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Novel Psychometric tools for the diagnosis and treatment of Mild Cognitive Impairment and Alzheimer's Disease

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Ph.D. Thesis

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List of abbreviations

AD	Alzeimer Disease
ADL	Activities of Daily Living
AES	Apathy Evaluation Scale
ALS	amyotrophic lateral sclerosis
aMCI	Amnestic mild cognitive impairment
APOE	Apolipoprotein E
APP	β-Amyloid Precursor Protein
Aβ	Amyloid peptide
BDM	Battery for Mental Deterioration
BPSD	Behavioral and Psychological Symptoms of Dementia
CBI	Caregiver Burden Inventory
CBS	Cornell-Brown Scale for Quality of Life in Dementia
ChEIs	cholinesterase inhibitors
CPM	Coloured Progressive Matrices
CTE	chronic traumatic encephalopathy
DMT	Disease modifying therapies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FAB	Frontal Assessment Battery
FTD	Frontotemporal Dementia
GPCOG	General Practitioner Assessment of Cognition
HDRS	Hamilton Psychiatric Rating scale for Depression
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
LLD	Late-life depression
MCFA	Multiple group confirmatory factor analysis
MCI	Mild cognitive impairment
MDD	Major Depressive Disorder
MMSE	Mini-mental State Examination
MoCA	Montreal Cognitive Assessment
MS	multiple sclerosis

naMCI	Non-amnestic mild cognitive impairment
NFT	Neurofibrillary tangles
NIA-AA	National Institute in Aging - Alzheimer's Association
NMDA	N-methyl-D-aspartate
NPS	Neuropsychiatric symptoms
NPT	Non-pharmacological treatment
PM	Progressive Matrices
PSEN1	Presenilin 1
PSEN2	Presenilin 2
P-tau	phosphorylated tau
QOL-AD	Quality of life in Alzheimer’s disease
RCT	randomized controlled trial

ABSTRACT

Alzheimer's is characterized by cognitive and affective symptoms with several challenges regarding its early diagnosis and the intervention to be implemented. Given the recent focus on apathy as a marker of cognitive decline and the transition to dementia, we examined the psychometric properties and the invariance of the Italian Version of the AES-C conducted on a sample composed of an experimental group of amnestic MCI and AD patients (N = 107) and a control group (N = 107) constituted by Age- and Sex-matched healthy controls. Results confirm the goodness of the scale. Confirmatory factory analysis confirmed that the AES-C Italian Version presents the same stability of one second-order factor and three first-order factors identified in the original version, and all items are predicted by a single general factor; the scale was found to be invariant across both populations and reliability and discriminant analysis showed good values. Our data demonstrated the validity of the Italian version of the AES-C for the assessment of apathy both in MCI and in AD patients. Then we focused our attention on measuring the impact of Cholinesterase Inhibitors (ChEIs) on the progress of cognitive decline in AD patients in an early phase of the disease. In our study we assess the validity of MMSE compared to MoCA for monitoring the impact of ChEIs treatment on cognitive decline in a sample of 33 mild AD patients. We therefore examined the impact of ChEIs treatment on global cognitive function in AD patients both at 6 months (Group1=17 patients) and at 9 months (Group2=16 patients) by using a psychometric approach including MMSE, MoCA, Frontal assessment Battery (FAB), Hamilton Depression Rating Scale (HDRS). Overall, our data suggest that the combined use of MMSE with MoCA can improve the evaluation of clinical efficacy of ChEIs in clinical practice. We believe that nowadays, when the challenge is to arrive at the earliest possible diagnosis of this disease, the use of new psychometric protocols can become essential to intervene promptly and start with an early treatment finally improving the quality of life of patients with AD.

INTRODUCTION

1. Alzheimer's disease

Alzheimer's disease (AD), is a chronic neurodegenerative disease characterized by an irreversible deterioration of cholinergic neurons, in particular in the cerebral cortex and hippocampus (Albert, 2007) and by the presence of β-amyloid in the senile plaques, intracellular aggregates of tau protein in the neurofibrillary tangles (Hardy, 2009). In general, the first symptoms manifest themselves in the cognitive sphere with memory alterations and behavioural problems and there is an increasing neuropsychological impairment with progressive decline of memory, language, executive function and visuospatial skills, able to interfere with the quality of life and normal daily activities (Cummings, McPherson, 2001). In particular short-term memory deficit is the pre-eminent characteristic of the disease of which it constitutes the real clinical onset. The autobiographical memory and that relating to historical, not recent and long-term events are initially unaffected. Disorientation occurs constantly during the course of the disease and tends to worsen. Among the earliest symptoms we should also consider concentration and attention deficits. Furthermore, in AD there is often also the presence of language impairments, with the appearance of anomies, paraphasias, and late aphasias too. AD patients may also present a clinical phenotype with gnotic, praxic, and visuospatial disorders. Finally, executive disorders and alterations in abstract thinking, which in some cases are already present at the onset of symptoms, compromise the ability to plan, criticize and judge as the disease progresses. (Berardelli, Cruccu, 2019). AD is characterized also by neuropsychiatric symptoms, such as anxiety, delusions, hallucinations, aggression (verbal and physical), irritability, inappropriate social behavior, disinhibition, sleep disturbances, eating disorders (Berardelli, Cruccu, 2019), depression, psychosis and agitation and evidence demonstrated that they are a common precipitant of institutional care (Ballard et al., 2008). Recently, particular attention has been paid to the construct of apathy, understood as a loss of will, interest and motivation in acting, emotional dulling and affective flattening. Apathy can be considered as a prodromal sign of AD and it has been shown to have a strong impact on its course as it accelerates cognitive decline (Perri et al. 2018) AD represents the first cause of dementia and in Italy there are about 600,000 patients who are affected by this disease (Berardelli, Cruccu, 2019).

According to the studies conducted in the last 30 years, it has been possible to identify different pathologic findings that characterize AD. First of all, the presence of amyloid plaques (Aβ) (Selkoe, 1994). It depends on the abnormal cleavage of the amyloid precursor protein (APP) resulting in Aβ monomers which aggregate to form oligomeric Aβ and eventually aggregate into Aβ fibrils and plaques (Tiwari, 2019; Chen, et al. 2017). The normal processing of the APP sequence consists of the non-amyloidogenic proteolysis of APP via α-secretase and λ-secretase, producing soluble fragments When APP is cleaved by λ-secretase and erroneous β-secretase, it leads to amyloid peptides insoluble that aggregate in the brain to form -amyloid plaques (Selkoe, Hardy, 2016; Kinney et al., 2018), characterized by an excess of deposition of Aβ-42. The pathogenetic role of Aβ-42 in the development of AD disease has been confirmed by the study of the genetically determined forms of the disease (Berardelli, Cruccu, 2019). In fact, the presence of mutations in one of three genes have been identified as factors causing the development of AD: amyloid precursor protein (APP), presenilin 1, (PSEN1) or presenilin 2 (PSEN2) (Bateman et al., 2011). The role of Aβ in this pathologic condition still remains an issue to be explored, as several studies have shown that Aβ plaques can accumulate up to 10 years before the onset of clinically-relevant symptoms (Kinney et al. 2018).

Another pathologic hallmark that characterised AD is the hyperphosphorylation of tau protein. Normally, tau phosphorylation plays a critical role in intracellular trafficking to remove tau from microtubules, allowing for transport, followed by dephosphorylation to return tau to microtubules. In Alzheimer's disease, on the other hand, the tau protein is phosphorylated in a greater number of sites with consequent removal of tau from the microtubules; this causes the collapse of microtubule structures and destruction of a series of cellular processes ranging from protein trafficking to overall cell morphology. Furthermore, the hyperphosphorylated tau (p-tau) aggregates into coupled helical fragments which form neurofibrillary tangles. Accumulation of such p-tau tangles and impaired cell function leads to loss of neuronal function and ultimately to neuronal apoptosis (Sadigh-Eteghad 2015; Kinney et al., 2018; Chen et al., 2017; Šimić et al. 2016).

Several studies have shown that Aβ deposits are already present in a substantial number of subjects yet in the preclinical phase of the disease. This means that despite subjects appear cognitively healthy they have an increased grey matter brain atrophy, especially within the hippocampus, a key region affected in AD dementia (Ewers et

al. 2011, Villemagne et al., 2013). Consequently, although clinically the first symptoms tend to appear after the age of 65, there is increasing evidence that AD pathology starts depositing in the brain in midlife.

Recently, literature have led to a third characteristic concerning the pathogenesis of AD: the neuroinflammatory hypothesis (Calsolaro, Edison, 2016; Breijyeh, Karaman, 2020), according to which an inflammatory response is activated in the brains of AD patients. This acute inflammatory response would be similar to the sustained immune responses already present in other diseases (Parkinson's disease, traumatic brain injury associated with chronic traumatic encephalopathy (CTE), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) (Kinney et al., 2018) and could contribute to neuronal death over time, facilitating Aβ and NFT- related diseases (Kinney et al. 2018).

According to these evidences, it is possible to consider AD as a pathology that develops along a temporal continuum that also includes a long asymptomatic (preclinical) phase in which neuropathological changes occur without compromising normal cognitive functioning (Dubois, et al., 2010). Then there is a symptomatic phase (prodromal or pre-dementia) of progressive cognitive decline, and finally in the last phase a functional impairment and real overt dementia (Amieva, 2008).

In 2011 biomarkers for the diagnosis of AD have been introduced in the most recent diagnostic criteria proposed by the National Institute in Aging - Alzheimer's Association (NIA-AA) (Jack Jr, et al., 2018). This allowed to increase the diagnostic accuracy and to identify three different degrees of clinical expression of the disease (Berardelli, Cruccu, 2019):

- Preclinical AD: asymptomatic phase of the disease; all the pathogenic mechanisms are in place, but the extent of the damage is not such as to determine the development of symptoms. In clinical practice it is difficult to identify this phase; however, it can be recognized in those who are asymptomatic, but carry the mutations that cause AD.
- Prodromal AD: initial symptomatic phase of the disease; the damage induced by the disease slightly compromises some cognitive functions, but without interfering in the overall functioning of the individual. This phase includes a clinical picture called Mild Cognitive Impairment which we will analyse shortly.

- Clinical AD: full-blown phase of the disease. The level of neuropathological alteration is severe and impairs autonomy and many cognitive functions.

However, it is important to underline that, despite these diagnostic categories reflect the continuum of AD, their use is only recommended in the context of research. (Ibidem)

Currently, according to the diagnostic criteria of the DSM-5, we can find two cognitive syndromes: major neurocognitive damage and mild neurocognitive damage. The diagnosis of severe neurocognitive impairment requires objective cognitive decline that interferes with activities of daily living and is not attributable to delirium or other neurological, medical, or psychiatric disorders. Patients with mild neurocognitive impairment have a milder symptom picture of cognitive decline: they are still able to lead an independent lifestyle and carry out complex daily activities (DSM-5, 2013). It is important to emphasize that in DSM-5 the criteria no longer require the presence of memory disturbances to establish the diagnosis of neurodegenerative dementia, as was the case in previous editions. We are therefore witnessing the recognition of other types of dementia in which memory deterioration is not considered an early symptom (Apostolova, 2016). This facilitates the clinician even more in the specific diagnosis of Alzheimer's disease.

Diagnostic Criteria	***Major Neurocognitive Disorder***	***Minor Neurocognitive Disorder***
A	*Significant* cognitive decline in one or more cognitive domains, based on: 1. Concern about *significant* decline, expressed by individual or reliable informant, or observed by clinician. 2. *Substantial* impairment, documented by objective cognitive assessment.	*Modest* cognitive decline in one or more cognitive domains, based on: 1. Concern about *mild* decline, expressed by individual or reliable informant, or observed by clinician. 2. *Modest* impairment, documented by objective cognitive assessment.
B	Interference with independence in everyday activities.	No interference with independence in everyday activities, although these activities may require more time and effort, accommodation, or compensatory strategies.

C	Not exclusively during delirium.
D	Not better explained by another mental disorder.
E	▪ Specify one or more etiologic subtypes, "due to": ▪ Alzheimer's disease ▪ Cerebrovascular disease (Vascular Neurocognitive Disorder) ▪ Frontotemporal Lobar Degeneration (Frontotemporal Neurocognitive Disorder) ▪ Dementia with Lewy Bodies (Neurocognitive Disorder with Lewy Bodies) ▪ Parkinson's disease ▪ Huntington's disease ▪ Traumatic Brain Injury ▪ HIV Infection ▪ Prion Disease ▪ Another medical condition ▪ Multiple etiologies

Adapted from: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association; 2013

2. Mild Cognitive Impairment

The term "Mild Cognitive Impairment" has generally been used to identify individuals who have some cognitive impairment, but not so severe to constitute dementia. In particular, it is based on the finding of a mild cognitive deficit which is greater than what would be expected for the age and education level of the individual, but which does not cause any interference in the performance of the activities of daily life. (Berardelli, Cruccu, 2019). It was introduced in the International Classification of Diseases (ICD-10) of the OMS to indicate a deterioration of cognitive functions that do not meet the criteria for dementia (Petersen, 1995). Often the symptoms that characterize these individuals are so mild that it is very difficult for the clinician to distinguish these functional problems from those that characterize age-related cognitive decline (Petersen, 2004). For this reason, MCI can be considered as an intermediate state between normal aging and dementia and as a prodromal disorder for the transition to AD. But, it does not only concern memory disorders, but it could affect various aspects of cognitive functioning such as language, executive functioning, visuospatial abilities (Petersen, 2004).

There are in fact two subtypes of MCI. Amnestic MCI (aMCI) is characterized by memory impairment, especially episodic; Non-amnestic MCI (naMCI) is characterized by the absence of memory impairment, but the presence of impairment

in one or more of the other domains, such as executive functions / attention, language, visuospatial skills (Petersen et al., 2014). Furthermore, MCI can manifest itself as impairment in a single domain or in multiple cognitive domains. The extent of impairment across domains is critical to understanding both the severity of the disease and the likelihood of progression to dementia (Roberts, Knopman, 2013). There is a hypothesis that single- or multiple-domain aMCI progresses into AD if there is an underlying degenerative etiology. (Petersen, et al. 2009). In contrast, naMCI can progress to other forms of non-AD dementia, based on the impairment of one or more domains.

It is possible to find in the literature multiple studies that investigate MCI and the risk factors involved in the transition to AD. In particular, if we focus on the pathogenesis of MCI, it is possible to state that among the main risk factors associated with mild cognitive decline, we find advanced age and a low level of education (Yaffe, 2018).

Regarding genetic studies, an overlap was found in the results of the alleles of the APOE-4 gene with studies focusing on the pathogenesis of AD, suggesting common causes for both the diseases (Boyle et al., 2010; Lopez, et al. 2003). Several studies also examined the comorbidity between MCI and vascular diseases, demonstrating the increased probability of MCI onset in the presence of cerebrovascular diseases (Roberts, et al., 2010; Di Carlo, et al. 2000). As regards the cognitive functions, the disorder most commonly attributable to MCI concerns prospective and episodic anterograde memory, especially for the amnestic subtype (Spìndola, Brucki, 2011; Wang, et al. 2012). Impairment of executive functions is found in both forms of amnestic and non-amnestic MCI (Aretouli, Brandt, 2010), in particular for working memory skills, planning and problem solving, but not for judgment skills that remains preserved (Brandt, et al. 2009).

There is a vast literature regarding the role of neuropsychiatric symptoms, especially in relation to depression. Depression is associated with a risk of progression to MCI, especially of the amnestic type, in the population with normal cognition (Hu, et al. 2020)

A systematic review by Ma (Ma, 2020) on neuropsychological characteristics and conversion rates to dementia among MCI patients, identified among the most frequent disorders besides depression, anxiety and apathy. Anxiety is common in MCI patients; the prevalence varies between 9.9% and 52%. Furthermore, there is a high comorbidity with depression in MCI patients. The symptoms of anxiety can represent a diagnostic

indicator of MCI as they are closely correlated with executive and cognitive dysfunction (Ma, 2020). The prevalence of apathy in MCI subjects is between 10.7% and 44.8%, with a difference based on the type of MCI: amnestic of 6.9% and multidomain of 14.7% (Ma, 2020). Chilovi and colleagues (Chilovi et al. 2009) identified several neuropsychiatric symptoms in MCI patients so as to categorize four subgroups: normal MCI, depressed MCI, depressed-apathetic MCI and apathetic MCI. It was found that the latter subgroup had the highest percentage of conversion to AD, around 60%. Martin and Velayudhan (2020), through a longitudinal study with 397 MCI patients without major depression, found that the prevalence of apathy was 44.8% and that they had a higher risk of progression to AD. Therefore, today the focus of attention has shifted towards apathy especially in the attempt to identify specific treatments in early AD patients (Gallagher, et al, 2017).

The conversion rate to dementia for MCI patients is a controversial topic as prevalence and incidence rates of dementia depend on multiple factors.

Several studies confirm that patients diagnosed with MCI have a greater risk of developing various types of dementia, including AD, with an annual conversion rate of 10-20% against 1-2% of subjects cognitively healthy (Amieva et al. 2004; Mitchell, Shiri-Feshki, 2009). In particular, aMCI seems to be the phenotype that evolves more frequently towards Alzheimer's dementia, while the other types of MCI seem to evolve towards other forms of dementia (such as frontotemporal dementia, Lewy body dementia or Parkinson's dementia) (Albert, et al. 2011; Subramanyam, Singh, 2016; Geda, 2012).

Based on this evidence, Mild Cognitive Impairment is identified as a precursor of AD, although not all patients progress to dementia within 5-7 years (Petersen, 2004). Many MCI patients can remain stable and do not develop dementia (Gomersall, et al. 2017), but there are also patients who may return to normal (Petersen, 2010).

So, when planning a timely diagnosis of AD, the focus of intervention is now focused from the moderate and severe stages of dementia to the early phases of the disease, in particular the stage of mild AD, but above all of MCI due to AD; in fact, the prevalence of MCI ranges from 16% to 22.2% worldwide, and approximately 10% -15% of older adults with MCI progress to dementia annually (Song, et al. 2021). The overall annual conversion rate to dementia is approximately 1% -3% in the elderly. Given the lack of effective pharmacological treatments for dementia, i.e. that have a regressing effect on the disease, the clinician's top priority is to improve or preserve the residual cognitive

function of older adults with MCI (Song et al. 2021). To reach this clinical outcome, it is certainly necessary to take the first step of a correct diagnosis of cognitive decline so as to be able to prevent or delay the transition from MCI to dementia, through an adequate neuropsychological examination (Di Nuovo, Vianello, 2013).

3. Neuropsychological Evaluation in MCI and AD

When referring to neuropsychological evaluation, it is essential to discuss the use of various psychometric tools that we will shortly present, but we cannot ignore the clinical interview with the patient who must be evaluated. The neuropsychological examination has the objective of obtaining a global assessment of the patient that allows the detection of residual and impaired cognitive functions, allowing the construction of diagnostic hypotheses. This aim cannot be reached exclusively on the basis of the score on a psychological test, since it is that same score that will be interpreted and examined in order to make the right diagnosis, with any further details of the case or pharmacological prescriptions and so on. It is therefore essential that during the neuropsychological interview with the patient, the degree of impairment of the subject should be investigated in order to understand how to set up the assessment (i.e. what type of tools to use) through the formulation of very specific questions that investigate the different cognitive abilities that they could be impaired by pathology, such as verbal comprehension, disease awareness, critical sense, general knowledge and motivation, and so on. Often, the presence of a family member is useful for the neuropsychological examination, both for verifying the reliability of the information provided by the patient, and for collecting additional information and investigating the degree of compliance and support for any treatment.

When considering AD patients, but especially patients with amnestic MCI at increased risk of developing AD, neuropsychological tools in combination with biological markers play a central role in early diagnosis (Caraci et al. 2013).

There is no standardized procedure with respect to the tools to be used to diagnose AD or MCI. The tools used in the diagnostic process of dementia should include informative questionnaires on autonomy in the activities of the subject's daily life such as the Activities of Daily Living / Instrumental Activities of Daily Living (ADL / IADL) tests through which discrimination can be established between dementia and mild neurocognitive disorder, or mild cognitive decline, as indicated in the DSM-5.

Clearly, in the case of these pathologies it is certainly important to investigate the general cognitive level (in particular executive functions, attention, language, memory and visuospatial skills). For the assessment of cognitive function, it would be optimal to use global cognitive function tests, in paper form and as short as possible, which allow the evaluation of the general mental state.

Among the main tools of global cognitive assessment, we should consider:

1. The Battery for Mental Deterioration (BDM: Caltagirone, et al., 1979), an instrument developed in Italy that includes 7 tests that require approximately 45 to 75 minutes for the administration. The battery evaluates different aspects of memory (short and long term, semantic-lexical), praxic-constructive skills, and linguistic skills. 8 scores are obtained, four for the processing of verbal material and four for the processing of visual-perceptual material (Caltagirone, et al., 1979).
2. Mini Mental State Examination (MMSE: Folstein, et al., 1975; Italian version: Measso, et al. 1993; Magni et al. 1996) screening tool for AD. The MMSE represents one of the most used tools, about 60%, in the diagnosis of MCI, followed by the clinical interview around 54%, within primary care (Pirani, et al. 2020). The test consists of 11 items, which investigate different cognitive areas (space-time orientation, language through naming tests, repetition, writing and understanding and execution of oral and written commands, immediate and recall memory, attention and calculation, praxia visual-constructive). However, although it is very widespread, it has some limitations: it does not consider the multidimensional structure of cognitive functions, for example memory, for which it evaluates areas less sensitive to deterioration than others and underestimates the visual-spatial areas; moreover, it appears not very sensitive in the evaluation of MCI, especially in the case of patients with high cognitive reserve (Pirani, et al. 2020).
3. Montreal Cognitive Assessment (MoCA: Nasreddine, et al. 2005; Italian version: Santangelo, et al., 2015; Conti et al. 2014) was created for rapid screening and early detection of mild cognitive impairment. It can be used as an alternative or in addition to MMSE and evaluates different cognitive domains such as attention and concentration, executive functions, memory, language, visual-constructive skills, abstraction, calculation and orientation. It appears to be the best screening tool for MCI detection, showing a sensitivity

of 83-97% (Abd Razak, et al. 2019). The MoCA shows better performance than the MMSE with a sensitivity of 89% and a specificity of 75% (Abd Razak, et al. 2019). Moreover, Pinto et al. highlighted that out of 34 articles, more than 80% showed that MoCA is superior to MMSE in discriminating individuals with Mild Cognitive Impairment from cognitively healthy individuals (Pinto, et al. 2019). Furthermore, the MoCa allows a differential diagnosis, as it contains items that investigate the functions of the frontal lobe, which in AD and Frontotemporal Dementia (FTD) patients obtain very different scores. The results of tests such as verbal fluency and speech production, orientation and delayed recall also allow to differentiate AD patients from FTD patients (Larner, 2018).

4. The General Practitioner Assessment of Cognition (GPCOG) is a short screening test for cognitive impairment introduced by Brodaty and colleagues in 2002, it represents a very short and easy to use screening tool (Brodaty et al. 2002).

In addition to tools for assessing global cognitive functioning, there are numerous neuropsychological tests to assess specific cognitive functions. Some of these are described below:

1. Frontal Assessment Battery (FAB: Dubois, et al. 2000; Italian version: Appollonio et al. 2005): It proposes a simple and rapid protocol through six cognitive and behavioral tests including: conceptualization, cognitive flexibility, motor programming, sensitive to interference, control of inhibition, environmental autonomy.
2. Raven Progressive Matrices (PM), which with elderly subjects has a simplified colored version (CPM, Raven, 1947, 1954; Italian version: Spinnler & Tognoni, 1987). The test is made up of incomplete figures in which the subject must identify the figure that completes the drawing among the alternatives proposed. It highlights analytical ability independent of previously learned concepts, analysing the cognitive domains of spatial skills and reasoning.
3. Rey's 15-word test: explicit verbal memory test (Rey, 1958); has the objective of quantifying the capacity for immediate and delayed recall.
4. Rey-Osterrieth Complex Figure Copy Test (Rey, 1959; Italian calibration: Caffarra, et al., 2002). The figure of Rey foresees the copy of the figure and then its reproduction by heart after a few minutes, thus allowing to evaluate the

"loss" of memory with respect to the efficiency of the visual-perceptual reproduction, its perceptual organization, the visual memory and the working memory.

In addition to the psychological tools that evaluate cognitive functions, there are tests that evaluate the neuropsychiatric symptoms, fundamental in the case of MCI and AD since in addition to being a risk factor for these disorders, they represent one of the causes of conversion to dementia. For this purpose, it is possible to use different psychometric tools, among the most used we should consider:

1. Hamilton Psychiatric Rating scale for Depression (HDRS: Hamilton,1960).
2. Apathy Evaluation Scale (AES) (Marin, 1991)
3. Cornell-Brown Scale for Quality of Life in Dementia (CBS: Ready et al., 2002)
4. Quality of life in Alzheimer's disease (QOL-AD: Logsdon et al., 2002)
5. Caregiver Burden Inventory (CBI: Novak and Guest, 1989).

4. Current pharmacological treatment

To date, there are no effective drug therapies available for AD and MCI, which remain incurable diseases. The authorized treatments involve the use of "symptomatic" drugs, which act on symptoms of cognitive decline without intervening, on the pathogenic mechanisms. Between these drugs we can find cholinesterase inhibitors (ChEIs) (donepezil, galantamine, rivastigmine) and the NMDA antagonist (memantine) (Atri, 2019). An early impairment of cholinergic pathways has been demonstrated in AD; AChEIs seem to improve central cholinergic neurotransmission thus tending to reduce cognitive decline, at least during the first year of treatment. However, once treatment with these drugs is stopped, it is possible to see rapid cognitive decline as well as rapid deterioration leading to a greater risk of autonomy loss (Howard et al., 2015) ChEIs have been shown to be efficacious in delaying cognitive decline, stabilizing cognition or maintaining daily living activities in RCT placebo studies for up to 52 weeks (Atri 2019, Rountree 2019). In particular, donepezil and rivastigmine have been approved for mild and moderate AD, while memantine has been approved for moderate and severe AD (Yiannopoulou, Papageorgiou, 2020).

Memantine is a non-competitive low-affinity open-channel blocking NMDA receptor and affects glutamate transmission (Yiannopoulou, Papageorgiou 2013). Memantine is used for moderate and severe AD, either as monotherapy or in combination with an ChEIs (Scheltens, et al. 2016) When given as monotherapy, different studies have

shown that memantine has long-term benefits for patients with moderate and severe AD (Tricco, et al. 2018). However, scientific evidence shows that when administered in combination with ChEIs, AD patients show an increased benefit compared to monotherapy (Na, et al. 2019; Kishita et al., 2019) also showing an improvement in global functions and daily activities (Calvo-Perxas, 2017) As discussed above, neuropsychiatric symptoms can occur both before and after the onset of MCI or AD; often these symptoms also require specific and validated pharmacological treatments. Antidepressants and antipsychotics are the main treatment for BPSD (Bessey, 2019).

5. Non-pharmacological treatment

As already discussed, the pharmacological therapies currently approved and available for the treatment of Alzheimer's have a reduced clinical effectiveness, as demonstrated in several studies, and cannot always guarantee a long-term effect and certainly cannot lead to a regression of the disease. The treatment of AD must therefore be understood as aimed at managing the disease and improving or maintaining the best quality of life for the patient. For this reason, recently, the attention of researchers has also focused on different types of interventions, that is the non-pharmacological treatment (NPT) also defined as "ecopsychological intervention" (Zeisel, et al., 2016). Non-pharmacological treatment includes interventions on the cognitive, social, psychological and relational aspects of the subject, using different modalities such as group activities, therapeutic dialogues, meditation, sensory, physical and physiological stimulation. The goal of this type of intervention is to improve the quality of life through the strengthening of cognitive, psycho-affective and social skills, reducing neuropsychiatric symptoms, preserving the patient's social activity, restoring confidence and self-esteem and promoting autonomy (Zuchella, et al., 2018).

According to the American Psychiatric Association, non-drug treatments for AD can be divided into 4 groups: cognition-oriented treatments; emotion-oriented treatments; behaviour treatment; stimulation-oriented treatment (i.e. art and music therapy, physical exercise). Cognition-oriented treatments are the most studied and used in the treatment of Alzheimer's since they aim at the maintenance and exercise of cognitive functions. Carrion and colleagues (2018) conducted a systematic review with the aim of investigating the scientific evidence supporting the efficacy of cognitive therapies in dementia. The results showed that stimulation of cognitive functions among people with dementia through skills training or a mix of reality orientation and skills training

is effective in increasing cognitive functioning. However, no evidence was found to support the effectiveness of reality orientation. However, the authors highlighted many limitations of their research. Great attention has recently been given to physical activity for the prevention of cognitive decline and therefore as a novel non-pharmacological treatment for MCI and AD. In fact, it seems that physical activity has the ability to improve cognitive and functioning plasticity; promote cardiovascular health; increasing dopamine and acetylcholine levels, which play a key role in cognitive functions (Szeto, Lewis, 2016). Fonte et al. (2019) conducted a study on cognitive treatment and physical activity in MCI and AD patients with the aim of comparing the two types of treatment. They found that both cognitive treatment and physical activity have a positive effect in reducing the cognitive decline that characterizes MCI and AD; they have also shown that both treatments are able to maintain cognitive functions. Also, occupational therapy has been demonstrated to have a good effect on autonomy, improvement in quality of life and decrease of psychological symptoms, although the effect that occupational therapy may have on depressive and anxious symptoms is still unclear (Bennett, et al., 2018). Finally, it is also shown that art therapy, in particular music therapy, has a positive effect on patients suffering from dementia. In their meta-analysis Moreno-Morales et al. (2020) investigated the effect of music therapy on cognitive functions, quality of life and the depressive state of subjects with dementia. The results showed an improvement in cognitive function and a positive outcome for the long-term treatment of depression. Furthermore, music therapy appears to improve the quality of life of people with dementia when evaluated immediately after surgery. However, it does not have a long-lasting effect.

6. The role of apathy

Apathy can be defined as a specific dimension of behavior characterized by a lack of motivation (Marin, 1993) in which motivation is a superordinate concept referring to the psychological structure and the determinants of goal-directed behavior (Bindra, 1959; Madsen, 1973). Apathy in often associated with poor treatment response, reliance on caregivers to initiate activities, more rapid cognitive and functional decline and increased mortality (Ruslan, L. et al., 2013). For clinical purpose apathy is often considered as a symptom of other syndromes, such as depression or dementia. (Marin, 1993). However, it can be considered as a syndrome itself and conceptualized as a

syndrome of diminished motivation in which the lack of motivation is not attributable to diminished level of consciousness, emotional distress, or cognitive deficits (Marin, 1991).

The prevalence of apathy is well documented in different neuropsychiatric disorders (Padala, 2005), especially in MCI and AD.

Apathy is a multidimensional construct that can include both the emotional and the social sphere and presents three separate dimensions consisting of cognitive, affective and behavioural symptoms. (Robert, 2009) although there is heterogeneity in the degree in which each dimension could be present. As stated above, Marin standardized the concept of apathy and proposed a three-dimensional model (Marin, 1991) that includes emotional responsiveness, goal-directed cognition and purposeful behaviour, which can be detected with the Apathy Evaluation Scale (AES) (Marin, 1990; Marin, 1991) and animated the 2009 International Apathy Workgroup Consensus Diagnostic Criteria (Robert, 2009) which considered the decrease of motivation as a central feature of apathy and provided operational definition of the affective, cognitive, and behavioral dimensions and asserted time and impact criteria. These rules allowed to discriminate apathy from pathologies with similar symptoms (Lanctôt, 2017). In fact, the differential diagnosis of apathy is not simple since some of its characteristics are similar to those of other NPS. In particular, depressive disorders are frequent in patients with AD, (Novais,2015). but its clinical phenotype is different from that of major depressive disorder. In fact, in AD-related depression, the symptomatology is milder and less persistent compared to major depression (Olin, 2002) and includes anhedonia, psychomotor retardation, fatigue / hypersomnia and lack of insight (Ishii, 2009). Somatic symptoms in AD-related depression are associated with the severity of cognitive impairment (Troisi, 1993).

Recent studies have shown that the higher the level of apathy, the more it is a predictor of the transition to dementia (Lanctot, 2017). Most of the epidemiological studies on apathy in the AD context refer to studies on the prevalence or change of apathy symptoms over time (Brotady, 2010). Apathy is predominant both in MCI and dementia. This prevalence is positively related to the severity of dementia (Lanctôt, 2017). A 3-year observational study of 332 MCI subjects has shown a higher incidence of dementia in subjects with apathy ([HR] =1.62) (Pink, et al. 2015). A more recent investigation using the Apathy Evaluation Scale (AES) in elderly with normal

cognition and MCI showing that apathy progression over time predicted transition from MCI to dementia (Guercio, et al. 2015).

On the basis of this evidence apathy can be considered as a marker of cognitive decline and transition to dementia. This has prompted the field to flag it as a high-value neuropsychiatric risk state in the latest guidelines for preclinical AD from the National Institute on Aging (Sperling, et al. 2011). An unresolved question is to understand whether apathy can be considered as a psychological marker of preclinical AD in amnestic MCI patient and the neurobiological and clinical links between apathy and depression in AD. Furthermore, it is not clear whether apathy can influence the rate of cognitive deterioration or the response to cholinesterase inhibitors in MCI and mild AD independently from the presence of depressive disorders.

Dysfunction in dopaminergic system seems to play a central role in the pathophysiology of apathy (D'Amelio, et al. 2018). Dopaminergic dysfunction might be caused also by a progressive loss of cholinergic neurons in strict compliance with the cholinergic hypothesis (D'Amelio, al. 2018). Pharmacologic challenge has shown that AD patients with apathy have a blunted subjective reward after administration of the dopaminergic agent dextroamphetamine (Lanctôt et al. 2008). A recent 6-week multicenter, double-blind, placebo-controlled RCT investigating the treatment of low-dose methylphenidate (20 mg/day) for apathy in patients with mild-moderate AD reported significant improvement in apathy and on a modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change in the active treatment group versus placebo (Rosenberg, et al. 2013).

Antidepressant drugs have not been found to improve apathy (Berman, et al. 2012) although not specific studies have been conducted with second-generation antidepressant drugs such as fluoxetine and bupropione. Evidence from RCTs suggests that cholinesterase inhibitors can improve apathy (Winblad et al.1999; Cummings et al. 2005) and delay its onset (Waldemar et al. 2011), although further studies are needed to better understand how apathy can influence the rate of cognitive decline both in MCI and mild AD as well as the response to cholinesterase inhibitors and second-generation antidepressant drugs.

Chapter I

Cognitive dysfunction in late life depression and Alzheimer Disease: the impact of physical activity.

In recent years, an increased attention has been given to therapies other than pharmacological ones in the treatment of various psychiatric disorders. This new interest may have been stimulated by the evolution of the concept of health that no longer sees the healthy subject as a person without physical symptoms, but who instead enjoys psychological health as well. Indeed, it has been clearly established that pharmacological treatment have positive effects on mental health, but several studies have also shown the effectiveness of new methods and non-pharmacological approaches to treat CNS pathologies. Among these, one of the most studied and observed is physical activity and its potential benefits for the cognitive functions and mood of depressed and AD subjects. For this reason, we conducted the following review on the possible links between physical activity and the reduction of depressive symptoms to examine the possible synergy between pharmacological and non-pharmacological treatment to rescue cognitive function both in depressed and AD patients.

Antidepressant Drugs and Physical Activity: A Possible Synergism in the Treatment of Major Depression?

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Abstract

Major depressive disorder (MDD) is a severe mental illness that affects 5–20% of the general population. Current antidepressant drugs exert only a partial clinical efficacy because approximately 30% of depressed patients failed to respond to these drugs and antidepressants produce remission only in 30% of patients. This can be explained by

the fact that the complex pathophysiology of depression has not been completely elucidated, and treatments have been mainly developed following the "monoaminergic hypothesis" of depression without considering the key role of other factors involved in the pathogenesis of MDD, such as the role of chronic stress and neuroinflammation. Chronic stress acts as a risk factor for the development of MDD through the impairment of neurotrophins signaling such as brain-derived neurotrophic factor (BDNF) and transforming-growth-factor-b1 (TGF-β1). Stress-induced depressive pathology contributes to altered BDNF level and function in MDD patients and, thereby, an impairment of neuroplasticity at the regional and circuit level. Recent studies demonstrate that aerobic exercise strongly increases BDNF production and it may contribute as a non-pharmacological strategy to improve the treatment of cognitive and affective symptoms in MDD. Here we will provide a general overview on the possible synergism between physical activity and antidepressants in MDD. Physical activity can synergize with antidepressant treatment by rescuing neurotrophins signaling in MD patients, promoting neuronal health and recovery of function in MDD-related circuits, finally enhancing pharmacotherapeutic response. This synergism might be particularly relevant in elderly patients with late-life depression, a clinical subgroup with an increased risk to develop dementia.

Keywords: depression, physical activity, stress, affective symptoms, cognition, brain-derived neurotrophic factor, transforming-growth-factor-b1
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Introduction

Major depressive disorder (MDD) is a severe and a common mental illness affecting more than 264 million people worldwide (Gbd 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). The World Health Organization (WHO) describes depression, also indicated as MDD or clinical depression, as a mental disorder characterized by sleep and appetite disturbances, variation of mood, loss of energy, and psychomotor retardation[1].

Among the different hypotheses that have been proposed to explain MDD pathophysiology, the "monoaminergic hypothesis" has been initially validated with the development of monoaminergic antidepressants. Based on this hypothesis an impairment of monoaminergic systems [serotonin (5-HT), noradrenaline, and

dopamine] has been considered a primary event for the onset of affective and cognitive symptoms in MDD (Hirschfeld, 2000; Hamon and Blier, 2013). Therefore, the majority of antidepressant drugs have been developed according to this hypothesis, representing a useful therapeutic tool (Lopez-Munoz and Alamo, 2009); unfortunately around 30% of depressed patients are considered treatment resistant (Caraci et al., 2018a), probably because emerging additional factors involved in the pathophysiology of MDD, such as chronic stress and neuroinflammation, should be considered (Caraci et al., 2018b). The pathological effects of stress on hippocampus have contributed to the development of the so-called "neurotrophic hypothesis" according to which neurotrophic factors play a key role in the etiology of depression (Altar, 1999; Duman and Li, 2012; Jaggar et al., 2019). This hypothesis suggests that depression derives from decreased neurotrophic support resulting in neuronal atrophy, decreased hippocampal neurogenesis, and loss of glial cells (Duman and Monteggia, 2006). A hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis has been found in the 50% of depressed patients (Krishnan and Nestler, 2008) and several evidences identify chronic stress, linked to an impairment of neurotrophins such as brain-derived neurotrophic factor (BDNF) and transforming-growth-factor-b1 (TGF-b1) (Caraci et al., 2018b), as a risk factor for the development of MDD (Pittenger and Duman, 2008; Caraci et al., 2010). A significant decrease of BDNF levels has been demonstrated in animal models of depression stress-induced (Berry et al., 2012) as well as in depressed patients (Angelucci et al., 2005). Likewise, a decrease of TGF-b1 levels has been observed in hippocampus and cortex of animal models of depression (Yu et al., 2011); furthermore, several studies carried out in depressed patients have demonstrated that plasma TGF-b1 levels are reduced and correlate with depression severity (Myint et al., 2005; Rush et al., 2016). A chronic treatment with first- and second-generation antidepressants rescues BDNF levels in different preclinical models of depression (Duman and Monteggia, 2006), while selective serotonin reuptake inhibitors (SSRIs) drugs and the new multimodal antidepressant vortioxetine are able to reverse the depressive-like phenotype and memory deficits induced by amyloid-b (Ab) in mice by the rescue of TGF-b1 (Torrisi et al., 2019). Furthermore, antidepressant drugs exert immunoregulatory effects reducing the production of proinflammatory cytokines and stimulating the synthesis of TGF-b1 in depressed patients (Sutcigil et al., 2007).

Noteworthy, it has been shown that epigenetic mechanisms such as DNA methylation, microRNAs, and histone modifications are able to influence the

development of depression (Lin and Tsai, 2019) and, with specific regard to BDNF, their altered activity can in turn affect the expression and the activity of this neurotrophic factor (Hing et al., 2018).

Several studies have demonstrated that aerobic exercise (AE) could represent a non-pharmacological strategy to improve the treatment of depression, decreasing, at the same time, the burden of somatic comorbidity of this pathology (Mura and Carta, 2013; Josefsson et al., 2014). Since the 1980s, several papers have reported on the beneficial effects played by exercise and physical activity in the treatment of depression, effects comparable to those of antidepressants (Martinsen et al., 1985; Babyak et al., 2000; Belvederi Murri et al., 2018; Lopez-Torres Hidalgo, 2019). This increased interest in this field has led to the proposal that physical exercise may serve as an alternative or integrative approach in combination with monoaminergic drugs for the treatment of MDD (Martinsen, 2008).

In the present review we will provide a general overview on the possible synergism between physical activity and antidepressants in treatment of MDD, analyzing the possible benefits of physical activity both at a neurobiological level and clinical level focusing in particular on the treatment of affective and cognitive symptoms in MDD.

The Pathophysiology of Depression: the role of Neurotrophic factors and the possible impact of physical activity

MDD shows a complex pathophysiology that has been only partially elucidated in the last 10 years (Caraci et al., 2018a). Chronic stress, reduced synaptic plasticity, impairment of adult hippocampal neurogenesis, and hippocampal neurodegeneration along with the well-known dysregulation of the monoaminergic system contribute to explain the pathophysiology of MDD (Jaggar et al., 2019; Vu, 2019). Epidemiological studies support the pivotal role played by chronic stress in MDD (Pittenger and Duman, 2008); in fact, the exposure to stressful life events contributes to the development of this disease (Czeh and Lucassen, 2007). Chronic stress leads to an impaired negative feedback of glucocorticoids (GR) on the activity of HPA axis, which results in elevated cortisol levels (de Kloet et al., 2005). Excess of GR is able to induce neuronal death at hippocampal level (Yu et al., 2008) as well as dysfunctional changes in the prefrontal cortex (PFC), two regions critically involved in the cognitive symptoms of depression (Krishnan and Nestler, 2008). Stress also exerts its effects by

reducing the synthesis of factors essential for neuronal homeostasis such as BDNF (Nowacka and Obuchowicz, 2013), a neurotrophin fundamental for the maintenance of dendritic spines (Vigers et al., 2012), the regulation of adult hippocampal neurogenesis (Vilar and Mira, 2016), cognitive and mood-related behavior and aging (Castren and Kojima, 2017). Reduced levels of BDNF have been connected to dendritic atrophy, neuronal apoptosis, and inhibition of neurogenesis in MDD (Nowacka and Obuchowicz, 2013). Stress decreases BDNF concentrations in hippocampus and PFC of animal models of depression (Smith et al., 1995; Duman and Monteggia, 2006; Filho et al., 2015), in line with the reduced expression of this neurotrophic factor observed at cortical, hippocampal, and peripheral level of depressed patients (Thompson Ray et al., 2011; Reinhart et al., 2015). Stress exposure also leads to an impairment of TGF-b1 signaling in different brain regions (hippocampus, cortex, and hypothalamus) (You et al., 2011; Caraci et al., 2015). This impairment has been connected to the onset of a depressive-like phenotype in mice (Torrisi et al., 2019). Lastly, a correlation between reduced TGF-b1 plasma levels, depression severity, and treatment resistance in MDD has been proved (Sutcigil et al., 2007; Caraci et al., 2018a).

In addition to HPA axis hyperactivation, immune system dysregulation and neuroinflammation play a central role in the pathophysiology of depression (Caraci et al., 2010), underlining the great impact of immune system activation on the central nervous system and in particular on the overall activity of
monoaminergic systems (Caraci et al., 2018a). An increase of two well-known pro-inflammatory cytokines, called interleukin (IL)-1b and tumor necrosis factor-a (TNF-a), as well as a decrease of anti-inflammatory cytokines (e.g., IL-10, IL-4, and TGF-b1) have been observed in hippocampus and cortex of animal models of depression (You et al., 2011) and MDD patients (Farooq et al., 2017; Caruso et al., 2019).

Antidepressant drugs, such as sertraline and fluoxetine, exert immunomodulatory effects, reducing the production of proinflammatory cytokines and stimulating the synthesis of TGF- b1 in depressed patients (Sutcigil et al., 2007; Maes et al., 2016; Caraci et al., 2018a). Furthermore, the ability of some antidepressant drugs to induce the synthesis and the release of BDNF and TGF-b1 has been demonstrated both in vitro and in vivo studies (Caraci et al., 2010), suggesting that the long time required for BDNF restore could, at least in part, contributes to explain the therapeutic latency (2–4 weeks) of these drugs (Racagni and Popoli, 2010). Recent

studies have demonstrated the rapid and long-lasting antidepressant effects of TGF-b1 as well as the key role of TGF-b1 released from microglia in mediating the antidepressant activity of (R)-ketamine (10 mg/kg) in a mouse model of depression (Zhang et al., 2020). (R)-ketamine is a novel drug under study for treatment-resistant MDD patients. Interestingly this drug rescued the expression of TGF-b1 and its receptors in the PFC and hippocampus, whereas inhibition of TGF-b1 signaling (i.e., SB431542) or neutralizing antibody of TGF-b1 blocked the antidepressant effects of (R)- ketamine, thus suggesting the essential and novel role of TGF-b1 as antidepressant.

According to the neurotrophic hypothesis of depression, which could be the impact of physical activity on the neurobiology of depression considering recent evidence in MDD patients?

Physical activity as an add-on strategy to the traditional treatment of depression is able to reduce the relapse risk, increase adherence to pharmacological treatment, and promote the management of side effects with a 60–80% of success (Neumeyer-Gromen et al., 2004; Silveira et al., 2013; **Figure 1**).

Interestingly a recent study conducted by Murri et al. (2018), has demonstrated that physical exercise, in combination with the SSRI sertraline, reduces affective symptoms and psychomotor retardation in MDD. Furthermore, the beneficial effects of AE as an add-on strategy in the treatment of moderate to severe depression has been shown in a study carried out by Imboden et al. (2019), considering different psychological and biological variables (e.g., BDNF, HPA axis activity, cognitive symptoms) besides depression severity.

Physical activity exerts beneficial effects on pre- and postnatal brain development (Gomes da Silva and Arida, 2015), stimulates neurogenesis and synaptic plasticity by increasing BDNF synthesis and release (Walsh and Tschakovsky, 2018), and reduces HPA axis hyperactivation (Nabkasorn et al., 2006). In particular, it has been proposed, as a proof of musclebrain crosstalk, that irisin, produced during exercise through the cleavage of fibronectin type III domain-containing protein 5 (FNDC5) membrane protein and able to cross the bloodbrain barrier, induces BDNF expression at brain level, which in turn will lead to an increased hippocampal neurogenesis, and therefore to enhanced learning, memory, and mood (Pedersen, 2019). With regard to TGF-b1, the plasma concentration of this neurotrophin increases in response to exercise (1 h of treadmill running) (Heinemeier et al., 2003). In a

different study enrolling healthy people and Parkinson subjects, the immunomodulatory effects of moderate intensity on plasma neurotrophins levels was investigated (Szymura et al., 2020). Szymura et al. (2020) demonstrated that after completion of the 12 weeks training program the concentration of TGF-b1 as well as of other neurothophic factors (nerve growth factor and BDNF) were found to be increased only in training groups. Furthermore, in a study considering a total of 29 athletes, the serum levels of TGF-b1 were higher in athletes with high relative Vo2peak (relVo2peak) values, a measure of the athletes' cardiovascular fitness and aerobic endurance, compared to low relVo2peak (Weinhold et al., 2016). No studies have been conducted yet in MDD patients to assess whether SSRIs can synergize with AE to increase TGF-b1 signaling, although preliminary available evidence suggests the existence of common biological targets.

All together, the above mentioned evidence suggests a synergistic effect between AE and antidepressant drugs for the treatment of depression (Figure 2), reducing the cognitive deficits that compromise the working activities of MDD patients and influence their relapse risk (Albert et al., 2016). This synergism might be particularly relevant in elderly patients with late-life depression (LLD), a clinical sub group with an increased risk to develop dementia, improving patients' cognitive outcomes (Neviani et al., 2017).

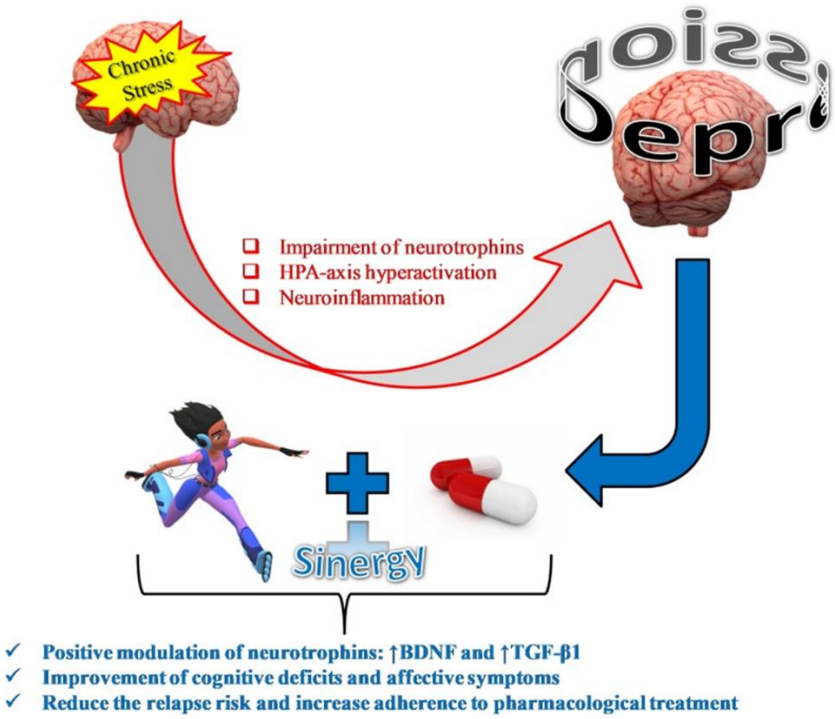

FIGURE 1 | Physical activity as an add-on treatment strategy to antagonize stress-induced depression.

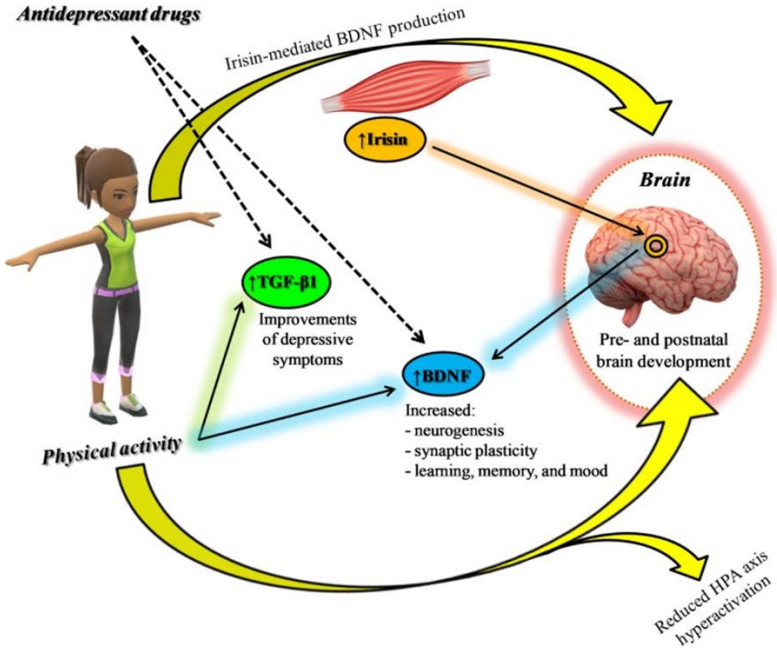

FIGURE 2 | Synergic effect between physical activity and antidepressants: positive modulation of neurotrophic factors.

Impact of physical activity on affective symptoms in MDD

Apart from biological and genetic risk factors (Hammen, 2018), physical inactivity has been identified as a risk factor for the development of depression (Adamson et al., 2016; Hammen, 2018). Along this line different studies have shown that physical activity is able to provide mental health benefits in patients with severe mental illness, reducing depressive symptoms and improving social and cognitive functions (Rosenbaum et al., 2014). In a recent global systematic review and meta-analysis including 69 studies, Vancampfort et al. (2017) have examined sedentary behavior and levels of physical activity in patients with MDD or other severe mental disorders. After the analysis of the studies, it was clear as the physical activity was connected to health benefits in healthy controls while the level of activity as well as the related benefits were low in people with severe mental illnesses (Vancampfort et al., 2017). Indeed, as confirmed in different studies, regular physical activity of moderate intensity, such as walking or cycling, is enough to give significant benefits for health and plays a protective role in preventing different mental disorders (Ashdown-Franks et al., 2019); whereas lack of exercise represents a major cause of chronic diseases, including depression (Booth et al., 2012). Several studies have focused their attention on the potential benefits of physical activity to prevent the development of this disease. The "HUNT Cohort Study" investigated whether exercise provides protection against new-

onset depression, the importance of both intensity and amount of physical activity and existing associations between them (Harvey et al., 2018). The results based on a healthy cohort of 33,908 adults followed for 11 years suggested that regular leisure-time exercise of any intensity provides protection against future depression development. Very recently Bennie et al. (2020) showed in a study employing a large sample (23,635) of German adults that AE is associated with a lower likelihood of depressive symptoms severity, as assessed by eightitem Patient Health Questionnaire depression scale (PHQ-8). In a case report published by Büyükturan et al. (2017), AE was able to improve physical conditions and to dramatically decrease depressive symptoms (sadness, anhedonia, reluctance to getting out of house, memory complaints) in a 76 years old female patient. Before enrolment in the study, she followed a 6-months treatment with antidepressants without getting any improvement. She followed a special 4-weeks exercise program consisting of 10 min warm-up (jogging, breathing, upper, and lower extremity active exercises), 20–25 min flexibility, balance and strengthening exercise, and 10 min cool-down exercise periods.

It has been shown that regular physical activity is able to reduce sleep disturbances (Chen et al., 2010) and improve somatic, affective, and cognitive symptoms in depressed patients, especially by enhancing the psychological health and social relationships (Babyak et al., 2000). Netz (2017), by the analysis of different randomized controlled trials in which physical exercise and pharmacologic treatment were compared, found in all studies considered, except one, that patients performing physical activity as an adjunctive treatment for depression have a significant improvement of depressive symptoms and a better clinical response after the exercise period.

An additional meta-analysis, carried out by Kvam et al. (2016), shows as different types of exercise (e.g., walking, running, cycling) could represent a viable adjunct treatment in combination with antidepressants. They demonstrate that the effects of exercise as an independent treatment were evident, with maximum efficacy showed when compared to no intervention, suggesting that physical activity may represent an alternative approach in non-responder patients. As discussed above, a regular physical activity is also able to reduce depressive symptoms by different neurobiological mechanisms. In fact, it can increase monoaminergic neurotransmission (Stenman and Lilja, 2013), reduce cortisol levels simultaneously

increasing hippocampal neurogenesis (Rethorst et al., 2009; Blake, 2012; Niwa et al., 2016), and increase b-endorphin and BDNF levels (Ernst et al., 2006). Since in the brain, neurons are a significant source of BDNF, whose synthesis occurs in regions fundamental for emotional and cognitive functions (Sasi et al., 2017), these preliminary evidence suggests that physical activity, when performed in combination with pharmacological antidepressant treatment, may improve affective symptoms in MDD patients.

Impact of physical exercise on cognitive symptoms in MDD

MDD could be considered as the most common mental illness among elderly people with an estimated prevalence ranging from 4.6 to 9.3% (Luppa et al., 2012). Rates of MDD are by and large lower in healthy community-dwelling elderly people than in younger adult populations, in a range from 1 to 3% (Kessler et al., 2010). However, these rates can increase on the basis of increasing medical and psychiatric comorbidity as well as in relation to various social conditions (Espinoza and Kaufman, 2014). LLD, occurring in people with an age $\geq$ 60 years, is often associated to cognitive dysfunction (Taylor, 2014). Cognitive dysfunction can affect one or multiple cognitive domains such as attention, working memory, verbal fluency, visuospatial abilities, and executive function (Murrough et al., 2011). Furthermore, this clinical sub-group presents a higher risk to develop dementia, in particular Alzheimer's disease and vascular dementia (Caraci et al., 2010; Diniz et al., 2013). LLD clinical manifestations are individual suffering, increased morbidity, premature mortality, and greater healthcare utilization (Diniz et al., 2013; Meijer et al., 2013), compromising the geriatric patients' life quality (Morimoto et al., 2015). Moreover, LLD is a condition often accompanied by significant impairment in physical and social functioning as well as disability (Blazer, 2003; Chang et al., 2016). Longitudinal studies have shown that LLD worsens the outcomes of physical illnesses and the likelihood of frailty in elderly people (Butters et al., 2008; Vaughan et al., 2015). Research community has focused its attention on physical exercise as a potential non-pharmacological treatment to improve cognitive function in depressed elderly patients. Since 1990s, several studies have been carried out to demonstrate the efficacy of physical exercise as an intervention for clinical depression in these patients (Dupuis and Smale, 1995; Blumenthal et al., 1999). In a randomized controlled trial, Singh et al. (2001) demonstrated the effectiveness of a 20 weeks physical exercise program as a long-term

treatment for clinical depression in elderly patients. The same year, in a different study, the effectiveness of a structured exercise program on specific areas of cognitive functioning (e.g., attention, concentration, executive processes, figural memory) compared to antidepressants treatment has been proved (Khatri et al., 2001). In 2012, Bridle et al. (2012) showed that structured physical exercise tailored to individual ability reduces depression severity in older people with clinically significant symptoms of depression. More recently, Heinzel et al. (2015) demonstrated that all investigated types of physical exercise, such as AE, resistance training, dancing, and alternative forms of exercise (Qi Gong and Tai Chi), may serve as a feasible and additional intervention for depression in elderly people. This preliminary evidence was strengthened by a meta-analysis of randomized controlled trials carried out by Schuch et al. (2016), suggesting that previous meta-analyses have underestimated the benefits of exercise and therefore structural physical exercise should be considered as a routine component of the management of depression in older adults.

This evidence shows how physical exercise could improve the effectiveness of pharmacological treatments in elderly depressed patients (Mura and Carta, 2013; Murri et al., 2015). An improvement in memory and executive functions that persists for up to 24 months was demonstrated in elderly depressed patients who followed an integrative approach consisting of combined physical activity and pharmacological treatment (Bragin et al., 2005). Murri et al. (2015), in a study of 24 weeks employing 121 primary care patients (>65 years) with major depression, demonstrated the synergism between the antidepressant sertraline and two different types of physical exercise in improving the outcomes related to LLD. In particular, a higher remission rate (primary outcome) was observed for the higher intensity, progressive AE plus sertraline group (81%), showing an increment of +8% (and shorter time to remission) and +36% compared to lower-intensity, non-progressive exercise plus antidepressant and sertraline alone, respectively.

Neviani et al. (2017) performed secondary analyses on data from the Safety and Efficacy of Exercise for Depression in Seniors study, a trial comparing the effectiveness of sertraline, in the absence or in the presence of progressive or non-progressive exercise. The results of 121 patients (mean age 75 years) showed improvements of Montreal Cognitive Assessment (MoCA) total scores and visuospatial/executive functions for sertraline plus progressive exercise group, showing how the addition of aerobic, progressive exercise to antidepressant drug

treatment may offer significant advantages over standard treatment with regard to cognitive abilities and disability (Neviani et al., 2017).

Conclusion

Physical activity stimulates neurogenesis and synaptic plasticity through BDNF synthesis and release, induces physiological changes in endorphine and monoamine levels, increases the plasma concentration of TGF-b1, and reduces cortisol levels; it can also act as an "anti-inflammatory factor" increasing IL-10 levels and suppressing TNF-a production, thus exerting "antidepressant-like effects". Therefore, we can assert that physical activity modulates many mechanisms and systems involved in the pathophysiology of depression. Physical activity has also proved able to act on the core symptoms of depression, decreasing sadness, anhedonia, and sleep disturbances, improving metabolic control and cognitive functions such as attention and concentration, and also decreasing the risk of depression and dementia development. Lastly, different clinical trials have highlighted the effects of physical activity as add-on treatment for MDD patients with moderate to severe depression, underlining the existing synergism between AE and the traditional pharmacological treatment. This synergism might be particularly relevant in elderly patients with LLD, a clinical sub-group characterized by an increased risk to develop dementia.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Chapter II

The link between Apathy and Alzheimer's Disease: the role of psychometric tools and the possible implications for the treatment

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Abstract

Abstract Alzheimer's Disease (AD) represents a critical challenge because of its increasing neuropsychological impairment with progressive cognitive decline accompanied by Behavioral and Psychological Symptoms of Dementia (BPSD) in almost 90% of patients. BPSD represent relevant clinical problems, leading to a worsening in the general conditions of patients. More specifically, apathy is often associated with a poor response to treatment, a faster cognitive and functional decline and an increased mortality rate.

Apathy can be considered as a common symptom of AD and as an early marker of cognitive decline and transition from mild cognitive impairment to dementia. Recent studies have shown different neurobiological and clinical links between apathy and AD. Evidence discussed in the present article suggests a strong clinical link between apathy and AD as well as the relevance of psychometric tools, such as the Apathy Evaluation Scale (AES), to better diagnose and treat apathy in patients with AD. The

aim of this review was thus to provide a general overview of the neurobiological and clinical links between apathy and AD, with the purpose of evaluating the impact of apathy on the health of AD patients, focusing on the role of psychometric tools and the possible implications for treatment. A multimodal intervention should be promoted as an innovative approach for the future treatment of apathetic AD patients.

Keywords: Apathy; Alzheimer; Psychometric tools; Treatment.

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1. Introduction

Alzheimer's Disease (AD) can be defined as a progressive and remediless neurodegenerative disease that affects an increasing number of subjects over the age of 65 (Albert, 2007). It is the most common form of dementia (Herrera, Caramelli, Silveira, & Nitrini, 2002; Hirtz, Thurman, Gwinn-Hardy, Mohamed, Chaudhuri, & Zalutsky, 2007) and in recent years it has been demonstrated (Isaacson, Ganzer, Hristov, Hackett, Caesar, Cohen et al., 2018) that late-onset AD begins decades before a diagnosis, with a long preclinical and prodromal phase often beginning in midlife (Frisoni, Winblad, & O'Brien, 2011). AD represents a critical challenge to the health care system with the aging population (Robert, Ferris, Gauthier, Ihl, Winblad, & Tennigkeit, 2010) because of its increasing neuropsychological impairment with a progressive decline of memory, language, executive function and visuospatial skills (Cummings & McPherson, 2001). The characteristics of the disease, of cognitive and functional decline, are accompanied by Behavioral and Psychological Symptoms of Dementia (BPSD) in almost 90% of patients (Guimarães, Levy, Teixeira, Beato, & Caramelli, 2008). BPSD are symptoms of disturbed perception, thought content, mood, and behavior that occur frequently in patients with dementia; they are common precipitators of institutional care (Mitchell, Herrmann, & Lanctôt, 2011) and significantly contribute to decreasing the quality of life of caregivers (Lyketsos, Lopez, Jones, Fizpatrick, Breitner, & Dekosky, 2002; Banerjee, Smith, Lamping, Harwood, Foley, Smith et al., 2006). BPSD, including apathy, agitation, delusion, irritability, anxiety, disinhibition and hallucinations (Cummings & McPherson, 2001), represent significant clinical problems, leading to an accelerated functional decline, the distress

of caregivers and aggression towards patients and possibly to an increased mortality rate, as reviewed by Guimarães and colleagues (2008).

Apathy can be defined as a specific dimension of behavior, characterized by a lack of motivation (Marin, Firinciogullari, & Biedrzycki, 1993), in which motivation is a superordinate concept referring to the psychological structure and the determinants of goal-directed behavior (Bindra, 1959; Madsen, 1973). Apathy in often associated with a poor response to treatment, the reliance on caregivers to start activities, a more rapid cognitive and functional decline and an increased mortality rate (Ruslan, Teerenstra, Smalbrugge, Vernooij-Dassen, Bohlmeijer, Gerritsen et al., 2013). For clinical purposes apathy is often considered as a symptom of other syndromes, such as depression or dementia (Marin et al., 1993). However, it can be considered as a syndrome in itself and conceptualized as a syndrome of reduced motivation in which the lack of motivation is not attributable to a reduced level of consciousness, emotional distress, or cognitive deficits (Marin, 1991). Apathy is a multidimensional construct that can include both the emotional and the social sphere and presents three separate dimensions consisting of cognitive, affective and behavioral symptoms (Robert, Onyike, Leentjens, Dujardin, Aalten, Starkstein et al., 2009) although there is heterogeneity in the degree in which each dimension could be present. The prevalence of apathy is well documented in different neuropsychiatric disorders (Padala, Frederick, & Subhash, 2005), especially in Mild Cognitive Impairment (MCI) and AD. In fact, from an epidemiological point of view, apathy can be considered as a common symptom of AD (Rea, Carotenuto, Fasanaro, Traini, & Amenta, 2014). Recent studies have shown that the higher the level of apathy, the more it is a predictor of the transition to dementia (Lanctôt, 2017). Most of the epidemiological studies on apathy in the context of AD refer to studies on the prevalence or change of apathy symptoms over time (Brodaty, Altendorf, Withall, & Sachdev, 2010). Apathy is predominant both in MCI and dementia and its prevalence is positively related to the severity of dementia (Lanctôt, 2017). It can determine high levels of distress in caregivers (Samus, Rosenblatt, Steele, Baker, Harper, Brandt et al., 2005) and, as in the case with AD, it can provoke several conflicts and unpleasant emotions, like anger and exhaustion, between patients and caregivers. On the basis of this evidence apathy can be considered as an early marker of cognitive decline and transition to dementia. This has prompted the field to flag it as a high-value neuropsychiatric state of risk, as has been highlighted in the latest guidelines for preclinical AD from the National Institute on

Aging (Sperling, Aisen, Beckett, Bennett, Craft, Fagan et al., 2011). But already in 2008, The European Alzheimer's Disease Consortium had drawn guidelines for the diagnosis of apathy (Winbald, Frisoni, Frolich, Johannsen, Johansson, Kehoe et al., 2008). To make a correct diagnosis of apathy the reduced motivation clinical picture must persist for no less than four weeks, and two of the following three dimensions should be present: (I) reduced goal-directed behavior, (II) reduced goal-directed cognitive activity, and (III) reduced emotions. In a recent work, Robert and collaborators (Robert, Lanctôt, Agüera-Ortizc, Aaltend, Bremonda, Defrancescof et al., 2018) proposed new diagnostic criteria for apathy to be adopted both in the clinical and the research domain (see Tab. 1).

TAB.1 New Diagnostic Criteria For Apathy 2018.

CRITERION A: A quantitative reduction of goal-directed activity either in behavioral, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient himself/herself or by observation of others.

CRITERION B: The presence of at least 2 of the 3 following dimensions for a period of at least four weeks and present most of the time

B1. BEHAVIOUR & COGNITION Loss of, or diminished, goal-directed behaviour or cognitive activity as evidenced by at least one of the following: General level of activity: the patient has a reduced level of activity either at home or work, makes less effort to initiate or accomplish tasks spontaneously, or needs to be prompted to perform them. Persistence of activity: He/she is less persistent in maintaining an activity or conversation, finding solutions to problems or thinking of alternative ways to accomplish them if they become difficult. Making choices: He/she has less interest or takes longer to make choices when different alternatives exist (e.g., selecting TV programs, preparing meals, choosing from a menu, etc.) Interest in external issue: He/she has less interest in or reacts less to news, either good or bad, or has less interest in doing new things Personal wellbeing: He/she is less interested in his/her own health and wellbeing or personal image (general appearance, grooming, clothes, etc.).

B2. EMOTION Loss of, or diminished, emotion as evidenced by at least one of the following: Spontaneous emotions: the patient shows less spontaneous (self-generated) emotions regarding their own affairs, or appears less interested in events that should matter to him/her or to people that he/she knows well. Emotional reactions to environment: He/she expresses less emotional reaction in response to positive or negative events in his/her environment that affect him/her or people he/she knows well (e.g., when things go well or bad, responding to jokes, or events on a TV program or a movie, or when disturbed or prompted to do things he/she would prefer not to do). Impact on others: He/she is less concerned about the impact of his/her actions or feelings on the people around him/her. Empathy: He/she shows less empathy to the emotions or feelings of others (e.g., becoming happy or sad when someone is happy or sad, or being moved when others need help). Verbal or physical expressions: He/she shows less verbal or physical reactions that reveal his/her emotional states.

B3. SOCIAL INTERACTION Loss of, or diminished engagement in social interaction as evidenced by at least one of the following: Spontaneous social initiative: the patient takes less initiative in spontaneously proposing social or leisure activities to family

or others. Environmentally stimulated social interaction: He/she participates less, or is less comfortable or more indifferent to social or leisure activities suggested by people around him/her. Relationship with family members: He/she shows less interest in family members (e.g., to know what is happening to them, to meet them or make arrangements to contact them). Verbal interaction: He/she is less likely to initiate a conversation, or he/she withdraws soon from it Homebound: He /She prefer to stays at home more frequently or longer than usual and shows less interest in getting out to meet people.

CRITERION C These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

CRITERION D The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to a diminished level of consciousness, to the direct physiological effects of a substance (e.g. drug of abuse, medication), or to major changes in the patient's environment.

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The recent evidence thus suggests a key role of apathy in AD. Along this line the aim of this review was to provide a general overview of the neurobiological and clinical links between apathy and AD, with the purpose of giving the clinicians the opportunity to evaluate the impact of apathy on the health of AD patients, focusing on the role of psychometric tools and the possible implications for treatment.

2. Neurobiological links between apathy and Alzheimer's Disease

In recent years, apathy has been deeply investigated, due to its high prevalence in neuropsychiatric disorders, especially in AD. Several studies have demonstrated its anatomical and neuropsychological correlates, in particular through neuroimaging studies. An association was found, for example, between apathy and the dysfunction in both the dorsolateral and orbitofrontal areas of the prefrontal regions and sub-regions within the basal ganglia (Eslinger, Moore, Antani, Anderson, & Grossman, 2012). In particular, an association between apathy and atrophy was revealed in AD concerning many different frontal regions, such as the anterior cingulate cortex (ACC) (Apostolova, Akopyan, Partiali, Steiner, Dutton, Hayashi et al., 2007; Bruen, McGeown, Shanks, & Venneri, 2008; Grambaite, Selnes, Reinvang, Aarsland, Hessen, Gjerstad et al., 2011; Tunnard, Whitehead, Hurt, Wahlund, Mecocci, Tsolaki et al., 2011; Mori, Shimada, Shinotoh, Hirano, Eguchi, Yamada et al., 2014), the medial frontal cortex (Apostolova et al., 2007; Mori et al., 2014), the orbitofrontal cortex (Holthoff, Beuthien-Baumann, Kalbe, Lüdecke, Lenz, Zündorf et al., 2005; Tunnard et al., 2011; Mori et al., 2014), the pars triangularis and insula (Tunnard et al., 2011;

Moon, Moon, Kim, & Han, 2014; Mori et al., 2014), the lower inferior temporal cortical thickness (Donovan, Wadsworth, Lorius, Locascio, Rentz, Johnson et al., 2014; Guercio, Donovan, Ward, Schultz, Lorius, Amariglio et al., 2015), as well as the fronto-parietal control network connectivity (Munro, Donovan, Guercio, Wigman, Schultz, Amariglio et al., 2015). Moreover, as recently reviewed by Starkstein and Brockman (2018), the decreased density of grey matter in the right superior frontal gyrus, in the bilateral middle and inferior frontal gyrus, the ACC and the basal ganglia (bilateral putamen and head of the caudate) has found to be correlated to an increased risk to develop apathy. These areas are critically involved in affective modulation and in sensory and emotional information processing (Tekin & Cummings, 2002; Levy & Dubois, 2006). A great attention has been given to the anterior cingulate cortex because it is involved in the systems of motivation and reward as a part of a frontal striatal circuit; moreover, it has been demonstrated that this circuit is correlated with symptoms of apathy (Tekin & Cummings, 2002; Blundo & Gerace, 2015). Levy and Dubois (2006) examined the correlation between the dimensions of apathy (emotional, affective, cognitional and auto-activation) and the anatomical regions of the brain. They found that three different areas of the brain could be attributed to their physiopathology; emotional-affective apathy was found to be typically associated with the damage of circuits linking the orbito-medial prefrontal and limbic cortex to the basal ganglia. Cognitive apathy was, instead, generally correlated to the dysfunction of the dorsolateral prefrontal cortex and related portions within the basal ganglia, while auto-activation apathy was related to the associative and limbic territories of the internal portion of the globus pallidus.

Finally, the hypofunction of the dopaminergic system should also be taken into consideration as a relevant neurobiological link between apathy and AD. As reviewed by Mitchell and colleagues (2011), in AD patients there seems to be a correlation between the pathophysiological changes to the DAergic neurons in the reward system and the onset of apathy. Indeed, DA mediates feelings of motivation, but it has been shown that there is a dysfunction of the dopaminergic system at an early stage of the pathogenesis of AD with a central role in the pathophysiology of memory deficits and apathy in AD (D'Amelio, Puglisi-Allegra, & Mercuri, 2018).

3. Psychometric tools to evaluate apathy in AD

Whereas apathy can be considered as a preclinical manifestation of the disease and AD patients can have a more rapid cognitive decline (Starkstein, Jorge, Mizrahi, & Robinson, 2006) and a more rapid loss of autonomy in the activities of daily life, a rapid recognition and diagnosis are needed to plan an appropriate treatment. An accurate assessment is essential to improve the management of apathy and its associated symptoms and conditions. Several psychometric tools for apathy are present in the literature, but we will describe the ones, which are most widely adopted (Clarke, Ko, Kuhl, van Reekum, Salvador, & Marin, 2011) and that have been validated on the AD population (Radakovic, Harley, Abrahams, & Starr, 2015; Mohammad, Ellis, Rau, Rosenberg, Mintzer, Ruthirakuhan et al., 2018; see Tab. 2 for details).

TAB. 2 Selection of validated psychometric tools to assess Apathy in AD

Full name	Abbreviation	n. Item	Authors
Apathy Evalutation Scale	AES (AES-C; AES-I; AES-S)	18	Marin, 1991
Apathy Scale	AS	14	Starkstein, 1992, 1995
Short Version Of Apathy Evaluation Scale		10	Lueken, et al. (2007)
Neuropsychiatric Inventory - Apathy Subscale	NPI - Apathy Subscale	8	Cummings, et al. 1994
Apathy Inventory	IA	3	Robert, et al. 2002
Dementia Apathy Interview and Rating	DAIR	16	Strauss, Sperry, 2002

The Apathy Evaluation Scale (AES) was developed by Marin and colleagues (Marin, Biedrzycki, & Firinciogullari, 1991), on the basis of the definition of apathy according to Marin, which describes a syndrome of loss of motivation as reflected by

the acquired changes in affection (mood), behavior and cognition (Marin *et al.*, 1991). It is measured through a four-point Likert-scale, composed of 18 items that assess and quantify the emotional, behavioral and cognitive aspects of apathy. There are three different ways of measuring the scale: through a self-report (AES-S), an informant report (AES-I) or a clinician interview (AES-C). The AES-C, in particular, includes a semi-structured open-ended interview that helps the clinician to collect information from the patient concerning his/her typical day activities, hobbies and interests, which reveals the degree of the subject's motivation and directs the clinician in providing his/her own rating of the individual's level of apathy on each item. Every item is rated on a 4-point response scale (0 = not at all true/characteristic to 3 = very much true/characteristic). Higher scores indicate more severe apathy (Marin *et al.*, 1991). The AES-C version takes between 10-20 minutes to be completed (Marin *et al.*, 1991).

Different studies (Mohammad *et al.*, 2018) demonstrated good to excellent internal consistency of all the versions of the AES, varying the values for convergent validity and good discriminant validity. However, as Marin and colleagues noted (Marin, Biedrzycki, & Firinciogullari, 1991; see also Mohammad *et al.*, 2018), only the AES-C and AES-S versions were able to discriminate apathy from depression. Moreover, the AES has been employed in three Randomized Clinical Trials (RCTs) as a primary outcome in patients with apathy and AD (Herrmann, Rothenburg, Black, Ryan, Liu, Busto *et al.*, 2008; Rosenberg, Lanctôt, Drye, Herrmann, Scherer, Bachman *et al.*, 2013; Padala, Padala, Lensing, Ramirez, Monga, Bopp *et al.*, 2018).

Two different scales were developed on the basis of the first version of the AES. Starkstein and colleagues (Starkstein, Mayberg, Preziosi, Andrezejewski, Leiguarda, & Robinson, 1992) developed a 14-item Apathy Scale, which is a short and slightly modified version of Marin's AES, and they validated it on the stroke, Parkinson's and AD population (Starkstein, Migliorelli, Manes, Teson, Petracca, Chemerinski *et al.*, 1995; Starkstein, Jorge, & Mizrahi, 2006). Lueken and co-workers (Lueken, Seidl, Volker, Schweiger, Kruse, & Schroder, 2007), instead, developed an abbreviated version of Marin's instrument, reducing the items from 18 to 10. This scale demonstrated a moderate convergent validity with the Neuropsychiatric Inventory (NPI)-apathy and an excellent internal consistency (Mohammad *et al.*, 2018). The aforementioned authors reduced the items considered to be redundant (Starkstein *et al.*, 1992) or inappropriate (Lueken *et al.*, 2007) according to experts with a special

knowledge of the population being assessed. As with the original Apathy Evaluation Scale, each item is measured with a four-point Likert scale.

The NPI was developed by Cumming (Cummings, Mega, Gray, Rosenberg-Thompson, Carusi, & Gornbein, 1994; Cummings, 1997) as a multidimensional instrument to assess neurobehavioral disorders in dementia. The NPI has a specific 8-item subscale to measure apathy, which lies in a general screen item rated on a yes-versus-no basis. Its scores have a scale ranging from 0 to 12, and higher scores indicate a more severe presence of apathy (Cummings *et al.*, 1994; Cummings, 1997). The NPI and NPI-apathy subscale were used and validated on multicultural sample patients with dementia and AD (Clarke *et al.*, 2011).

The Apathy Inventory (AI) (Robert, Clairet, Benoit, Koutaich, Bertogliati, Tible *et al.*, 2002) is based on Marin and colleagues' diagnostic criteria of apathy (Marin, 1991; Marin *et al.*, 1991), which means lack of emotional response, self-initiated actions, and interest in things. This is why the AI includes 3 different items for the assessment of emotional blunting, lack of initiative, and symptoms of loss of interest. The AI involves two versions: a clinician-administered interview to the caregiver (AI-caregiver) or the patient (AI-patient). The frequency is rated on a four-point Likert scale and the severity on a three-point Likert scale. The AI validation was carried out in a mixed sample consisting of normal controls, MCI patients and AD patients (Robert *et al.*, 2002). The internal consistency reported for the caregiver-based version is of good quality and the between-rater and test-retest reliability were excellent and demonstrated favorable values for all three items on the scale (Robert *et al.*, 2002; Mohammad *et al.*, 2018).

The Dementia Apathy Interview and Rating (DAIR) (Strauss & Sperry, 2002) is an informant-based unidimensional 16-item clinician-administrated scale to measure changes in motivation, engagement, and emotional response in MCI patients with apathy. The scale is administered to a caregiver using a structured interview with questions concerning apathy in the patient over the past month. Each item is rated on a 4-point scale (0 = no or almost never to 3 = yes or almost always) with higher scores corresponding to a greater severity in apathy. Only items representing a change in behavior are included in the final apathy score. The DAIR has very good internal consistency and the two-month test-retest reliability and the inter-rater reliability also demonstrated to be very good (Strauss & Sperry, 2002).

The presence of valid and reliable apathy scales are essential to assess and plan treatment of the apathy syndrome in the AD population. As we have seen and thoroughly described, there are a lot of well-structured, valid and reliable psychometric tools for the evaluation of apathy that can be used in conjunction with other clinical tools of assessment and that provide altogether a more complex and complete clinical evaluation of the subject. However, a gold standard of apathy assessment is still lacking.

4. Pharmacological treatment of apathy in AD

The pharmacological treatment of apathy appears to be essential to take care and manage AD patients, although it still represents an unmet clinical need. Different studies have investigated the role of different psychotropic drugs on the pharmacological treatment of apathy. Concerning donepezil and rivastigmine, evidence from Randomized Clinical Trials (RCTs) suggests that cholinesterase inhibitors can improve apathy (Winblad, Engedal, Soininen, Verhey, Waldemar, & Wimo, 1999; Cummings, Koumaras, Chen, & Mirski, 2005) and delay its onset (Waldemar, Gauthier, Jones, Wilkinson, Cummings, Lopez *et al.*, 2011). In a recent RCT, the authors compared the apathy scores of 113 mild to moderate AD patients treated for 24 months with donepezil plus a cholinergic precursor (choline alphoscerate) with those of patients who were administered to donepezil alone (Rea, Carotenuto, Traini, Fasanaro, Manzo, & Amenta, 2015). The results demonstrated that the combination of donepezil with choline alphoscerate was more effective than donepezil alone in reducing apathy in AD patients. Lopez and colleagues (Lopez, Mackell, Sun, Kassalow, Xu, McRae *et al.*, 2008) conducted a multi-center, open-label, 12-week study to evaluate the efficacy and safety of the administration of donepezil in 106 mild to moderate AD Hispanic patients treated with donepezil 5 mg/day for 6 weeks followed by 10 mg/day for another 6 weeks. The authors demonstrated that the NPI "apathy/indifference" subdomain showed a statistically significant improvement in donepezil-treated patients. Other studies confirmed that donepezil could improve apathy symptoms in patients with mild-severe AD (Drijgers, Aalten, Winogrodzka, Verhey, & Leentjens, 2009). A validation of the hypothesis that the rescue of the cholinergic system can be a useful approach for the treatment of apathy comes from other relevant studies conducted with cholinesterase inhibitors, such as rivastigmine and galantamine. In an open-label, multi-center study (Gauthier,

Juby, Dalziel, Re´hel, Schecter, & EXPLORE Investigators, 2010) the efficacy of rivastigmine on apathy was evaluated in a sample of 4460 AD patients, demonstrating that the percentage of patients showing an improvement vs. a deterioration in apathy at month 6 was in the order of 42.8 vs. 7.2%, respectively. Galantamine can also be used for the treatment of apathy in AD. In 2004, Cummings and colleagues (Cummings, Schneider, Tariot, Kershaw, & Yuan, 2004) assessed the efficacy of galantamine at different doses (8, 16, or 24 mg/day) in a 21-week, multi-center RCT in 978 patients with mild to moderate AD. This study demonstrates a significantly less appearance of apathy in patients treated with galantamine and without specific behavioral symptoms. Monsch and colleagues (Monsch, Giannakopoulos, & GAL-SUI Study Group, 2004) investigated the effects of galantamine (escalated from 8 to 24 mg/day over 8 weeks) in a 3-month, open-label, multi-center study conducted on 124 AD patients. The authors demonstrated a 27% reduction in the apathy score, as assessed by the NPI at the end of the period of treatment. Freund-Levi and co-workers (Freund-Levi, Jedenius, Tysen-Backstrom, Larksater, Wahlund, & Eriksdotter, 2014) recruited subjects with diagnoses of probable dementia (88%) or MCI (12%) from a memory clinic. The aim of the randomized, open-label trial, was to explore the effects of the administration of galantamine and risperidone on the overall neuropsychiatric symptoms (NPS) and global function. Both galantamine and risperidone treatments were able to produce a small non-significant reduction of apathetic behaviors, as measured by the NPI-apathy subscale, also over time.

In 2006 (Cummings, Schneider, Tariot, & Graham, 2006) an exploratory analysis of a 24-week, double-blind, placebo-controlled trial was conducted in order to compare memantine (20 mg/day) treatment with placebo in 404 moderate to severe AD patients, which were already treated with donepezil; the authors did not detect significant effects on apathy as assessed with the NPI, whereas an improvement in the NPI-apathy score (-11.3%) was observed following treatment with memantine by Schmidt and colleagues (Schmidt, Baumhackl, Berek, Brücke, Kapeller, Lechner *et al.*, 2010) in a 16-week, open label study conducted on 53 AD patients.

Moreover, a recent 6-week, multi-center, double-blind, placebo-controlled RCT, investigating the treatment of low-dose methylphenidate (20 mg/day) for apathy in patients with mild-moderate AD, reported a significant improvement in apathy in the group of active treatment vs. placebo on a modified ADCooperative Study – Clinical Global Impression of Change (Rosenberg et al., 2013). Padala and colleagues

(2018) conducted a 12-week, double-blind, randomized, placebo-controlled survey on 60 elderly veterans in a community dwelling. They used the AES-C to assess apathy as well as to evaluate the impact of the treatment on apathy. The authors demonstrated that the methylphenidate group experienced a significantly greater improvement than the placebo, both in terms of apathy (at 4, 8, and 12 weeks) and in terms of cognition, functional status, caregiver burden and depression (not until 12 weeks).

Pharmacological challenge has shown that AD patients with apathy have a blunted subjective reward following the administration of the dopaminergic agent dextroamphetamine (Lanctôt, Herrmann, Black, Ryan, Rothenburg, Liu et al., 2008), suggesting that a hypofunction of the dopaminergic system can contribute to the pathophysiology of apathy in the AD brain. Antidepressant drugs have not been found to improve apathy (Berman, Brodaty, Withall, & Seeher, 2012) although no specific studies have been conducted with second-generation antidepressant drugs, such as fluoxetine and bupropione, to evaluate the impact of these drugs alone or in combination with cholinesterase inhibitors.

5. Non-pharmacological treatment of apathy in AD

As discussed above, pharmacological therapies have demonstrated their efficacy in the management of apathy associated with AD. More specifically, donepezil and methylphenidate have demonstrated to be the most efficient drugs in reducing the level of apathy in the AD population. But alongside pharmacological treatment, several studies have investigated alternative types of interventions. Non-Pharmacological Treatment (NPT), also defined "ecopsychological intervention" (Zeisel, Reisberg, Whitehouse, Woods, & Verheul, 2016), has been recently considered as a new essential path (Theleritis, Siarkos, Politis, Katirtzoglou, & Politis, 2018) to be explored for the management of apathy. Non-pharmacological treatment includes interventions on cognitive, social, psychological, and relational aspects of the subject, using different methods, such as group activities, therapeutic dialogs, meditation, and sensory, physical, and physiological stimulation. The aim of this type of intervention is to improve the quality of life of the patient by strengthening his/her cognitive, psycho-affective, and social skills, reducing the psycho-behavioral symptoms, preserving the patient's social activity, restoring confidence and self-esteem, and promoting autonomy (Zuchella, Sinforiani, Tamburin, Federico, Mantovani, Bernini *et al.*, 2018). A multiplicity of NPTs has shown to be effective on the treatment of apathy in AD. Occupational therapy and physical activity, inserted within a multidisciplinary intervention, have revealed to be effective in the treatment of apathy in

patients suffering from dementia compared with pharmacological treatments alone (Treusch, Majic, Page, Gutzmann, Heinz, & Rapp, 2015). Maci and colleagues (Maci, Pira, Quattrocchi, Di Nuovo, Perciavalle, & Zappia, 2012) conducted an interesting study in a 14-patient RCT, which included physical activity as NPT, in order to assess the effect of a 3-month program of physical activity, cognitive stimulation and socialization versus usual activities at home. Maci and collaborators (2012) demonstrated a significant improvement in the AES scores. Moreover, in 2015, Telenius and co-workers confirmed that a high intensity functional exercise program in nursing home patients with dementia decreased the level of apathy following the intervention versus a control group (Telenius, Engedal, & Bergland, 2015). Several recent studies have considered the key role of exercise in the treatment of various neuropsychiatric disorders (Guerrera, Furneri, Grasso, Caruso, Castellano, Drago *et al.*, 2020). Physical activity, associated with drug treatment, allows to expand the range of rehabilitation interventions dedicated to demented patients. Furthermore, art therapies are also used as NPTs due to their efficacy in improving the levels of apathy compared with learning therapy (Hattori, Hattori, Hokao, Mizushima, & Mase, 2011). Raglio and colleagues (Raglio, Bellelli, Traficante, Gianotti, Ubezio, Villani *et al.*, 2008) conducted a study in which they included 60 participants: a music therapy experimental group (n = 30) and a control group (n = 30). After 4 weeks, the NPI scores for apathy were significantly improved in the experimental group. Moreover, Ferrero-Arias and colleagues conducted a RCT, which included 146 patients, divided into two groups: an intervention group, with music, art therapy and psychomotor activity, opposed to a control group, which were simply asked to perform free activities in a room during the day. They used the DAIR scale to assess apathy and they found a significant difference between the intervention and control groups, especially in patients with moderated apathy. They thus came to the conclusion that a structured, non-pharmacological, short-term occupational therapy intervention can improve apathy in mild or moderate dementia patients (Ferrero-Arias, Goñi-Imízcoz, González-Bernal, Lara-Ortega, da Silva-González, & Díez-Lopez, 2011).

More recently, it has been demonstrated that a multi-component psychological intervention after 6 months allows to register an improvement in the apathy NPI score versus a standard occupational therapy intervention (Fischer-Terworth & Probst, 2012). In 2016, Di Domenico and colleagues recruited 26 AD patients and 26 healthy controls (Di Domenico, Palumbo, Fairfield, & Mammarella, 2016). The experimental group followed a brief emotional shaping intervention, which was developed to reduce apathy (assessed with the AES) and increase the "willingness to do" in AD patients. The results

demonstrated that the patients of the experimental group showed a significant increase in motivation.

Finally, great relevance has been recently given to Information and Communication Technologies (ICT) with the aim to train cognitive functions, promote communication, reduce loneliness, improve physical functions and the emotional state in apathetic and non-apathetic patients (Manera, Abraham, Agüera-Ortiz, Bremond, David, Fairchild *et al.*, 2020). An interesting study (Manera, Petit, Derreumaux, Orvieto, Romagnoli, Lyttle *et al.*, 2015) had the aim of demonstrating the efficacy of employing serious games (SGs), in this case "Kitchen and Cooking", for the assessment and rehabilitation of elderly people with MCI and AD. Twenty-one patients were recruited and results demonstrated that apathetic participants were motivated and interested in the activities, as the non-apathetic group, confirming that this game was useful in the case of presence of apathy. Moreover, Moyle and colleagues (Moyle, Cooke, Beattie, Jones, Klein, Cook *et al.*, 2013) conducted a pilot cross-over RCT with 18 demented patients and used the AES to assess apathy; the authors found no improvement of apathy with the use of a robot companion. In contrast, other studies (Valentí Soler, Agüera-Ortiz, Olazarán Rodríguez, Mendoza Rebolledo, Pérez Muñoz, Rodríguez Pérez *et al.*, 2015) demonstrated that the use of social robots in 60 patients with dementia resulted in an improvement in the NPI apathy scores.

6. Conclusions

The neurobiological and clinical links between apathy and Alzheimer's Disease are essential when considering apathy as one of the main common neuropsychiatric symptoms of AD. Apathy was initially considered only as a symptom of the Major Depressive Disorder, but today, more than ever, it seems important to investigate apathy as a syndrome in itself, in order to be able to specifically intervene promptly on it and improve patients' quality of life. The connection between brain regions involved in both apathy and Alzheimer's is quite clear and the common involvement of the cholinergic system can explain why drugs currently used in AD patients (i.e. cholinesterase inhibitors) can also be effective in the treatment of apathy. Evidence discussed in the present review suggests a strong clinical link between apathy and Alzheimer's Disease as well as the relevance of psychometric tools, such as the AES, to better diagnose and treat apathy. We believe that only by considering every single aspect of the patient's clinical picture can the clinician plan a multi-component intervention that has effects on health, defined as a state of complete physical, mental and social well-being (World Health Organization). In fact, several studies have shown the efficacy in reducing apathy also through non-

pharmacological treatments centred on individual autonomous, psychological and social functioning, but a major unmet question remains open as to how we can better integrate pharmacological and non-pharmacological treatments. A multimodal intervention is the innovative approach that we believe might be proposed in the next future for the treatment of apathetic AD patients.

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Chapter III

The Apathy Evaluation Scale (AES-C): Psychometric properties and invariance of Italian version in Mild Cognitive Impairment and Alzheimer's disease

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Abstract

Apathy is a neuropsychiatric symptom observed in different neurological and psychiatric disorders. Although apathy is considered a symptom, it has been recently reconsidered as a syndrome characterised by three dimensions: cognitive symptoms, affective symptoms and behavioural symptoms. Recent studies have shown that apathy can be considered as a prodromal symptom of Alzheimer's disease (AD), but also an

indicator of the transition from mild cognitive impairment to AD. According to this scenario, an early detection of apathy in subjects with Mild Cognitive Impairment (MCI) and Mild AD can be a valid psychometric strategy to improve an early diagnosis and promote a prompt intervention. The Apathy Evaluation Scale is a validated tool composed of 18 items that assess and quantify emotional, behavioural and cognitive aspects of apathy. The aim of this study is to assess the specific reliability and validity of the Italian version of the Apathy Evaluation Scale—Clinician Version (AES-C) to detect apathy both in amnestic MCI and mild AD patients. In the present paper, we therefore examined the psychometric properties and the invariance of the Italian Version of the AES-C conducted on a sample composed of an experimental group of amnestic MCI and AD patients (N = 107) and a control group (N = 107) constituted by Age- and Sex-matched healthy controls. Results confirm the goodness of the scale. Confirmatory factory analysis confirmed that the AES-C Italian Version presents the same stability of one second-order factor and three first-order factors identified in the original version, and all items are predicted by a single general factor. Moreover, the scale was found to be invariant across both populations. Moreover, reliability and discriminant analysis showed good values. We found in the experimental group a negative correlation between the AES-C and Frontal Assessment Battery (FAB) ($rs = -0.21$, $p < 0.001$) and Mini Mental State Examination (MMSE) ($rs = -0.04$, $p < 0.001$), while a positive correlation was found between the AES-C and Hamilton psychiatric Rating scale for Depression (HAM-D) scores ($rs = 0.58$, $p < 0.001$) Overall, our data demonstrated the validity of the Italian version of the AES-C for the assessment of apathy both in MCI and in AD patients.

Keywords: apathy; AES-C; validation; reliability; psychometric properties; Alzheimer; MCI

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1. Introduction

Apathy is a neuropsychiatric symptom (NPS) observed in different neurological and psychiatric disorders [1,2]. Etymologically, its name comes from the Greek word ἀπάθεια (apatheia), meaning lack (a-) of emotions (-pathos), and some of our Greek and Roman ancestors, in the frame of stoic philosophy, considered it as a virtue. So far

from this perspective, the current scientific point of view regards apathy as a prodromal symptom in different diseases such as multiple sclerosis, amyotrophic lateral sclerosis, psychosis, traumatic brain injury and all type of dementia, especially in both Alzheimer's disease (AD) and vascular dementia (VaD) [3].

Apathy's main feature is a deficit in motivation, which is displayed through reduced interest, emotions and goal-directed behaviours. Differently from depression, apathy is characterised by emotional neutrality rather than negative emotions [4]. It is a multidimensional construct that includes the emotional and social sphere and is characterised by three dimensions: cognitive symptoms, affective symptoms and behavioural symptoms [5]. Apathy has often been regarded as a symptom of other syndromes (e.g., depression or dementia) [6], but it can itself be defined as a syndrome characterised by decreased motivation in which the lack of motivation is not attributable to a decreased level of consciousness, emotional distress or cognitive deficits [7].

In the last two decades, the interest about the association between apathy and dementia has increased due to the predictive role of apathy on dementia. AD is a progressive and irreversible neurodegenerative disease that usually affects people over the age of 65 [8] and is the most common form of dementia [9,10]. The onset of AD begins many years before the actual diagnosis [11] and is characterised by a preclinical and prodromal phase that can begin as early as middle age [12] AD is characterised by its increasing neuropsychological impairment with a progressive decline in memory, executive functions, language and visuospatial skills [13]. In almost all patients, the cognitive and functional decline of the disease is accompanied by behavioural and psychological symptoms (BPSD) [14] such as apathy, agitation, disappointment, irritability, anxiety, disinhibition and hallucinations [13], i.e., symptoms of disturbed perception, thought content, mood, and behaviour [15] which significantly reduce the quality of life of patients and caregivers [16,17]. According to this scenario, it is now widely demonstrated that apathy can act as a risk factor which can promote the conversion from Mild Cognitive Impairment (MCI) to dementia.

Chilovi et al. [18] classified MCI patients in four subgroups, namely (1) MCI normal, (2) MCI depressed, (3) MCI depressed-apathetic and (4) MCI apathetic. They found the highest percentage of conversion to dementia among the apathetic group (60%), followed by MCI normal (24%), MCI depressed-apathetic (19%) and MCI depressed (7.9%). Similarly, in a sample of 1713 MCI patients, it was observed that

apathetic subjects have a greater risk of developing dementia than those with depression only [19]. More recently, with a cohort of 2137 MCI patients, Roberto et al. [20] found fairly the same results. They divided the sample in four classes based on the predominant NPS symptoms: (1) irritability, (2) apathy, (3) anxiety/depression, (4) asymptomatic. While irritability and apathy were predictors of dementia, anxiety/depression did not constitute a risk factor. These results are confirmed by a recent systematic review [21] that investigated the impact of apathy, depression and anxiety on the progression from MCI to AD. The authors underlined that for MCI patients, apathy is a 'more important indicator' among the two other neuropsychiatric symptoms in the evolution to dementia.

Thus, an early assessment and identification of apathy are extremely useful for clinicians to understand the possible evolution from MCI to Mild AD better and therefore design tailored prevention and treatment programs.

Different tools are available in the literature as psychometric tools for assessing apathy. The Neuropsychiatric Inventory (NPI), for example, developed by Cumming [22,23], is a multi-dimensional instrument to assess neurobehavioural disorders in dementia. In particular, it presents a specific eight-item subscale to measure apathy: higher scores indicate a more severe presence of apathy [22,23]. Robert et al. [24] developed the Apathy Inventory (AI) on the basis of Marin and colleagues' diagnostic criteria of apathy [6,7], but also Starkstein and colleagues [25] and Lueken et al. [26] settled two different and modified short versions of the Marin instrument. Strauss and Sperry [27] developed the Dementia Apathy Interview and Rating (DAIR) which is an informant-based unidimensional scale that measures changes in engagement, motivation and emotional response in MCI patients. The Lille Apathy Rating Scale (LARS) is based on a structured interview. It includes 33 items, divided into nine domains. Responses are scored on a dichotomous scale. The scale was validated with a sample of 159 patients with probable Parkinson's disease and 58 healthy controls [28]. In subsequent studies, LARS was also administered to other disease populations, such as AD and MCI patients [29].

Radakovic and Abrahams [30] created a multi-dimensional scale based on Levy and Dubois' [31] apathetic subtypes. The Dimensional Apathy Scale (DAS) is composed of 24 items and 3 subscales—Executive, Emotional and Behavioural/Cognitive Initiation. DAS is suitable for application in different pathologies.

In the present work, we performed the validation and psychometric analysis of the Italian Version of the Apathy Evaluation Scale—Clinician Version (AES-C) on MCI and Mild AD patients starting from the evidence that AES is based on a definition of apathy that is closer to a syndrome in and of itself rather than as a symptom of other syndromes. The Apathy Evaluation Scale (AES) was developed by Marin and colleagues [32] and was conceived and built based on the definition of apathy according to Marin: syndrome of loss of motivation as reflected by acquired changes in affect (mood), behaviour and cognition [32]. The AES is a four-point Likert-Scale measure, composed of 18 items that assess and quantify emotional, behavioural and cognitive aspects of apathy. AES presents three available administration forms of the scale: self-report (AES-S), informant report (AES-I) and clinician interview (AES-C). Only in the AES-C is a semi-structured open-ended interview present: it helps the clinician to collect information from patients about their typical day and hobbies and interests; this interview allows the clinician to investigate the subject's degree of motivation and direct him in providing his own rating of the individual's level of apathy on each item. Every item is rated on a four-point response scale (0 = not at all true/characteristic to 3 = very much true/characteristic). Higher scores indicate more severe apathy [32]. The AES-C version takes between 10 and 20 min to be completed [32].

The AES-C has been employed in three randomised controlled trials (RCTs) as a primary outcome in those with apathy and AD [33–35]. However, only the AES-C and AES-S versions were able to discriminate apathy from depression [32]. However, it is important to notice that different studies [36] confirmed good to excellent internal consistence of all the versions of the AES-C, with varying values for convergent validity and good discriminant validity. From the literature examined, it seems that the Apathy Evaluation Scale possesses these characteristics and can be validated on the AD population also in the Italian language. So, the aim of this study is to assess the specific reliability and validity of the Italian version of the AES-C scale to detect apathy both in amnestic MCI and mild AD patients. In the present paper, we therefore examined the psychometric properties and the invariance of the Italian Version of the AES-C in a sample of 107 amnestic MCI and AD patients compared with Age- and Sex-matched healthy controls.

2. Materials and Methods

2.1. Participants and Procedure

The study involved 214 participants (Table 1), divided into two groups. The experimental group consisted of 107 patients (34 males, 73 females) recruited from the U.O.S. Centro Alzheimer e Psicogeriatria, DSM ASP3, Catania, Italy where the new diagnostic criteria of the National Institute of Aging (NIA) and Alzheimer's Association work group (2011) have been adopted both for AD and amnestic MCI patients. All patients selected for the present work were firstly recruited on their first access to the service, where they received the diagnosis for the first time. We tested 306 patients on their first access to the centre, but only 107 were included in the study based on the inclusion and exclusion criteria. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was authorised by the Internal Ethics Review Board of the Department of Educational Sciences (Section of Psychology) of the University of Catania; research procedures followed all the indications provided by the guidelines of the AIP (Italian Association of Psychology) and its Ethical Council. The inclusion criteria included a diagnosis of MCI or probable Mild AD. As a screening for general cognitive impairment, we used the Italian standardised version of the Mini Mental State Examination (MMSE) [37,38], and included in the study patients with a total age and educational adjusted score ≥18 and ≤ 28. Patients with a recent history of cerebral ischaemia and/or a recent history of psychotic episodes were excluded. The control group was made up of 107 subjects (29 males, 78 females) of healthy volunteers, with MMSE scores ≥ 28. The neuropsychological evaluation involved the administration of various psychological tools. Questionnaires were administered individually: the scale was administered by the clinician to the patient without further interviews or input from the caregiver. Global cognitive function assessment has been carried out in MCI and AD patients by using the MMSE and Montreal Cognitive Assessment (MoCA) [39,40]. The Frontal Assessment Battery [41,42] was used to evaluate executive functions. Severity of depression was measured by means of the Italian version of the Hamilton Depression Rating Scale (HAMD-17) [43]. Apathy was assessed by the Apathy Evaluation Scale (AES-C). The HAM-D and AES-C were compiled by a clinician after a semi-structured interview with the patient to prevent depressed or apathetic subjects from being unable to report their symptoms adequately. Psychometric assessments were performed by two psychologists with a

long experience in neuropsychological assessment and in particular in the field of behavioural and psychological symptoms of dementia.

Table 1. Demographic and clinical characteristics of the sample

Group	Gender	No.	Age (mean ± DS)	Mild AD (No.)	MCI (No.)
Experimental					
	Male	34	75.62 ± 5.736	12	22
	Female	73	76.03 ± 7.297	19	54
	Tot.	107	75.90 ± 6.82	31	76
Control					
	Male	29	75.00 ± 6.984	-	-
	Female	78	73.70 ± 6.841	-	-
	Tot.	107	74.1 ± 6.87	-	-

2.2. Measures

2.2.1. Mini Mental State Examination

The Mini Mental State Examination [37,38] constitutes a rapid and sensitive test for quantifying residual cognitive abilities for the documentation of their modification over time as a result of neurodegeneration. It is made up of twelve items through which seven cognitive functions are explored: time orientation, spatial orientation, immediate memory, attention and calculation, recall memory, language, visual-constructive praxis. Its administration requires a variable time from 5 to 15 min. It is a less demanding test, but it allows us to have a measure of global cognitive function that can also be used with the progression of the disease.

2.2.2. Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) [39,40] evaluates different cognitive domains: attention and concentration, executive functions, memory, language, visualconstructive skills, abstraction, calculation and orientation. The test administration time is 10 min; the maximum possible score is 30 points; a score equal to or higher than 26 is considered normal.

2.2.3. Frontal Assessment Battery

The FAB [41,42], or Frontal Assessment Battery, is a short bedside cognitive and behavioural battery to assess frontal lobe functions. It consists of 6 cognitive and behavioural subtests: conceptualisation, mental flexibility, motor programming,

sensitivity to interference, inhibitory control and environmental autonomy. In Apollonio's [42] correction, the cut-off score is 13.50/18. The Frontal Assessment Battery is easy to administer at the bedside and is sensitive to frontal lobe and executive dysfunction.

2.2.4. Hamilton Psychiatric Rating Scale for Depression

The Hamilton psychiatric Rating scale for Depression, i.e., HDRS or HAM-D, is undoubtedly the best known and most used psychometric tool in the world to evaluate depression's severity. In its original formulation [43], the HAM-D was composed of 17 items, brought to 21 in the subsequent version [44]; besides these, numerous other versions have circulated with more or less arbitrary variants, the best known of which is the 24-item one (the added items are the feeling of helplessness, the loss of hope and the feeling of uselessness). The most widely used version is probably the one published in the NIMH "ECDEU Assessment Manual" [45]. It investigates 21 different areas that are crucial for the assessment of the subject's depressive state. Areas are: depressed mood, guilt, suicidal thoughts, initial insomnia, intermediate insomnia, prolonged insomnia, work and interests, slowing of thought and speech, agitation, psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, somatic symptoms, genital symptoms, hypochondria, introspection, weight loss, diurnal symptomatology variation, depersonalisation, paranoid symptomatology, obsessive symptomatology. Each of the 21 areas represents a single item of the scale, to each of which the examiner, during the interview, must assign a score ranging from 0 (absent) to 4 (severe), or from 0 to 3 (clearly present), depending on the items and the severity of the symptoms. The score thus obtained indicates a possible depression if it is between 10 and 15 points, mild depression if it is between 16 events 25 points, moderate depression if it is between 26 and 28 points and severe depression if it is greater than 28 points.

2.2.5. Apathy Evaluation Scale

The Apathy Evaluation Scale (AES-C) is a 4-point Likert scale consisting of 18 items. It requires 10–20 min to administer depending on the subject's abilities and the version used. In the Clinician Version, a categorisation of items is indicated in the right column: B = behavioural item; C = cognitive item; E = emotional item. Items are worded with positive or negative syntax (+ or -); most are positive. The rating of Self-

evaluation (SE) and quantifiable (Q) items are denoted in the right column of the AES-C. Scores for the AES-C range from 18 to 72. The cut-off score is 39–41, depending on which version of the AES is used. A clinical correlation suggests that these cut-offs are probably slightly low. In this work, the AES-C was compiled by a clinician after a semi-structured interview with the patient in order to prevent depressed or apathetic subjects from being unable to report their symptoms adequately. A back-translation procedure has been used during the adaptation to the Italian language, following the recommendations made by Beaton et al. [46]. The procedure was as follows: translation and adaptation of the original scale from English to Italian, back translation, and review committee. A bilingual Italian-English interpreter translated the English version of the AES-C into Italian. So, it was then translated back to English by a bilingual psychologist with a doctoral degree. The differences that emerged from the comparison between the two versions were discussed and addressed by the research group. Revisions were made to the Italian translation of the AES-C. No substantial difference has been highlighted between the final Italian version and the original English one.

2.3. Data Analysis

Linear structural equations models [47] were calibrated to test the hypothesised model. Tests were completed in AMOS 26.0 [48] by applying the maximum likelihood (ML) method. A sequence of CFA analyses was carried out on the dataset, to establish the best factor model to fit the data. The models' goodness of fit was evaluated using the Tucker Lewis Index (TLI), the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA) and the Standardised Root Mean Square Residual (SRMR). Furthermore, 2 values and D2 values between the competing models are presented, but they are sensitive to sample size [49], so the Akaike Information Criterion (AIC) was also presented along with the Bayesian Information Criterion (BIC) (lower values indicate a better fit). DCFI was also used, with values not exceeding 0.01 indicating that the models are equivalent in terms of fit [50]. Moreover, we conducted a confirmatory factor analysis (CFA) to confirm the factor structure of the AES-C. Next, a series of multiple group CFA were run, in which different, and progressively more stringent, forms of measurement equivalence were tested [51,52]. By establishing whether factor loadings, intercepts and residual variances are equivalent in a factor model that measures a latent concept, we can assure that

comparisons that are made on the latent variable are valid across groups or time [53]. Other well-known analytical tools such as correlations were also used, which were implemented by using SPSS 27.0.

3. Results

3.1. Confirmatory Factor Analysis

At first, a model with one second-order factor and three first-order factors (Model 1: second order=1-factor, Apathy; first order: 3-factors, Behavioural, Cognitive and Emotion) was measured, the results of the fit showed in Table 2 revealed that the model was good [$\chi 2(129)=241.388$, SRMR=0.05, RMSEA=0.06, CFI=0.93, TLI=0.92, AIC=325.388, BIC=466.759]. Model 1 was then compared with a three-factor model (Model 2: first order = 3-factors, Behavioral, Cognitive and Emotional), composed of three first-order factors with co-variances between them where the lower-level variables are observed variables con-taining errors [$\chi 2$ (132)=349.059, SRMR=0.05, RMSEA=0.09, CFI=0.84, TLI=0.81, AIC=472.059, BIC=603.332]. The first model of the two showed the best fit to the data, based on fit indexes, AIC and delta Chi-square value ($\Delta\chi^2$M2- M1(3)=107.67). Model 1 was then compared to a one-factor Model (Model 3: all 18 items predicted by a single factor), in which all the items were predicted by a single factor [$\chi 2(135)=404.847$, SRMR=0.06, RMSEA=0.10, CFI =0.83, TLI=0.80, AIC=476.847, BIC=698.023] and it showed again the best fit to the data ($\Delta\chi^2$M3- M1(6)=163.459). Moreover, all factor loadings were significant at $p < 0.001$. Fit indexes for the tested models are presented in Table 2.

Table 2. Fit indexes for models tested in CFA (Study 1).

	χ2	df	SRMR	RMSEA	RMSEA 90%-C.I.	CFI	TLI	AIC	BIC
Model 1[a]	241.388*	129	.05	.064	.051-.076	.93	.92	325.388	466.759
Model 2[b]	349.059*	132	.05	.096	.086-.108	.84	.81	472.059	603.332
Model 3[c]	404.847*	135	.06	.10	.089-.112	.83	.80	476.847	698.023

Note. [a] Model 1: one second-order factor and three first-order factors.[b] Model 2: three first-order factors with covariances among them. [c] Model 3: all the items were predicted by a single factor.*: $p < .001$

Results showed that Model 1 is the one with the best goodness of fit compared to the Italian sample we analysed. This means that the Italian version of the AES-C confirmed the same factorial structure of the original version by Marin and colleagues.

3.2. Descriptive statistic normality of distribution and factor loading of model 1

Next, in Table 3 we report the list of items, the overall means with the standard deviations and the means by gender, the normality of the distribution and the factor loading of model 1 considered the most parsimonious, confirming the factorial

structure of the scale. Critical values that exceed +2.00 or that are smaller than −2.00 indicate statistically significant degrees of non-normality. Descriptive statistics in Table 3 show that data were normally distributed, with good skewness and kurtosis values. The results confirm the good-ness of the scale and the normality of the distribution.

Table 3. Descriptive statistic (mean (M), standard deviation (SD), skewness, kurtosis) and factor loading of model 1.

	M	**SD**	**Female (151)**		**Male (63)**		**Skewness**	**Kurtosis**	**Factor loading Model 1**
			M	*SD*	*M*	*SD*			
1. S/he is interested in things.	1.90	.89	1.86	.91	1.91	.89	.80	-.07	**.905**
2. S/he gets things done during the day.	1.66	.81	1.54	.78	1.71	.82	1.13	.68	**.950**
3. Getting things started on his/her own is important to him/her.	1.92	.99	1.81	.99	1.96	.99	.78	-.56	**.500**
4. S/he is interested in having new experiences.	2.45	1.14	2.56	1.10	2.41	1.16	.03	-1.42	**.532**
5. S/he is interested in learning new things.	2.39	1.19	2.41	1.17	2.38	1.20	.10	-1.51	**.549**
6. S/he puts little effort into anything.	1.85	.99	1.79	.94	1.87	1.02	.85	-.48	**.691**
7. S/he approaches life with intensity.	2.00	.98	1.87	.94	2.05	1.02	.69	-.61	**.613**
8. Seeing a job through to the end is important to her/him.	1.45	.70	1.30	.56	1.51	.75	1.50	1.66	**.719**
9. S/he spends time doing things that interest her/him.	1.84	.88	1.89	.83	1.82	.92	.74	-.36	**.810**
10. Someone has to tell her/him what to do each day.	1.71	.94	1.63	.88	1.74	.96	1.13	.22	**.797**
11. S/he is less concerned about her/his problems than s/he should be.	1.99	.96	2.08	.94	1.95	.96	.55	-.78	**.674**
12. S/he has friends.	1.79	.96	1.67	.86	1.83	1.00	1.07	.13	**.901**
13. Getting together with friends is important to her/him.	1.62	.82	1.54	.74	1.66	.85	1.16	.56	**.740**
14. When something good happens, s/he gets excited.	1.43	.714	1.46	.69	1.42	.72	1.56	1.68	**.749**
15. S/he has an accurate understanding of her/his problems.	1.72	.78	1.89	.90	1.65	.71	.90	.32	**.630**
16. Getting things done during the day is important to her/him.	1.53	.76	1.65	.88	1.48	.70	1.29	.85	**.665**
17. S/he has initiative.	1.92	1.003	1.98	1.04	1.89	.99	.73	-.66	**.810**
18. S/he has motivation.	1.95	.99	1.98	.99	1.93	.98	.71	-.62	**.797**

3.3. Convergent and Discriminant Validity

The convergent and discriminant validity of the AES-C was tested using the measures of MMSE, MOCA, FAB and Hamilton. Table 4 shows descriptive statistic and correlation matrix for the study variables. The data are reported by distinguishing the re-sults between two different groups: control group and experimental group (MCI and AD patients). There is a high negative correlation in experimental group between AES-C and FAB (rs=-.21, p<.001) and MMSE (rs=-.04, p<.001), while there is a positive correlation be-tween AES-C and HAM-D scores (rs=.58, p<.001) and MOCA (rs=.46, p <.001). These data are in line with Marin's first AES validation study, in which Moderate but statistically significant correlations were found between the AES-C and the HAM-D (r=0.39) and the AES-C and the Hamilton Rating Scale for Anxiety (r=0.35) indicating adequate discrimi-nant validity. This confirms the fact that apathy, in addition to being considered as a symptom dimension of depression, presents itself as a construct connected to a psycho-pathological core but different from depression.

In the control group we found a high pos-itive correlation between AES-C and HAM-D (rs=.22, p<.001) and MOCA (rs=.17, p<.001), and negative correlation between AES-C and FAB (rs=-.22, p<.05). This latter result reflects the nature of the effects of frontal lobe dysfunction on the emotional aspects of evaluated subjects. There is in fact an anatomical correlation and a neurobiological link between frontal injury and the appearance of apathy [54-55]. Consequently, the negative correlation between AES-C and FAB suggest that in the absence of frontal lesions the levels of apathy in healthy subjects are less elevated. The positive correlation between AES-C and MoCA in the control group was an unexpected result. We hypothesize that this data could be linked to the presence of apathetic symptoms also in the subjects of the control group, included in the study exclusively on the basis of their normal cognitive functions. In fact, high apathy scores are compatible with a high score on the MoCA (general cognitive efficiency) rather than on the FAB which measures frontal functions only.

Table 4. Descriptive statistics and inter-correlations (N=214)*.

	Control group		**Experimental group**		**α**	**1**	**2**	**3**	**4**	**5**
	M	*SD*	*M*	*SD*						
1. MMSE	29.20	1.15	23.50	3.27	.89	-	-.10	.09	.11	-.16**
2. MOCA	28.53	1.57	18.33	4.38	.77	.63**	-	-.11	.02	-.17**
3. FAB	16.24	1.33	11.31	3.28	.87	.52**	.55**	-	-.09	-.22**
4. Hamilton	4.37	2.58	10.29	7.35	.76	.14	.08	-.10	-	.22**
5. AES-C	28.35	7.8	37.58	11.0	.91	-.04	.46**	-.21**	.58**	-

Notes: MMSE=Mini Mental State Examination; MoCA=Montreal Cognitive Assessment; FAB=Frontal Assessment Battery; Hamilton=Hamilton psychiatric Rating scales For Depression; AES-C=Apathy Evaluation Scale – Clinician Version; p scores: * <.05, ** <.001. *Correlations among experimental data are below diagonal, correlations among control group data are above the diagonal.

3.4. Multiple-Group Confirmatory Factor Analysis (MCFA)

Cross-validation comparisons were conducted by running a series of multiple-group CFA, in which different, and progressively more stringent, forms of measurement equivalence were tested [51]. We considered six models (configural, metric, scalar, error, variance and covariance) to test for measurement invariance across gender and type of group. The first multiple-group analysis tested a model of configural invariance (Model 1) by simultaneously evaluating the fit of male and female samples. The fit indices (2(258) = 421.58, p < 0.001; CFI = 0.91; SRMR = 0.043; RMSEA = 0.061) indicated a good fit for this model, supporting an equivalent solution made of one second-order factor with three first-order factors for the AES-C in the Italian context

in Table 5. The fit of this configural model provides the baseline value against which all subsequently specified equivalence models are compared [56].

Model 2 was tested for metric invariance; D2M2−M1(17) = 27.94 and DCFI = 0.001 suggested that Model 2 could be considered equivalent to Model 1 (Table 5). Thus, metric invariance was supported.

Table 5. Fit statistics for measurement invariance by gender.

Model	χ2(df)	CFI	SRMR	RMSEA [90% CI] *p*close	ΔCFI
1. Configural Invariance	421.58(258)	.91	.04	.06 (.045-.064)	-
2. Metric Invariance	449.52 (275)	.90	.04	.06 (.045-.064)	.001
3. Scalar Invariance	453.74 (278)	.90	.04	.06 (.045-.064)	.000
4. Measurement error Invariance	523.58 (300)	.90	.04	.06 (.045-.064)	.002
5. Structural Variance Invariance	553.11 (315)	.90	.04	.06 (.045-.064)	.001
6. Structural Covariance Invariance	566.02 (322)	.90	.04	.06 (.045-.064)	.001

Moreover, measurement scalar invariance (as tested by Model 3) and error invariance (Model 4) were found (Δχ2M3-M2(3)=4.22, ΔCFI=.000; Δχ2M4-M3(22)=69.84, ΔCFI=.002.

The equivalence in factor variances was tested (Model 5) and it was found to be tenable (Δχ2M5-M4(15)=29.53, ΔCFI=.001). Finally, the equivalence in factor covariances was tested (Model 6) by nesting the respective model with Model 5, and the result was that it was supported (Δχ2M6-M5(7)=12.91, ΔCFI=.001).

A second multigroup tested a model of configural invariance (Model 1) by simultaneously evaluating the fit of experimental group and control group. The fit indices [χ2(96)=452.91, p< .001; CFI=.90; SRMR=.054; RMSEA=.062] indicated a good fit for this model, supporting an equivalent solution made of one second-order factor with three first-order factors for AES-C in the data sets for experimental group and control group (Table 5).

Model 2 was tested for metric invariance (Table 6). More importantly, Δχ2M1-M2(17)=13.92 and ΔCFI=.000 suggested that Model 2 could be considered equivalent to Model 1. So, metric invariance was supported.

Table 6. Fit statistics for measurement invariance by experimental group and control group.

Model	χ2(df)	CFI	SRMR	RMSEA [90% CI] *p*close	ΔCFI
1. Configural Invariance	452.91 (256)	.90	.05	.06 (.051-.069)	-
2. Metric Invariance	466.83 (273)	.90	.05	.06 (.054-.080)	.000
3. Scalar Invariance	481.56 (291)	.90	.05	.06 (.054-.080)	.000
4. Measurement error Invariance	501.16 (302)	.90	.05	.06 (.054-.080)	.000

5. Structural Variance Invariance	523.19 (317)	.90	.06	.06 (.054-.080)	.000
6. Structural Covariance Invariance	560.31 (325)	.90	.06	.06 (.054-.080)	.000

The equivalence of the model is present also for error invariance (as tested by Model 3) and scalar invariance (Model 4) were found ($\Delta\chi$2M2-M3(18)=14.73, ΔCFI=.000; $\Delta\chi$2M3-M4(11)=19.6, ΔCFI=.000.

Finally, the equivalence in factor variances (Model 5) and in factor covariances (Model 6) were tested and the result were that it was supported ($\Delta\chi$2M5-M4(15)=22.03, ΔCFI=.000); ($\Delta\chi$2M6-M5(8)=37.12, ΔCFI=.000).

Results were totally satisfactory as the model fit proved to be invariant across both populations (Table 6).

4. Discussion

Starting from the evidence that apathy can represent both a prodromal symptom and a risk factor for AD, in the present manuscript we analysed the psychometrics properties and invariance of the Italian Version of the Apathy Evaluation Scale—Clinician Version in a sample of 107 Italian MCI and AD patients. For this reason, different procedures were used, and different analyses were carried out. Confirmatory factory analysis confirmed that the AES-C Italian Version presents the same stability of one second-order factor and three first-order factors identified in Marin's original study. Moreover, as in the original study, all items are predicted by a single general factor. So, in general, we can affirm that our results confirm the goodness of the scale. In 2007, Clarke and colleagues [57] conducted a review study of publications between January 1983 and December 2004 about AES-C psychometric properties. The authors provided detailed information about both reliability and validity, concluding that the scale has good psychometric properties, as firstly demonstrated by the original study by Marin et al. The original study [32] reported high internal consistency, with Cronbach's alpha (α)=0.90. This result was confirmed by subsequent studies where exceeded 0.8, indicating that the scale is homogeneous. Marin et al. [32] also reported a good test-retest reliability, with a coefficient of 0.88 and a good inter-rater reliability (ICC = 0.94). Besides, there is strong evidence for good validity of the scale [57–59]. Content validity is supported by the judgement of various experts and by the fact that the AES-C has been used in many studies and across several health conditions. In different studies, convergent validity was assessed by comparing results of other

measures of apathy, namely the AES-C self-rated, AES-C informant-rated and Apathy subscale of the Neuropsychiatric Inventory (NPI) [32,60,61]. Moreover, statistically significant correlations were observed between the AES-C and negative symptoms of the HAM-D, specifically, psychomotor retardation, lack of energy and insight and diminished work/interest. A similar result regards the correlations between the AES-C and reduced initiative, lack of emotional responsivity and inattention, as measured by the Montgomery and Asberg Depression Rating Scale (MADRS), as well as with the emotional withdrawal item of the Positive and Negative Syndrome Scale [62,63].

Our data agree with these findings and confirm the validity of the AES as a clinically relevant psychometric tool to detect apathy in MCI and mild AD patients. The convergent and discriminant validity of the AES-C was tested using the measures of cognitive impairment and the HDRS. In particular, it was planned to administer the Hamilton test, as in the original study, in order to evaluate also in the Italian version the ability of the AES to discriminate depression from apathy as a construct in and of itself. The results are in line with what was stated in the original article by Marin: in fact, the moderate but significant correlation between the AES-C and HAM-D confirms that apathy can not only be considered as a symptom of depression, but that it should be considered as a separate syndrome for which to intervene selectively to improve the quality of life of the subjects. Several previous studies showed the difference between the construct of apathy and that of depression. Already in 1998, Levy et al. [64] carried out research on a sample of subjects suffering from different neuropsychiatric diseases, showing that there was no correlation between apathy and depression and therefore confirming the separation of the two constructs, but they also found that apathy was strongly correlated with a low cognitive level measured by the Mini Mental State Examination. Successively, Starkstein et al. [65] have suggested that apathy is a behavioural dimension independent of depression. This seems very important considering that recent studies have shown that the higher the level of apathy, the more it is a predictor of the transition to dementia [2]; apathy alone or both apathy and depression are major risks to develop AD in MCI patients when compared to those with no NPS, as reported by Ruthirakuhan et al. [19]. Most of the epidemiological studies on apathy in the AD context refer to studies on the prevalence or change in apathy symptoms over time [66]. Apathy is predominant both in MCI and dementia. This prevalence is positively related to the severity of dementia [2]. A 3-year observational study of 332 MCI subjects showed a higher incidence of dementia

in subjects with apathy ((HR) = 1.62) [67]. Moreover, an investigation using the Apathy Evaluation Scale (AES) in elderly individuals with normal cognition and MCI showed that apathy progression over time predicted the transition from MCI to dementia [68]. A very recent study on the predictivity of apathy for the transition to dementia was carried out by Roberto et al. [20], who identified and explored the predictivity of the conversion to dementia of four NPS profiles, distinguishing apathy from depression and demonstrating that apathy was a predictor of the conversion to dementia, as opposed to depression. Other studies have examined the discriminant validity by comparing AES-C scores and measures of depression and anxiety. Significant correlations were found between the AES-C and Hamilton Rating Scale for Anxiety; HAM-D scores of depressed mood, guilt or hopelessness, suicide and vegetative symptoms of depression; depressed mood symptoms on the MADRS; the Calgary Depression Scale for Schizophrenia (CDSS) and the NPI depression subscale. Other results that gave support to the construct validity are the significant negative correlations between the AES-C and physical arousal measures such as heart rate reactivity, diastolic blood pressure and mean arterial pressure [68].

Our study also examined for the first time the psychometric link between apathy and executive function. Specifically, when considering the healthy control group, interestingly we found a negative correlation between the AES-C and FAB. This result suggests that apathy is connected to damage of the prefrontal cortex and other brain structures [55]. In healthy subjects without brain damage, therefore, the score on the apathy test correlates negatively with that of the FAB, demonstrating the presence of a link between apathy and brain injury. Multiple-Group Confirmatory Factor Analysis (MCFA) was performed for measurement invariance across gender and type of group. Results showed that the same factor solution was invariant across gender (men, women), and they were totally satisfactory as the model fit proved to be invariant across both populations.

When moving to MCI and mild AD patients, it is well known that the availability of a valid and reliable psychometric tool for the measurement of apathy appears to be fundamental for evaluating and planning the treatment of apathy syndrome in the AD population, and in particular in an early phase of AD pathogenesis, such as amnestic MCI. A recent study demonstrate that the AES-C sub-scale can predict the progression from MCI to AD dementia [69] Other studies have evaluated the AES-C in mild and moderate AD patients. Radakovic et al. [70]

examined the correlation between apathy and AD in a sample of 102 AD patients and 55 healthy controls. The aim of the study was to determine the validity and reliability of a multidimensional apathy measure, the Dimensional Apathy Scale (DAS) compared to the Apathy Evaluation Scale (AES), Geriatric Depression Short form (GDS-15), and Lawton Instrumental Activities of Daily Living (LIADL). The authors found in both subsamples a positive significant correlation between the DAS total score and AES ($r = 0.75$; $p < 0.001$), showing that apathy profiles in AD are heterogeneous, with additional specific impairments relating to awareness dependent on the apathy subtype [70]. The AES is a unidimensional measure, whereas apathy is established as a multidimensional construct. When considering the diagnostic criteria of apathy and in particular diminished motivation, reduced goal-directed cognitive activity and functional impairments, other psychometric tools such as the DAS should be used in combination with the AES in future clinical studies in early AD patients to evaluate the various dimensions of apathy better as well as additional specific impairments and specific clinical phenotypes such as the Executive-Initiation apathy detectable with the DAS eventually in combination with the AES-C.

Starting from the evidence of the key role of apathy as a risk factor for AD and the future development of disease-modifying strategies in amnestic MCI patients, the availability of a validated Italian version of the AES-C represents an essential step to plan future clinical studies in this field. Previous studies have found that the AES-S is a psychometrically sound measurement tool for assessing levels of apathy in a cognitively healthy middle-aged cohort at risk for AD [70], but our study demonstrates for the first time that the AES-C can be a useful tool to detect both apathy and executive dysfunction in amnestic MCI patients.

Despite the goodness of the results obtained, the study has some limitations. One of these concerns the sample. Although the presence of a higher number of women than men confirms the literature, according to which AD disease is more frequent in the female gender, a more homogeneous sample between men and women would perhaps have been more adequate to represent a sample of the AD and not. Another limitation concerns the influence of the pharmacological interventions to which the subjects of the study could be subjected (such as antidepressants or cholinesterase inhibitors). This limitation is not present on our study, because no patients with a current depressive episode or treated with antidepressants were recruited in the study. Furthermore, we recruited only AD patients that did not receive a treatment with

cholinesterase inhibitors, a drug class which might influence apathy scores. This might be considered as a limitation of our study, but it also helped us to exclude the impact of cholinesterase inhibitors on apathy scores in our AD sample. Further studies are needed to understand the impact of cholinesteraseinhibitors on AES scores. A mixed sample of MCI and AD subjects all belonging to the same reference centre was used. Future studies could investigate the difference in the perception and presence of apathy in subjects undergoing treatment versus those not undergoing treatment, also to assess the impact of pharmacological vs. non-pharmacological treatments better. Finally, our control subjects showed high apathy scores. We cannot exclude the possibility that the presence of apathy in the control group may be related to the SARSCoV-2 pandemic period during which the AES was administered.

5. Conclusions

From the results of the psychometric analyses conducted, it is possible to affirm the validity of the Italian version of the AES-C for the assessment of apathy both in MCI and in AD patients. Despite the limitations, our study leads to a real advance for future research and interventions. Considering the study and early identification of apathy in Alzheimer's patients can be of fundamental importance to intervene promptly and improve the quality of life of MCI patients in an early phase of AD pathogenesis. This study allowed us to show that the AES-C shows good discriminating, convergent, criterion and construct values, excellent wearability and good reliability, and presents itself as an adequate tool in the Italian context to assess apathy both in MCI and AD subjects.

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Review Board of the Department of Educational Sciences (Section of Psychology) of the University of Catania (n. Ierb-Edunict-2020.14.10 approved on 14.10.2020); research procedures followed all the indications provided by the guidelines of the AIP (Italian Association of Psychology) and its Ethical Council.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request. The data are not publicly available due to privacy restrictions.

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Chapter IV

The combined use of Mini-Mental State Examination with Montreal Cognitive Assessment to evaluate the clinical efficacy of cholinesterase inhibitors in Mild Alzheimer's disease patients

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Abstract

Alzheimer's disease (AD), is a chronic, progressive and neurodegenerative disease characterized by an irreversible cognitive decline and neuropsychiatric symptoms which strongly affect the quality of life of these patients. Current available drugs such as cholinesterase inhibitors (ChEIs) exert only a symptomatic activity against cognitive decline without interfering with the underlying pathogenic mechanisms. The clinical use of these drugs in AD patients required the use of different and combined psychometric tools such as Mini-Mental State Examination and Montreal Cognitive Assessment to better measure their impact on the progress of cognitive decline. The aim of this retrospective observational study was to assess the the validity of MMSE compared to MoCA for monitoring the impact of ChEIs treatment on cognitive decline in a sample of 33 mild AD patients. In the present paper we therefore examined the impact of ChEIs treatment on global cognitive function in AD patients both at 6

months (Group1=17 patients) and at 9 months (Group2=16 patients) by using a psychometric approach including MMSE, MoCA, Frontal assessment Battery (FAB), Hamilton Depression Rating Scale (HDRS). We did not find significant changes in Group 1 in MMSE scores ($z = -1.105$; $p = 0.132$)., whereas a significant reduction was detected with MoCA at 6 months ($z = -2.105$; $p = 0.035$). At 9 months we observed a significant reduction both in MMSE ($z = -3.755$; $p < 0.001$) and MoCA scores ($z = -2.732$; $p = 0.006$) as well as in FAB scores ($z = 2.969$; $p = 0.003$). ChEIs did not reduce the severity of depressive symptoms in both groups. Overall, our data suggest that the combined use of MMSE with MoCA can improve the evaluation of clinical efficacy of ChEIs in clinical practice.

Key words: Cognitive decline, drugs, Alzheimer, MMSE, MoCA, cholinesterase inhibitors

1. Introduction

Alzheimer's disease (AD), is a chronic, progressive and neurodegenerative disease (Albert, 2007) characterized by an irreversible deterioration of patient's cognitive functions and autonomy (APA, 1994). First symptoms appear in cognitive sphere with memory deficits and neuropsychiatric symptoms; there is an increasing neuropsychological impairment with progressive decline of memory, language, executive function and visuospatial skills, able to interfere with the quality of life and normal daily activities (Cummings, McPherson, 2001). To date, AD remains an incurable disease, and several studies have shown that cognitive impairment in AD are closely related to cholinergic deficiency (Lucchi et al., 2004) and also to an impairment of the monoaminergic systems (Caraci et al., 2018). Along this line, current available drugs such as cholinesterase inhibitors (ChEIs) exert only a "symptomatic" action against cognitive decline without interfering with the pathogenic mechanisms. ChEIs improve central cholinergic neurotransmission thus decreasing cognitive decline, at least during the first year of treatment (Howard et al., 2015; Cummings et al. 2000; Rogers et al. 2000; Wilcock et al. 2000, Rösler et al. 1999). The clinical use of these drugs, developed for the treatment of cognitive symptoms in AD, posed the great issue of monitoring their clinical efficacy and measure the response to drug treatment in AD patients. According to this scenario, it becomes essential the use of different psychometric tools to measure the impact of this drug class on the progress of cognitive

decline in AD patients in an early phase of the disease . A recent meta-analysis (Knight et al., 2018) focused on the use of the Mini-Mental State Examination (MMSE) (Folstein, et al., 1975) as the tool of choice for monitoring the effect of the ChEIs on cognitive decline. Different studies (Knight et al. 2018; Coin et al. 2009; Peng et al. 2002) have shown an improvement in MMSE scores in the first 6 months of ChEIs treatment. However, the same authors identified the use of the MMSE also as a limitation for their own studies due to the existing debates on the dubious correlation and poor convergent validity with other neuropsychological tests (Lucchi et al., 2004) and its both floor and ceiling effects (Knight et al. 2018). The objective of the present study is to examine the validity of the MMSE for monitoring drugs effects on cognitive decline of mild AD patients compared with another psychometric tool, the Montreal Cognitive Assessment (MoCA) to assess whether their combined use can improve the evaluation of clinical efficacy of ChEIs in clinical practice. To verify this hypothesis, we carried out a pilot retrospective observational study on a sample of 33 mild AD patients, where a battery of psychometric instruments was administered to monitor the effect of the ChEIs on global cognitive function.

2.Materials and Methods

2.1 Participants and Procedure

The study involved 33 participants, recruited from the U.O.S. Centro Alzheimer e Psicogeriatria, DSM ASP3, Catania, Italy where the new diagnostic criteria of the National Institute of Aging (NIA) and Alzheimer's Association work group (2011) have been adopted for mild AD patients. All patients selected for the present work were firstly recruited on their first access to the service, where they received the diagnosis for the first time. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was authorised by the Internal Ethics Review Board of the Department of Educational Sciences (Section of Psychology) of the University of Catania; research procedures followed all the indications provided by the guidelines of the AIP (Italian Association of Psychology) and its Ethical Council. The inclusion criteria included a diagnosis of probable Mild AD. As a screening for general cognitive impairment, we used the Italian standardised version of the Mini Mental State Examination (MMSE) (Crum et al., 1993; Magni et al., 1996), and in the study were included patients with a total age and educational adjusted score ≥16 and

≤25. All patients were treated with ChEIs for at least 6 months (donepezil 5-10 mg /die, rivastigmine patch 4.6-9.5 mg/die). Patients with a recent history of cerebral ischaemia and/or a recent history of psychotic episodes were excluded. The neuropsychological evaluation involved the administration of various psychological tools before pharmacological treatment (T_0) and after 6 months (group 1) and at least 9 months (group 2) of treatment (T_1). Global cognitive function assessment has been carried out in AD patients by using both the MMSE and MoCA (Nasreddine et a., 2005; Santangelo et al., 2014). The Frontal Assessment Battery (FAB) (Dubois et al., 2000; Apollonio et al., 2005) was used to evaluate executive functions. Severity of depression was measured by means of the Italian version of the Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960).

Table 1. Demographic characteristics of the sample.

	No.	**Age (Mean ± DS)**	**Gender**	
Group 1	17	76,29 ± 6,87	*Female*	14
			Male	3
Group 2	16	76,38 ± 5,965	*Female*	11
			Male	5

2.2 Measures

Mini Mental State Examination

The Mini Mental State Examination (Crum et al., 1993; Magni et al., 1996) is a measure of global cognitive function whose administration requires from 5 to 15 minutes. It can also be used with the progression of the disease. It is made up of 11 items through which different cognitive functions are explored: time orientation, spatial orientation, immediate memory, attention and calculation, recall memory, language, visual-constructive praxis.

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005; Santangelo et al., 2014) evaluates global cognitive function through different domains: attention and

concentration, executive functions, memory, language, visual-constructive skills, abstraction, calculation and orientation.

Frontal Assessment Battery

Frontal Assessment Battery (FAB) (Dubois et al., 2000; Apollonio et al., 2005) assess frontal lobe functions. It consists of 6 cognitive and behavioural subtests: conceptualisation, mental flexibility, motor programming, sensitivity to interference, inhibitory control and environmental autonomy.

Hamilton Psychiatric Rating Scale for Depression

The Hamilton psychiatric Rating scale for Depression (Hamilton, 1960; Hamilton, 1996; Guy, 1976), i.e., HDRS or HAM-D, is the most used psychometric tool to evaluate depression's severity. It evaluates 21 different areas (depressed mood, guilt, suicidal thoughts, initial insomnia, intermediate insomnia, prolonged insomnia, work and interests, slowing of thought and speech, agitation, psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, somatic symptoms, genital symptoms, hypochondria, introspection, weight loss, diurnal symptomatology variation, depersonalisation, paranoid symptomatology, obsessive symptomatology) that exert a key role for the assessment of the subject's depressive state.

2.3 Data Analysis

Statistical analysis was carried out using non-parametric tests for paired data, using SPSS version 27 for Windows 64bit software. Wilcoxon's test for paired data was used. Statistical analysis was performed on group 1 and group 2 at baseline and at 6 months and 9 months respectively from the start of drug treatment; *p* has been attributed a significance value of <0.05.

4.Results

We first evaluated the impact of the pharmacological treatment with ChEIs (donepezil 5-10 mg /die, rivastigmine patch 4.6-9.5 mg/die) on global cognitive function in AD patients at 6 months. In Group 1, the comparison between t0 and t1 showed no statistically significant differences on the MMSE scores ($z = -1.105$; $p = 0.132$). These results are in accordance with other available evidence literature, where MMSE is adopted as the best tool for monitoring drug's effects and an increase in the MMSE

scores was detected in some studies after the first six months of treatment (Knight et al. 2018; Coin et al. 2009; Peng et al. 2002). We also examined FAB scores, that did not show a statistically significant variation (z = -1.662; p = 0.097). We then analysed the impact of pharmacological treatment on MoCA scores. Interestingly we found a significant reduction of MoCA scores and the differences between t0 and t1 in the MoCA score emerged already at 6 months from the start of treatment (z = -2.105; p = 0.035). These results suggest the greater ability of MoCA, compared to the MMSE, to detect an early phase of cognitive decline in mild AD patients, even when MMSE show no changes. Instead, it seems that the use of ChEIs for six months had no impact on the depressive symptoms in AD patients with a slight, but not statistically significant, reduction of HDRS scores (z = -1.194; p = 0.233).

Table 2. Descriptive statistics and change in group 1

Measure	Baseline (t0) Mean ± SD	6 months (t1) Mean ± SD	P Wilcoxon	Median of differences
MMSE	20,42 ± 2,278	21,34 ± 3,291	0,132	0,000
MoCA	16,47 ± 3,815	14,58 ± 4,634	0,035	-1,000
FAB	10,65 ± 3,457	9,765 ± 3,413	0.097	0,000
HDRS	12,12 ± 7,999	10,47 ± 6,463	0,233	0,000

We than examined the impact of ChEIs treatment on global cognitive function in AD patients at 9 months. Interestingly, in group 2, the comparison between t0 and t1 scores instead highlighted statistically and clinically-relevant differences in all the psychometric tools used for the evaluation of cognitive function (MMSE, MoCA, FAB). In fact, as regards the MMSE score, a high significance emerged (z = -3.755; p <0.001), demonstrating a drop in the score that seemed to have persisted in the first 6 months. A significant difference also emerged in the MoCA (z = -2.732; p = 0.006) and FAB (z = 2.969; p = 0.003) scores. Even in this group, however, there are no significant differences between t0 and t1 for HDRS scores (z = -0.338; p = 0.736), suggesting again that ChEIs did not reduce the severity of depressive symptoms in our sample of mild AD patients.

Table 3. Descriptive statistics and change in group 2

Measure	Baseline (t0) Mean ± SD	≥ 9 months (t1) Mean ± SD	P Wilcoxon	Median of differences
MMSE	20,72 ± 3,012	17,72 ± 2,241	<0,001	-3,000
MoCA	16,14 ± 3,300	12,94 ± 3,431	0,006	-3,500
FAB	10,93 ± 2,718	8,363 ± 2,957	0,003	-2,500
Hamilton	12,94 ± 7,672	13,56 ± 10,88	0,736	1,500

5.Discussion

Mini Mental State Examination (Folstein, et al.,1975) represents one of the most validated and used psychometric tools for the evaluation of global cognitive dysfunction both in a screening phase as well as in the first diagnosis of AD. It is an instrument for general cognitive evaluation and it is used also for the diagnose of the different stages of AD from mild to moderate and severe ones (Vertesi et al., 2001). Despite presenting itself as a valid tool for the study of cognitive impairment and disease progression and also used for monitoring the effect of drug treatment (Siqueira et al., 2019), the MMSE shows several limitations as we have observed in the present study. It has a ceiling effect and a limited range of performance for individuals with age-related cognitive decline: this means that subjects with still subjective memory deficits can obtain scores within the normal range.

MMSE is more useful for mild and moderate dementia and probably not sensitive or specific enough for diagnosis of MCI (Caraci et al., 2014), with different studies showing 70% sensitivity and specificity using a cutoff of 26 or less for cognitive impairment (Loewenstein et al. 2000). Furthermore, MMSE is not sensitive to MCI detection due to the absence of executive function items (Trzepacz, 2015). The Montreal Cognitive Assessment (MoCA) was recently developed as a novel cognitive screening test for milder forms of cognitive impairment, having surpassed the well-known limitations of the MMSE (Larner, 2012).

According to this evidence, in the present study we evaluated for the first time the ability of MMSE, compared to MoCA, for the evaluation of global cognitive function in the first stage of AD (mild AD) to assess whether the combined use of these two instruments can improve the assessment of drug's treatment (i.e. ChEIs).

In fact, as we have shown in Group 1, the comparison between t0 and t1 showed no statistically significant differences on the MMSE score ($z = -1.105$; $p = 0.132$), demonstrating that the MMSE shows an increase in its score in the first six months of treatment as reported by other studies available in literature (Knight et al. 2018; Coin et al. 2009; Peng et al. 2002). MMSE has been used in double-blind placebo-controlled studies for the evaluation of ChEIs symptomatic efficacy and their approval from regulatory agencies (Mielke et al., 2012). Nevertheless, it remained unresolved the question whether a no change or a slight increase in MMSE scores can be considered a valid and sufficient primary outcome measure to demonstrate the symptomatic efficacy of ChEIs, especially in the first stage of AD progression. It becomes therefore essential to combine MMSE with novel available tools such as MoCA to better monitor the response to ChEIs in clinical practice. Our results only partially confirm the efficacy of MMSE as a valid tool for monitoring the effect of ChEIs at 6months, because when we used MoCA then detected clinically-relevant differences between t0 and t1 with a significant reduction in MoCA scores, suggesting that MoCA can better detect global cognitive decline in mild AD compared to MMSE. These results are further validated by the analysis of the group 2 data, when extending time monitoring with the same psychometric tools at 9 months. We observed a significant drop in MMSE scores that we did not observe at first 6 months, but was predicted instead by MoCA scores change at the same time frame. Our results suggest the greater ability of MoCA compared to the MMSE to identify cognitive decline in the first stage of AD.

As discussed above, it is known that MoCA was developed as a psychometric tool aimed at detecting previous states of dementia (Nasreddine et al., 2005) and in particular MCI stage, but it can also be used for the identification of the early stages of AD. It is also presented as a global screening tool for cognitive functions (included executive function), but it possesses a greater complexity than the MMSE and it seems also to possess ideal psychometric properties to monitor drug's response in the first stage of AD. Several studies report a better performance of MoCA compared to MMSE for the diagnosis of the early phase of cognitive decline in AD. Larner (2012) examined whether the combination of MMSE and MoCA could increase the diagnostic power of these tools both for AD and MCI. They found that that MoCA had a higher sensitivity in identifying MCI, but the combination of the two instruments did not add a diagnostic gain. Furthermore, Larner et al. suggest that in the presence of subjects showing cognitive decline without a functional impairment, it is preferable to proceed

with the administration of MoCA, since the MMSE could produce a normal score generating a false negative. Along this line, Ciesielska's meta-analysis (2016) found that MoCA is better than MMSE in meeting the criteria as a screening test able to detect MCI among over 60 years old patients. Recent studies also show that MoCA is a very useful psychometric tool not only for MCI, but also for the detection of early stages of AD. Cecato and colleagues (Cecato et al. 2015), conducted a cross-sectional study of 136 community-dwelling elderly participants using MMSE and MoCA to investigate which test was best able to discriminate between healthy controls, MCI and AD. They found that MoCA had markers of more severe impairments ie. rhino naming, serial 7, clock numbers and hands, word recall and orientation subtest, that can discriminate participant with MCI from AD patients. Pinto et al. (2019) conducted a systematic review with the aim of comparing the MMSE and the MOCA in the accuracy of identifying MCI and AD and found that MoCA was superior to MMSE for the greater complexity of the MoCA (given by the presence of more complex items such as the design of the cube and clock design). Furthermore, we cannot forget that MoCA administration is more difficult by the longer length of time it takes to assess delayed recall; in fact, this could cause a higher percentage of errors in elderly subjects with a mild cognitive deficit. Pinto et al (2019) suggest that MoCA should be chosen over MMSE as the primary test for screening cognitive functions in the elderly. De Roeck et al. (2019) in their systematic review demonstrate that MoCA is the most suitable instrument to detect MCI and early AD thanks to its specific items for the assessment of cognitive functions and visuospatial skills, which are not investigate by MMSE. All this evidence suggest that MoCA is a more sensitive tool compared to MMSE for tracking cognitive decline in the early phase of AD pathophysiology (Siqueira et al., 2019). Moreover, our study suggests, for the first time, that MoCA is a promising tool to better detect both cognitive decline and the response to ChEIs after 6 months treatment, when compared to MMSE. ChEIs are a drug class with a symptomatic efficacy, but also well-known side effects (Matsunaga et al. 2019). It becomes therefore essential to monitor the response to these drugs, especially in the first stage of AD, to better personalize the pharmacological treatment and select the appropriate dose. Further long-term observational studies are needed in larger samples of mild AD patients to confirm the validity of our retrospective observational study conducted in a small sample of mild AD patients.

Conclusion

The present retrospective observational study confirms the validity of MoCA as a novel psychometric tool for assessing cognitive decline in the first stage of AD in combination with MMSE and FAB. Furthermore, our study suggests an innovative psychometric protocol for future clinical studies with the inclusion of MoCA to better evaluate both the rate of cognitive decline and the clinical efficacy of ChEIs in mild AD patients. When considering both the clinical relevance of early detection of AD and the efficacy and safety issues related to ChEIs treatment, the use of combined psychometric tools such as MMSE and MoCA can become essential to intervene promptly and improve the quality of life of AD patients.

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GENERAL DISCUSSION AND CONCLUSIONS

AD is a progressive neurodegenerative disease that affects an increasing number of subjects over the age of 65 (Albert, 2007). It is the most common form of dementia (Herrera et al 2002; Hirtz, et al., 2007) and its prevalence is increasing globally (Ferri et al. 2005). AD was first described in 1906 by neuropathologist Alois Alzheimer, who presented the case of a 51-year-old woman with an unknown form of dementia (Alzheimer, A., 1995) describing her symptoms in this way:

"*Her memory is seriously impaired. If objects are shown to her, she names them correctly, but almost immediately afterwards she has forgotten everything. When reading a test, she skips from line to line or reads by spelling the words individually, or by making them meaningless through her pronunciation. In writing she repeats separate syllables many times, omits others and quickly breaks down completely. In speaking, she uses gap-fills and a few paraphrased expressions ("milk-pourer" instead of cup); sometimes it is obvious she cannot go on. Plainly, she does not understand certain questions. She does not remember the use of some objects*."

Today it seems evident that these symptoms can be interpreted as the first neuropsychological description of Alzheimer's disease. However, at that time it was only the observation of post mortem brain histological analyses that made it possible to identify the neurofibrillary tangles, neuritic plaques and amyloid angiopathy which we now know are the main neuropathological features of AD. However, although many years have passed since these discoveries and scientific research has made great strides regarding the study of Alzheimer's disease, the mechanisms underlying the evolution of this disease and especially the methods of treatment are still not well known. The World Health Organization recognized AD as a global health public priority (Rabbito et al., 2020) because it represents a critical challenge to the health care system with the aging population (Robert, et al., 2010). Over the years, there has been an increase in the number of people affected by Alzheimer's worldwide, from an estimated 27 million in 2006 (Brookmeyer et al., 2007) to an estimated 35 million in 2010 (Alzheimer's Association, 2010). Moreover, its incidence is estimated to triple by 2050, predicting one AD patient for every 85 persons (Brookmeyer et al., 2007).

Therefore, if we consider that in Europe 17.6% of the population is over 65, it is easy to imagine how the possibility of incidence of Alzheimer's disease can increase (De Roeck, et al. 2019). For this reason, over the years, many countries have established intervention plans to prevent and improve the early diagnosis of this disease (Pinto et

al. 2018). Unfortunately, the drugs currently approved for the treatment of AD and related cognitive decline are only 4 and above all they are "symptomatic" drugs, that is, they provide purely short-term symptomatic benefits, but do not influence the pathogenic mechanisms underlying the disease, despite the fact that a neuroprotective potential has been proposed for some of these drugs such as memantine (Salomone et al. 2012): for mild to moderate AD they includes cholinesterase inhibitors (donepezil, rivastigmine, galantamine) while for moderate to severe AD the NMDA receptor antagonist (memantine) is indicated. However, clinical trials for both drug classes have shown limited efficacy in promoting the improvement of cognitive functions and slowing the progression of cognitive decline (Berardelli, Cruccu, 2019). In fact, although patients benefit from these drugs, most AD patients, including those treated appropriately, continue to experience progressive cognitive decline (Liss, et al. 2021). There is therefore a need to develop new drugs, called disease-modifying drugs, that can act by actually slowing down or blocking cognitive decline. The modern challenge of AD research is to use a drug treatment in the early stages of AD in order to intervene on the modification of the biomarkers characteristic of Alzheimer's disease. Disease modifying therapies (DMT) are characterized by their ability to modify the evolution of a disease by acting on its pathogenic mechanisms and preventing neuronal death (Caraci, Drago, 2013). The disease-modifying drug slows progression of structural damage, ensuring a persistent effect that remains even after the end of the treatment. Its action is therefore opposed to that of the symptomatic drug which does not alter the progression of the disease, but only relieves the symptoms, also showing a reversibility of its effect in case of interruption of the treatment. To evaluate the effectiveness of disease modifying therapies, there must be a clear and validated definition of the biomarkers underlying AD, which would be the target of this type of drug (Salomone et al. 2012). However, the slow progress of Alzheimer's disease hinders the ability to quickly assess the effectiveness of disease modifying therapies, which instead take years. To date, there is no modifying drug available for AD due to unsatisfactory results on the effectiveness of these drugs. Indeed, the non-specificity of biomarkers directly correlated with cognitive decline makes the markers themselves only potential predictors of a possible clinical benefit (Cummings, Fox, 2017). One of the possible failures of the potential neuroprotective drugs in Phase II/II clinical trials lies in the sample included in the studies, often characterized by an already manifest and advanced cognitive decline. To demonstrate the clinical efficacy of these drugs as

neuroprotectanys, these drugs must be studied and used in the very early stages of AD, that is, before the pathogenic mechanisms that cause neuronal degeneration are activated (Berardelli, Cruccu, 2019; Salomone et al. 2013).

According to this evidence, it seems increasingly important and necessary to focus attention and studies on the early diagnosis of cognitive decline and therefore of Alzheimer's disease. In fact, recently, the interest of scientific literature has shifted from intervention to the secondary prevention in AD focusing on the early stages of the disease.

Along this line, the role of neuropsychology seems fundamental. Neuropsychological assessment is an indispensable part of diagnosing AD. In fact, thanks to the use of psychological tools it is possible to investigate the residual functions present in the patient, from the cognitive functions to the psychological and behavioural symptoms typical of this pathology and therefore to frame the subject and his autonomous functioning within one of the degrees of pathology, from mild to severe. The measurement of cognitive decline assumes a central role in the assessment of AD. In the literature there are many psychological tools and batteries that have been developed precisely with the aim of investigating both global and more specific cognitive functions. In particular, the cognitive tools that we have mostly used in our research works and on which we have paid the most attention are the MMSE and the MoCA. The MMSE is one of the most used tools in the world for the assessment of global cognitive functions. Different studies have shown that MMSE is the preferred and validated tool not only for the assessment of cognitive impairment in AD patients, but also as the main tool for monitoring the subject's response to drug treatment. Numerous studies, in fact, use the MMSE to evaluate cognitive functions and the consequent trend of cognitive decline in subjects undergoing pharmacological treatment, especially with ChEI.

In 2005, the Montreal Cognitive Assessment was created as an appropriate tool to assess cognitive decline in subjects who presented mild symptoms, but who did not fall within the category of Alzheimer's disease: subjects with Mild Cognitive Impairment. The MoCA thus appears to be a more sensitive tool than the MMSE in identifying a slight cognitive decline, at a time when the subject still retains most of his cognitive functions and all his autonomies. The MoCA is also presented as a test for assessing the individual's global cognitive functions, but it compensates for the shortcomings of the MMSE, such as the assessment of frontal functions, proving to be

a more accurate tool in the assessment of cognitive decline. Starting from this evidence, we conducted our retrospective observational study to assess the validity of MMSE compared to MoCA and their combined use for monitoring the impact of ChEIs treatment on cognitive decline in a sample of 33 mild AD patients. We wondered if, given the scientific evidence regarding the better performance of the MoCA compared to the MMSE in the assessment of cognitive impairment, the MoCA could represent also an adequate tool also in monitoring the response to the drug. In the literature there were no previous works of this kind and further research would be necessary to deepen the subject, but our study shows promising and interesting results. In fact, the MoCA was able to detect the progression of cognitive decline in patients on drug treatment with ChEIs for 6 months, when the MMSE on the contrary showed no change in its scores. For this reason, we believe that the MoCA could be a better tool combined with MMSE also for monitoring the efficacy of the drug and therefore allow an improvement in the pharmacological treatment of the AD patients. Our study confirms the validity of MoCA as a novel psychometric tool for assessing cognitive decline in the first stage of AD in combination with MMSE and FAB. Furthermore, our study suggests an innovative psychometric protocol for future clinical studies with the inclusion of MoCA to better evaluate both the rate of cognitive decline and the clinical efficacy of ChEIs in mild AD patients. When considering both the clinical relevance of early detection of AD and the efficacy and safety issues related to ChEIs treatment, the use of combined psychometric tools such as MMSE and MoCA can become essential to intervene promptly and improve the quality of life of AD patients. However, cognitive decline, although the main one, is only one of the symptoms of Alzheimer's disease. Indeed, cognitive and functional decline is accompanied by behavioural and psychological symptoms (BPSD) in almost 90% of patients (Guimarães, et al., 2008). BPSDs are characterized by disturbances in perception, thought content, mood and behaviour that occur frequently and are common precipitators of institutional care (Mitchell, et al., 2011) significantly contributing to decreasing the quality of life of patients and their caregivers. Among the BPSDs we find apathy, agitation, disappointment, irritability, anxiety, disinhibition and hallucinations (Cummings, McPherson, 2001): all these symptoms accelerate the patient's functional decline and can contribute to the increase in mortality rates in AD patients.

Depression is certainly one of the most studied BPSDs in the literature. In fact, several studies have shown that depression is among the most frequent psychiatric comorbidities in dementia even if there is an overlap between AD symptoms and depressive symptoms. Surely the relationship between depression and dementia still needs further investigation, but it is clear that depression can be considered as a risk factor, a consequence but also a prodromal symptom of AD. (Caraci et al. 2018; Babulal, et al., 2018; Bennett, Thomas,2014; Ownby, et al., 2006; Novais, Starkstein, 2015; Mizukami, 2013).

But recently different studies have focused particularly on apathy. Apathy defines a specific dimension of behaviour characterized by a lack of motivation. it has often been regarded as a symptom of other syndromes, particularly depression. However, it can be considered as a multidimensional construct (three separate dimensions made up of cognitive, affective and behavioural symptoms) in its own right that has a great impact on both the emotional and social spheres and has three separate dimensions made up of cognitive, affective and behavioural symptoms. Recent studies have shown that the higher the level of apathy, the more it is a predictor of transition to dementia (Lanctôt, 2017) Apathy is predominant both in MCI and dementia and its prevalence is positively correlated with the severity of dementia (Lanctôt, 2017). Based on this evidence, we considered apathy as an early indicator of cognitive decline and the transition to dementia. This prompted the field to report it as a high-value neuropsychiatric risk state in the National Institute on Aging's latest guidelines for preclinical AD (Sperling et al., 2011), albeit as early as in 2008, the European Alzheimer's Disease Consortium had drawn up guidelines for the diagnosis of apathy (Winblad, et al., 2008). Based on this scientific evidence, our attention has focused on the link between apathy and Alzheimer's and in one of our works we have set ourselves the goal of providing a general overview of the neurobiological and clinical links between apathy and AD, with the aim of give clinicians the opportunity to assess the impact of apathy on the health of AD patients by focusing on the role of psychometrics tools available to evaluate it and the possible implications for treatment. In our review we analysed the neurobiological and clinical links between apathy and Alzheimer's disease highlighting their importance when considering apathy as one of the main common neuropsychiatric symptoms of AD. Although at first apathy was considered only as a symptom of Major Depressive Disorder, today it seems necessary to

investigate apathy as a syndrome, in order to be able to intervene in a targeted and timely manner on it and improve the quality of life of patients.

Based on our studies and our evaluations on the clinical relevance of apathy we decided to focus our attention on the Italian validation of the Apathy Evaluation Scale Clinical Version, on a sample of MCI and Mild AD subjects.

Starting from the evidence that apathy can represent both a prodromal symptom and a risk factor for AD, in our paper we analysed the psychometric properties and the invariance of the Italian version of the apathy rating scale - clinical version in a sample of 107 Italian MCIs and patients with AD. In general, it is possible to say that our results confirm the goodness of the scale. In 2007, Clarke and colleagues conducted a publication review study between January 1983 and December 2004 on the psychometric properties of the AES-C. The authors provided detailed information on both reliability and validity, concluding that the scale has good psychometric properties, as first demonstrated by the original study by Marin et al. The validity of the content is supported by the judgment of various experts and the fact that AES-C has been used in many studies and in various health conditions. In several studies, convergent validity was evaluated by comparing the results of other measures of apathy, and statistically significant correlations were observed between AES-C and negative HAM-D symptoms, in particular psychomotor retardation, lack of energy and and decreased work / interest. Our data are consistent with these findings and confirm the validity of AES as a clinically relevant psychometric tool for detecting apathy in patients with MCI and mild AD. The convergent and discriminating validity of AES-C was tested using measures of cognitive impairment and HDRS. In particular, it was planned to administer the Hamilton test, as in the original study, in order to evaluate also in the Italian version, the ability of AES to discriminate depression from apathy as a construct in and of itself. The results are in line with what was stated in the original article, i.e. apathy cannot be considered only as a symptom of depression, but must be considered as a syndrome in its own right for which selectively intervene to improve the quality of life. of the subjects. Several previous studies have shown the difference between the construct of apathy and that of depression and have suggested that apathy is a behavioural dimension independent of depression.

Our study also examined for the first time the psychometric link between apathy and executive function. In particular, when considering the healthy control group, it is interesting to note that we found a negative correlation between AES-C and FAB. This

finding suggests that apathy is linked to damage to the prefrontal cortex and other brain structures (Moretti, et al. 2016). In healthy subjects without brain damage, therefore, the apathy test score correlates negatively with that of the FAB, demonstrating the presence of a link between apathy and brain damage. Multiple group confirmatory factor analysis (MCFA) was performed to measure invariance by gender and group type. The results showed that the same factor solution was gender-invariant (men, women) and were totally satisfactory as the model fit was found to be invariant in both populations. When moving to patients with MCI and mild AD, it is known that the availability of a valid and reliable psychometric tool for measuring apathy appears to be essential for evaluating and planning the treatment of apathy syndrome in the AD population, and in particular in an early stage in the pathogenesis of AD, such as amnestic MCI. A recent study demonstrates that the AES-C subscale can predict progression from MCI to AD dementia (Clarke, et al. 2007). Starting from the evidence of the key role of apathy as a risk factor for AD and from the future development of disease-modifying strategies in patients with amnestic MCI, the availability of a validated Italian version of the AES-C represents an essential step for plan future clinical studies in this field. Furthermore, our study demonstrates for the first time that AES-C can be a useful tool for detecting both apathy and executive dysfunction in patients with amnestic MCI. Future studies could investigate the difference in the perception and presence of apathy in treated versus non-treated subjects, also to better evaluate the impact of pharmacological treatments compared to non-pharmacological ones. Finally, our control subjects showed high apathy scores. We cannot rule out the possibility that the presence of apathy in the control group may be related to the SARSCoV-2 pandemic period during which AES was administered.

We believe that only by considering every single aspect of the patient's clinical picture, the clinician can plan a multi-modal intervention that has significant impact on health, defined as a state of complete physical, mental and social well-being (World Health Organization). In fact, several studies have shown efficacy in reducing apathy also through non-pharmacological treatments centred on individual autonomous, psychological and social functioning.

With a research team from ASP 3 Catania, we conducted a pilot study, publishing an abstract entitled "Cognitive rehabilitation in patients with MCI and mild AD: a focus on apathy".

In the face of the increasingly evident limits of the clinical efficacy of pharmacological treatment alone, in recent years greater attention has been placed on the usefulness of combining pharmacological treatment with a cognitive rehabilitation process, especially in the early and moderate stages of AD, in order to improve the quality of life of patients and their families. Starting from these assumptions, the hypothesis was formulated that cognitive rehabilitation, planned as cognitive stimulation, can rescue not only cognitive functions, but also had a relevance in the manifestation and containment of apathy, finally improving the quality of life of these patients. We therefore carried out a pilot study with the aim of verifying whether there were any differences in Apathy Evaluation Scale (AES) test scores between subjects with MCI and mild AD included in a rehabilitation program and subjects who on the contrary, did not carry out any activity of this type. The study involved the recruitment of two groups of patients at the U.O.S DIP. Alzheimer's and Psychogeriatrics Center ASP3 Catania:

1. study group with patients who underwent rehabilitation planned as cognitive stimulation, composed of 31 subjects (F = 21; M = 10) aged between 65 and 90 years (mean ± sd: 76.71 ± 7.862), with a score at the MMSE with an average of 23.76 and s 3.114; 2. control group with patients not undergoing rehabilitation composed of 31 subjects (F = 22; M = 9), aged between 65 and 90 years (Mean ± sd: 77.16 ± 7.847) with MMSE score with mean 23,32 and ds 3.712. Both groups were given AES-C. Statistical analysis was then performed using the Mann-Whitney test for unpaired data. The preliminary results obtained show that there is a significant difference equal to P = 0.0183 between the two groups. In particular, the analysis of the scores on the AES-C test shows that there is a lower degree of apathy in subjects undergoing rehabilitation with cognitive stimulation. Our results confirm the hypothesis that cognitive rehabilitation in subjects with MCI and mild AD can improve the quality of life of the subjects, also as regards the emotional sphere, especially the construct of apathy, characteristic of this pathological picture. Furthermore, it has been hypothesized that improving the patient's quality of life may make the relational dynamics between patients and caregivers more manageable. Further studies on the construct of apathy could allow us to further consolidate our results.

There are numerous studies that have investigated the effectiveness of other non-pharmacological interventions on other psychiatric syndromes. In particular, we conducted a systematic review on the effects of physical activity against cognitive

decline and the possible synergism between pharmacological treatment and physical activity both in major depressive disorder and AD patients. Indeed, it appears that physical activity can synergize with antidepressant treatment by rescuing neurotrophins signaling in MDD patients, promoting neuronal health and recovery of cognitive function in MDD-related circuits, finally enhancing the response to antidepressant drugs. When considering late life depression, we can hypothesize that this synergism might be particularly relevant in elderly patients with late-life depression, a clinical subgroup with an increased risk to develop dementia. Late-life depression occurs from the age of 60 and is often associated with cognitive dysfunction (Taylor, 2014) of one or more cognitive domains (attention, working memory, verbal fluency, visuospatial skills, and executive function) (Murrough et al., 2011). It is relevant remember that this the clinical subgroup shows a higher risk of developing Alzheimer's disease and vascular dementia (Caraci et al., 2010; Diniz et al., 2013). Longitudinal studies have shown that LLD worsens outcomes physical illnesses and the likelihood of frailty in the elderly (Butters et al., 2008; Vaughan et al., 2015). Over the years, several studies have been carried out to demonstrate the effectiveness of physical exercise as an intervention for clinical depression in these patients (Dupuis, Smale, 1995; Blumenthal et al., 1999) demonstrating the effectiveness of a structured exercise program on depressive symptoms and suggesting the need and the benefit of combining physical exercise with the daily routine of the elderly subject and any pharmacological treatment with antidepressants.

Physical activity can also be used effectively in the treatment of apathy in AD subjects. Maci et al. (Maci, et al., 2012) conducted an interesting study including physical activity as NPT, in order to assess in a 14-patient RCT the effect of a 3-month program of physical activity, cognitive stimulation and socialization versus usual activities at home. Maci et al. (2012) demonstrated a significant improvement in AES scores. Moreover in 2015, Telenius et al. (2015) confirmed that a high intensity functional exercise program in nursing home patients with dementia decreased level of apathy after the intervention versus a control group. Several recent studies have considered the key role of exercise in the treatment of various neuropsychiatric disorders (Guerrera, Furneri, et al., 2020). The clinical relevant issue to keep in mind is that physical activity, associated with drug treatment, allows to expand the range of rehabilitation interventions dedicated to demented patient especially in the early phase of the disease. Several studies seem to have demonstrated the efficacy of ChEIs and

other drugs in reducing apathy, while antidepressant drugs have not been found to improve apathy (Berman et al. 2012) although non-specific long-term observational studies have been conducted with second-generation antidepressant drugs such as fluoxetine and bupropion both in MCI and mild AD to evaluate the response to cholinesterase inhibitors and second-generation antidepressant drugs.

Certainly, more clinical studies are needed to investigate the effects of different drug treatments on reducing apathy. In particular, with the availability of a psychometric tool validated in Italy from our group for the assessment of apathy in AD patients, we believe that long-term observational study can now be planned, in mild to moderate AD patients, to examine the effect of ChEIs on AES-C scores, in order to evaluate how this drug class can reduce apathy and improve the quality of life in AD patients.

In conclusion, this study allows to remark the importance of neuropsychological evaluation in the context of Alzhaimer's disease, both for cognitive and affective evaluation and for monitoring the response to the drug. Only by considering every aspect of the patient and his symptoms, will it give the clinician the possibility of using a multi-modal intervention that can support the patient in dealing with and managing this disease. I believe that nowadays, when the challenge is to arrive at the earliest possible diagnosis of this disease, the use of new psychometric protocols can become essential to intervene promptly and improve the quality of life of patients with AD.

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