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Behavioral and Psychological Symptoms in Mild Cognitive Impairment subtypes: BPSD and Neuroimaging Correlation

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1. Introduction

Behavioural and psychological symptoms are common in dementia. These symptoms include depression and anxiety, psychotic symptoms, wandering, agitated behaviour and sleep disorders, and are collectively known as the behavioural and psychological symptoms of dementia (BPSD). These symptoms confer a large proportion of the social burden of dementia [1,2], and are important targets for intervention in dementia patients [3]. Yet these symptoms are not restricted to those with dementia. Many behavioural and psychological problems are also present in a significant proportion of the non-demented older population [4,5]. Behavioural and psychological symptoms have been associated with cognitive impairments not sufficient for a diagnosis of dementia, although their prevalence and relationship to cognitive impairments are not clear. Two recent reviews have highlighted the variation in estimates of the prevalence of behavioural and psychological symptoms in those with mild cognitive impairment (MCI) and suggested that differences in the settings of studies, the characteristics of participant groups, and the definitions of symptoms and of MCI contribute to this variation [6,7]. In this work we use data from the population representative Cognitive Impairment Through Aging Study (CogItA) to explore the relationship between behavioural and psychological symptoms with the different classifications of MCI and in different neuroimaging pattern .

2. Mild cognitive impairment

Improvements in health care over the past 50 years have extended average life expectancy, which has resulted in a substantial increase in the numbers of individuals over 65 years of age.(8) Many elderly people complain of impaired memory (9) and do less well than the young in various cognitive tasks, particularly those that assess memory; (10) these findings suggest that memory impairments are a common consequence of the ageing process.

Careful cross-sectional examination of cognitive function among elderly people, however, reveals a range of cognitive impairment including deficits in various domains in the absence of clinically defined dementia. (11,12)

Gradual decline in cognitive ability is characteristic in longitudinal studies of elderly people. Although this is consistent with the hypothesis that normal ageing is accompanied by mental decline, differences between individual trajectories of change suggest that much of the age-related cognitive decline reflects the inclusion of individuals with incipient dementia.(13)

The notion that incipient dementia is common among elderly individuals is further supported by neuropathological studies that reveal evidence of Alzheimer's disease (AD) years before clinical symptoms present.(14,15) Extensive AD pathology can rarely be found in individuals with no detectable symptoms.(14,16) AD pathology is, however, more likely to occur in patients that show memory impairment, even if they're not demented yet.(15)

Clinical studies of elderly individuals with memory impairment also reveal a rapid rate of conversion to AD, reaching as high as 15% per year. This evidence suggests that significant memory impairment, short of dementia and often denoted as mild cognitive impairment (MCI), in elderly people may be a transition phase between the normal ageing process and AD.(17,18)

Although many individuals with MCI complain of memory loss, impairments in other cognitive domains also occur,(19) and not all MCI patients go on to develop AD,(10) particularly when MCI is studied in the general population.(20)

The assumption that MCI may represent a transition state between normal cognitive decline due to ageing and dementia offers possibilities for early diagnosis and potential treatment with the aim of delaying the onset or preventing dementia.(14)

2.1 Background and conceptual development

Many attempts have been made to define the clinical entity of declined cognitive abilities associated with ageing. In the early part of the 19th century, Prichard (22) identified the earliest stage of dementia as impairment of recent memory with intact remote memory.

More than a century later, Kral (23) espoused a contrasting point of view, with his description of benign senescent forgetfulness, in which fairly unimportant data and parts of an experience are not recalled and in which the forgotten data seem to belong to the remote past rather than the recent past. Recognition that dementia can have a long prodromal phase has led to active investigation of individuals with cognitive impairment without dementia. Work in this area has created many definitions (table 1).(26,31, 39. 44)

Clinical definitions of cognitive-impairment syndromes

Term	Initial description	Diagnostic criteria
Benign senescent forgetfulness	Kral[18]	Memory complaints
Age-associated memory impairment	Crook and co-workers[19]	Subjective memory impairment with objective memory impairment compared with that of a young adult
Late-life forgetfulness	Blackford, LaRue[20]	Age-associated memory impairment plus age-adjusted deficits in four or more specific cognitive tests
Aging-associated cognitive decline	Levy[21]	Age-adjusted impairment on any cognitive task
Age-related cognitive decline	DSM IV[22]	Objective decline in cognitive function not otherwise specified
Mild cognitive decline	ICD-10[23]	Impairments in cognitive tests of learning, memory, or concentration secondary to defined illness
Mild neurocognitive decline	DSM IV[22]	Impairments in memory, learning, perceptual-motor, linguistic, or executive functioning
Cognitive impairment–no dementia	Graham and co-workers[5]	Impairments in memory, learning, perceptual-motor, linguistic or executive functioning in the absence of clinically defined dementia
MCI	Petersen and co-workers[10]	Subjective complaint of memory impairment with objective memory impairment adjusted for age and education in the absence of dementia

Tab.1 Definition of MCI

In 1982, two clinical staging systems were published, which continue to be used today by clinicians to assess the boundaries of ageing and dementia. These are the clinical dementia rating (CDR) (24) and the global deterioration scale for ageing and dementia (GDS). (25) The CDR distinguishes a stage of questionable dementia (CDR 0·5) from people defined healthy (CDR 0) and those with mild dementia (CDR 1). Individuals at CDR 0,5 have mild consistent forgetfulness and doubtful or mild impairment in independent function at the usual level in job, shopping, business and financial affairs, and volunteer and social groups.

Definitions of dementia were published in 1980 by the American Psychiatric Association (26) and in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA), (27) which remain today as benchmarks for clinicians.

The American Psychiatric Association's primary degenerative dementia definition notes that the diagnosis should be restricted "to cases in which there is clear evidence of progressive and significant deterioration of intellectual and social or occupational functioning". (26)

The definition by McKhann and colleagues (27) also notes that a diagnosis of probable Alzheimer's disease should include deficits in two or more areas of cognition, with progressive worsening of memory and other cognitive functions.

Diagnosis is lent support by impaired activities of daily life. Hence, from these definitions, the CDR 0·5 stage of questionable dementia includes mild dementia and mild cognitive impairment, but allows for such affected individuals to have measurable deficits in several areas of cognition without meeting criteria for dementia.

The term mild cognitive impairment was first used in association with stage 3 of the GDS. (25, 28) This scale identifies seven clinical stages, of which four range from normality to mild dementia. Stage 1 individuals are free of both subjective and objective clinical deficits. Those at stage 2 have subjective deficits only, such as self-perceived difficulties remembering names. Perhaps the best current terminology for this disorder is subjective cognitive impairment.

People at GDS stage 3 have subtle deficits in cognition and may have some impairment in executive functioning that affects complex occupational and social activities. GDS stage 4 individuals have clear deficits in cognition and functioning with reduced performance in instrumental activities of daily life, such as preparing meals and managing personal financial affairs. People at GDS stage 4 fulfil criteria for mild dementia.

According to Reisberg, (25) the GDS 3 description of mild cognitive impairment accords with that subsequently formulated by an international working group (29) and describes a severity range of cognitive and functional impairment largely in keeping with other subsequent definitions described below.

Petersen (30) says it is important to note that the GDS and the CDR are severity rating scales and not diagnostic instruments. Some investigators have equated GDS 3 or CDR 0,5 to mild cognitive impairment, but Petersen believes that this practice might not always be correct, stating that: "as severity scales, these stages may correspond to mild cognitive impairment or may describe individuals with very mild dementia." As such, Petersen believes that the rating scales are not synonymous with the syndrome of mild cognitive impairment.

Reisberg and associates disagree with respect to the GDS 3 stage, which they believe to be fully consistent with, for example, the definition of mild cognitive impairment posed in the opening statement of this report.

As noted above, the CDR 0,5 stage of questionable dementia is a broad category that encompasses mild dementia and mild cognitive impairment. Reisberg points out that the global staging definition of mild cognitive impairment has advantages of inclusivity, whereas other definitions of the disorder are frequently more restrictive—eg, from an epidemiological standpoint.

For example, the amnestic subtype of mild cognitive impairment described below and in the panel requires memory complaints. (30) Many individuals with mild cognitive impairment deny they have the disorder and do not report symptoms, although they nevertheless show signs of cognitive impairment consistent with the disorder that are evident to clinicians or informants.

The GDS 3 definition of mild cognitive impairment—unlike the preceding GDS 2 stage of subjective cognitive impairment and the amnestic subtype of mild cognitive impairment—does not require memory complaints; only signs of the disorder are required for GDS stage 3 assignment. Hence the GDS stage 3 definition of mild cognitive impairment is more encompassing of individuals with these clinical signs than, for example, the amnestic category.

The model of cognitive impairment no dementia (CIND) includes all individuals falling in between healthy and demented states, and has been used in population-based epidemiological studies such as the Canadian Study of Health and Aging(31) and the Indianapolis Study of Health and Aging.(32) As originally derived by the investigators of the Canadian study, this model encompasses many disorders, from circumscribed memory impairment to chronic alcohol and drug use, psychiatric illness, mental retardation, and vascular pathologies.

CIND represents cognitive impairment that may or may not progress to dementia. Another perspective on this model, described by Petersen (33) and Winblad and colleagues, (29) is that although previous criteria for mild cognitive impairment were specific to isolated deficits in memory, developments have extended them so that the definition of mild cognitive impairment now includes a broad range of cognitive deficits and clinical subtypes with many potential causes.

In other words, mild cognitive impairment and CIND could previously be distinguished by the fact that mild cognitive impairment referred to isolated memory deficits—now called amnestic mild cognitive impairment—whereas CIND included global cognitive impairment and deficits in several cognitive domains.

Currently, attempts are being made (33) to broaden the definition of mild cognitive impairment to include non-memory deficits and impairment in several cognitive domains, with causal mechanisms including degenerative, vascular, and psychiatric factors.

Findings of longitudinal population studies, which have been undertaken using various definitions of mild cognitive impairment adapted to epidemiological research, have shown a prevalence in the general elderly population between 3% and 19%, with an incidence of 8–58 per 1000 per year, and a risk of developing dementia of 11–33% over 2 years.(34)

Conversely, findings of population-based studies have shown that up to 44% of patients with mild cognitive impairment at their first visit were estimated to return to normal a year later.(34, 35)

These epidemiological studies underline the fact that there are many factors affecting cognition performance in elderly populations apart from neurodegenerative disorders, including education, vascular risk factors, psychiatric status, genetic background, hormonal changes, and use of anticholinergic drugs, and that these factors can account for why many cases of mild cognitive impairment are reversible.

Patients referred to memory clinics and other specialised centres are unlike the general population in that they are seeking services for a perceived memory disorder. At these centres, they are diagnosed after detailed, systematic, clinical and neuropsychological assessments. In these clinical research settings, individuals with mild cognitive impairment have been shown to progress to dementia (generally Alzheimer's disease) at a rate of 18% per year. (36)

Similarly, those diagnosed with amnestic mild cognitive impairment with the research criteria defined by Petersen and colleagues (tab.2), (30) who also fulfil exclusion criteria for various medical, psychiatric, and neurological disorders, have a high rate of progression to dementia, particularly Alzheimer's disease.

In a 3-year multicentre randomised clinical trial, a 16% per year rate of progression to Alzheimer's disease was noted with the definition of amnestic mild cognitive impairment. (37)

Amnestic subtype of mild cognitive impairment
Memory complaint, preferably corroborated by an informant
Memory impairment relative to age-matched and education-matched healthy people
Typical general cognitive function
Largely intact activities of daily living
Not clinically demented

Tab.2 Peterson's MCI Criteria

This rate accords with findings of previous studies in which similar inclusion and exclusion criteria were used.(38) Findings of another study, in which the same definition of amnestic mild cognitive impairment was used for patients referred on the basis of history of progressive memory changes, showed a progression rate to Alzheimer's disease of 41% after 1 year and 64% after 2 years.(39) Thus, application of the same amnestic criteria can lead to different progression rates despite baseline similarity in cognitive performance.

This finding suggests a need to broaden clinical criteria for amnestic mild cognitive impairment (and probably mild cognitive impairment at large) to include history and duration of symptom progression and more explicit acknowledgment of the exclusion criteria applied in various studies.

The category of mild neurocognitive disorder in the diagnostic and statistical manual, 4th edition, is similar, but not identical, to the syndrome of mild cognitive impairment. Research criteria for mild neurocognitive disorder include the presence of two or more disturbances, including impairment in memory, executive function, attention or speed of processing, perceptual-motor abilities, and language.

Two cognitive domains must show decline and cause impairment in social, occupational, or another area of function. Objective evidence has to be present of a neurological or general medical disorder that is judged to be caused by the cognitive disturbance.

In summary, patients defined by the terms CDR 0,5, GDS stage 3, CIND, and mild cognitive impairment represent a large segment of the population older than age 65 years. The prognosis in terms of progression to dementia is more heterogeneous in population studies than in the setting of specialised clinics and is driven by the nosological and exclusionary criteria being used in either setting.

2.2 Pathophysiology

Much clinical evidence exists for the detrimental effects of anticholinergic drugs on cognition.(40) A central cholinergic deficit is thought to be present in amnestic mild cognitive impairment, related to loss of neurons in the nucleus basalis of Meynert, (41) although findings of a post-mortem study showed upregulation of choline acetyl transferase activity in the frontal cortex and hippocampus.(42)

This upregulation could be a compensatory mechanism, which is suggested by recruitment of memory and attentional networks, shown by functional magnetic resonance imaging.(43) The role of cerebrovascular disease in mild cognitive impairment is probably under-represented, particularly in population studies in which brain imaging has not been undertaken.(44)

Findings of the Religious Order Study (45) indicated that cerebrovascular involvement in mild cognitive impairment is intermediate between that seen in ageing and early Alzheimer's disease. Both cerebrovascular disease and neurodegenerative features were shown to contribute to mild cognitive impairment.

The importance of white-matter lesions and small lacunar infarcts is becoming increasingly apparent in vascular cognitive impairment.(46) In view of the fact that cerebrovascular disease is frequent in elderly individuals, and that treatment of cerebrovascular risk factors constitutes one of the most important prevention strategies for Alzheimer's disease and vascular dementia, more research is needed on vascular mild cognitive impairment or vascular CIND.

These disorders need to be defined operationally, as was done for mild cognitive impairment associated with subcortical cerebrovascular disease.(47) The role of amyloid deposition and neurofibrillary tangle formation in mild cognitive impairment has not been studied extensively yet.

Pathological findings of neurofibrillary tangles in the mesial temporal structures do correlate with mild cognitive impairment. (48, 49) Compared with people with dementia and those without cognitive impairment, individuals with mild cognitive impairment have intermediate amounts of Alzheimer's disease pathological findings identified by silver stain, (48) with amyloid deposition and tau-positive tangles (50) in the mesial temporal lobes.

Mutations in apolipoprotein E alleles clearly raise the risk of progression from amnestic mild cognitive impairment to Alzheimer's disease. (37, 51, 52) This mutation alters cholesterol transport and synaptic plasticity.(53)

Other gene mutations are likely to be identified, which will be of relevance to the progression of mild cognitive impairment towards dementia.

In summary, a combination of causal factors are interacting in patients with mild cognitive impairment, including cholinergic dysfunction, white-matter lesions and cerebral infarctions, extracellular amyloid deposition, and intracellular neurofibrillary tangle formation. Apolipoprotein E4 allele status can increase the risk of progression from mild cognitive impairment to Alzheimer's disease.

2.3 Diagnosis

In terms of research diagnostic criteria, there is uncertainty about whether a lumping-together approach to mild cognitive impairment (54) is preferable to a splitting approach, with various categories of the disorder. (55)

Prospective cohort studies are underway to establish whether amnestic and non-amnestic subtypes of mild cognitive impairment (figure) (56) have different prognoses for progression to dementia and which type of dementia they predict (56) and their effect on survival times. (57)

It is possible that all progressive dementias have their own predementia states.(58) The operational definition of amnestic mild cognitive impairment proposed by Petersen (tab. 2)(9) has been used repeatedly in randomised controlled trials, with some variations on the test for delayed recall and cut-off scores to distinguish people with mild cognitive impairment from healthy individuals. (37, 38,59, 60)

These apparently minor differences in entry criteria for the level of memory impairment are associated with different rates of progression to Alzheimer's disease, ranging from 5% to 16% per year. Other factors affect the rate of progression, such as the number of people carrying the apolipoprotein E4 allele.

It should be noted that these trials applied inclusion and exclusion criteria similar to those proposed by McKhann and colleagues (27) for Alzheimer's disease, with the important exception of the presence of dementia and the size of the cognitive and functional decline.

An international working group on mild cognitive impairment formulated specific recommendations for criteria, including: (22) the individual is neither normal nor demented; (23) there is evidence of cognitive deterioration, shown by either objectively measured decline over time or subjective report of decline by self or informant in conjunction with objective cognitive deficits; and (24) activities of daily life are preserved and complex instrumental functions are either intact or minimally impaired. (9)

These criteria serve to expand the construct of mild cognitive impairment to involve cognitive domains other than memory and make it a prodrome to multiple types of dementia.

Standard neuropsychological tests have established that poor performance on delayed recall and executive function tests indicate a high risk of progression to dementia,(28, 61, 62) particularly delayed recall, since this measure was a highly accurate predictor of progression to Alzheimer's disease in longitudinal studies of 2–10 years' duration in clinical samples (63, 64) and large epidemiological samples.(65)

There is a need for sensitive but user-friendly cognitive tests for clinicians, such as the Montreal cognitive assessment. (66) This test is a useful complement to the mini-mental state examination,(67) which is within the normal range in most patients with mild cognitive impairment.

Informant rating scales significantly improve the accuracy of the mini-mental state examination in predicting progression to Alzheimer's disease.(68)

Although cognitive symptoms and tests have been the core features of mild cognitive impairment up to now, there is increasing awareness of a behavioural component, which includes anxiety, depression, irritability, and apathy. (69, 70)

The presence of behavioural and psychological signs, including depression, predicts a high likelihood of progression to dementia. (71) A semi-structured interview to psychiatric symptoms and use of standardised scales such as the neuropsychiatric inventory (72) have shown an important contribution of behavioural changes to mild cognitive impairment in a clinical trial setting.(60)

Depressive symptoms can contribute to mild cognitive impairment and have been shown to modify positive predictive value, specificity, and sensitivity in randomised controlled trials.(73) It is likely that future formulations of the broader definition of mild cognitive impairment will include non-cognitive symptoms that might be important in the prodrome of disorders such as frontotemporal dementia and Lewy body dementia.

Difficulties remain in defining the boundaries between normal ageing and mild cognitive impairment, and between mild cognitive impairment and mild dementia.(74) Many of these distinctions depend on the degree of functional impairment.

Findings of epidemiological studies have shown that subtle difficulties in the performance of everyday activities (eg, complex hobbies, finance handling) are common in individuals with mild cognitive impairment 2 years before a diagnosis of dementia, (63) whereas overt difficulties in certain abilities (use of the telephone, finances, transportation, drugs) signal the onset of dementia. (75)

The lack of awareness of such impairments in people with mild cognitive impairment has been postulated to be predictive of progression to dementia. (76)

Individuals with memory complaints and informants should be asked about performance on hobbies, executive level tasks, and instrumental activities of daily life. (77, 78)

Mild cognitive impairment is also accompanied by other changes, such as balance and coordination. (79) A structured assessment of functional capacities will become increasingly important in determining the point at which people with mild cognitive impairment progress to dementia. Analysis of data from randomised controlled trials such as the Memory Impairment Study (80) could help in this respect.

Neuroimaging and electrophysiological tests for the workup of mild cognitive impairment could be the same as those used in early dementia. Several methods are sensitive for mild cognitive impairment, including brain imaging with MRI, (81, 82) positron emission tomography, (83, 84) and quantitative electroen cephalography. (85, 86)

Medial temporal lobe atrophy on magnetic resonance imaging and hypometabolism on fluorodeoxyglucose-positron emission tomography have been recorded in people with mild cognitive impairment compared with cognitively normal individuals, (82, 88) and presence of these signs has a high predictive value for progression to dementia. (89, 90)

Biomarkers in cerebrospinal fluid under study include total tau, phosphotau epitopes, and the 42 aminoacid form of β amyloid. (91, 92) Specific phosphotau epitopes have met criteria for an ideal biological marker candidate, with properties for both classification and early diagnosis.(82, 93)

Evidence suggests that phosphotau 231 and isoprostane can increase the diagnostic accuracy of conventional cognitive and magnetic resonance assessments in people with mild cognitive impairment.(92)

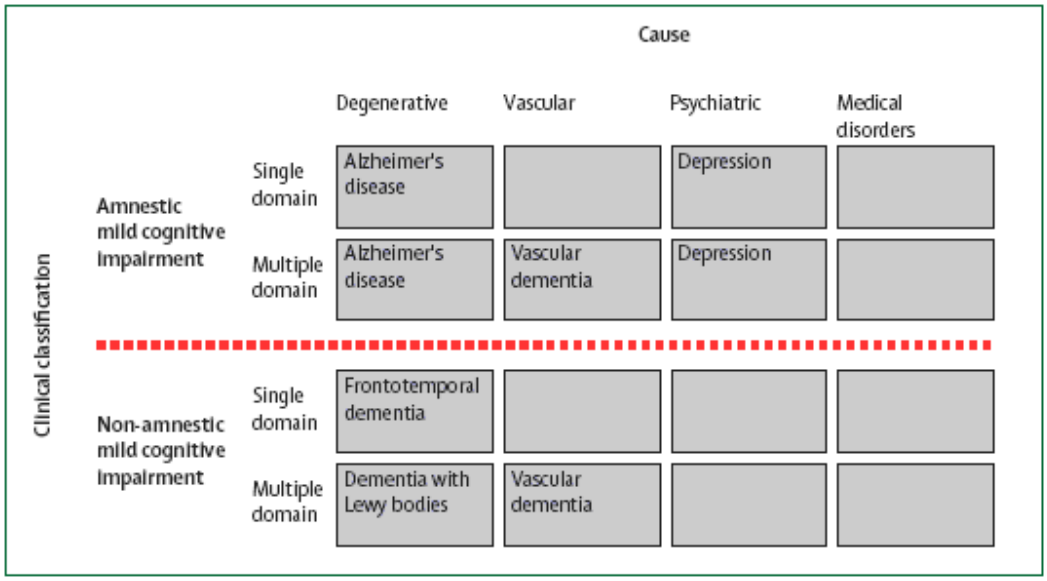
Many of these biomarkers have been selected by the National Institute on Aging biological markers working group (95) as feasible core biomarkers suitable for multicentre longitudinal studies of Alzheimer's disease with special consideration given to mild cognitive impairment.

A large study from the Alzheimer's Disease Neuroimaging Initiative has just begun investigating the role of imaging measures and biomarkers in predicting progression to dementia in individuals with mild cognitive impairment.

In summary, research diagnostic criteria are being validated for the different subtypes of mild cognitive impairment, with emphasis on amnestic mild cognitive impairment. Until such validation is available from prospective cohort studies, a pragmatic approach to mild cognitive impairment has been proposed by Gauthier and Touchon (96) to distinguish subtypes in clinical practice, based on the most prominent feature at a given time, from amnestic to dysphoric, vascular, or associated with other medical disorders.

It might be time to consider revisions of the international classification of mental and behavioural disorders and of the diagnostic and statistical manual of mental disorders, to include specific diagnostic criteria for mild cognitive impairment or its different subtypes.

Furthermore, an update to the NINCDS/ ADRDA criteria for Alzheimer's disease (27) should be considered, to include a prodromal or very early stage of Alzheimer's disease that would correspond to amnestic mild cognitive impairment, as defined in the clinical trials described in the next section.



Tab.3 Outline the syndrome of mild cognitive impairment.

Figure swos MCI with predominant amnestic versus non-amnestic neuropsychological feautures, potential prodrome to neurodegenerative disorder such as Alzheimer's desease, frontotemporal dementia, Lewy Body disease, or caused by vascular cognitive impairment, psychiatric disordersuch as depression or as a prodrome to other medical disorder, including metabolic and nutritional deficiencies, upper airway obstruction, andhead trauma.(56)

2.4 Management

The first wave of clinical trials aimed at symptomatic drug treatment for amnestic mild cognitive impairment over 6 months to 3 years have been largely unsuccessful.(97) Results from the Memory Impairment Study (37) showed no significant differences in the probability of progression from amnestic mild cognitive impairment to Alzheimer's disease in patients allocated vitamin E or donepezil, compared with placebo, during the 3 years of treatment, although significant differences were recorded favouring the donepezil group on various measures during the first 12 months of the study including delay of diagnosis of Alzheimer's disease.(37)

Furthermore, there was a prolonged response to donepezil over 24 months in the apolipoprotein E4 carrier subgroup. Potential reasons for the apparent lack of sustained benefit of the cholinesterase inhibitors might be the compensatory upregulation of central cholinergic

activity, lack o sensitivity of the cognitive outcomes (ceiling effects), and heterogeneity of patients. If there is benefit from these inhibitors, it seems to be limited and transient. (98)

Conversely, randomised controlled trials of cholinesterase inhibitors and other pharmacological drugs are worth pursuing in mild cognitive impairment, possibly targeting populations at high risk of progression to dementia, since there are indications that postponement between mild cognitive impairment and manifest dementia could result in short-term economic benefis of US$5300 per patient per year (99) and advantages for individuals with mild cognitive impairment and their families.

It should be noted that resource use and costs attributable to the disorder during the mild cognitive impairment phase are low, and possibilities to detect intervention effects on direct costs are also low during this phase.

However, many people with mild cognitive impairment retire from their occupations and other productive activities as the disorder progresses, and economic models should take into consideration productivity losses.

Additionally, from clinical experience, it is known that depressive symptoms are common in people with mild cognitive impairment.

However, the extent to which these symptoms cause resource use in terms of informal care is not known. Encouraging results have been reported from uncontrolled studies using cognitive training.(100, 101)

Large effect sizes have been noted within the range for healthy elderly people (102) and better than that for patients with Alzheimer’s disease.(103)

The success of cognitive training seems to be dependent on the level of severity across the range of normal ageing to dementia.

These findings in individuals with mild cognitive impairment need to be confirmed in randomised controlled trials.

The management of patients with mild cognitive impairment is currently non-specific: control of vascular risk factors; treatment of concomitant disorders such as depression and hypothyroidism; and phasing out anticholinergic drugs.

Many people with mild cognitive impairment are very aware of their difficulties and seek information about the nature of their disorder and their outlook. They are also interested in coping strategies, particularly if they are in demanding occupational settings.

Since these patients are at higher risk of dementia and death than usual, they need sensitive counselling about such risks and the current lack of certainty in predicting prognosis.

It would not be appropriate to falsely reassure them that they are healthy, since they should have the opportunity to make future plans while fully competent to do so, including advance directives for power of attorney in case of incapacity.

A caregiver burden has already been identified for spouses of people with mild cognitive impairment, for which selective preventive interventions to keep psychological wellbeing to a maximum should be considered.(104)

Currently, there is debate about whether the term mild cognitive impairment should be used at all in clinical practice, in view of the heterogeneity of progression to dementia and the possibility of reverting back to normal.

Caution should thus be exercised in using this term. Some researchers are attempting to broaden the discussion about mild cognitive impairment to the political, philosophical, and economic implications of anti-ageing drugs.(105)

Systematic screening for mild cognitive impairment in asymptomatic elderly people is not recommended because of insufficient data about its usefulness. On the other hand, spontaneous memory complaints from people older than 50 years, particularly if corroborated by an informant, should lead to a medical assessment as per standard clinical practice for individuals suspected of early dementia.

Mild cognitive impairment is regarded as a medical diagnosis by some clinicians, as suggested in the American Academy of Neurology practice parameter statement that “patients with a mild cognitive impairment should be recognized and monitored for a cognitive and functional decline due to their increased risk for subsequent dementia”, (106) a state of risk considered by other authors, possibly amenable to prevention.

However, in view of the variation in specificity with respect to the outcome of amnestic mild cognitive impairment, one must be cautious in presenting a diagnosis such as incipient Alzheimer’s disease prematurely.

2.5 Prevention

Although no specific disease-modifying treatment has yet been shown to be effective for any of the degenerative dementias, control of risk factors might prove useful. The best evidence available so far is in the control of isolated systolic hypertension. (44)

The idea of interventional epidemiology proposed by Ritchie (34) for mild cognitive impairment will probably lead to international randomised controlled trials linking the consortia of investigators interested in the causes and treatment of mild cognitive impairment and dementia (European Alzheimer's disease consortium, Alzheimer's disease cooperative study in the USA, and consortium of Canadian centres for clinical cognitive research).

2.6 Clinical continuum of cognitive decline

The advent of current understanding of mild cognitive impairment and the clear findings that the disorder is a frequent precursor of overt dementia raises the question of the antecedents of mild cognitive impairment.

Is mild cognitive impairment in general, and the impairment that precedes Alzheimer's disease in particular, one step in a process that has additional clinical antecedents?

Support for this view can be extrapolated from findings of neuropathological studies, which show that Alzheimer's disease-related neuropathological findings, including neurofibrillary changes, seem to occur decades before the overt appearance of dementia. (107)

It has been recognised for many years that many healthy older people have subjective complaints of cognitive decline. As noted earlier in this Seminar, the GDS staging procedure differentiates individuals with such symptoms, but who are otherwise free of clinical signs from healthy older people who are free of complaints of impairment.

In 1986, a US National Institute of Mental Health workgroup proposed an entity—age-associated memory impairment— to characterise healthy individuals at least 50 years of age with subjective complaints of memory loss and performance on a recent memory test at least 1 SD below the mean established for young adults. (108)

A similar entity with somewhat modified specific psychometric and other criteria has been proposed by Levy.(109) The prognostic relevance of subjective cognitive complaints in older people, without reference to psychometric test data, has been investigated in several studies, most of which have noted relations between subjective complaints and future cognitive decline.(110, 113)

For example, Reisberg and associates (114) are finding a fivefold greater likelihood of decline to mild cognitive impairment or dementia, over a 7-year mean follow-up interval, in people with subjective complaints compared with similarly aged individuals who are free of subjective complaints of impairment.

Wolf and co-workers (115) reported a significant difference in urinary cortisol concentrations between older individuals with and without subjective complaints, perhaps, in part, a marker of concerns of older people about these self-perceived deficits, since cortisol concentrations are a well-known marker of stress.

As an entity that precedes mild cognitive impairment, studies are presently noting that about 7–8% of otherwise healthy older people with subjective cognitive impairment progress to mild cognitive impairment or overt dementia every year. (114, 116)

Hence, findings of several longitudinal studies lend support to the belief that mild cognitive impairment, with subtle but manifest clinical signs, is a stage in a clinical process that might be subjectively evident many years earlier.

Although, current estimates need to be examined in much greater detail in future studies, it has been suggested that the subjective cognitive impairment stage before mild cognitive impairment could last for about 15 years.(117)

Hence, the appearance of mild cognitive impairment seems to be on a clinical continuum that is preceded by subjective cognitive impairment.

3. AIMS

Although MCI encompasses a broad variety of subjects at elevated risk for subsequent progression to dementia, this population remains relatively heterogeneous and includes many subjects whose cognitive and functional abilities may remain stable or even improve. Therefore, the main purpose of neurologist, psychiatrist and genecitist is to identify as soon as possible which are the variables linked to a high risk of developing dementia as well as to start treatments of delaying dementia.
Among the various proposed tools for identifying the MCI individuals with high-risk to develop dementia, such as neuroimaging, CSF biomarkers, the role of neuropsychological assessment and behavioural evaluation have been suggested.

Accordingly the general aims of this study were:

1. **First** (main aim). To evaluate the frequency and the relationship between behavioral and psychological symptoms in different MCI subtypes after stratification for age, education and sex

Particularly specific aims of this research are:

- **Second.** To evaluate if the severity of BPSD correlates with the degree of cognitive deficts in different tasks of cognition

- **Third** To evaluate the association between behavioral and psychological symptoms in different neuroimaing pattern.

4. MATERIALS AND METHOD

4.1 THE COGNITIVE IMPAIRMENT THROUGH AGEING (CogItA) STUDY

The study sample included subjects will be selected from the *Cognitive Impairment Through Aging S*tudy *(CogItA)* a longitudinal, memory clinic study regarding aging, cognitive impairment and dementia carried out in subjects aged 50 or over who were recruited over a 10-year period at the Memory Clinic, Dept. of Neurology and Rehabilitation, AOUP. "P. Giaccone", University of Palermo (Chief: Prof. Rosolino Camarda) from 2000 to 2011.

All included subjects have been evaluated with a multidimensional protocol including demographic characteristics, medical history, pharmacological treatments, clinical, neuropsychological and neurological examination, standard laboratory blood tests and neuroimaging study. When available, subjects were evaluated annually. The study at baseline comprised over 3548 subjects; approximately for one-third of these 3-year follow-up data are available. Written informed consent has be obtained from healthy subjects enrolled in the study as well as from caregivers of subjects with MCI at study enrolment.

For this research we recruited only the healthy patients and patents with a clinical diagnosis of MCI according to the common criteria established by Winblad et. al. (2004) in the first K Symposium about mild cognitive impairment and the controls. (118)

4.2 **MULTIDIMENSIONAL PROTOCOL FOR MCI**

Neuropsychological tests were administered in an approximately one hour and half session. Cognitive and functional test scores are recorded in the database for each participant at baseline and annually. This protocol was administered by trained physicians and neuropsychologists in a quite environment.

Specifically the multidimensional protocol includes the following:

a. The **Global Cognitive Assessment** was composed by the Mini Mental State Examination (119) and the Montreal Cognitive Assessment (120).
b. **Functional Scales** included the Activity of Daily Living and the Instrumental Activity of Daily Living.
c. **Behavioural Scales** included: the Neuropsychiatric Inventory (121)**.**

d. Finally **Neuropsychological Testing** includes tests evaluating memory, attention and concentration, visuo-spatial ability, language, praxic and executive functioning.

a. Global Cognitive Assessment

Mini Mental State Examination

The MMSE is a widely clinical instrument used for the preliminary screening of cognitive status in adults. The MMSE has demonstrated validity and reliability in psychiatric, neurologic, geriatric, and other medical populations. It is a brief test (takes only 5-10 minutes) composed by 11-question that tests five areas of cognitive function: orientation in time, orientation in place, registration, attention and calculation, recall, and language.

The maximum score on the Mini Mental State Exam is 30. The normal value is also corrected for degree of schooling and age.

In general, scores fall into four categories:

24-30: normal range

20-23: mild cognitive impairment or possible early stage/mild disease

10-19: middle stage/moderate dementia

0-9: late stage/severe dementia

The MMSE has lacked sensitivity to mild degrees of impairment (119). With the conventional cut-off level at 24 for dementia, the test has only a 6-point scale for discrimination between MCI or very mild dementia and normal functioning, with score overlap and skew as a result of the test's ceiling. The MMSE has become a benchmark against which newer tests are compared to establish their improved sensitivity to mild degrees of impairment. (122)

Montreal Cognitive Assessment

The MoCA is a 30-point test administered in 10 minutes and evaluate multiple cognitive domains.

Details on the specific MoCA items are as follows:

- The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes.

- Visuo-spatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point).
- Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points).
- Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each).
- Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task.
- Finally, orientation to time and place is evaluated (6 points).

The MoCA has been found to have good internal consistency and test-retest reliability and was able to correctly identify 90% of a large sample of a-MCI subjects from two different clinics (120).

b. Functional Scale

Activity of Daily Living

Reflects basic and important general tasks (such as bathing, dressing, eating, transferring in or out of a bed or chair and using the toilet). The score ranges from 0 (total dependence) to 6 (complete independence).

Instrumental Activity of Daily Living

It includes activities essential for making an independent life in the community (such as managing money, doing heavy or light housework, taking medication, shopping, preparing meals and use telephone). The score ranges from 0 (total dependence) to 8 (complete independence).

c. Behavioural Scale

Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) (tab.5) was developed to assess psychopathology in dementia patients. It is a structured interview of caregiver and assess 12 behaviours on the basis of frequency and severity in the past month such as delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, wandering, night-time behavior disturbances, and appetite and eating abnormalities.

Each sub-scale has an entry question inquiring whether the disturbance had been present in the last month. If the answer is affirmative, the caregiver is asked to rate specific neuro-behavioural symptoms within each sub-scale on a four-point frequency and on a three-point severity scale. Frequency and severity scores are multiplied for each sub-scale (composite score) and added together for the total NPI score. The composite score of each sub-scale ranges between 0 and 12, and the total composite score between 0 and 144 according to the severity and frequency of NPS. For the purpose of the study, NPS were recorded both as continuous than as present (NPI score $\geq$1) or absent (NPI score = 0). The scale has a high level of internal consistency reliability, inter-rater reliability and the test–retest reliability, and has been validated in Italian subjects (121, 123).

d. Neuropsychological Tests

Neuropsychological testing (tab.4) has been conducted using some cognitive test included in the Mental Deterioration Battery (MDB) (124) as well other tasks such as Token (126) and Visual Search (126) previously validated in Italian subjects.

For each test of the battery, Italian normative data for score adjustment based on sex, age and education were available and for each test a normative cut-off score corresponding to the lower limit of the tolerance interval on a 95% one-tailed test, for a confidence level of 95%, was calculated on the scores obtained by the healthy subjects of the standardisation sample (125; 126).

Briefly cognitive tests used were:

Memory: the Rey Auditory-Verbal Learning Test (RAVLT) immediate and delayed and the Story Prose (127), which measure the learning capacity and long term memory and the prose memory respectively.

The RAVLT takes approximately 10 to 15 minutes to administer and consists of five presentations of a 15-word list, followed by a free recall trial after a 15 minute delay. Score on this test range from (0-75 points).

The Story Recall requires the immediate and delayed recall of a short story, exploring the memory of 27 complex verbal stimuli (127). Subjects are asked to recall as many items of the story as possible soon after initial presentation, then the examiner repeats the whole story at the subject but the delayed recall is evaluated fifteen minutes later without further repetition. Score on this test range from (0-27 points).

While the first test evaluate long term memory as well as short term memory, the second evaluate only the long term memory and the capacity to retain new information about events or facts, enabling retrieval when needed at a future time.

Executive functions: we used the Raven Coloured Matrices, the Phonemic Fluency Test (127) and the Frontal Assessment Battery (128);

The Raven's Progressive Matrices are a series of multiple-choice items that evaluate abstract non-verbal reasonin. It consists of three sets (A, B, Ab) from the standard matrices and each set includes 12 items. Score range from 0 to 36. Most of the items are presented on a coloured background to make the test more conspicuous for the participants. But the last few items in set B are kept black on white background.

Phonemic Fluency Test assess the timed production of words after phonemic cues (A, F and S). The number of words reported in 1 minute for each letter was recorded. A cumulative score for the three letters was calculated (127).

The Frontal Assessment Battery (128) consists of six subtests exploring the following: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. It takes approximately 10 minutes to administer. Score range from 0 to 18.

Attentive functions: we used the Trail Making Test and the Visual Search (126)*;*

The Trail Making Test consisted of two parts. Part A, which required the subject to sequentially connect with a pencil 25 circled numbers irregularly distributed on a paper sheet, principally assessed psychomotor speed. Part B, which required the subject to connect circled letters and numbers alternating between the two sequences, assessed the mental flexibility needed for continuously shifting between the alphabetical and numerical series. The time required to complete each part of the task was recorded. The extra-time required to complete part B with respect to part A reflects shifting ability subtracted from psychomotor speed involved in both tasks.

The Visual Search Test measures the recognition of visual stimuli (digits) arranged randomly on a matrix made up of 13 rows and 10 digits for each row. There are three different subtests, each with a number of stimuli to be recognized. This test evaluates selective visual attention and control of impulsiveness towards recognizing the wrong stimulus. The score is given by the number of correct answers (range 0-60) and omissions (range 0-60).

Language: the Token Test (126) and the Aachener Aphasie Test.

The Token Test (126) detects speech receptive disturbances in aphasics. It requires 20 tokens, varying in shape (circle and square), size (small and large), and colour (red, yellow, green, blue and white). The test has 36 commands, each of which requires the manipulation or the attention to one or more tokens. The items are simple and complex and the score for each item is 0 if the answer is wrong, 0.5 if an item is missed initially but is correct after the repetition, 1 if the answer is correct.

The Aachener Aphasie Test is a battery composed by six tests. It measures aphasia (a disturbance of comprehension and formulation of language). It results from disturbance of the translation from words into thoughts and vice versa. Aphasia is produced by damage of cortical regions which are related to language functions.

In our neuropsychological battery we used only the fifth test, the confrontation naming test (score range: 0 to 120) that evaluates the capability of the patient to describe things or situations or actions with the right words. It consists of four subtests (score range: 0 to 30 points): nouns, colour terms, compound nouns, sentences.

Visuo-spatial abilities: the Visual Object and Space Perception*;*

The VOSP consist of nine tests each designed to assess a particular aspect of object or space perception. In our neuropsychological battery we used the subtest 7 (position discrimination) that consists of two adjacent horizontal squares, one with a black dot (5 mm)

printed exactly in the centre and one with a black dot just off centre. It is composed by twenty stimuli and the score range from 0-20 in relation with a correct choises.

Praxic function were investigated by using the Costructive Praxic (126). It assess the capacity of the subject to copy simple and complex geometric figures. The score ranges from 0 to 14.

Memory Assessment Clinics-Questionnaire: for detecting the degree of subjective awareness of the memory deficit we have used the Memory Assessment Clinics-Questionnaire **(MAC-Q)** (129). Subjects were asked to rate their present ability with six daily memory activities (e.g., remembering telephone numbers or where they put objects) in respect to the past. For each item the score ranged from 1 (ability better than in the past) to 5 (ability greatly worsened with respect to the past) with the overall score ranging from 5 to 30. A score ≥ 25 gives a measures of significant subjective cognitive complain.

e. Neuroimaging Assessment

The subject was assessed with CT or MRI by different neuroimaging pattern specifically:
Normal: Normal imaging
Vascular: Leukoaraiosis and/or lacunae
Degenerative: Atrophy (cortical and/or subcortical)
Mixed: Vascular plus degenerative lesions

MEMORY	**Rey words immediate and delayed recall (Rey, 1958)**
	Story Recall (Novelli et al, 1986)
EXECUTIVE	**Raven Coloured Matrices (Raven, 1938)**
	Letter Fluency (Novelli et al, 1986)
	Frontal Assessment Battery (Dubois et al, 2000)
ATTENTION	**Trail Making Test (Reitan, 1958)**
	Visual Search (Spinnler e Tognoni, 1987)
LANGUAGE	**Token Test (Spinnler e Tognoni, 1987)**
	Aachener Aphasie Test (De Bleser et al, 1986)
VISUO-SPATIAL ABILITY	**Visual Object and Space Perception (K. Warrington, 1991)**
PRAXIC	**Constructive Apraxia (Spinnler e Tognoni, 1987)**

(Tab. 4 Neuropsychological Battery)

	NA	Never	Frequency				Severity			S x F
Delusion	X	0	1	2	3	4	1	2	3	_____
Hallucination	X	0	1	2	3	4	1	2	3	_____
Agitation	X	0	1	2	3	4	1	2	3	_____
Depression	X	0	1	2	3	4	1	2	3	_____
Anxiety	X	0	1	2	3	4	1	2	3	_____
Euphory	X	0	1	2	3	4	1	2	3	_____
Apathy	X	0	1	2	3	4	1	2	3	_____
Disinibition	X	0	1	2	3	4	1	2	3	_____
Irritability	X	0	1	2	3	4	1	2	3	_____
Wandering	X	0	1	2	3	4	1	2	3	_____
Sleep	X	0	1	2	3	4	1	2	3	_____
Appetite	X	0	1	2	3	4	1	2	3	_____
Total										|__|__|__|

Frequency

0= Never **3= Frequently**

1= Rarely **4= Almost always**

2= Sometimes

Severity 1= light (not caused disorder in patients)

2= moderate (caused disorder in patients)

3= severe (Drugs, more serius for patients)

(Tab. 5 Neuro Psychiatric Inventory)

4.3 INCLUSION and EXCLUSION CRITERIA FOR MCI DIAGNOSIS

As previously stated, MCI was diagnosed according to revised criteria proposed by Winblad et al. (2004) (118). General criteria include:

- MMSE: score ≥ 23,75 (119)
- CDR: score range 0.5 (questionable dementia)
- Normal functioning in the activities of daily living with none of slight impairment in the instrumental activities of daily living
- At least deficit in one of the neuropsychological tests that evaluate cognitive domains. Subjects were considered to have impaired performance in the cognitive domains if their performance on at least one test was at least 1.5 standard deviations below published age and education matched normative means

The MCI diagnosis was classified as follows:

1) a-MCI, subjects with memory deficits, defined as a pathological score in at least 1 standardized memory test, with no deficits in other cognitive tests;
2) snm-MCI, subjects with deficit in one single non-memory domain, defined as an abnormal test performance (under normality cut-off) in 1 non-memory test;
3) md-MCI-a, subjects with 1 abnormal test in at least 2 domains, one of which was memory impairment;
4) md-MCI-na, subjects with 1 abnormal test in at least 2 domains, excluding memory.

Inclusion criteria for healthy control subjects will be a MMSE score ≥27. Exclusion criteria for all included groups will be the presence of clinically severe psychiatric or systemic disease, mental retardation, severe sensory impairment (blindness, deafness), other

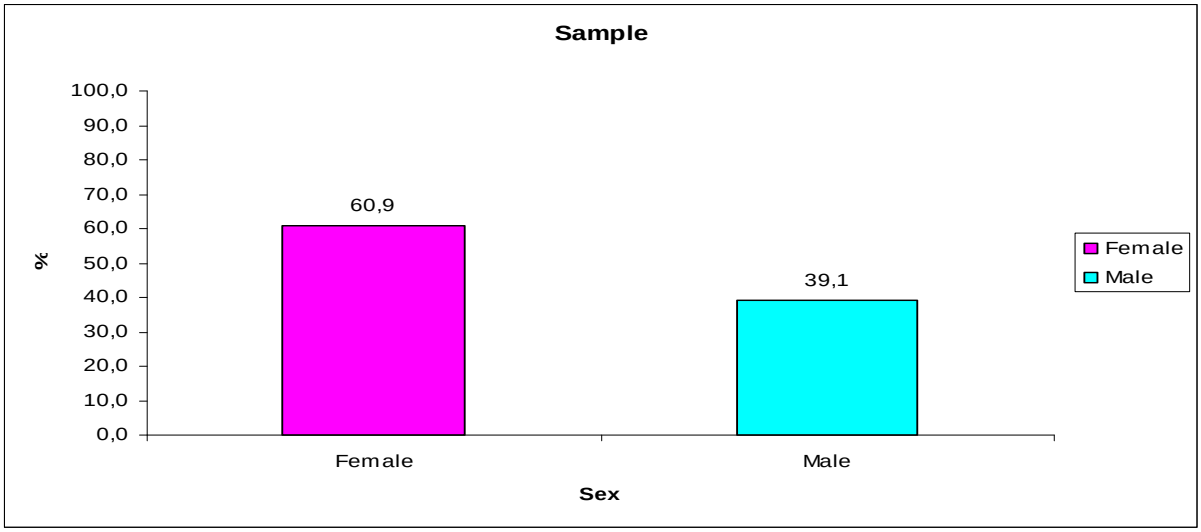
neurological conditions associated with cognitive impairment, a history of alcohol or substance abuse or dependence, head injury with loss of consciousness.

4.4 STATISTICAL ANALYSES

T-tests (and χ^2-tests when appropriate) and one-way ANOVA were used to compare demographic and neuropsychological variables between groups. All analyses were performed through the software SPSS *(SPSS Inc., Chicago, III, USA)*.

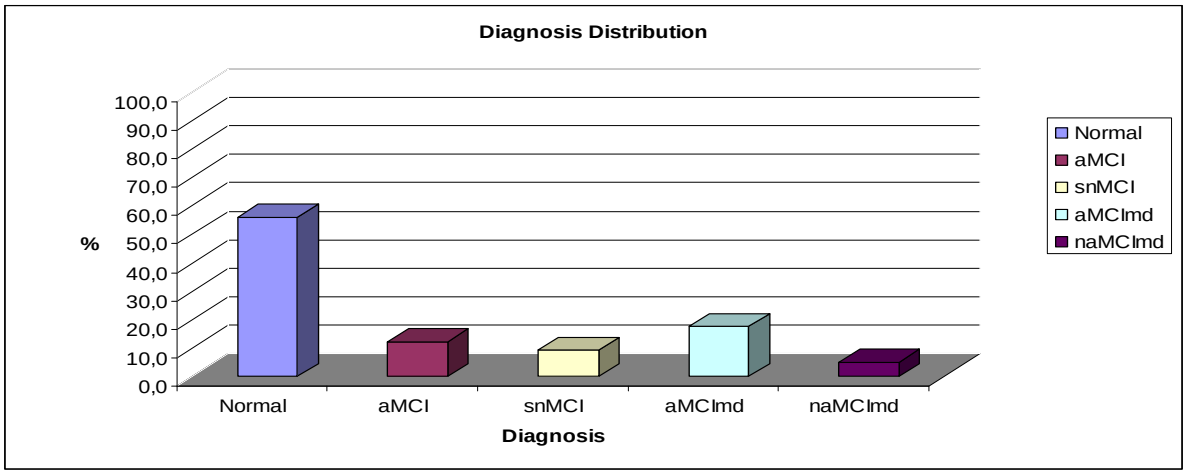
4.5 GENERAL CHARACTERISTIC OF INCLUDED SUBJECTS

The study sample includes patients that completed all the neuropsychological battery in day-hospital regime and was composed by five groups of subjects, as follows:
The group was composed by 3548 subjects: 2162 (60,9%) female and 1386 (39,1%) male (Tab.6). This research was composed by two parts we named Study I and Study II.

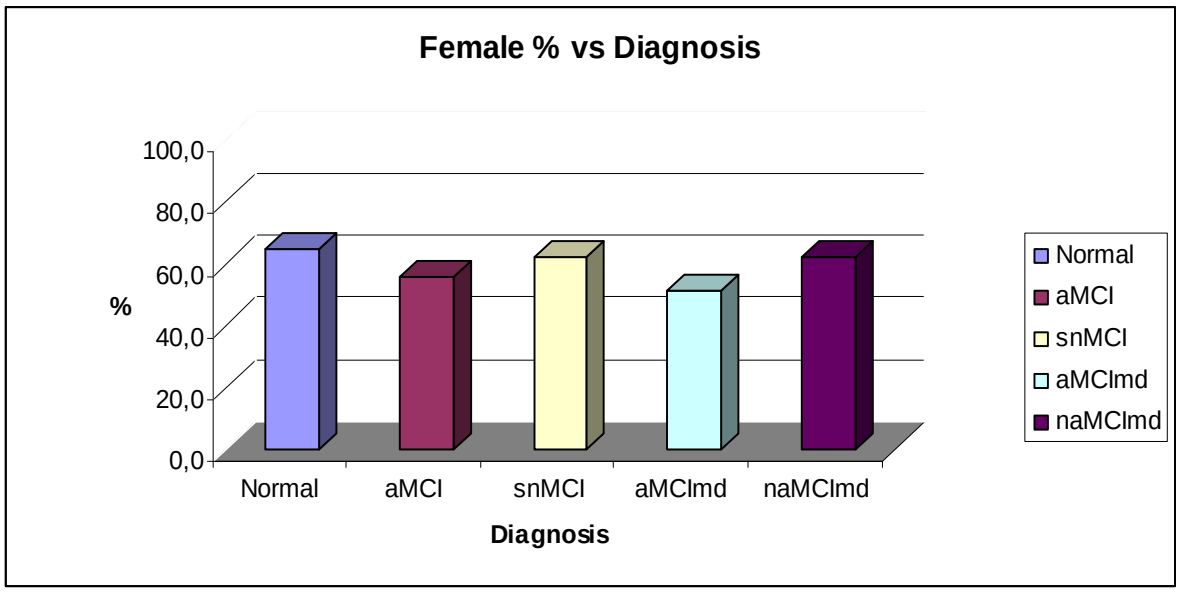


(Tab. 6 Sex Distribution of Sample)
In the Study I the sample was composed by 5 diagnostical group (Tab.7): amnestic MCI single domain (aMCI), amnestic MCI multiple domain (aMCImd), single non memory MCI (snMCI), non amnestic MCI multiple domain (naMCImd) and control group.

The first group with diagnosis amnestic MCI (aMCI) was composed by 433 (12,2%) subjects (56% female). The second group with diagnosis of amnestic MCI multiple domain (aMCImd) was composed by 621 (17,5%) subjects (51,4% female). The third group with diagnosis of non amnestic MCI single domain (snMCI) was composed by 324 (9,1% female) subjects (62,3% female). The fourth group with diagnosis of non amnestic MCI multiple domain (aMCImd) was composed by 174 (4,9%) subjects (62,3% female) The fifth group Control Group was composed by 1996 (56,1%) subjects (64,7% female) (Tab 8). The statistical distribution of sex showed that the memory complain was more frequently in male than in female, and in male the memory domain was more frequently associated with other pathological domain.

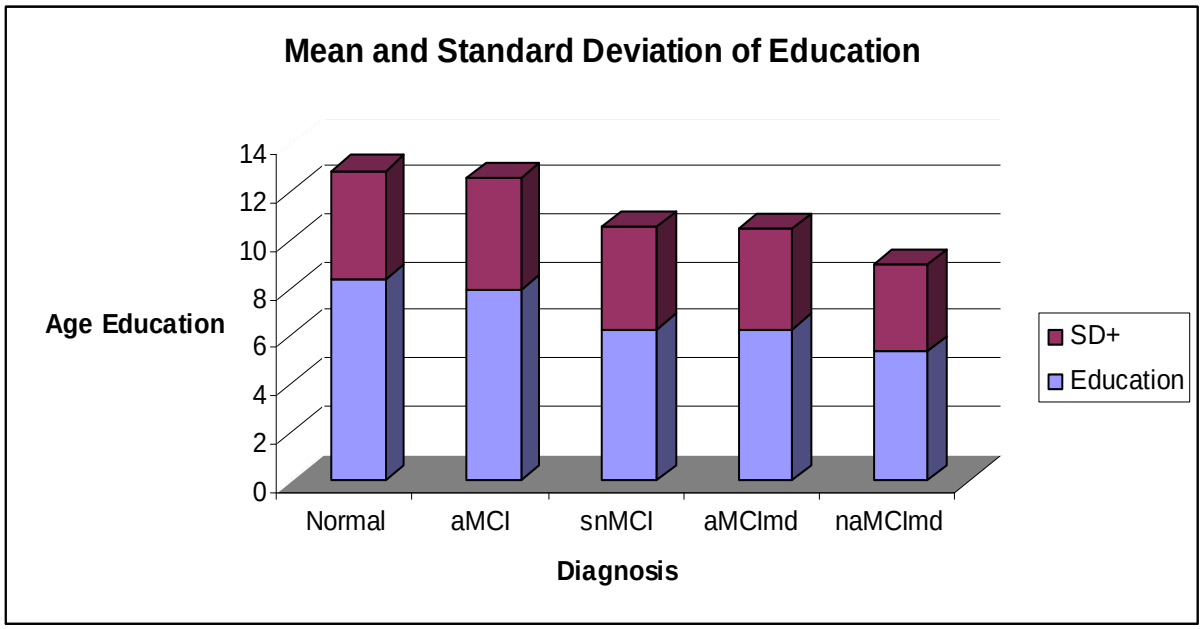


Tab.7 Diagnosis Distribution



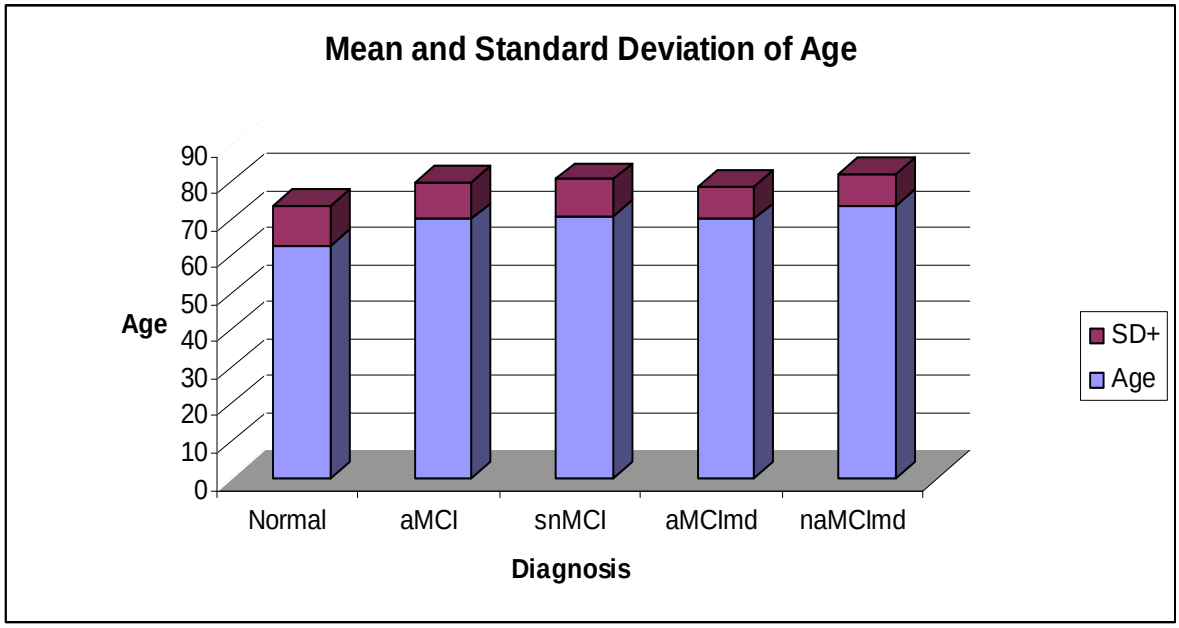
Tab.8 Sex Distribution in MCI and Normal Sample

The education of participants ranged between 0 (illiterate) to 17 (graduate). As we will see by the statistical analysis of the demographic characteristic our sample showed lower education level in MCI than in Control Group. More specifically the mean of age in aMCI is 7,9 (±4,7) years of education, in the aMCImd group is 6.3(±4,2) years of education, in the snMCI is 6,3 (±4,3) years of education, in the naMCImd is 5,4 (±3,6) years of education, and in the Control Group is 8,4 (±4,5) years of education (Tab 9).



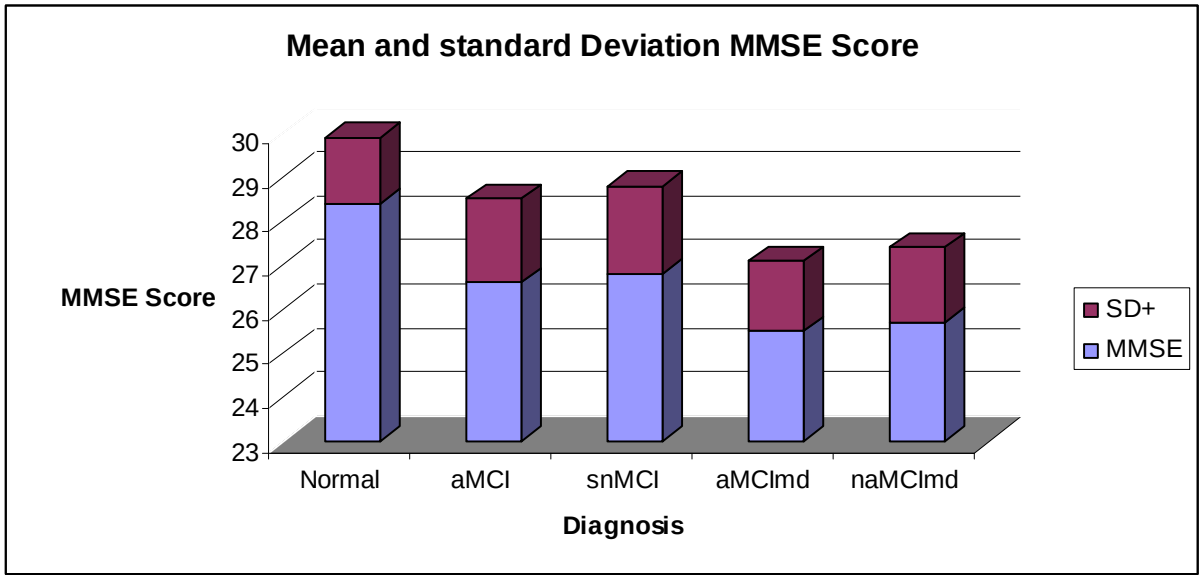
Tab.9 Education distribution in MCI and Normal Sample-mean and standard deviation

Age of participants ranged between 50 and 90 years. The age's means in aMCI subjects was 62,7±10,7, in aMCImd subjects was 69,7±9,0, in snMCI subjects was 70,7±9,9, in naMCImd subjects was 73,4±8,8 and in Control Group is 62,7±10,7. Totally the MCI Group is more elderly than Control Sample, and the naMCImd was more elderly than other MCI subtypes (Tab. 10).



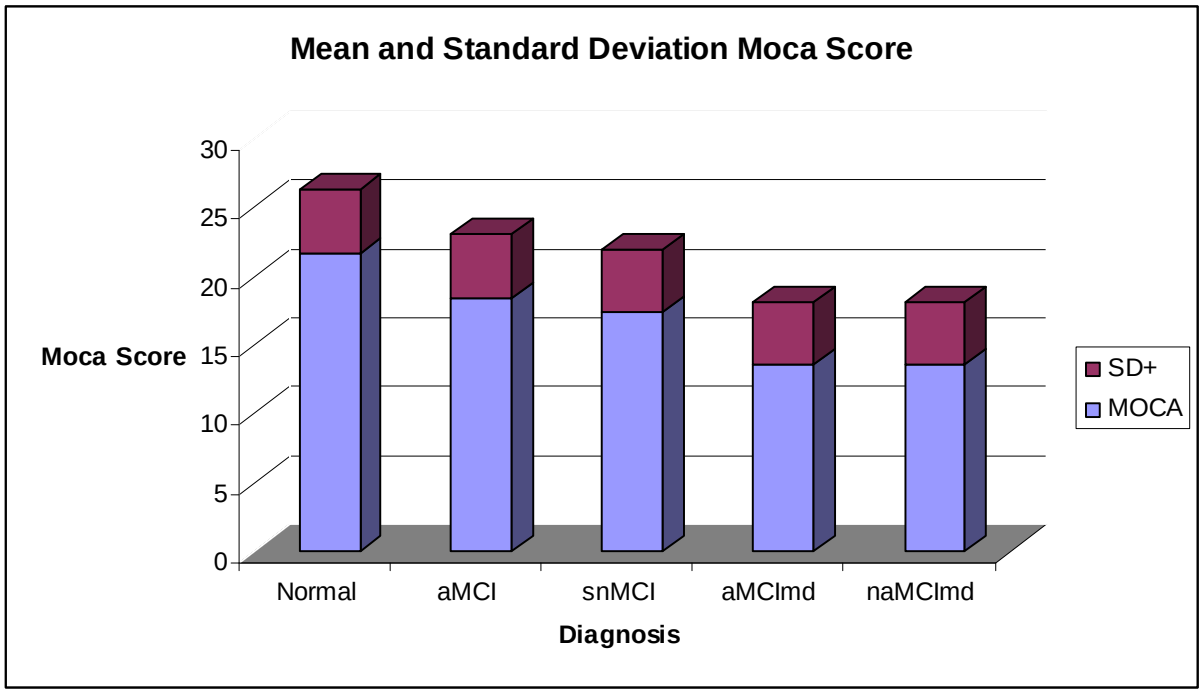
Tab.10 Age distribution in MCI and Normal Sample-mean and standard deviation

The cognitive characteristics of the sample, as expected, showed that the MMSE score was significantly higher in controls than in all MCI groups, and in those who showed an impairment of only one cognitive domain compared to those who showed a multiple domain impairment. More specific the means of MMSE in aMCI is 26,6 ± 1,9, in aMCImd is 25,5± 1,6, in snMCI is 26,8±2,0, in naMCImd is 25,7±1,7 and in Control Group is 28,4±1,5 (Tab.11).



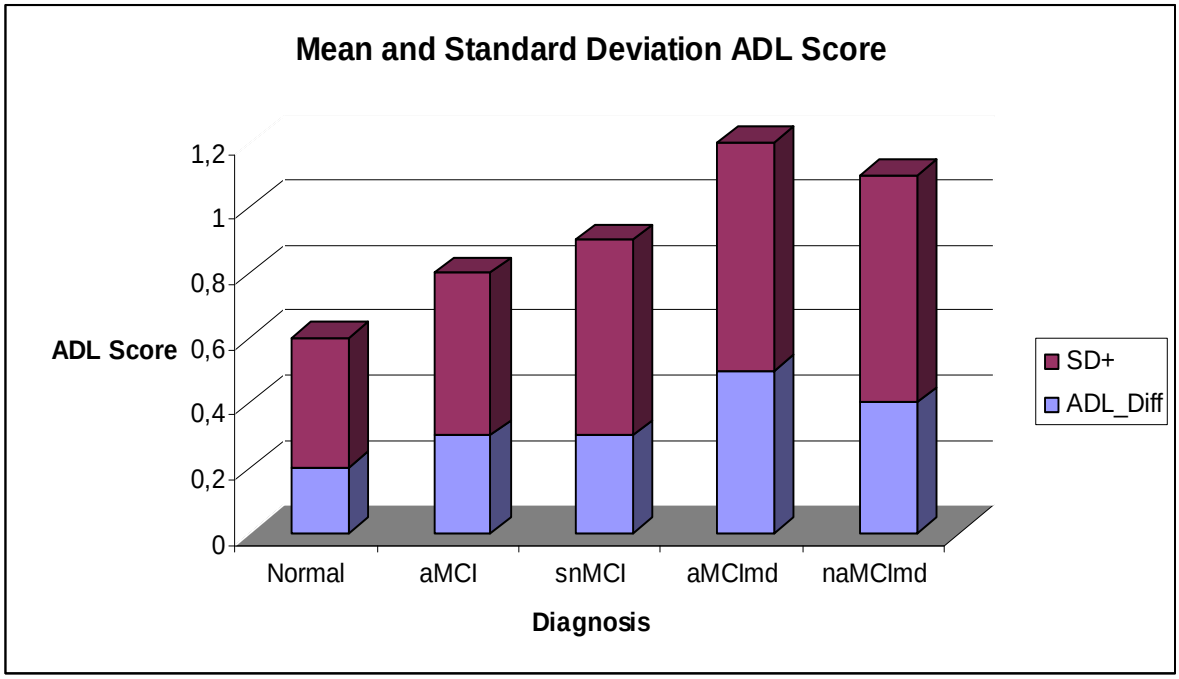
Tab.11 MMSE Score in MCI and Normal Sample-mean and standard deviation

The same characteristic was have been shown in Moca test. More specifically the means of Moca in aMCI was 18,4±4,7, in aMCImd was 13,6±4,5, in snMCI was 17,4±4,5, in naMCImd was 13,6±4,5 and in Control Group was 21,7±4,6 (Tab.12).

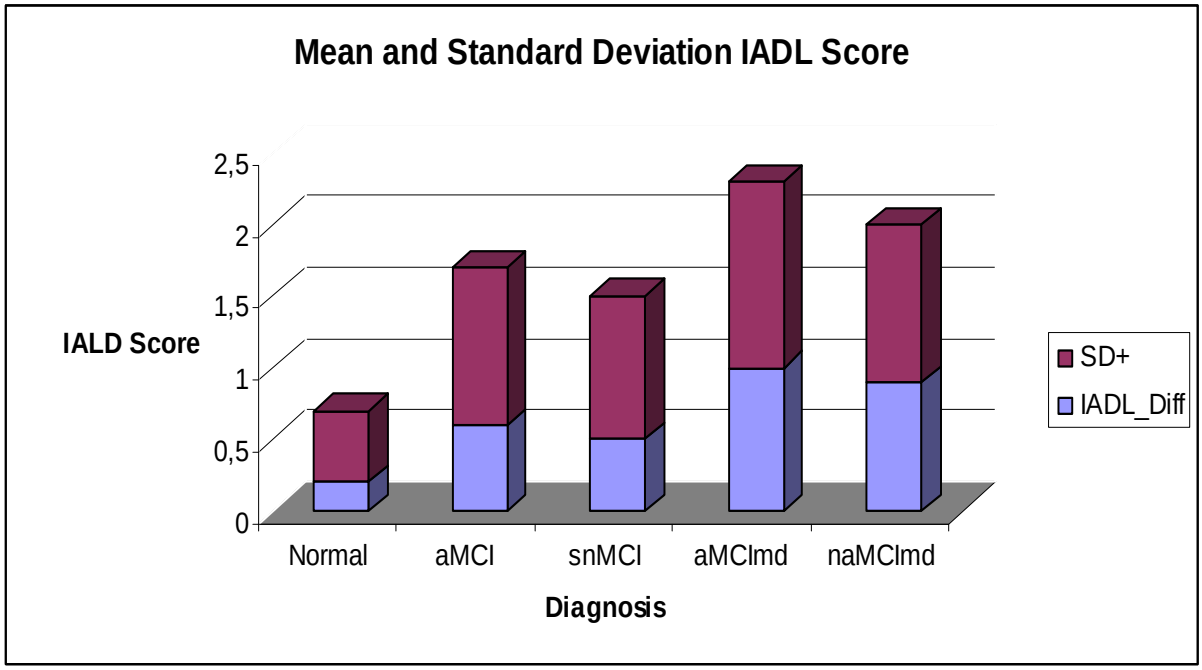


Tab.12 Moca Score in MCI and Normal Sample-mean and standard deviation

The daily base ability was more significantly preserved in Control Group than in MCI subjects, and in aMCI than MCI with more domain compromise, whereas daily instrumental ability was more preserved in control group than MCI, and it was more compromise in MCI multiple domain than in MCI with deficit in a single domain. More specifically the means of compromise items ADL in aMCI was 0,3±0,5, in aMCImd was 0,5±0,7, in snMCI was 0,3±0,6, in naMCImd was 0,4±0,7 and in Control Group was 0,2±0,4, and the means of compromise items IADL in aMCI was 0,6±1,1, in aMCImd was 1,0±1,3, in snMCI was 0,5±1,0, in naMCImd was 0,9±1,1 and in Control Group was 0,2±0,5 (Tab.13; Tab. 14).



Tab.13 ADL Score in MCI and Normal Sample-mean and standard deviation



Tab.14 IADL Score in MCI and Normal Sample-mean and standard deviation

	Normal	aMCI	snMCI	aMCImd	naMCImd	P
	1996	433	324	621	174	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Age	62,7±10,7	69,7±9,9	70,7±9,9	69,7±9,0	73,4±8,8	0,000
Education	8,4±4,5	7,9±4,7	6,3±4,3	6,3±4,2	5,4±3,6	0,000
Sex F %	64,7	56,0	62,3	51,4	62,3	0,000
MMSE	28,4±1,5	26,6±1,9	26,8±2,0	25,5±1,6	25,7±1,7	0,000
ADL_Diff	0,2±0,4	0,3±0,5	0,3±0,6	0,5±0,7	0,4±0,7	0,000
IADL_Diff	0,2±0,5	0,6±1,1	0,5±1,0	1±1,3	0,9±1,1	0,000
MOCA	21,7±4,6	18,4±4,7	17,4±4,5	13,6±4,5	13,6±4,5	0,000

Table 15 (Demographical and cognitive feature in MCI and Control Same -mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

The study II was composed by two parts, in the first part we selected only MCI sample. The MCI was classificated in aMCI+, composed by aMCI and aMCImd, and naMCI+ composed by snMCI and naMCImd.(Tab.16)

Tot N. 1552	N. naMCI+	N. aMCI+	
	N. 498	N. 1054	**P**
	Mean±SD	Mean±SD	
Age	71,7±9,6	69,7±9,4	0,000
Education	6±4,1	6,9±4,5	0,000
MMSE-Z	26,4±2,0	26±1,8	0,000
MOCA	16,2±4,9	15,5±5,2	0,107
ADL	0,4±0,6	0,4±0,7	0,827
IADL	0,7±1,1	0,9±1,3	0,005
Sex F%	62,5	53,7	0,001

Table 16 (Demografical and cognitive feature in aMCI+ and naMCI+ -mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

The first group with diagnosis of amnestic MCI Plus (aMCI+) was composed by 1054 subjects (53,6% female). The second group with diagnosis of non amnestic MCI plus (naMCI+) was composed by 498 subjects (62,5% female). The statistical distribution of sex showed that the memory complain was more frequently in male than in female and the aMCI+ was younger

than naMCI+. The age's means in aMCI+ is 69,7±9,4, in naMCI+ is 71,7±9,6 (Tab. 4). The instrumental ability was more preserved in naMCI+ than in aMCI+, indeed IADL means in aMCI+ was 0,9±1,3 and in naMCI+ was 0,7±1,1. the MMSE score was more elevated d in naMCI+ than in aMCI+.

In the second part of Study II we selected MCI subjects with neuroimaging report (N.895) and for each MCI group we selected MCI with normal, degenerative and vascular neuroimaging report obtaining: aMCI+ with normal (N.243), degenerative (N.145) and vascular (N.223) neuroimaging report and naMCI+ with normal (N.122), degenerative (N.45) and vascular (N.117) neuroimaging report.

The sample with Normal neuroimaging report naMCI+ differed from aMCI+ only by MMSE score, in fact in aMCI+ the MMSE mean was 26,3±1,8 while in naMCI+ means was 26,7±2,0; so aMCI+ obtained worse score in MMSE than naMCI+ (Tab.17).

Normal	**naMCI**	**aMCI**	**P**
N.366	N.122	N.244	
Age	64,8±9,4	63,6±8,9	0,241
Edu	6,2±4,2	6,9±4,4	0,128
MMSE-Z	26,7±2,0	26,3±1,8	0,031*
MOCA	18,4±4,7	17±4,9	0,084
ADL_Diff	0,3±0,5	0,3±0,5	0,671
IADL_Diff	0,4±0,9	0,5±0,9	0,229
sex F	66,4(81)	62,7(153)	0,488

Table 17 (Demografical and cognitive feature in aMCI+ and naMCI+ in Normal imaging Pattern-mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

In the sample with Degenerative neuroimaging report naMCI+ differed from aMCI+ only by age, in fact in aMCI+ the age's mean was 72,4±7,9 while in naMCI+ age's means was 76,4±8,1; so naMCI+ was more elderly than naMCI+(Tab.18).

Degenerative			
N.200	**naMCI**	**aMCI**	**P**
	N.47	N.153	
Age	76,4±8,1	72,4±7,9	0,003*
Edu	6,5±3,9	6,7±4,6	0,822
MMSE-Z	26±1,8	25,6±1,7	0,231
MOCA	14,7±5,9	12,5±4,4	0,097
ADL_Diff	0,3±0,6	0,3±0,7	0,957
IADL_Diff	0,6±1	0,9±1,4	0,130
sex F	63,8(30)	57,5(88)	

Table 18 (Demografical and cognitive feature in aMCI+ and naMCI+ in Degenerative imaging Pattern-mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

In the sample with Vascular neuroimaging report naMCI+ differed from aMCI+ by MMSE score, in fact in aMCI+ the MMSE mean was 25,8±1,7 while in naMCI+ means was 26,8±2,0; so aMCI+ obtained worse score in MMSE than naMCI+. The aMCI+ group was younger than the MCI+ in fact age's mean of naMCI+ was 68,3±9,3 and age's mean of aMCI+ was 66,2±9,4. Moreover the male subjects was more frequently associated with amnestic decline, in particular 48,9 % of aMCI+ and 62,9 % of naMCI+ was female.(Tab19)

Vascolar	naMCI	aMCI	P
N.339	N.116	N.223	
Age	68,3±9,3	66,2±9,4	0,046*
Edu	6,1±4	6,9±4,6	0,122
MMSE-Z	26,8±2	25,8±1,7	0,000*
MOCA	15,8±4,6	16,2±5,3	0,593
ADL_Diff	0,4±0,6	0,4±0,7	0,745
IADL_Diff	0,7±1,1	0,9±1,3	0,401
sex F	62,9(73)	48,9(109)	0,014*

Table 19 (Demografical and cognitive feature in aMCI+ and naMCI+ in Vascular imaging Pattern-mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

4.5 NEUROCOGNITIVE CHARACTERISTIC OF INCLUDED SUBJECTS

The Neurocognitive Characteristics of the sample were investigated by a comprensive Battery of Neuropsychologic test. The Battery was included test to examinated Memory, Executive, linguistic, attentive and praxic function.

In Study I as we expected the Normal subject to obtain better score in all screening and amnestic MCI obtain worse score in memory tests. Executive functions, attention, praxic and linguistic functions seemed more preserved in aMCI than in the other MCI subtype, and in snMCI than in aMCImd and naMCImd, although naMCImd showed worse attention performance. The visuopercective performance was preserved in MCI with normal memory performance (Tab.20).

In the first part of Study II the aMCI+ group showed better performance in executive, attentive and praxic functions than naMCI+. As we expected the memory performance was more impaired in aMCI+ than in naMCI+, of course this impairment was evident in all different Neuroimaging pattern. Whereas in Normal and Degenerative pattern the aMCI+ persisted the worse performance of attention in naMCI+ than in aMCI+(Tab. 21, 22, 23, 24).

	Total	Control	aMCI	snMCI	aMCImd	naMCImd	P
	N. 3547	N.1995	N.433	N.324	N.621	N.174	
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Memory	REYImm	39,4±6,1	27,9±5,7	35,7±5,6	26,1±4,7	34,3±4,5	0,000
	REYDiff	8,5±4,1	4,5±2,1	7,7±1,9	4,2±1,8	6,9±1,5	0,000
	BrRac	13,2±2,9	7,9±3,0	12,4±3,0	7,9±3,7	11,8±2,5	0,000
	FlSeT	14,4±7,5	14,6±6,0	16,1±7,5	12,5±5,5	15,8±8,0	0,000
	MACQ	25,2±4,3	27,3±4,5	25,2±5,2	27,3±5,4	25,4±6,1	0,000
Executive	FAB	16,3±1,9	15,6±2,1	14,1±2,4	12,4±2,7	12,2±2,6	0,000
	Rav	26,5±4,4	25,5±4,5	23,3±4,9	21,1±4,9	19,9±4,7	0,000
	FlFoT	33,6±7,5	26,2±6,7	23,2±6,5	20,3±6,9	19,3±6,5	0,000
Language	Aech	114,4±5,2	110,7±7,2	107,4±9,2	102±13,7	102,1±13,2	0,000
	TokTest	31,7±1,8	30,7±2,0	29,4±3,0	27,2±4,1	27,3±4,3	0,000
Attention	MAt_P	45,3±7,3	41±6,4	37,5±8,2	33,5±8,5	33,3±8,2	0,000
	TrMTA	60,4±25,8	69,1±29,2	125,5±78,9	147,3±84,0	187,5±87,1	0,000
	TrMTB	112,6±71,3	150,7±91,3	240±154,7	265,5±132,3	329±144,2	0,000
	TrMTBA	55±60,2	85,1±79,9	145,2±123,6	150,1±109,3	182,2±117,9	0,000
Visuospatial Prassic	VOSP	19,3±1,4	18,9±1,5	18,3±2,1	17,3±3,1	17,1±2,9	0,000
	AprCo	11,9±1,6	11,8±1,3	11±1,8	10,8±2,3	10,4±2,3	0,000

Table 20 (Neuro-cognitive feature in MCI and Normal sample-mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

		naMCI	aMCI	
	N.1584	**N.504**	**N.1080**	**P**
Memory	**REYImmC**	35,3±5,3	26,7±5,2	0,000*
	REYDiffC	7,4±1,8	4,3±1,9	0,000*
	Racconto	12,2±2,9	7,9±3,4	0,000*
	F-semant	16±7,6	13,3±5,8	0,000*
	MACQ	25,3±5,5	27,3±5,1	0,000*
Executive	**FAB**	13,3±2,7	13,4±2,9	0,517
	Raven	22,1±5,1	22,9±5,2	0,006*
	F-fonem	21,9±6,8	22,7±7,4	0,044*
Language	**Aechener**	105,5±11,0	105,6±12,2	0,850
	Token	28,7±3,6	28,7±3,8	0,962
Attention	**Matrici**	36,1±8,4	36,6±8,5	0,256
	Trail-A	146±86,8	117,9±78,4	0,000*
	Trail-B	266,3±156,3	203,7±125,5	0,000*
	Trail B-A	156,3±122,3	115,2±99,8	0,000*
Visuospazial Praxic	**VOSP**	17,8±2,5	17,8±2,9	0,686
	Apr Cost	10,8±2,0	11,2±2,0	0,002*

Table 21 (Neuro-cognitive feature in aMCI+ and naMCI+ -mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

Normal Neuroimaging		naMCI+	aMCI+	
N. 366		N.122	N.244	P
		Mean±SD	Mean±SD	
Memory	REYImmC	35,4±5,8	27±5,6	0,000*
	REYDiffC	7,4±2	4,7±2,1	0,000*
	Racconto	11,9±2,9	8±3,1	0,000*
	F-semant	15,6±7,9	13,3±6,2	0,005*
	MACQ	26,7±5,5	27±5,2	0,661
Executive	FAB	14,3±2,8	14±2,8	0,535
	Raven	22,9±5,4	23±5,2	0,858
	F-fonem	22,9±7,2	23,6±7,3	0,386
Language	Aechener	108,7±9	107,9±11,9	0,539
	Token	29,6±3,3	29±3,8	0,173
Attention	Matrici	36,1±7,5	37,6±8,5	0,083
	Trail-A	115,4±67,6	97,7±64,8	0,081
	Trail-B	246,4±158,8	175,9±121,7	0,006*
	Trail B-A	146,6±120,4	100,6±96,1	0,020*
Visuospazial Praxic	VOSP	18,1±2,4	17,9±3,1	0,657
	Apr Costrut	10,9±2,3	11,3±1,9	0,083

Table 22 (Neuro-cognitive feature in aMCI+ and naMCI+ in Normal imaging Pattern-mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

Degenerative Neuroimaging		naMCI+	aMCI+	
N.200		N.47	N.153	P
		Mean±SD	Mean±SD	
Memory	REYImmC	35,8±5,2	26,8±5,2	0,000*
	REYDiffC	7,5±1,8	4±1,7	0,000*
	Racconto	11,4±2,2	7,5±3,3	0,000*
	F-semant	18,1±9,3	14,2±6,8	0,004*
	MACQ	22,8±9	27,9±4,4	0,000*
Executive	FAB	12,7±2,9	13,1±2,7	0,579
	Raven	21,8±6	22,1±5,1	0,757
	F-fonem	21,9±7,3	22,6±7,3	0,564
Language	Aechener	104,7±8	104,8±12,2	0,946
	Token	28,9±2,8	28,3±3,8	0,363
Attention	Matrici	35,6±9,4	36,1±7,7	0,735
	Trail-A	162,4±81,2	124,4±67,1	0,023*
	Trail-B	332,9±183,7	255±145,9	0,120
	Trail B-A	203,1±154,9	155,7±131	0,273
Visuospatial Praxic	Apr Costrut	11,4±1,9	11,2±2,1	0,551
	VOSP	18,3±2,5	18±2,4	0,679

Table 23 (Neuro-cognitive feature in aMCI+ and naMCI+ in Degenerative imaging Pattern-mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

Vascular Neuroimaging		naMCI	aMCI	P
N.339		**N.116**	**N.223**	
		Mean±SD	**Mean±SD**	
Memory	**REYImmC**	36,2±5,3	26,5±5,2	0,000*
	REYDiffC	7,7±2	4,3±2	0,000*
	Racconto	12,4±2,7	8,3±3,5	0,000*
	F-semant	15,8±2,7	12,8±5,6	0,000*
	MACQ	25,9±2	28,3±4,7	0,000*
Executive	**FAB**	13,2±4,2	13,3±3	0,944
	Raven	22,5±7,6	22,8±5,2	0,591
	F-fonem	22±4,9	22,1±8	0,914
Language	**Aechener**	105,3±7,1	106±11,7	0,624
	Token	28,5±12,8	28,4±3,7	0,892
Attention	**Matrici**	37,6±3,8	36±8,5	0,091
	Trail-A	142,4±90,4	118,3±85,5	0,082
	Trail-B	200,5±127,6	196,7±131,3	0,888
	Trail B-A	107,8±93,7	108,2±104,2	0,986
Visuospatial Praxic	**Apr Costrut**	10,7±8,4	11,1±2	0,106
	VOSP	17,6±2,7	17,5±2,8	0,899

Table 24 (Neuro-cognitive feature in aMCI+ and naMCI+ in VascularNormal imaging Pattern-mean and standard deviation-Anova-one way for continuous data and χ^2 for dicotomic data)

5. RESULTS AND DISCUSSIONS

5.1 RESULTS AND DISCUSSION OF STUDY 1

The aim of the Study I was to evaluate the presence of BPSD in four subtypes of MCI and a Control Group. We correlated the scores obtained in specific NPI (frequenty x severity) (the results are showed in the table IV). Among NPI items, we have evaluated the correlation between 12 items (Delusions, Hallucinations, Agitation/Aggression, Depression, Anxiety, Euphoria, Apathy, Disinhibition, Irritability, Wandering, Sleep, Eating Disorder) and the different types of diagnosis (aMCI, aMCImd, snMCI, naMCImd and Control Group) and the total score and the different types of diagnosis (Tab. 25).

	Normal (A)	aMCI (B)	aMCImd (C)	snMCI (D)	naMCImd (E)	P	
Mood related features							
NPI_Depression	2,9	3,3	3,9	3,3	3,3	0,001	A<C
NPI_Anxiety	3,1	3,2	3,7	3,3	3,6	N.S.	
NPI_Apathy	0,8	1,7	2,8	1,7	2	0,001	A<B,C,D,E C>B,D
Psichothyc related features							
NPI_Delusion	0,05	0,2	0,3	0,1	0,3	N.S.	
NPI_Alllucination	0,05	0,1	0,3	0,1	0,3	N.S.	
Frontal related features							
NPI_Euphory	0,03	0,1	0,1	0,1	0,05	N.S.	
NPI_Agitation	0,2	0,6	0,7	0,6	0,8	0,001	A<C,E
NPI_Disinibition	0,1	0,3	0,3	0,2	0,2	N.S.	
NPI_Irritability	1	1,6	2,3	1,8	2,2	0,001	A<B,C,D,E B<C
Other related features							
NPI_Wandering	0,05	0,35	0,44	0,06	0,4	N.S.	A<C
NPI_Sleep	2,71	2,72	2,86	2,94	2,87	0,001	
NPI_Appetite	0,41	0,74	1,28	0,91	0,99	0,001	A<C
NPI_Total	11,4	14,9	18,8	14,7	16,9	0,001	

Table 25 (Behavioural feature in MCI+ and in Normal Sample- χ^2 for dicotomic data)

Totally the Normal subjects presented a lower NPI total score than MCI subject, and MCI with only one cognitive domain deficit presented total score lower than MCI multiple domain

deficit. We divided the NPI item in four categories: Mood related features included Depression, anxiety and apathy; psychotic related features included delusion and hallucination; frontal related features included agitation, irritability, euphoria, disinhibition, and other related features include wandering, sleep and appetite.

In Mood relates features depression was most significantly present in aMCImd than in Normal subjects, and apathy was most significantly present in MCI than in Normal subjects and in aMCImd than in MCI with only one cognitive domain deficit. According to Frontal related features agitation score was more elevated in MCI with more cognitive deficits than in Normal group and irritability score was more elevated in MCI than in Normal group and in aMCImd than in aMCI. Finally in Other related group wandering and appetite was more presented in aMCImd than in Normal group.

5.2 RESULTS AND DISCUSSION OF STUDY II

The study II was composed by two part: in the first part we selected the MCI subject (N.1552) in two group: MCI with amnestic deficit (N. 1054) (aMCI+) and MCI without amnestic deficit (N.498) (naMCI+). The aim of the first part of second study was to evaluate the presence of BPSD in this two subtypes of MCI (aMCI+ and naMCI+).

According to first step of the Study II the subjects aMCI+ shows more elevated level of depression, euphoria, apathy, and appetite than naMCI+. (Tab. 26)

N. 1552	**naMCI+**	**aMCI+**	**P**
NPI %	**N. 498**	**N. 1054**	
Delusion	1,7	3,1	0,106
Hallucinations	1,9	3,0	0,204
Agitation	10,0	9,0	0,535
Depression	51,0	58,0	0,011*
Anxiety	50,8	54,8	0,151
Euphoria	0,4	1,7	0,035*
Apathy	26,3	35,1	0,001*
Disinhibition	2,7	3,7	0,330
Irritability	26,5	28,9	0,330
Wondering	1,9	6,4	0,000*
Sleep	42,5	41,7	0,760
Appetite	11,7	16,9	0,009*
NPI Tot	79,8	83,5	0,075

Table 26 (Behavioural feature in aMCI+ and naMCI+ χ^2 for dicotomic data)

In the second part we selected MCI with neuroimaging report (N.895) and for each MCI group we selected MCI with normal, degenerative and vascular neuroimaging report, so we obtained: aMCI+ with normal (N. 243), degenerative (N.145) and vascular (N.223) neuroimaging report and naMCI+ with normal (N. 122), degenerative (N.45) and vascular (N.117) neuroimaging report. The aim of this second part was evaluated the presence of BPSD in this two subtypes MCI according to the different neuroimaging pattern (tab. 26, 27, 28).

Normal Neuroimaging	naMCI+	aMCI+	P
N. 366	N.122	N.244	
NPI %			
Delusion	0,0	2,1	0,118
Hallucinations	0,9	1,7	0,548
Agitation	8,6	7,5	0,705
Depression	51,7	57,7	0,289
Anxiety	50,9	57,7	0,225
Exaltation	No	No	
Apathy	23,3	22,1	0,801
Disinibition	2,6	2,1	0,760
Irritability	20,7	24,2	0,465
Wondering	1,7	3,3	0,389
Sleep	46,6	42,5	0,470
Appetite and weight	8,6	12,9	0,234
NPI Tot	78,4	79,3	0,861

Table 26 (Behavioural feature in Normal Image aMCI+and naMCI+ χ^2 for dicotomic data)

Degenerative Neuroimaging	naMCI+	aMCI+	P
N.200	N.47	N.153	
NPI %			
Delusion	2,3	2,1	0,923
Hallucinations	0,0	1,4	0,437
Agitation	7,0	6,9	0,994
Depression	37,2	57,6	0,019
Anxiety	44,2	48,6	0,610
Exaltation	0,0	2,8	0,269
Apathy	14,0	38,9	0,002
Disinibition	0,0	1,4	0,437
Irritability	16,3	31,3	0,055
Wondering	2,3	6,9	0,259
Sleep	39,5	38,9	0,936
Appetite and weight	9,3	17,4	0,200
NPI Tot	74,4	88,9	0,018

Table 27 (Behavioural feature in Degenerative Image aMCI+ and naMCI+ χ^2 for dicotomic data)

Vascular Neuroimaging	naMCI+	aMCI+	P
N.339	**N.116**	**N.223**	
NPI %			
Delusion	0,9	1,8	0,499
Hallucinations	0,9	2,7	0,261
Agitation	12,2	10,4	0,624
Depression	53,0	62,0	0,114
Anxiety	56,5	59,7	0,571
Exaltation	1,7	1,8	0,963
Apathy	26,1	38,5	0,023
Disinibition	1,7	5,0	0,144
Irritability	31,3	33,0	0,748
Wondering	0,9	5,0	0,054
Sleep	45,2	46,2	0,870
Appetite and weight	13,9	21,3	0,101
NPI Tot	81,7	88,2	0,103

Table 28 (Behavioural feature in Degenerative Image aMCI+and naMCI+ χ^2 for dicotomic data)

According to Normal Neuroimaging pattern there wasn't difference in BPDS between aMCI+ and naMCI+. Instead the Degenerative pattern and in Vascular Pattern apathy was more frequently present in aMCI+ than in naMCI+, in fact in Vascular pattern the 38,5% of aMCI+ was apathetic while in naMCI the apathetic was 26,1%, and in Degenerative pattern the apathy's frequency in aMCI+ was 38,9 % while in naMCI+ it was 14%. In the latter pattern the aMCI+ appeared more depressed than naMCI+ in particular the depression's frequency in aMCI+ was 57,6% and in naMCI+ was 37,2%.

6. Conclusion

A review of behavioural symptoms in different dementia subtypes found an increase in the risk of depression, emotional labiality, anxiety and apathy in vascular dementia compared to AD, while delusions, delusional misidentification, wandering and restlessness were less frequent in vascular dementia compared with Alzheimer's disease (130). In our study of the population with MCI presented elevated frequency of BPSD than Normal group, in depression, apathy, irritability, agitation, wondering and appetite, and aMCImd present more elevated frequency of non cognitive characteristic. In amnestic compromise MCI the presence of vascular and degenerative disease significantly increased the frequency of apathy. While the presence of degenerative disease was associated with depression in aMCI+, suggesting that apathy as a preclinic symptom of dementia. Recent reviews have demonstrated a large variation in estimates of the prevalence of behavioural and psychological symptoms in MCI (6,7). This variation can in part be explained by different diagnostic criteria for MCI and use of different study settings. Most symptoms are less prevalent in the population than in clinical samples (6). Behavioural and psychological problems are common in dementia (4) and have become accepted as central characteristics of the disorder. Behavioural and psychological symptoms in dementia are at least as problematic for patients and caregivers as cognitive impairments, significantly affecting quality of life and cost of care of people with dementia (1,2). Furthermore, they currently offer greater opportunities for intervention and management than does cognitive impairment (3). Current definitions of MCI focus entirely on cognition and may exclude those with psychiatric symptoms on the basis that psychiatric disorders might underlie cognitive impairment which should then not be considered an indicator of incipient Alzheimer's disease. Yet we have shown that many behavioural and psychological symptoms are present in those with mild cognitive impairments with a similar pattern of occurrence to that seen in individuals with dementia. Behavioural and psychological symptoms should be assessed as possible targets for management in cognitively impaired older people. Several studies in patients with MCI have shown that those with behavioural and psychological symptoms have an increased risk of dementia incidence and suggest that noncognitive symptoms should be a consideration when identifying those in the earliest stages of dementia (6,7). It remains difficult to differentiate patients with psychological symptoms as a consequence of early dementia from those in whom cognitive impairment is secondary to other psychological conditions. Further population-based longitudinal studies are needed to

establish whether behavioural and psychological symptoms can be used alongside memory and other cognitive impairment to improve the identification of those at highest risk of dementia incidence.

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