations between total symptom and distress scores 0.80 and 0.94 respectively; interscale correlation between the NPI total score for all domains and the NPI-Q severity total was 0.91.[35]

Sample Selection

The present study included patients with MCI (N=7,118) diagnosed at the Diagnostic Unit of *Fundació ACE* (ACE). All participants were assessed by a neurologist, a neuropsychologist and a social worker. Diagnoses and reassessments were made via consensus by all the different professionals in a clinical committee as explained above.[36,37] In order to test the hypothesis of the study, a selection of subjects was defined by the following criteria: (i) at least one follow-up visit (n=4,645); (ii) older than 44 years old (n=3,417); (iii) a MMSE total score higher than 23 (n=2,793);[38] (iv) more than 6 months of follow-up (n=2,470); and (v) administration of NPI-Q at their basal visit (n=2,137), which requires presence of an informant. The final sample used for the present study was therefore of 2,137 patients diagnosed as MCI.

Analytical Approach

LCA provides a flexible analytical approach that allows researchers to study patterns of observations in data and to make inferences about unobserved sources of population heterogeneity.[39] The strategy becomes a person-centred analytic tool focused on similarities and differences among people instead of relations among variables.[40] The main target of this strategy is to assemble participants sharing similar characteristics (person-centred

approach) into distinct profiles, based on their expressions on a number of variables that are intercorrelated.[41] LCA uses patterns of responses on dichotomous variables to estimate two different parameters, called latent class probabilities and conditional probabilities. Latent class probabilities become prevalence of each class and conditional probabilities are rates of each analysed variable given membership in each latent class. Thanks to these estimations it is possible to have an individual probability of affiliation in every latent class, according to their pattern of symptoms and their modal class membership.

Firstly, dichotomous ratings on each of the 12 NPI-Q domains were obtained (0=0; 1> 1 to 3). Aimed not to introduce noise in the LCA data processing, only neuropsychiatric conditions observed at least in the 3% of participants were included. Thus, Agitation/aggression (agitation), depression/dysphoria (depression), anxiety (anxiety), apathy/indifference (apathy), disinhibition (disinhibition), irritability/lability (irritability), sleep and night-time behaviours (sleep), and appetite and eating disorders (appetite) were the final domains included in our analysis. The final LCA model was determined using a consensus of several fit criteria. Lowest value of BIC,[42] Entropy value (a number close to one suggests a clear classification),[43] LRT and adjusted LRT were performed to estimate whether a model with k profiles fitted the data significantly better than a model with k - 1 profiles.[44] An optimal application of LCA needs the consideration that variables included in the analysis are independent between them after conditional class membership is created. This assumption was tested using standardized bivariate residuals,[45] contrasting the observed symptom patterns to respect those predicted by the model. Once LCA was performed and the most parsimonious number of classes was determined, each participant was assigned to the class according the highest membership probability. Subsequently, Cox proportional hazards models, using the resulting latent class solution as main predictor, were executed in order to determine their survival effect on conversion to dementia. Given that not all patients had been genotyped for *APOE-ε4*, comparability of this subsample with the sample without this measure was measured by means of χ^2 contrasting the distribution for all NPS classes. All neuropsychiatric domains were

statistically comparable between these subsamples. Lastly, in order to explore the frequency distribution of our four main variables of study (NPS-classes) we obtained a contingency table to ascertain different frequencies within type of dementia for each class. LCA was run using MPlus v8.4 and Cox analysis with SPSS V26.

Data Availability Statement

Data used for this study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

NR, MJP, LT, MB and SV conceived the idea, designed the study and wrote the protocol and methodology. MM, MA, IH, AM, MRR, CA, EEA, SG, JPT, LV, AE, GO, APC, AS, AO, IR, SMG and LM acquired all the data, performed technical procedures and managed the data set. NR, MM and AR managed previous literature searches. NR, MJP and SV contributed to the statistical analysis, interpretation of the results and writing of the first draft of the manuscript. MA, AB, AR, LT, and MB revised the manuscript critically for intellectual content. All authors contributed to the writing of the final version and approved the manuscript.

COMPETING INTERESTS

All authors have stated that they have no conflicts of interest to report.

4.2. Neuropsychiatric profile as a predictor of cognitive decline in MCI.

Roberto N, Portella MJ, Marquié M, Alegret M, Hernández I, Mauleón A, Rosende-Roca M, Abdelnour C, Esteban de Antonio E, Tartari JP, Vargas L, López-Cuevas R, Bojaryn U, Espinosa A, Ortega G, Pérez-Cordón A, Sanabria Á, Orellana A, de Rojas I, Moreno-Grau S, Montrreal L, Alarcón-Martín E, Ruíz A, Tárraga L, Boada M, Valero S. Neuropsychiatric Profile as a Predictor of Cognitive Decline in Mild Cognitive Impairment. *Frontiers is Aging Neuroscience*. 2021 Dec 8;13:718949.

Abstract

Introduction:

Mild cognitive impairment is often associated with affective and other neuropsychiatric symptoms (NPS). This co-occurrence might have a relevant impact on disease progression, from MCI to dementia.

Objective:

The aim of this study was to explore the trajectories of cognitive decline in an MCI sample from a memory clinic, taking into consideration a perspective of isolated cognitive functions and based on NPS clusters, accounting for the different comorbid symptoms collected at their baseline visit.

Methods:

A total of 2137 MCI patients were monitored over a 2.4-year period. Four clusters of NPS (i.e., Irritability, Apathy, Anxiety/Depression and Asymptomatic) were used to run linear mixed models to explore the interaction of cluster with time on cognitive trajectories using a comprehensive neuropsychological battery (NBACE) administered at baseline and at the three subsequent follow-ups.

Results:

A significant interaction between cluster and time in cognitive decline was found when verbal learning and cued recall were explored (p=0.002 for both memory functions). For verbal learning, the Irritability cluster had the largest effect size (0.69), whereas the Asymptomatic cluster showed the smallest effect size (0.22). For cued recall, the Irritability cluster had the largest effect size among groups (0.64), and Anxiety/Depression had the smallest effect size (0.21).

Conclusions:
In MCI patients, the Irritability and Apathy NPS clusters shared similar patterns of worsening in memory functioning, which could point to these NPS as risk factors of a faster cognitive decline, acting as early prognostic markers and helping in the diagnostic process.

Key words: mild cognitive impairment, cognitive decline, neuropsychiatric symptoms, irritability, apathy, anxiety, depression.

INTRODUCTION

Biological changes bonded to impairment of cognitive functions are shown as humans age (Glisky, 2007). In the elderly, some cognitive skills such as attention, memory, executive functions or processing speed suffer from subtle changes associated with the normal aging process (Park et al., 2002; Park and Reuter-Lorenz, 2009), whereas others suffer a greater cognitive decline beyond expected, but not all decrement in cognitive functioning in this population is a precursor of disease. Therefore, it is important to distinguish between normal and pathological cognitive decline, mainly because it could affect the patient's daily functioning (Ginsberg et al., 2019) worsening their quality of life. The accurate measurement of cognitive decline over time is of utmost importance as it could help in the diagnosis and posterior prognosis of different neurodegenerative diseases and other syndromes (Grober et al., 2008; Wise et al., 2019).

Cognitive impairment is often associated with affective symptoms, such as anxiety or depression (Geda et al., 2008; Hermida et al., 2012; Singh-Manoux et al., 2017), which have been widely reported in different populations. While more is known about the former in relation to cognitive decline (Gonzales et al., 2017), there is still not much agreement about other neuropsychiatric symptoms (NPS) that could interfere with or relate somehow to a worsening in neuropsychological measures over time in early stages of different diseases. Some studies demonstrate the co-existence of both factors, with NPS being the predecessors of cognitive decline, often for many years (Wise et al., 2019; Tsunoda et al., 2020). There is no consensus on the order of appearance of both neural insults; previously, it was thought that cognitive deficits were the main reason for medical consultation, while studies increasingly claimed that NPS were the precursors initially

detected before any cognitive decline is shown (Mortby and Anstey, 2015; Ismail et al., 2018). In any event, it is important to delve into early cognitive decline and try to elucidate the factors favouring it. At this early stage, another important feature to keep in mind is that comorbid NPS are often found in the clinical practice, and this co-occurrence of NPS and cognitive decline might have a cumulative effect on disease progression (Geda et al., 2013). Many attempts have been made to identify specific profiles of NPS associated with Alzheimer's disease (AD). Some studies have explored the existence of neuropsychiatric subsyndromes or the genetics of NPS that could be the basis of AD, but no clear conclusions have been raised so far (Canevelli et al., 2013; Huang et al., 2020). A high prevalence of NPS in AD has commonly been associated with a worsening in the patient's functionality (Karttunen et al., 2011).

It is well known that NPS seem to play a critical role in early clinical stages of the dementia continuum (Karttunen et al., 2011; Burhanullah et al., 2020), such as in Mild Cognitive Impairment (MCI) (Lyketsos et al., 2002; Geda et al., 2008; Peters et al., 2012). In a search of profiles of clustered symptoms that could serve as markers of disease progression in early stages, NPS would act as early clinical manifestations of an emergent process of neurodegeneration (Gallagher et al., 2017). In particular, affective NPS (depression, apathy, anxiety and irritability) were associated with a more rapid progression to AD in older adults with MCI (Jang et al., 2020), and those have also even shown synergic effects with the APOE ε4-allele (Valero et al., 2020). Recently, some attempts have been made to investigate grouped NPS as possible predictors of cognitive decline along the progression of MCI towards dementia (Palmer et al., 2007; Edwards et al., 2009). In a recent two-year prospective study, and according to the three classes found in terms of NPS trajectories (*stable, improved* and *worsened*) in MCI patients, it was found that the NPS *worsened* class suffered the greatest cognitive and functional decline, as well as the highest conversion rate in comparison with the *stable* class and the *improved* class (David et al., 2016). Other clinical studies exploring associations of NPS by using factor analysis in MCI and mild AD dementia were focused on conversion to dementia and/or its relation to the severity of cognitive decline, but not specific cognitive domains (Siafarikas et al., 2018; Liew, 2019). There are two studies

in the same line exploring NPS clusters and conversion to dementia in cognitively healthy volunteers (Leoutsakos et al., 2015; Forrester et al., 2016). However, there is still no consensus in the findings, probably due to dissimilarities in the design and methodology of these studies (different diagnostic criteria, sample selection or neuropsychological assessment applied) (Ma, 2020). Likewise, there is a conceptual void when exploring the most common NPS in patients with MCI and their implications in cognitive decline in a long-term follow-up to analyse patients' progression in specific domains. Only a few studies in neurological patients, such as those with Parkinson's and Huntington's diseases (Pirogovsky-Turk et al., 2017), are going in this direction of assessing NPS in the MCI population and their implications for cognitive decline (Weintraub et al., 2015; Donaghy et al., 2018).

Therefore, this longitudinal study aims at investigating the existence of different trajectories of domain specific cognitive decline over time in an MCI sample from a memory clinic, taking into account baseline NPS clustering.

MATERIAL AND METHODS

Participants

The study was conducted at the Memory Clinic of Fundació ACE, *Institut Català de Neurociències Aplicades* (Barcelona, Spain), a private non-profit institution focused on the diagnosis, care and research of cognitive disorders and providing services to the Catalan Public Health Service (*Xarxa Hospitalària d'Utilització Pública*, XHUP) (Boada et al., 2014).

A total of 2137 patients diagnosed with MCI were selected from a pool of patients evaluated at the Memory Clinic, see (Roberto et al., 2021) for more information; MCI subtypes diagnoses were based on modified Petersen's criteria and Lopez and colleagues' classification, defined as amnestic (aMCI) or non-amnestic (naMCI), and possible or probable MCI due to AD, respectively (Petersen et al., 1999; Lyketsos et al., 2002; Petersen, 2004). All patients had to fulfil the following inclusion criteria: i) more than 44 years old; ii) a Mini-Mental State Examination (MMSE) total score of 24 or above; iii) a Clinical Dementia Rating (CDR) score of 0.5; iv) a Global Deterioration Scale (GDS) score of 3 or below; v) at least six

total years of formal education; vi) absence of severe visual or auditory disturbances that could hinder the neuropsychological examination; vii) presence of an informant or relative to complete the baseline administration of the NPI-Q; and, viii) a baseline neuropsychological visit completed along with at least one follow-up. All clinical data were collected from January 2006 to June 2017. In all cases, the date of the MCI diagnosis was taken as the starting point or inclusion date for this study. Patients were followed up approximately annually with a clinical assessment that included a neurology and a neuropsychological visit.

Cognitive measures

Cognitive data were collected at baseline and at every follow-up visit, using *The Neuropsychological Battery of Fundació ACE* (NBACE). The NBACE is a 50-minute battery designed to assess cognitive domains especially affected in the elderly when dementia due to AD or other neurodegenerative processes is suspected (Alegret et al., 2012). The NBACE was proposed as a brief, easy-to-administer and goal-directed compilation of globally-used neuropsychological tests in our target population, provided that it is focused on verbal memory and learning, visual perception, and executive functions, which are affected early in the course of the disease. However, these are not the only explored domains. In our study we included tests sensitive to the following cognitive domains: attention, working memory, processing speed, executive functions, verbal memory, language, gnosis, visuospatial skills and praxis. ~~Details of the battery,~~ Normative data and cut-off scores of the NBACE subtests for individuals more than 44 years old can be found elsewhere (Alegret et al., 2013).

Processing speed was measured with the Automatic Inhibition subtest of the *Syndrome Kurtz Test* (SKT; Erzigkeit, 1989), using execution time as the raw score. **Attention and working memory** scores were obtained by means of the digit span forward and backward subtests of the *Wechsler Adult Intelligence Scale–Third Edition* (WAIS–III; Wechsler, 1997a). **Verbal learning and memory** were measured through the word list learning test from the *Wechsler Memory Scale–Third Edition*. Verbal learning trials, long-term retention and cued-recall were used as raw scores; the interference list was not included in the battery (WMS–III; Wechsler, 1997b). Verbal learning was

composed of the sum of raw scores obtained in the 4 trials of the learning phase ($\Sigma 1^{st}+2^{nd}+3^{rd}+4^{th}$); long-term retention was the total amount free recalled words; and cued-recall was the total number of words correctly recognized among the correct items and the same amount of 'interference' items. **Language** was measured with the 15-item version of the *Boston Naming Test* (BNT; Kaplan, Goodglass, & Weintraub, 1983). **Gnosis,** with a single score, was evaluated by means of *the Poppelreuter test* (Della Sala, Laiacona, Trivelli, & Spinnler, 1995). **Visuoconstructive praxis** was evaluated with the abbreviated *block design* subtest of the *Wechsler Adult Intelligence Scale–Third Edition* (WAIS–III; Wechsler, 1997a). **Visuospatial skills** were measured with *Luria's Clock Test* (Golden, 1980), providing a single score. Finally, **executive functioning** was measured through different tests: the Automatic Inhibition of the SKT accuracy score of inhibition ability; phonetic, semantic and verb fluencies, obtaining three scores derived from the number of words recalled; and the abbreviated similarities subtest of the WAIS-III for abstract reasoning.

NPS measures

NPS were evaluated at the baseline clinical assessment using the Neuropsychiatric Inventory-Questionnaire (NPI-Q) (Boada et al., 2002). The NPI-Q is a simplified and widely-used scale that assesses 12 behavioural disturbances including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep and night-time behaviours, and appetite and eating disorders, in the dementia-related population. The NPI-Q was completed through information provided by a patient's reliable informant (family member or caregiver). A change during the previous month in each one of the 12 behavioral domains was recorded as a dichotomized measure (present or absent). For more details on this measure and procedures see (Roberto et al., 2021).

Analytical approach

The present study is based on the results of a previous Latent Class Analysis (LCA) for clustering participants by means of a dichotomized NPI-Q measure

(Roberto et al., 2021). Each participant was assigned to the best fitting cluster with the highest membership probability using baseline NPS. A 4-cluster was considered the optimal solution: Class 1 = *Irritability*; Class 2 = *Apathy*; Class 3 = *Anxiety/Depression*; Class 4 = *Asymptomatic*. Then, linear mixed-effects models (LMMs) were executed to explore cognitive decline for specific domains including NPS clusters and time of assessment (four time points, baseline, 1-year, 2-year and 3-year follow-ups). Individual LMM models were calculated, one for each neuropsychological domain explored. Our independent variable was interaction of NPS cluster by time of assessment, considered the main effect of interest in the model, included as a fix and also as a random effect provided that assessment time points could vary among participants, and they also had different conditional probabilities of cluster belonging (see Roberto et al 2021), i.e., individual differences had to be modelled. Mean differences (SD) accounting for time between baseline and every follow-up (times of assessments) were as it follows: from baseline to the first follow up were 11.26 months (6.22); from baseline to the second follow-up were 22 months (7.48); and from baseline to the third follow-up were 32.21 months (9.01). Both random intercept and slopes were included in the analyses. Asymptomatic class was considered the reference category. Age, MMSE, educational level, sex, conversion to dementia (yes/no), MCI type (amnestic/non-amnestic), and MCI profile (possible/probable) were also included in the models and were considered in the models as fixed factors. Only when a significant interaction (cluster x time) was obtained in a specific cognitive domain, simple effects were calculated contrasting differences among clusters across the time points. Syntax of LMM is provided in **Supplementary Material.**

RESULTS

According to previously published findings from our group (Roberto et al., 2021), the whole sample of 2137 MCI patients was divided into four NPS clusters. Class 1-*Irritability* included 134 patients (6.3%) with high probability of irritability (.93), together with lower probability of anxiety (.64) and apathy (.63). Class 2-*Apathy* comprised 272 patients (12.7%) and it was strongly represented by this symptom (1). Class 3-*Anxiety/Depression* included 1056

patients (49.4%) who showed a high probability of depression (.95), anxiety (.93) and, by far, apathy (.61). Class 4-*Asymptomatic* included 675 patients (31.6%) with low probabilities (<.3) in all NPS.

Demographic and clinical characteristics of the sample stratified by NPS are shown in **Table 1.** There were significant differences in age, gender, educational level, MMSE total score, MCI type, MCI profile, and conversion rates to dementia among the four NPS clusters, thus those were included in the models and were considered as fixed factors. Differences among groups in age distribution showed that *Apathy* patients were the oldest (mean age 76.2). In relation to gender, women were more prevalent in the *Anxiety/Depression* and *Asymptomatic* classes (65.2% and 60.9%, respectively). Educational level attained was higher in patients in the *Apathy* class (8.04 years of education). In relation to MMSE score obtained, the *Anxiety/Depression* class had the highest results (MMSE mean 27.02). Regarding the MCI type (amnestic vs. non-amnestic), our sample was quite balanced in general terms, having percentages in the four classes ranging from approximately 51% to 66%. According to the classification of possible or probable MCI profile, the *Irritability* and *Apathy* classes had a higher percentage of patients with a diagnosis of probable amnestic (47% and 48.2%, respectively). Finally, patients in the *Irritability* and *Apathy* classes showed a higher proportion of conversion to dementia.

Table 1. Demographic characteristics and clinical variables of our final sample (n=2137) stratified by neuropsychiatric symptoms cluster (NPS cluster). Results are shown as mean (SD) for age, education and MMSE; whereas for gender, mild cognitive impairment (MCI) type and MCI profile data are showed as n (%). MMSE= Mini-Mental State Examination. MCI type= amnestic/ non amnestic. MCI profile= probable/possible. Conversion to dementia was reported independently of the etiology. Class is related to neuropsychiatric-cluster belonging (Class 1=Irritability; Class 2= Apathy; Class 3= Anxiety/Depression; 4= Asymptomatic).

	Irritability class	**Apathy class**	**Anxiety/ Depression class**	**Asymptomatic class**	**F/χ^2**	***p***
	n=134	n=272	n=1056	n=675		
Age (yrs)	75.17 (7.99)	76.20 (7.32)	73.82 (8.31)	75.23 (8.15)	8.30	<.001
Gender (% of females)	39 (29.1%)	112 (41.2%)	688 (65.2%)	411 (60.9%)	102.14	<.001
Education (yrs)	7.38 (3.80)	8.04 (4.23)	7.10 (3.79)	7.25 (4.08)	4.14	.006
MMSE (total score)	27.00 (1.72)	26.65 (1.74)	27.02 (1.69)	26.97 (1.76)	3.46	.016
MCI type (% of amnestic)	69 (51.5%)	180 (66.2%)	609 (57.7%)	417 (61.8%)	11.51	.009
MCI profile (% of probable)	64 (47.0%)	131 (48.2%)	292 (27.7%)	266 (39.4%)	59.86	<.001
Conversion to dementia	72 (53.7%)	149 (54.8%)	394 (37.3%)	264 (39.1%)	37.21	<.001

Table 2 shows the LMM results for cognitive domains accounting for cluster, time, and cluster by time interaction. Only the memory domain showed a significant interaction in cluster by time, with verbal learning and cued-recall in particular being the only processes showing significant differences.

Table 2. Linear mixed model results of cluster by time of interaction and main effects in cognitive domains.

	Cluster	Time	Interaction Cluster*Time
Attention			
Digit Span Forward (WAIS III)	1.59 (.191)	12.79 (<.001)	1.33 (.217)
Working Memory			
Digit Span Backwards (WAIS III)	.53 (.662)	14.30 (<.001)	1.27 (.246)
Processing speed			
Execution time in sec (SKT)	6.71 (<.001)	1.87 (.133)	.59 (.803)
Executive			
Phonetic fluency	8.63 (<.001)	5.80 (.001)	1.82 (.060)
Semantic fluency	9.74 (<.001)	55.53 (<.001)	.78 (.636)
Verbal fluency	5.42 (.001)	.69 (.557)	.74 (.669)
Inhibition ability (SKT errors)	3.71 (.011)	3.58 (.013)	1.48 (.149)
Abstract reasoning (WAIS III)	7.68 (<.001)	42.50 (<.001)	1.31 (.227)
Verbal memory			
Verbal learning (WMS III)	5.25 (.001)	45.35 (<.001)	2.92 (.002)
Long-term retention (WMS III)	3.43 (.016)	43.23 (<.001)	2.49 (.008)
Verbal recognition (WMS III)	3.15 (.024)	45.34 (<.001)	2.92 (.002)
Language			
Naming (BNT abbreviated)	.59 (.624)	43.83 (<.001)	1.12 (.349)
Gnosis			
Poppelreuter	1.34 (.259)	20.99 (<.001)	1.13 (.338)
Visuospatial skills			
Luria's Clock	3.14 (.024)	20.32 (<.001)	.82 (.597)
Praxis			
Block-design (WAIS III)	3.20 (.023)	18.34 (<.001)	1.30 (.230)
General Cognition			
Total score (sum)	10.52 (<.001)	141.43 (<.001)	2.63 (.005)

Note: Results are shown as follows: F/(*p*). After Bonferroni correction for multiple testing, an effect is significant when p<.003. Data was adjusted by age, gender, educational level attained, MMSE (Mini-Mental State Examination total score), MCI type (amnestic vs. non-amnestic), MCI profile (probable vs. possible), and conversion to dementia (independently of the etiology). WAIS = Wechsler Adult Intelligence Scale; SKT= Syndrom-Kurztest; WMS = Wechsler Memory Scale; BNT = Boston Naming Test. Cluster is the neuropsychiatric class (Class 1 = Irritability; Class 2 = Apathy; Class 3 = Anxiety/Depression; Class 4 = Asymptomatic). Time refers to the assessment at every follow-up for our study period.

Simple effects for these two cognitive functions comparing baseline with the third follow-up are displayed in **Table 3,** revealing significant results in all four clusters (p<.001). When differences between the final follow-up and the baseline scores were calculated in terms of verbal learning, a faster decline was shown in the *Irritability* class, with double the difference, versus a slower decline in the *Asymptomatic* class, with 3.66 and 1.34, respectively. With regard to effect size, the *Irritability* class had the highest score (0.69), whereas for *Apathy* and *Anxiety/Depression* classes the effect sizes were medium (0.49 and 0.31, respectively). The *Asymptomatic* class showed the smallest effect size (0.22). Similar results were obtained for cued-recall, but this time the *Irritability* and *Apathy* classes had quite similar differences between follow-up measures and the baseline (1.80 and 1.88, respectively), and the *Anxiety/Depression* class had the lowest score difference from the baseline. In terms of effect sizes, the *Irritability* class again showed the largest effect size (0.64), followed by the *Apathy* and *Asymptomatic* classes (0.46 and 0.30, respectively), with the *Anxiety/Depression* class having the smallest effect size (0.21).

Table 3. Simple effects and effect sizes of significant cognitive domains (i.e., verbal learning and recognition) between baseline (X_1) and third follow-up (X_4) measures.

	Cluster	Δ X_1-X_4	Confidence interval for difference (95%)	*p*	Cohen's d difference
Verbal learning	Irritability	3.66	2.48-4.84	<.001	0.69
	Apathy	2.54	1.59-3.48	<.001	0.49
	Anxiety/Depression	1.71	1.24-2.19	<.001	0.31
	Asymptomatic	1.34	0.76-1.92	<.001	0.22
Verbal recognition	Irritability	1.80	1.08-2.53	<.001	0.64
	Apathy	1.88	1.30-2.47	<.001	0.46
	Anxiety/Depression	0.70	0.40-0.99	<.001	0.21
	Asymptomatic	1.05	0.69-1.41	<.001	0.30

Note: Cluster reflects neuropsychiatric symptoms class: Class 1 = Irritability; Class 2 = Apathy; Class 3 = Anxiety/Depression; Class 4 = Asymptomatic. Confidence interval refers to mean differences. Adjusted by age, gender, years of education, MMSE (Mini-Mental State Examination total score), MCI type (amnestic vs. non-amnestic), MCI profile (probable vs. possible), and conversion to dementia. Δ X_1-X_4 = Difference of last follow-up from the baseline.

Cognitive decline for memory domains (learning and cued recall) were calculated for each cluster trajectory (see **Fig. 1** and **Fig. 2**, respectively). Slopes of the trajectories were also presented for each cluster. Fig. 1 and Fig. 2 show speed of decline, with the *Irritability* class being the faster decliner (cognitive slope -0.98) and the *Asymptomatic* class the slower decliner (cognitive slope -0.43) in relation to verbal learning. For cued-recall, the *Irritability* and *Apathy* classes had the same cognitive slope value, and the *Anxiety/Depression* class showed a slower decline in this memory domain.

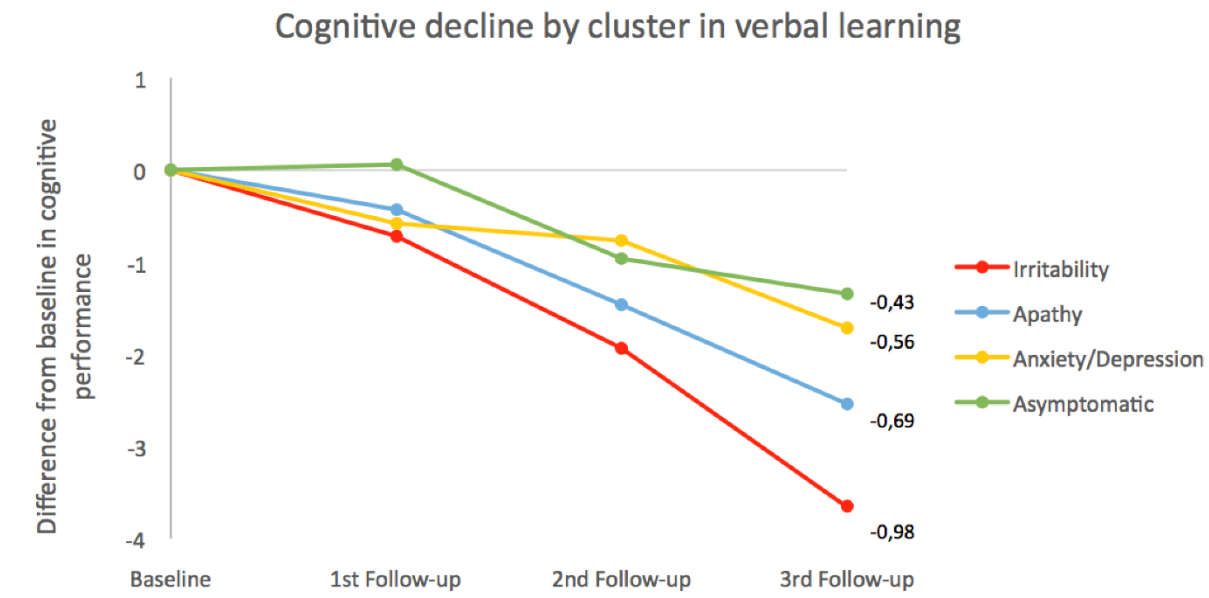

Fig. 1 Cognitive decline across clusters for verbal learning. Measures for each group were obtained using MM means by calculating differences between baseline and follow-ups for each time point. Slopes for each cluster were calculated using the 2-known points approach. Negative values correspond to decrements: the larger the absolute values the steeper the line. Numbers at the ends of the lines indicate the cognitive slopes for each class.

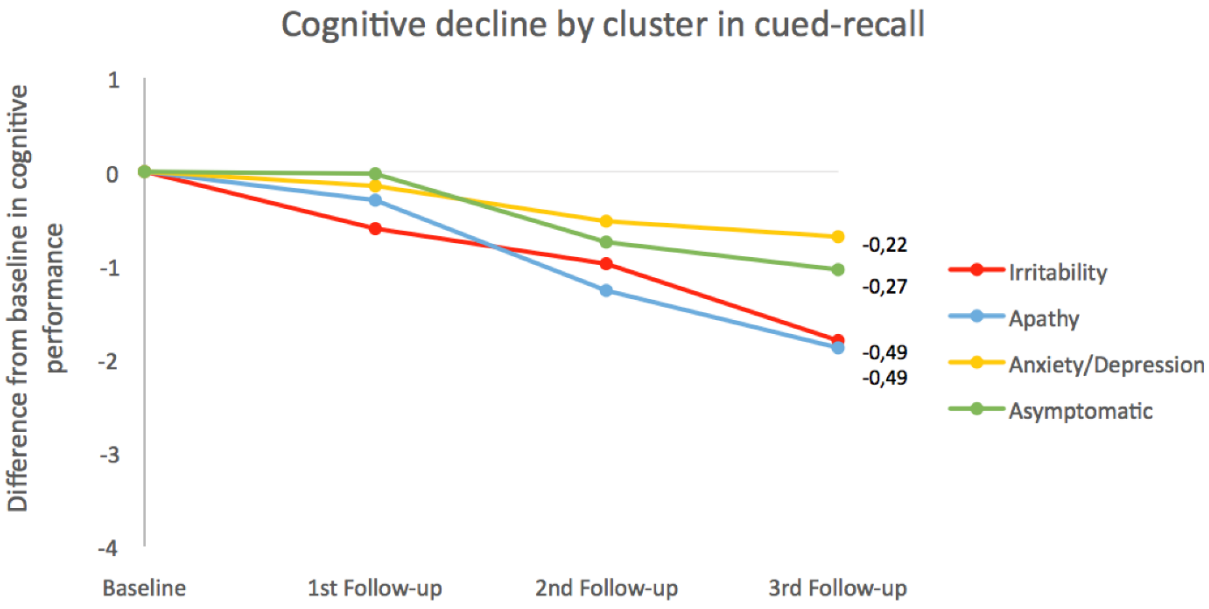

Fig. 2 Cognitive decline across clusters for cued-recall. Measures for each group were obtained using MM means by calculating differences between baseline and follow-ups for each time point. Slopes for each cluster were calculated using the 2-known points approach. Negative values correspond to decrements: the larger the absolute values the steeper the line. Numbers at the ends of the lines indicate the cognitive slopes for each class.

DISCUSSION

The findings in our study revealed different trajectories of cognitive decline in memory domains depending on NPS clusters (*Irritability*, *Apathy*, *Anxiety/Depression*, and *Asymptomatic*) in patients with MCI. In our sample of 2137 MCI patients, the *Irritability* and *Apathy* NPS classes shared a similar pattern of faster cognitive decline in two memory domains (verbal learning and cued-recall), compared to the *Anxiety/Depression* and *Asymptomatic* classes, which showed a slower cognitive worsening over the stipulated follow-up period. Even though *Irritability* was the least prevalent neuropsychiatric condition in this sample, it proved to be the NPS class with the worst and fastest cognitive decline. Therefore, the present findings suggest that although *Irritability* and *Apathy* are less frequent NPS in MCI, these symptoms should be taken into account to improve the quality and usefulness in diagnostic and prognostic evaluation of cognitive worsening in MCI patients, especially those with an amnestic profile.

Although irritability is included among the so-called affective NPS, there is no substantial literature reporting consistent results on how individuals evolve in terms of cognitive decline, neither in healthy controls (Lobo et al., 2008; Leoutsakos et al., 2015), nor in patients with MCI (Forrester et al., 2016), and/or dementia (Moran et al., 2004). Indeed, most of the studies in MCI have focused on other affective NPS such as anxiety, apathy and depression (Penna, 2013). However, some authors have postulated that irritability could be among the affective symptoms that foretell a faster decline in conversion to dementia (Ismail et al., 2017; Jang et al., 2020), but to date none have provided data on that. Therefore, the present results partially support this hypothesis, adding some novelty about which cognitive domains could be more affected, always taking into account that the resulting clusters are mainly constellations of NPS, in which one symptom is the most manifest. For instance, Irritability cluster embraced irritable symptoms (.93), but also anxiety and apathy to a lesser extent (both .63). Therefore, it is possible that the differential cognitive decline observed in individuals belonging to the Irritability cluster may be somehow influenced by anxious and apathic symptoms. In any case, with the present results, this is just speculative, but future

studies should explore the mechanistic process underneath the effect of NPS on cognitive decline. It can be speculated that the presence of irritability may confer extra vulnerability to a faster conversion to dementia. It is worth mentioning that the large sample size of this study allowed the detection of an *Irritability* class, and it is probable that previous studies failed to detect a consistent cluster comprising individuals with irritability due to the lower prevalence compared to other affective NPS.

In contrast, several studies have explored the relationship between apathy and cognitive decline. Some authors indicated an increased risk of progression from MCI to AD when apathy was presented in isolation (Vicini Chilovi et al., 2009; Richard et al., 2012), whereas others postulated the risk was even higher when combined with depressive symptoms (Ruthirakuhan et al., 2019). Strikingly, low isolated depressive symptoms were not associated with cognitive decline (Richard et al., 2012). Conversely, another recent study demonstrated that both apathy and anxiety were associated with cognitive decline when presented comorbidly (Johansson et al., 2020). Our results converged with these findings, as we observed a sharper cognitive decline suffered by patients in the *Apathy* class compared to *Anxiety/Depression*. Given that cognitive decline is one of the factors favoring conversion to dementia and it was adjusted in our analyses, the findings shed light on the NPS profiles that could entail an earlier risk of conversion, and thus act as isolated markers.

With regard to anxiety and depression, both are among the most prevalent affective NPS in MCI patients (Lyketsos et al., 2012), but their influence on cognitive decline is still controversial (Chan et al., 2011). Those symptoms have mostly been considered to be precursors of dementia, whereas only a few studies considered anxiety and depression to be a mere reaction to cognitive losses perceived by the patient (Simard et al., 2009; Di Iulio et al., 2010), which could be a consequence of and not an early marker for conversion to dementia. The present findings provided evidence of no clear association between anxious and depressive symptoms and faster cognitive decline; in contrast to other studies, both symptoms did not yield a worst prognosis in our sample. Note that the cognitive trajectory of the *Anxiety/Depression* class was comparable to the *Asymptomatic* class in

terms of showing no consistent cognitive decline for those two clusters, as reported by other researchers (Ismail et al., 2017; Martin and Velayudhan, 2020). These findings may suggest that although anxiety and depression are the most frequently detected and known affective NPS in patients with cognitive decline, clinicians should bear in mind other affective NPS beyond anxious and depressed manifestations that could be more relevant in the progression to dementia.

The classification of individuals by symptomatic classes rather than isolated symptoms seems to be more useful and informative as it better reflects day-to-day reality in a memory clinic. Among the different studies exploring MCI populations grouped according to comorbid NPS, significant differences exist in obtained cluster solutions, probably due to the methodological approaches used. For instance, some works used a volunteer sample (Leoutsakos et al., 2015; Forrester et al., 2016; Jang et al., 2020), whereas others used clinical samples (David et al., 2016; Siafarikas et al., 2018; Liew, 2019). The statistical approach and designs were also different among studies (i.e. LCA *vs*. factor analysis, techniques that group individuals vs. grouping characteristics respectively; or cross-sectional *vs*. longitudinal), which could have undermined the importance of taking affective NPS into consideration in diagnostic and prognostic evaluations. One of the abovementioned publications assessed cognitive decline across latent classes (David et al., 2016). However, the authors did not include affective NPS *per se*, but rather their severity, and they only evaluated memory and executive function domains, apart from the MMSE, to obtain a global cognitive measure. Therefore, the present study represents a step forward as cognitive decline was explored in assessing different cognitive processes.

A relevant finding of the present study is therefore that not all cognitive domains were affected equally at this early stage, but instead they behaved as isolated processes that showed subtle differences in cognitive decline when NPS classes were taken into account. Likewise, the results also revealed that an accurate assessment of MCI patients, contrary to previous work in already diagnosed dementia patients (Escudero et al., 2019), should cover cognitive performance by domains as well as NPS as these can guide the prognosis of MCI, especially now, when diagnosis can be sought earlier than ever. Interestingly,

different cognitive trajectories were observed according to early NPS instead of neurological symptoms, which could help clinicians be aware of a possible diagnosis of dementia or other neurodegenerative diseases (Geda et al., 2013; Dietlin et al., 2019; Wise et al., 2019), and consider what is necessary to slow down progression of the illness, where possible.

There are also limitations to be considered in the current study. First, there are the baseline differences in demographic characteristics and clinical variables among NPS clusters which could undermine the findings, even though the analyses were adjusted for these variables. Second, it is important to consider including medication records in future studies, as it could affect the evolution of an underlying neuropsychiatric condition. Also, a longer follow-up would be appropriate to determine how NPS and cognitive decline will interact in the long run, as well as to analyse the long-term stability of NPS classes. Also, the presence of early AD-related biomarkers would help achieve a more accurate etiological diagnosis, and to benchmark NPS observations. Finally, the estimated variances of the parameter estimates may have been biased because heteroscedasticity was not taken into account for the repeated measurements of individuals and consequently may have affected the precision of estimating the appropriate model. However, similar studies published so far have failed to account for heteroscedasticity and the findings are consistent.

CONCLUSIONS

The approach of this study explores specific cognitive decline trajectories based on affective NPS clusters in MCI patients from a memory clinic, adding some novelty with respect to previous works. Specifically, and according to our results, *Irritability* and *Apathy* classes share a similar pattern of faster cognitive decline in two memory domains (verbal learning and cued-recall), compared to the *Anxiety/Depression* and *Asymptomatic* classes. The present findings emphasize the relevance of including an assessment of affective NPS when starting a diagnostic process provided that such symptoms – and in particular irritability and apathy – might act as aggravating factors. Our findings appear to open a new avenue to use NPS assessment as a clinical tool of great value when it comes to detecting in advance which patients could suffer from a marked worsening in cognition.

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AUTHOR CONTRIBUTIONS:

NR, MJP, LT, MB and SV conceived the idea, designed the study and wrote the protocol and methodology. MM, MA, IH, AM, MRR, CA, EEA, SG, JPT, LV, AE, GO, APC, AS, AO, IR, SMG and LM acquired all the data, performed technical procedures and managed the data set. NR, MM and AR managed previous literature searches. NR, MJP and SV contributed to the statistical analysis, interpretation of the results and writing of the first draft of the manuscript. EAM helped in the statistical analysis and interpretation of the results. MM, MA, AR, LT, and MB revised the manuscript critically for intellectual content. All authors contributed to the writing of the final version and approved the manuscript.

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COMPETING INTERESTS

All authors have stated that they have no conflicts of interest to report.

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Discussion.

5. Discussion

By analysing the distribution of NPS in a sample of patients with a diagnosis of MCI, this thesis has provided evidence upon the existence of different clusters associated with distinct long-term outcomes. The main finding is that different trajectories of conversion to specific dementia subtypes depend onto NPS-cluster belonging. Moreover, different cognitive trajectories in memory domains are associated to each specific cluster. Therefore, the results of the two studies included in this dissertation determined discrete patterns of disease progression defined by pre-eminence of NPS soon after the diagnose of MCI was established.

Results from **Study 1** showed that the most common symptoms presented by MCI patients were depression, anxiety, apathy, irritability and sleep disturbances (ascending sorted), similarly to the those reported by other studies.[79,80] One of these studies found, however, that aggression instead of anxiety was more frequent in their sample of patients with MCI.[79] Depressive symptoms, by contrast, were invariably more frequently reported in both previous studies. In our sample, prevalence rates were greater in comparison with these two studies. May these differences be explained by the sample type: the current results were based on a clinical sample instead of both previous studies which were population-based. A systematic review already demonstrated that higher prevalence of NPS is to be found in clinical or hospital-based samples, compared to population-based ones.[128] Table 7 shows a summary of prevalence rates comparing the two previous works with Study 1.

	Lyketsos 2002 *(n=320)*	*Peters 2012* *(n=479)*	*Roberto 2020* *(n=2137)*
Anxiety	9.9	5.4	60.2
Apathy	14.7	6.9	46.3
Depression	20.1	16.9	60.7
Irritability	14.7	9.8	38.9
Sleep disturbances	13.8	7.6	8.8

Table 8. Most common NPS in MCI population (results are shown in %) and the prevalence rates as reported in different studies. Roberto 2020 refers to Study 1. Data are shown in percentages upon the whole sample (percentages do not sum up 100%).

Different NPS are often presented simultaneously, but the pre-eminence of a particular one is thought to mark the entire clinical manifestation in every individual. Although, comorbidity mirrors the reality of the daily clinical practice and it has to be taken into account to understand the underlying pathology, only a few studies have started to explore the existence of NPS clusters in MCI population so as to determine subgroups of patients who may progress differentially given their initially neuropsychiatric manifestations.[129–133] In Study 1 we explored clusters of patients with MCI from a Clinic by means of a LCA. We found four classes of patients, in whom several NPS were present, but each class was predominantly defined by one of them -the most prevalent symptom- according to what was expected. In detail, Cluster 1 was predominantly composed by patients with a high conditional probability of suffering irritability, although anxiety and apathy were also present to a lesser extent. Cluster 2 was primarily composed by patients with apathy as the core symptom. Cluster 3 was mainly assembled with patients suffering from anxiety and depression, but secondarily with apathy. Cluster 4 had no prevalent symptoms to highlight.

The number and characteristics of clusters vary among the studies published so far; one study found four groups (irritable, complex, depressed and asymptomatic),[129] while another one with a similar methodological approach found three groups (severe, affective, and asymptomatic).[130] Both studies were using volunteer samples with incident MCI, contrary to the well-established MCI diagnosis of our clinical sample. In this regard, another study found three groups depending on the severity of NPS (stable, worsened and improved).[131] By contrast, a more recent study found three clusters in MCI population (depression, agitation and psychosis),[132] which were replicated in mild-AD patients, indicating that pre-eminence of NPS account for illness progression. Similarly, another recent study with a substantially large sample size found three groups according to prominent symptoms (hyperactivity, affective and psychotic). Affective and psychotic clusters were associated with a higher risk of conversion to dementia, but it is to note that these authors only included psychiatric history, psychiatric drugs and GDS score as adjusting variables. Thus, our findings revealed that a more realistic approach which integrates relevant variables may provide more useful information of rates of conversion.[133] In this regard, the most recent study, found three NPS-clusters in the a

sample of MCI patients (asymptomatic, depressed/irritable and complex), in which symptomatic groups (depressed/irritable and complex) had a significantly increased risk of conversion to dementia in comparison to the asymptomatic cluster. However, our analysis approach was based in an integrated model of comorbid symptoms and other relevant characteristics such as education level, known to be closely related to cognitive attainment along life.[134] In any case, as suggested by previous and also by our studies, there exist different subgroups of MCI patients defined by NPS. Particularly, all studies have in common the presence of a predominantly asymptomatic group and a mainly characterized depressed one.

After our study period, almost half of our sample suffered from a remarkable worsening in their medical condition converting to dementia. Our results are mostly in line with those reporting specific conversion rates to dementia according aetiology.[48] The most frequent subtype of dementia according to our results was AD, followed by VD. The third cause of dementia were FTD and PD, followed closely by DPD. Being the less prevalent causes of dementia DLB and non-degenerative disorders according to our results. In comparison to worldwide prevalence rates, DLB was shown to be more frequent in other samples than in our memory unit.

Besides this, and consistent with our study hypothesis, findings showed that there were different patterns of conversion to dementia based on NPS-cluster belonging. *Irritability* and *Apathy* clusters were the faster converters in comparison to the *Anxiety/Depression* and the *Asymptomatic* clusters. The former ones had similar patterns of conversion, as well as the latter. Conversely to what is found in most studies, depressive symptoms did not predict better conversion to dementia as it has been reported in several studies.[135] Three different models were applied when exploring conversion to dementia with several adjusting variables. *Apathy* cluster emerged as the best predictor of conversion to dementia when cluster-belonging was included as the unique adjusting variable. It supports that apathy is a good prognostic marker of conversion, as already suggested.[76] By contrast, *Irritability* cluster predicted future conversion to dementia when all adjusting variables were included (age, gender, MMSE score, years of education and APOE-ε4). We hypothesized that the *Irritability* cluster emerged thanks to the large sample size, which could not be found in similar studies due to smaller samples. Other studies

exploring the risk of progression are not fully comparable to our results due to dissimilarities in detected clusters. Although there is a tendency towards affirming that the more severe and greater amount of symptoms, the earlier worsening of medical condition arises, there are some NPS that seem to be associated with a worse prognosis *per se*, regardless intensity and frequency.[76] Also, there appears to be an additive effect of NPS on cognitive worsening and speed of decline.[136]

Cognitive decline is the variable per excellence that represents greatest dysfunction in patient's autonomy and worsening in their medical condition. According to **Study 2**, we can affirm that NPS-clusters set the course of cognitive decline in memory domains. Specifically, verbal learning and cued-recall showed significant interaction of cluster and time effects, revealing that memory processes may be more susceptible to the presence of comorbid NPS in patients with MCI. That is, *Irritability* and *Apathy* clusters shared a similar pattern of faster cognitive decline when compared to the *Anxiety/Depression* and *Asymptomatic* clusters along time. Few studies reported irritability as having similar prognostic value as apathy in cognitive worsening of MCI patients.[129,130,137] Even that irritability has been less studied in comparison to anxiety or depression,[138] thanks to our results we can conclude that the former seems to predict a worse trajectory in terms of cognitive decline in some memory domains. It is worth to emphasize that the *Irritability* cluster was composed by a small number of patients, which is difficult to find unless a considerably sample size is available. Conversely, apathy has been widely reported in preclinical stages of dementia, but sometimes is misdiagnosed because it can be confounded with general depressive symptoms. Indeed, several studies link unquestionable symptoms of both, making it difficult to disentangle possible attributions of each symptom to the disease.[139,140] Present results highlight the importance of exploring NPS beyond most commonly reported symptoms (such as depressive and anxious ones), which strikingly provided no evidence on contributing to a faster and greater decline in cognition. Indeed, in the context of a memory clinic we propose that anxious and depressive symptoms could be related to patients' perceived deficits instead of being disease markers for dementia, taking into account that both shared a similar pattern with the *Asymptomatic* cluster.

Thus, NPS could subserve as warning signs for early diagnosis and posterior prognostic markers of the disease. But emphasis has to be placed in all NPS as clusters represent

constellations of such symptoms that need to be explored when there exists a suspicion of dementia.

The present doctoral thesis is not exempt from limitations. *First*, NPS collection was done cross-sectionally. To assess NPS uniquely at a specific point in time leaves us out of the possibility of exploring membership stability. Our study did not account for possible shifts between clusters along time. So it would be of interest for future studies to be able to monitor NPS clusters as MCI progresses. *Second*, individuals with intermittent or pharmacologically treated NPS might not have been identified, so it could be a source of misleading in the basal exploration on NPS. For future studies it is important to include pharmacological records. *Third*, neurobiological mechanisms underlying NPS in early clinical stages are not yet elucidated, so the pathophysiology of those symptoms is poorly understood to date. It would be interesting to explore NPS from an integrated perspective, combining clinical practice with the latest advances in research to answer these questions. *Fourth*, methodological decisions for the present work could have mislead our results, for example, dichotomization of values or inclusion of only more prevalent symptoms may have biased or resulted in loss of information. These decisions were made with the intention of representing our sample more realistically. *Lastly*, there is also a possibility of cohort effects in our sample which include a variety of influences on cognitive functioning. Even though, it mainly has to do with cross-sectional age trends, ergo this could affect NPS but not cognitive results in our case. Thus, more studies along these lines are needed to improve generalization of our results.

5.1. Implications for clinical practice

A better clinical exploration of the individuals in early stages including affective and behavioural exhaustive assessment should allow professionals to establish a more comprehensive therapeutic intervention. Considering the results presented in this thesis, it could be said that there is a need of considering differences according to the most prevalent NPS when presented comorbidly. This could help to understand and predict cognitive trajectories, as well as the possible associated diagnosis of a future dementia. Also, the findings support the idea of NPS evaluation as potential and useful source of information for the clinical management of MCI from the very beginning of complaints, expressed by both, patients and their relatives or close ones.

5.2. Implications for future research

The applicability of the results defended in this thesis is straight forward in terms of continuing this line of research: from now on, we advocate that studies of MCI and conversion to dementia will have to include NPS clusters so as to elucidate the pathophysiological mechanisms involved in this constellation of symptoms; and to discern how they influence in the development of future dementia.

In line with clustering NPS there has been an attempt of re-conceptualizing them in early stages. Recently, a new concept the so-called Mild Behavioural Impairment (MBI) has emerged to capture late-onset NPS. The International Society to Advance Alzheimer's Research and Treatment (ISTAART) has already included NPS in the MBI diagnosis, which cover five domains: decreased motivation, social inappropriateness, impulse control dysfunction, affective disturbances, and abnormal perception and thoughts.[84] This emerging separation of cognition and affection/behaviour diagnosis suggests a possible and practical differentiation for the search of neurobiological mechanisms in early stages.

To date, **Study 1** has already been cited in two works one about apathy and its prognostic use; and the other one focused on different factors surrounding a patient diagnosed with dementia, including NPS and how our *Irritability* and *Apathy* clusters could predict conversion to dementia by adding vulnerability.[141,142] Moreover, another work addressing heterogeneity in AD diagnosis, progression rates and implications for clinical trials has taken into account our results from **Study 2** by placing the focus of attention on NPS.[143]

In summary, the results of the present thesis highlight the need for an early exploration of NPS more systematically beyond cognitive complaints. It would be useful to detect possible NPS and to use them as early markers of dementia subtypes. Also, these symptoms could subserve as prognostic features in predicting future illness trajectories in terms of cognitive decline. MCI is considered an early clinical stage during which there may be an opportunity to preserve function and prevent cognitive impairment, raising the possibility of targeting effective treatments that slow down cognitive decline and diminish psychiatric morbidity.

Conclusions.

6. Conclusions

The overarching aim of this thesis was to advance the current scientific evidence on early markers of a specific dementia diagnosis while identifying prognostic markers based on cognitive trajectories, defined specifically by a decline of memory functions.

Below is a list of conclusions raised from the results:

- Patients with MCI were categorized in four clusters defined by the most pre-eminent NPS: *Irritability*, *Apathy*, *Anxiety/Depression*, and *Asymptomatic* clusters.
- The *Irritability* and the *Apathy* clusters were the best predictors of conversion to dementia, obtaining similar risk rates compared to the *Anxiety/Depression* and the *Asymptomatic* cluster.
- AD, VD and FTD are in ascending order the main causes of dementia according to its aetiology in prevalence rates.
- NPS are associated with a faster cognitive decline and conversion to dementia. Specifically, *Irritability* cluster predominantly tend to convert to non-AD dementia; while *Apathy*, *Anxiety/Depression* and *Asymptomatic* clusters mainly convert to AD, independently of age, gender, education, MMSE, and APOE-ε4.
- The *Irritability* cluster is the best predictor of conversion to dementia after adjusting for NPS-clusters, age, sex, education, MMSE, and APOE-ε4.
- There exist differential trajectories of cognitive worsening in verbal learning and cued-recall based on cluster membership along with time.
- The *Irritability* and *Apathy* clusters share similar patterns of cognitive decline in two memory domains (verbal learning and cued-recall) in comparison with *Anxiety/Depression* and *Asymptomatic* clusters at a 3-years follow up.

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7. Bibliography

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