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ADVANCED PSYCHOMETRIC APPROACHES TO THE ASSESSMENT OF COGNITIVE DECLINE AND RISK FACTORS: FROM SYMPTOMS INTERPLAY TO THERAPEUTIC INNOVATION

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GENERAL INTRODUCTION

1. Aging and cognitive decline

Recent demographic trends indicate a steady increase in life expectancy accompanied by a simultaneous decline in birth rates. Forecasts project that by 2070, the average age of the population will rise by approximately five years compared to current figures, with life expectancy reaching 86 years for men and 90 years for women (European Commission, 2021, 2024). As a result, the demographic structure will shift toward an increasingly older population, with the proportion of individuals aged 65 and older constituting the largest age cohort. These projections underscore the growing importance of geriatric health in medium- and long-term socio-healthcare planning, particularly in the context of supporting the biopsychosocial well-being of aging populations (World Health Organization, 2017).

Indeed, physiological aging is associated with significant alterations in cerebral metabolic processes, which in turn lead to disrupted connectivity and neuronal atrophy. These neurobiological changes manifest behaviorally through slowed learning processes, increased task execution times, and greater difficulty in problem-solving (Alicioglu & Karakas, 2021). In addition, aging is accompanied by impaired mechanisms of neural plasticity and reduced synaptogenesis (Appelbaum et al., 2022). Structural neuroimaging and volumetric studies consistently show that aging affects specific brain regions, particularly the prefrontal and temporal cortices, while also inducing substantial changes across several subcortical structures (Vinke et al., 2018).

At the cellular level, brain aging is characterized by an increase in neuroinflammation, oxidative stress, genomic instability, metabolic dysfunction,

and protein homeostasis imbalance, leading to the accumulation of cellular waste products (Mecocci et al., 2018). Autopsy studies of older individuals without a clinical diagnosis of neurodegenerative disease frequently reveal hallmark pathological features such as amyloid plaques, neurofibrillary tangles, Lewy bodies, synaptic dystrophy, neuronal loss, and global cerebral atrophy (Elobeid et al., 2016).

These neuropathological and molecular alterations inevitably result in cognitive consequences, variably affecting neuropsychological functions including memory, attention, language, calculation, praxis, gnosis, executive functioning, and spatiotemporal orientation.

In some cases, the trajectory of physiological cognitive decline may progress into Mild Cognitive Impairment (MCI), a clinical condition conceptualized as an intermediate stage between normal aging and overt dementia (Petersen et al., 2001). MCI is defined by measurable cognitive deficits, particularly evident through neuropsychological testing, that do not yet significantly compromise the individual's functional independence but do represent an elevated risk for progression to dementia (Jongsiriyanyong & Limpawattana, 2018). While estimates of the conversion rate from MCI to dementia vary across studies, particularly due to methodological inconsistencies, meta-analytical evidence suggests that between 10% and 20% of individuals with MCI progress to dementia each year, typically within a follow-up period of one to two years (Petersen et al., 1999; Ward et al., 2013). MCI affects between 6.7% and 25.2% of adults aged 60 and older (Petersen et al., 2018) and is considered a heterogeneous syndrome (Gutiérrez Rodríguez & Guzmán Gutiérrez, 2017). Clinically, it can be subclassified into amnestic MCI, primarily involving episodic memory deficits, and non-amnestic MCI, which is characterized by impairments in executive function, visuospatial abilities, or language. Furthermore, MCI can be classified by domain involvement into single-domain MCI, where only one

cognitive domain is affected, and multi-domain MCI, involving impairments across two or more cognitive domains (Glynn et al., 2021).

By contrast, the term dementia refers to a broad category of neurocognitive disorders marked by progressive, irreversible deterioration in mental functions such as memory, reasoning, judgment, and learning capacity, ultimately resulting in significant impairment of personal autonomy (American Psychiatric Association, 2022). According to the World Alzheimer's Report, ten hallmark symptoms distinguish dementia from normal aging, including memory loss, language difficulties, personality changes, disorientation, and inappropriate or destructive behaviors (Alzheimer's Disease International, 2024; Gauthier et al., 2021). These symptoms typically worsen over time, leading to a total loss of independence and necessitating full-time care. At present, no curative treatment exists for dementia, underscoring the imperative for early detection and intervention during the preclinical and high-risk stages.

Within the global aging context, dementia represents a critical and escalating public health challenge. It is currently estimated that approximately 47 million people worldwide are living with dementia, with nearly 8 million new cases diagnosed each year. If current trends persist, the number of individuals affected is projected to exceed 75 million by 2030 and could nearly triple by 2050 (World Health Organization, 2021). These figures highlight dementia as not only a medical priority but also a significant socio-economic concern, particularly within national healthcare systems.

In Italy, dementia has been formally recognized as a strategic priority. In response to the growing burden, the National Dementia Plan (Piano Nazionale Demenze) was launched in 2014, followed by the establishment of a Permanent Dementia Working Group in 2020 to ensure coordinated policy actions and resource allocation (Istituto Superiore di Sanità, 2021, 2024).

Recent updates to international syntheses and consensus documents have emphasized a biologically informed continuum of cognitive decline that links subjective cognitive decline, MCI and Alzheimer's disease, and explicitly recommend integrating biomarker evidence (amyloid/tau PET and fluid biomarkers) with neuropsychological and functional staging for improved early detection and risk stratification. The 2024 Lancet Commission update highlights newly recognized modifiable risk factors and reiterates the need for multimodal assessment frameworks that combine neuropsychological measures with accessible biomarkers and digital phenotyping for more precise prognostication and targeted prevention strategies (Livingston et al., 2024).

Indeed, as an intermediary condition, MCI represents a critical window for intervention. Early diagnosis and timely therapeutic strategies are essential, as patients in this stage are most likely to benefit from cognitive and pharmacological interventions aimed at mitigating decline (García et al., 2021).

Against this backdrop, considerable research efforts are now focused on identifying predictive factors that may signal the transition from healthy cognitive aging to Mild Cognitive Impairment (MCI), and subsequently from MCI to full-blown dementia. The overarching goal of this line of inquiry is to facilitate early diagnosis and prompt intervention, ideally during the prodromal phase, when only a risk profile is present and no overt pathology has yet emerged. Despite progress in this area, significant knowledge gaps remain. Therefore, further research is needed to delineate a comprehensive set of predictive risk factors capable of identifying individuals at high risk for developing dementia years before clinical symptoms manifest.

2. Modifiable risk factors

Building on this neurobiological and epidemiological foundation, recent evidence underscores the critical role of *modifiable risk factors* across the lifespan in mitigating the progression from physiological aging to Mild Cognitive Impairment and dementia.

Risk factors are conditions that may contribute to the development of a disease without being its direct cause. Gaining a comprehensive understanding of how such factors interact with cognitive functioning offers the opportunity to intervene early, not only through neuropsychological assessment and adaptation measures but also by screening general life characteristics of the individual well before the emergence of clinical symptoms.

The literature underscores the complexity of accurately identifying all risk factors associated with cognitive deterioration, largely due to its multifactorial etiology. Risk factors are generally categorized as modifiable or non-modifiable, with the former representing the primary targets of preventive strategies (Ashraf & Uddin, 2022). A systematic review conducted by Beydoun and colleagues highlighted the influence of modifiable risk factors - such as socioeconomic status, behavioral patterns, and dietary habits - on long-term cognitive performance, indicating their significant role in the incidence of cognitive decline (Beydoun et al., 2014).

Subsequent evidence has further reinforced this perspective. Indeed, the 2024 Lancet Commission update identified fourteen potentially modifiable risk factors that collectively account for an estimated 45 percent of all dementia cases, a significant increase from the prior estimate of 40 percent (Livingston et al., 2024).

Building on the Lancet Commission's life-course framework, each of the fourteen modifiable risk factors warrants individual consideration with respect to epidemiology, plausible mechanisms, and opportunities for intervention.

1. Low educational attainment (early life). Low formal education is consistently associated with higher dementia incidence, an effect frequently interpreted through the cognitive reserve model: greater educational exposure builds neural networks and compensatory strategies that delay clinical expression of neuropathology. Recent cohort and mediation studies confirm that education's protective effect is partly mediated by lifetime occupational complexity, lifestyle, and vascular risk profiles, underscoring both primary-prevention and social-policy implications (investing in equal access to quality education may have downstream neuroprotective effects decades later) (Nafilyan et al., 2024).

2. Hearing impairment (midlife onward). Hearing loss has emerged as one of the most robust mid-life risk factors. Longitudinal analyses and meta-syntheses report elevated hazard ratios for cognitive decline and dementia among individuals with untreated hearing impairment (Cantuaria et al., 2024; Liang et al., 2021). Proposed mechanisms include increased cognitive load, reduced social engagement, and accelerated brain atrophy in auditory and associative cortices; interventional studies are beginning to test whether hearing rehabilitation (hearing aids, cochlear implants) mitigates risk, but randomized evidence on dementia incidence is still limited, making hearing screening and timely treatment a high-yield target for translational research and public health programs (Machado et al., 2024).

3. Traumatic brain injury (TBI) (midlife). Robust meta-analytic evidence links moderate-to-severe TBI with substantially increased long-term dementia risk, with severity and repetition of injury amplifying hazard. Pathophysiologically, TBI can seed chronic neuroinflammation, tauopathy, and diffuse axonal injury that interact with aging processes. Prevention (helmet use, sports and

occupational safeguards), early rehabilitation, and systematic long-term follow-up of TBI survivors are therefore key clinical priorities (Mavroudis et al., 2024).

4. Hypertension (midlife). Hypertension in midlife is reproducibly associated with later cognitive impairment and dementia. Mechanistic pathways include small-vessel disease, white matter lesions, and cerebral hypoperfusion; randomized and individual-participant meta-analyses indicate that effective blood-pressure control reduces incidence of cerebrovascular events and appears to lower dementia risk, supporting aggressive midlife cardiovascular risk management as a dementia-prevention strategy (Lennon et al., 2023).

5. Excessive alcohol consumption (mid/late life patterns). The relationship between alcohol and dementia has proven complex: dose-response meta-analyses suggest a non-linear association, with heavy use increasing dementia risk and some observational studies reporting a J-shaped curve for light-to-moderate intake (Zarezadeh et al., 2024). However, recent causal inference and large-scale observational work increasingly questions protective findings and emphasizes that higher intake reliably increases risk; therefore, public-health guidance should prioritize limiting harmful alcohol use and clarifying risk across consumption patterns (Zheng et al., 2024).

6. Obesity (primarily midlife). Midlife obesity - particularly central/visceral adiposity - is associated with elevated dementia risk later in life. Mechanisms include chronic systemic and neuroinflammation, insulin resistance, and vascular comorbidity. Notably, the temporal window matters: higher BMI in midlife confers greater risk, whereas low BMI in late life may reflect preclinical disease (Yang et al., 2025). Interventions targeting weight reduction and metabolic health in midlife therefore hold promise for risk reduction (Park et al., 2024).

7. Tobacco smoking (throughout adult life). Smoking is a well-established risk factor for dementia, with cumulative exposure correlating with higher incidence

of both vascular and Alzheimer's-type dementia. Mechanisms include atherogenesis, oxidative stress, and cerebrovascular injury. Recent longitudinal analyses support cessation at any age as a strategy to attenuate future cognitive decline, and smoking control remains a high-impact, clinically actionable prevention target (Anstey et al., 2007).

8. Depression (mid- to late-life). Depression across the life course - particularly persistent or recurrent episodes in midlife - has been associated with an increased risk of subsequent dementia. Proposed mechanisms include chronic inflammation, hypothalamic–pituitary–adrenal axis dysregulation, and behavioral mediators (reduced activity, social withdrawal). While reverse causation (prodromal depressive symptoms) complicates interpretation, current evidence supports aggressive detection and treatment of depression as part of comprehensive dementia-risk reduction (Elser et al., 2023).

9. Social isolation and loneliness (late life). Social isolation and loneliness are independently linked to higher dementia incidence in longitudinal analyses (Shen et al., 2022). Pathways likely combine behavioral consequences (reduced cognitive and physical activity), psychological stress, and altered inflammatory profiles. Interventions that foster social connectivity and community engagement for older adults therefore constitute feasible population-level strategies to support cognitive health (Ng et al., 2025).

10. Physical inactivity / sedentary behavior (mid- to late life). Regular physical activity is among the most consistently protective lifestyle factors: cohort studies and meta-analyses associate higher cardiorespiratory fitness and sustained exercise with lower dementia risk and slower cognitive decline. Exercise promotes cerebrovascular health, neurogenesis, and neurotrophic factor expression; accordingly, scalable exercise programmes represent a cornerstone of multimodal prevention. Recent intervention trials also demonstrate cognitive

gains from combined exercise, diet, and cognitive training in at-risk older adults (Wang et al., 2025).

11. Diabetes (type 2) and glycemic control (midlife). Type 2 diabetes is strongly associated with higher dementia risk, mediated largely by vascular injury, glycemic extremes, and insulin-resistance-related neurodegeneration. Emerging pharmaco-epidemiologic evidence suggests that certain glucose-lowering agents (for example, SGLT2 inhibitors and GLP-1 receptor agonists) may confer cognitive benefits, but randomized dementia-prevention trials are lacking. Hence, optimal glycemic control and cardiovascular risk management in diabetic patients are pragmatic prevention priorities (Li et al., 2024; Seminer et al., 2025).

12. Air pollution (ambient particulate matter and nitrogen oxides) (life-course exposure). A growing body of high-quality evidence - including recent systematic reviews and a Lancet Planetary Health meta-analysis - links long-term exposure to PM2.5 and traffic-related pollutants with increased incidence of dementia. Biological plausibility is supported by translocation of ultrafine particles to the brain, neuroinflammation, and cerebrovascular injury. Reducing population exposure to air pollution therefore represents an important, structural prevention lever that complements individual-level interventions (Best Rogowski et al., 2025; Wilker et al., 2023).

13. High low-density lipoprotein (LDL) cholesterol (midlife). The 2024 Lancet report incorporated midlife elevated LDL cholesterol as a newly recognized risk factor. Epidemiological cohorts and lipid-variability analyses implicate dyslipidemia in later cognitive decline - likely via atherogenic and microvascular brain injury - suggesting that midlife lipid management (lifestyle and pharmacotherapy where appropriate) may reduce downstream dementia risk. Randomized trials specifically addressing dementia outcomes are sparse, but existing cardiovascular outcome data and observational analyses support lipid control as a plausible, actionable strategy (Livingston et al., 2024).

14. Untreated vision loss (late life). Untreated vision impairment has been newly recognized as a late-life risk factor for cognitive decline and dementia. Cohort and pooled analyses show higher dementia incidence among individuals with visual deficits, plausibly mediated by reduced sensory input, decreased activity and social participation, and shared systemic disease (e.g., diabetes). Importantly, vision loss is often correctable or remediable; therefore, systematic vision screening and timely ophthalmic treatment constitute concrete, evidence-informed prevention opportunities (Littlejohns et al., 2022).

Taken together, these recent scientific reports converge on three practical implications. First, timing matters: early-life (education), midlife (blood pressure, lipids, obesity, hearing), and late-life (sensory loss, social engagement) determinants require temporally targeted interventions. Second, mechanistic plurality - vascular injury, chronic inflammation, sensory deprivation, and reduced cognitive reserve - highlights the need for multimodal prevention strategies rather than single-axis solutions. Third, policy and clinical translation are both necessary: many of the risk factors identified are socially patterned (education, pollution, access to care), implying that population-level public-health actions will be essential to realize the projected reductions in dementia burden. These conclusions derive directly from the 2024 Lancet Commission synthesis and from contemporary systematic reviews, meta-analyses, and large cohort studies cited above (Livingston et al., 2024).

In sum, the convergence of recent Lancet data with mechanistic and interventional studies affirms that dementia onset is not an immutable consequence of aging. Instead, a life-course, multipronged prevention strategy - spanning education, cardiovascular health, sensory preservation, lifestyle modification, and social support - offers a promising framework for delaying or averting cognitive decline.

3. The psychometric challenges for a complex understanding of interactions

The multifactorial nature of cognitive decline, particularly in its prodromal stages, presents a formidable challenge for both clinical research and applied psychometric assessment (Livingston et al., 2024). Traditional statistical models in neuropsychology - often grounded in linear regression, factor analysis, or structural equation modeling - tend to conceptualize risk factors as independent or hierarchically structured contributors to an outcome variable (Brown, 2015; Kline, 2015). While these approaches have yielded valuable insights into main effects and latent constructs, they are inherently limited in their capacity to represent reciprocal, dynamic, and non-linear relationships among variables that evolve over time (Borsboom & Cramer, 2013; Bringmann et al., 2019). In the context of dementia research, where risk factors such as hypertension, depression, physical inactivity, and sensory impairments may mutually reinforce or buffer one another, a paradigm shift toward more interaction-sensitive methodologies is warranted. Without such a shift, psychometric models risk oversimplifying the etiological complexity of cognitive decline, potentially overlooking synergistic or cascading effects that could inform prevention and intervention strategies.

A critical psychometric gap emerges when the temporal and bidirectional interactions between modifiable risk factors is considered. For example, depression may increase the likelihood of social isolation, which in turn exacerbates physical inactivity, amplifying cardiovascular risk and thus accelerating cognitive deterioration (Kuiper et al., 2015; Rafnsson et al., 2020). Such feedback loops are ill-suited to representation in traditional latent variable models, which typically assume local independence and unidirectional causal pathways (Bollen, 1989; Brown, 2015). Furthermore, static measurement approaches neglect the fact that the network of risk factors is dynamic, with

relationships that may strengthen, weaken, or even reverse as individuals age or as health status changes (Epskamp et al., 2018). Capturing these evolving interdependencies requires a methodological framework capable of modeling variables not as isolated indicators of latent constructs, but as active components in a mutually influential system (Borsboom, 2017).

In this regard, network theory offers a promising conceptual and analytic solution (Borsboom & Cramer, 2013; Robinaugh et al., 2020). In a network approach, observed variables - whether they are neuropsychological test scores, biomarkers, or self-reported behavioral patterns - are represented as nodes, while the statistical relationships between them are represented as edges. These edges may be operationalized as zero-order correlations, partial correlations controlling for all other variables in the network, or other similarity metrics depending on the data structure (Epskamp & Fried, 2018). Importantly, in psychometric network models, edges are not interpreted merely as indicators of a shared latent cause; rather, they are conceptualized as potential direct interactions between observed variables. This shift in perspective has profound implications for understanding cognitive decline, as it allows us to map how one risk factor may directly influence another, independent of latent constructs (Bringmann et al., 2019).

From a statistical standpoint, the most common approach to estimating such networks in psychological research is the Gaussian Graphical Model (GGM) for continuous variables, which estimates a sparse partial correlation network by applying regularization techniques such as the graphical least absolute shrinkage and selection operator (gLASSO) (Epskamp et al., 2018; Friedman et al., 2008). The gLASSO imposes a penalty on the number of edges, effectively setting weaker connections to zero, thereby yielding a more interpretable and stable network structure. For categorical or mixed data, extensions such as the Ising Model or mixed graphical models are employed. These methods not only provide a

visualization of the global network topology but also allow for the computation of centrality metrics - such as strength, betweenness, and closeness - that identify the most influential nodes within the network (Opsahl et al., 2010). In the context of cognitive decline, a highly central node might represent a risk factor whose modification could lead to widespread downstream effects on the system (Robinaugh et al., 2020).

The temporal dimension can be integrated through the use of longitudinal network models, such as Vector Autoregressive (VAR) models and their multilevel extensions (mlVAR) (Bringmann et al., 2013; Epskamp et al., 2018). These models enable the separation of within-person (dynamic) and between-person (structural) networks, thereby distinguishing patterns that are consistent across individuals from those that are idiosyncratic. For example, within a given individual, increases in blood pressure might precede declines in executive function, which in turn precede increases in depressive symptoms; however, across the population, these relationships may average out to a weaker association (Sliwinski et al., 2018). By modeling both levels simultaneously, longitudinal network analysis can capture personalized dynamic systems of risk factors, opening the door to tailored preventive interventions.

From a psychometric perspective, network models align with the formative measurement model paradigm, in which the construct of interest - here, the "risk system" for cognitive decline - is constituted by the measured variables themselves rather than by a common latent cause (Borsboom, 2017). This is particularly appropriate in dementia research, where the co-occurrence of certain risk factors (e.g., hearing loss and social isolation) may collectively precipitate cognitive impairment, even in the absence of any single dominant latent variable. Moreover, network analysis can be applied to multimodal datasets, integrating cognitive test scores, neuroimaging measures, genetic markers, and ecological momentary assessment (EMA) data into a single unified

model. The integration of heterogeneous data sources is facilitated by recent advances in multilayer or multiplex networks, where each "layer" represents a different data modality, and inter-layer edges capture cross-domain interactions (e.g., how physical activity patterns relate to hippocampal volume changes over time) (De Domenico, 2017).

The statistical interpretation of network parameters also differs fundamentally from that of traditional psychometric models. In a regularized partial correlation network, the presence of an edge between two nodes suggests a unique association between those variables, controlling for all others in the network (Epskamp & Fried, 2018). This allows researchers to disentangle spurious correlations driven by shared relationships with other factors. Furthermore, bootstrapping methods have been developed to assess the stability of edge weights and centrality measures, addressing concerns about sampling variability - a critical step when dealing with high-dimensional neuropsychological data (Epskamp et al., 2018). The combination of regularization, bootstrapping, and longitudinal modeling positions network analysis as a robust, scalable, and conceptually aligned approach to the complex systems nature of cognitive decline.

The practical implications of adopting a network analytic framework in cognitive aging research are substantial. First, it enables the identification of potential intervention targets beyond those highlighted by traditional regression-based models. A node with high strength centrality - such as physical inactivity - may have numerous direct connections to other risk factors, suggesting that interventions aimed at increasing activity could have cascading benefits across the network. Second, network analysis allows for the detection of bridge nodes - variables that link otherwise distinct communities of nodes (e.g., a behavioral factor connecting vascular health and psychosocial functioning) (Jones et al., 2021). These bridge nodes are of particular interest in prevention research, as

they may represent critical leverage points for disrupting pathological feedback loops.

Methodologically, network analysis also encourages iterative refinement of measurement instruments (Borsboom, 2017). In a network model, the addition or removal of a variable changes the global topology, potentially altering the identified central nodes and clusters. This property can be leveraged to optimize neuropsychological batteries, ensuring that assessments capture not only the breadth of relevant domains but also the variables most critical for maintaining network stability. Furthermore, the visual and intuitive nature of network diagrams makes them an effective tool for communicating complex risk structures to multidisciplinary teams, policymakers, and even patients (Robinaugh et al., 2020), thereby enhancing the translational impact of research.

In conclusion, the psychometric challenges posed by the intricate web of risk factors for cognitive decline call for analytic strategies that move beyond the constraints of traditional latent variable models (Borsboom & Cramer, 2013). Network theory and network analysis provide a mathematically rigorous and conceptually congruent framework for modeling the dynamic, reciprocal, and system-level interactions among risk factors. By integrating longitudinal, multimodal data and focusing on the relational architecture of the system, network analysis holds the potential to transform our understanding of dementia risk from a static checklist of variables to a living, evolving system - one that can be mapped, monitored, and strategically modified to delay or prevent the onset of cognitive decline.

4. Current gaps in cognitive decline research and care

Despite notable advances in understanding the neurobiology and epidemiology of cognitive aging, substantial gaps persist in both research frameworks and applied care models. These gaps concern the integration of physical and cognitive dimensions of aging, the breadth of risk factors considered, the nuanced role of such factors in influencing treatment responsiveness, and the translation of technological innovation into sustainable, real-world interventions. Addressing these issues requires a paradigm shift toward multidimensional, life-course approaches that transcend disciplinary silos and linear cause-effect assumptions.

4.1 Toward an integrated body-mind framework

Current conceptualizations of cognitive decline have often been criticized for artificially separating physical and cognitive domains, thereby limiting their explanatory and predictive capacity (Kelaiditi et al., 2013). In reality, the physiological processes underpinning physical frailty - such as sarcopenia, systemic inflammation, and impaired metabolic regulation - are deeply intertwined with neurobiological mechanisms of cognitive deterioration (Soysal et al., 2017). The construct of cognitive frailty has emerged as a promising integrative framework, defined as the coexistence of physical frailty and Mild Cognitive Impairment in the absence of overt dementia (Kelaiditi et al., 2013). This dual-domain model aligns with evidence that body and mind are not independent aging systems but rather interconnected subsystems whose decline can be mutually reinforcing.

From a preventive perspective, embracing a body-mind framework compels researchers and clinicians to design interventions that simultaneously target physical robustness and cognitive resilience. For example, multimodal programs combining resistance training, cognitive stimulation, and nutritional optimization have demonstrated superior outcomes compared to single-

component interventions (Kivipelto et al., 2018; Ngandu et al., 2015). However, such integrated approaches remain underrepresented in clinical trials, and standardized assessment tools capable of capturing both domains in a unified metric are lacking. This methodological gap hinders the ability to accurately monitor intervention effects and to identify high-risk individuals before irreversible decline occurs.

4.2 Broadening the spectrum of risk factors

Another major gap lies in the scope of modifiable risk factors routinely investigated in cognitive decline research. As told before, the 2024 Lancet Commission identified 14 modifiable risk factors, yet some lifestyle and behavioral determinants remain relatively underexplored despite plausible mechanistic links to neurodegeneration. Three such factors, for instance - nutrition, sleep, and apathy - warrant particular attention.

Nutritional status is a determinant of both systemic and brain health, influencing neurogenesis, synaptic plasticity, and vascular integrity (Godos et al., 2023). Diets rich in polyphenols, omega-3 fatty acids, and antioxidants - such as the Mediterranean and MIND diets - have been associated with slower cognitive decline and reduced dementia incidence (Morris et al., 2015). Yet, dietary assessment remains inconsistently implemented in cognitive aging studies, and few randomized trials have tested the long-term cognitive impact of nutritional interventions in pre-dementia populations.

Similarly, sleep health exerts a bidirectional influence on cognition. Chronic sleep disturbances contribute to impaired glymphatic clearance of neurotoxic proteins such as β-amyloid, exacerbate neuroinflammation, and disrupt synaptic homeostasis (Lucey et al., 2019). Conversely, emerging evidence suggests that poor sleep may also reduce the efficacy of cognitive and pharmacological interventions by impairing neuroplasticity (Ramar et al., 2021). Despite these

insights, sleep assessment and management are rarely embedded as core components of dementia-prevention trials.

Apathy, often conceptualized as diminished motivation and goal-directed behavior, has traditionally been examined as a neuropsychiatric symptom secondary to cognitive impairment. However, longitudinal data indicate that apathy may precede and predict cognitive decline, functioning as both an early marker and an independent risk factor (van Dalen et al., 2018; Van Dalen et al., 2018). Its impact extends beyond onset: apathy can reduce adherence to treatment protocols, limit engagement in cognitively stimulating activities, and undermine rehabilitation outcomes. Despite this, apathy assessment is seldom incorporated into preventive screening or intervention design, representing a critical blind spot in current care models.

4.3 Risk factors and treatment responsiveness

A further gap is the insufficient consideration of how risk factors influence not only the onset but also the trajectory and treatment responsiveness of cognitive decline. Vascular risk factors such as hypertension and diabetes, for example, may diminish the neuroprotective effects of cognitive training or pharmacotherapy by sustaining microvascular damage and metabolic dysregulation (Gorelick et al., 2011). Similarly, sensory impairments - when unaddressed - can limit the effectiveness of interventions reliant on auditory or visual input (Deal et al., 2015).

Understanding these moderating effects requires integrating risk-factor profiling into both trial design and personalized care planning. This integration would enable the stratification of participants by modifiable risk burden, the tailoring of intervention components, and the identification of subgroups most likely to benefit. Such an approach resonates with precision-medicine paradigms and could improve both clinical outcomes and cost-effectiveness. Yet, current

research often treats risk factors as baseline covariates to be statistically controlled, rather than as dynamic variables shaping therapeutic potential.

4.4 Leveraging technology for autonomy and independence

Technological innovation offers unprecedented opportunities to address some of these gaps, particularly in promoting autonomy among older adults with cognitive frailty or early cognitive decline. Digital health tools - including mobile health (mHealth) applications, wearable sensors, and Internet-of-Things (IoT) platforms - can deliver personalized monitoring, feedback, and interventions at scale (Linn et al., 2021). For example, platforms such as My Active and Healthy Ageing integrate physical training, dietary planning, and cognitive exercises based on real-time sensor data (Rainero et al., 2021).

Gamified cognitive-motor training and virtual-reality-enhanced rehabilitation have shown promise in improving cognitive function and physical performance by enhancing neuroplasticity and user engagement (Bruni et al., 2022; Oliveira et al., 2021). Furthermore, social robots and human-robot interaction systems can support daily activities, provide companionship, and reduce social isolation (Søraa et al., 2023). However, their adoption is often hindered by barriers such as low digital literacy, limited interest, financial constraints, and usability challenges (Fadzil, 2023; Van Houwelingen et al., 2018).

Importantly, technological interventions must be adapted to the cognitive, sensory, and motivational profiles of target users. Apathy, sensory loss, or low self-efficacy can reduce engagement with digital tools, underscoring the need for assisted onboarding, ongoing support, and motivational design features (Vanoh et al., 2019). Without such user-centered adaptation, technology risks exacerbating rather than alleviating disparities in cognitive health.

5. Conclusion and structure of the thesis

In sum, several key gaps currently limit the effectiveness of cognitive decline research and care: the need of a complex methodological approach for the study of dynamic relationships, the lack of an integrated body-mind perspective, the narrow operationalization of modifiable risk factors and their assessment, the neglect of risk-treatment interactions, and the insufficient translation of technological potential into equitable, scalable solutions. Addressing these challenges requires interdisciplinary collaboration, longitudinal multimodal assessment, and a shift toward personalized, ecologically valid interventions. These themes will be further developed and empirically examined in the present dissertation.

While the Lancet Commission has identified a broad set of modifiable risk factors for dementia, the present thesis does not aim to provide an exhaustive examination of all of them. Instead, its innovative contribution lies in the targeted exploration of apathy as a potential novel risk factor, and in the empirical analysis of how depression, an established factor, modulates pharmacological outcomes. By integrating these affective dimensions into psychometric modeling and clinical evaluation, the thesis advances a more nuanced understanding of risk-treatment interactions that remain largely neglected in current research. This focused approach offers both theoretical innovation - by positioning apathy within the landscape of dementia risk - and practical implications, by highlighting how affective burden may influence the efficacy of therapeutic interventions. The assessment of apathy and the feasibility of technological supports for autonomy will be also addressed to provide a more comprehensive framework for prevention strategies and to inform the development of personalized, ecologically valid solutions for dementia care.

In more detail, the structure of the dissertation will consist of five chapters.

The first chapter will deal with a narrative review of the construct of cognitive frailty, surveying modifiable risk factors, neuropsychological profiles, assessment strategies, and technology-enabled supports, while mapping unresolved conceptual and methodological gaps that limit early detection and intervention.

Chapter two will adopt a network perspective on apathy across the continuum from healthy aging to MCI/early Alzheimer's disease, modeling apathy's behavioral, emotional, cognitive, and demographic components as an interconnected system; the analysis will identify symptom centralities and bridges most closely tied to cognitive/functional deterioration, proposing apathy as a candidate risk factor and target for tailored assessment and intervention.

Chapter three will aim to refine apathy assessment using Exploratory Graph Analysis (EGA) applied to the clinician-rated Apathy Evaluation Scale (AES-C), yielding a four-dimension solution with better psychometric performance and clinical interpretability than Marin's three-factor model and a traditional EFA, thus offering a more precise operationalization for clinical and research use.

Chapter four will report a longitudinal pilot study in mild Alzheimer's disease that compares the sensitivity of different psychometric tools to change during cholinesterase-inhibitor therapy (6- and 9-month follow-ups) and tests whether baseline depressive symptoms predict subsequent cognitive trajectories, evidence that supports affective burden as a potential modulator of pharmacological response.

Chapter five, finally, will investigate autonomy-supportive technologies through the lens of cognitive ergonomics, contrasting human-assisted versus robot-assisted task execution under varying demands and quantifying cognitive load with objective performance, subjective ratings, and physiological stress markers

(salivary cortisol), to clarify age-related differences and design principles for user-centered assistive solutions.

To sum up, the overarching goal of this dissertation is to advance the understanding and assessment of cognitive decline by applying innovative psychometric approaches. Specifically, it aims to (i) critically examine the construct of cognitive frailty and its modifiable risk factors, (ii) analyze apathy as a candidate risk factor for dementia, refining its measurement and conceptualization, (iii) investigate the role of depression in modulating pharmacological outcomes, and (iv) explore the potential of technological supports to sustain autonomy. Collectively, these objectives seek to bridge symptom-level dynamics with clinical and therapeutic innovation, fostering more precise, integrative, and personalized strategies for dementia prevention and care.

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CHAPTER ONE

Cognitive Frailty: a narrative review examining

modifiable risk factors, neuropsychological functioning,

assessment strategies, and technological supports

Preface

The first chapter explores the construct of *cognitive frailty* as a potential bridge linking physical decline and cognitive deterioration in the aging process. The use of a holistic conceptual framework, indeed, would allow a better explanation of the pathophysiological processes of impairment, and would promote an integrated action towards the risk factors involved. This review, therefore, considers different aspects of cognitive frailty: the conditions that may favor its onset, the characterizing neuropsychological profiles, the specific assessment strategies, and the rehabilitation approaches based on new technology.

Despite the promising directions opened by recent research, the field still lacks a unifying theoretical model capable of integrating biological, psychological, and social dimensions into a coherent framework. Furthermore, significant gaps remain in the standardization of diagnostic criteria, the validation of sensitive and specific assessment tools, and the evaluation of intervention efficacy over the long term. By synthesizing current evidence and identifying critical areas for future investigation, this chapter aims not only to clarify the conceptual boundaries of cognitive frailty, but also to contribute to the development of more effective preventive and therapeutic strategies that can ultimately enhance quality of life in older adults.

1. Introduction

In recent years, the concept of "frailty" has garnered significant attention within both clinical and research contexts. Among older adults, frailty is conceptualized as a heterogeneous disruption across biological, functional, genetic, cognitive, and social dimensions, leading to age-related declines in health and autonomy (Pilotto et al., 2020). The International Consensus Group on Cognitive Frailty, convened in Toulouse in 2013, defined frailty as a multidimensional geriatric syndrome characterized by increased vulnerability to stressors due to reduced capacity across various physiological systems (Kelaiditi et al., 2013). According to several authors, physical frailty is operationalized through indicators such as decreased muscle strength, slow gait speed, unintentional weight loss, exhaustion, reduced physical activity, and difficulties in basic functional tasks, including rising from a chair (Ensrud, 2008).

When physical frailty co-occurs with Mild Cognitive Impairment (MCI) in the absence of dementia, the term "cognitive frailty" is employed (Kelaiditi et al., 2013). Cognitive frailty can be further classified as reversible or potentially reversible. In the reversible form, physical frailty or pre-frailty coexists with subjective cognitive complaints or pre-MCI, while in the potentially reversible form, physical frailty or pre-frailty is accompanied by MCI (Sugimoto et al., 2018).

The adoption of the term "cognitive frailty" is supported by an extensive body of research examining the association between multimorbidity and MCI. For example, a 14-year longitudinal study demonstrated that multimorbidity is associated with cognitive decline (Wei et al., 2020), a finding corroborated by a systematic review (Hill et al., 2021). Consequently, a unified definition encompassing the coexistence of physical and cognitive impairment has gained preference in recent literature.

Despite these advancements, several aspects of the cognitive frailty construct remain insufficiently explored, particularly when compared to physical frailty (Kochlik et al., 2023). To date, there is no consensus regarding its prevention, underlying mechanisms, measurement, or support strategies (Jiao et al., 2023). Although numerous studies have investigated modifiable health and psychosocial risk factors contributing to the development of cognitive frailty, findings have been inconsistent (Zhang et al., 2022). This represents a critical gap in the literature, as evidence from the Italian Longitudinal Study on Aging indicates that cognitive frailty can be reversed in its early stages (Solfrizzi et al., 2017), provided that its contributing factors are thoroughly understood. This reversibility is linked to the dynamic nature of impairment, which is influenced by multidimensional factors, particularly lifestyle-related behaviors (Tang et al., 2021).

Additionally, a more detailed characterization of the neuropsychological profiles associated with cognitive frailty is warranted. While previous research has highlighted declines in attention, executive functioning, and instrumental activities of daily living (Delrieu et al., 2016), recent evidence suggests that cognitive frailty contributes to the motoric cognitive risk syndrome, characterized by subjective cognitive complaints and slow gait in the absence of dementia and overt mobility impairments (Corral-Pérez et al., 2023). However, neuropsychological functioning in cognitive frailty has not been comprehensively assessed, with the identification of cognitive profiles often relying solely on screening instruments (Facal et al., 2019).

The development of specific cognitive markers is closely tied to the need for dedicated diagnostic tools, which are currently lacking. Approximately two decades ago, a tool was proposed to assess frailty; however, it primarily focused on physical dimensions, neglecting cognitive aspects (Fried et al., 2001). Several authors have emphasized the importance of coupling psychometric evaluations

with specific motor performance assessments, including the use of wearable sensors (Razjouyan et al., 2020). Despite the existence of initiatives such as the FRAILTOOLS study, which aimed to validate and disseminate diagnostic protocols (Checa-López et al., 2019), there remains a need to systematize evidence regarding psychometric tools tailored to specific cognitive domains within the broader context of multidimensional frailty.

Another critical area of investigation pertains to rehabilitation strategies for cognitive frailty. The integration of new technologies, in particular, has become a significant focus due to their potential to expand and expedite healthcare delivery, especially in contexts characterized by limited staffing and the need for continuous monitoring. Robotics, for instance, has been utilized to support older adults by monitoring physical parameters (e.g., blood pressure) and assessing cognitive performance (Varrasi, Di Nuovo, et al., 2019; Varrasi, Lucas, et al., 2019). Furthermore, telerehabilitation protocols have been developed to aid in the reversal of frailty among older adults, utilizing a variety of platforms (Md Fadzil et al., 2022). However, beyond technical implementation, issues related to the acceptability and usability of these interfaces remain subjects of ongoing debate (Olde Keizer et al., 2019).

Investigating these themes is of paramount importance, as cognitive frailty is associated with adverse health outcomes, including depression, reduced quality of life, falls, dementia, hospitalization, and premature mortality (Zou et al., 2023). Addressing the gaps identified within the literature is essential for advancing strategies aimed at promoting healthy aging and mitigating the negative consequences associated with cognitive frailty.

2. Materials and Methods

2.1 Objectives

Given the previously identified gaps in the literature, the present chapter aims to review the available evidence and delineate existing shortcomings across the following thematic areas: (1) modifiable risk factors associated with cognitive frailty; (2) the neuropsychological functioning of older adults experiencing cognitive frailty; (3) the most effective tools for assessing this construct; and (4) technologies that can be leveraged to support the autonomy and rehabilitate individuals with cognitive frailty. The overarching objective is to clarify the current state of the art within each of these domains to identify critical research areas that warrant further investigation for a comprehensive understanding of cognitive frailty.

2.2 Methodology

This study was conducted as a narrative review of the literature. The review followed the methodological framework proposed by Egger, Smith, and Altman (Egger et al., 2001) and adhered to the guidelines outlined by Petticrew and Roberts (Petticrew & Roberts, 2006).

An initial selection of relevant literature was carried out by consulting the following indexed databases: PubMed, Scopus, Google Scholar, and Web of Science. Studies were included based on the following criteria:

- Peer-reviewed articles written in English;
- Publications dated from 2013, the year the construct of cognitive frailty was formally defined (Kelaiditi et al., 2013);
- Studies containing specific keywords tailored to each of the four thematic areas under investigation.

Specifically, the keywords for the exploration of modifiable risk factors included "cognitive frailty risk factors" and "predictors of cognitive frailty," yielding approximately 1.512 papers. For the investigation of neuropsychological functioning, the keywords "neuropsychological profile of cognitive frailty" and "cognitive domains in cognitive frailty" were used, resulting in approximately 1.240 papers. For the assessment tools theme, the keywords "cognitive frailty measurement tools," "cognitive frailty assessment," and "cognitive frailty tests" were employed, retrieving approximately 3.060 papers. Lastly, for the supportive technologies theme, the keywords "support technologies for cognitive frailty" and "cognitive frailty and robotics" were utilized, resulting in approximately 2.320 papers.

Following this initial selection, a secondary screening was conducted by two independent reviewers using a stepwise approach, examining the titles, abstracts, and full texts of the articles. The primary reasons for exclusion included studies that focused exclusively on physical frailty, unclear or inconsistent definitions of cognitive frailty that overlapped with other forms of cognitive impairment, and duplicate publications. Upon completion of this process, the articles selected by each reviewer were compared, and any discrepancies were discussed to reach a consensus on inclusion.

The final selection of papers for each thematic area was as follows:

- Modifiable risk factors: 33 papers;
- Neuropsychological functioning: 12 papers;
- Assessment tools: 20 papers;
- Supportive technologies: 17 papers.

3. Modifiable risk factors for cognitive frailty

The current literature indicates that several factors critically contribute to the risk of developing cognitive frailty. Among these, age stands out as one of the most significant, albeit non-modifiable, factors. Indeed, the prevalence of cognitive frailty increases with advancing age, particularly after the age of 80 (Navarro-Pardo et al., 2020). In contrast, there is less agreement regarding the role of sex as a non-modifiable risk factor. While some studies have identified sex as an independent risk factor for cognitive frailty (N. M. Chu et al., 2019), others have found no such association, with recent meta-analyses supporting the notion that sex does not play a significant role during the preclinical stages of dementia (Parnetti et al., 2019).

Given that cognitive frailty encompasses both physical and cognitive dimensions, modifiable risk factors include sociodemographic variables, health conditions, and lifestyle habits, reflecting an integrated perspective on the mind-body relationship. For example, educational attainment appears to be associated with cognitive frailty risk, with individuals receiving fewer than six to seven years of formal education demonstrating an elevated risk for impairment (Navarro-Pardo et al., 2020). More broadly, each additional year of formal education is positively correlated with better cognitive functioning and neuropsychological status in later life (Lövdén et al., 2020). However, the substantial heterogeneity in how educational levels are evaluated across studies complicates direct comparisons and the execution of meta-analyses (Zhang et al., 2022).

While Ruan et al. (2020) did not identify a significant association between marital status and cognitive frailty, social participation has been found to serve as a protective factor against cognitive decline (Coco et al., 2019; Xie et al., 2021). Notably, sensory impairments such as vision and hearing loss, which can lead to social isolation, represent risk factors for both frailty and dementia (S. Y. Lee et al., 2023). Evidence from the English Longitudinal Study of Ageing further

indicates that frailty may contribute to an increased risk of loneliness (Gale et al., 2018). Individuals with greater social engagement often have more opportunities for physical activity, which is protective against cognitive frailty, whereas sedentary lifestyles are associated with increased risk (Zhang et al., 2022). Different types of activities, including outings, cognitive and physical exercises, and multidomain tasks, have been shown to exert varied positive effects on cognition (Katayama et al., 2021). These findings align with evidence highlighting the beneficial impact of physical exercise on both frailty and cognitive reserve in older adults (Lyu et al., 2023). Overall, social participation and the presence of instrumental or emotional support can mitigate frailty among older adults and prevent its more severe consequences (W.M. Chu et al., 2023).

Mental health also emerges as a significant factor in this context (Platania et al., 2023). Individuals with depression exhibit a higher prevalence of cognitive frailty (Rivan et al., 2020), and depression and anxiety frequently co-occur with frailty (C. L. Li et al., 2020). Low mood is commonly associated with sleep disturbances, which themselves constitute risk factors for cognitive frailty, particularly insomnia and hypersomnolence (C. Yuan & Zhang, 2023). Sun et al. (2020) estimated that approximately 15% of cognitive deficits may be attributable to sleep problems, and individuals with frailty often report sleep disturbances (Nishikawa et al., 2020). These conditions share several underlying mechanisms with cognitive impairment, including chronic inflammation, cerebrovascular disease, oxidative stress, mitochondrial dysfunction, and increased pro-inflammatory cytokines (Platania et al., 2020). Such biological markers have been shown to affect the dopaminergic system, resulting in symptoms such as fatigue, psychomotor slowing, and cognitive deficits, which are characteristic of frailty (De Labra et al., 2015; Guerrera et al., 2024). Furthermore, individuals with cognitive frailty and comorbid depression are 57% less likely to revert to a state of cognitive impairment alone compared to those without depression (M. Yuan et al., 2022). Within this framework, apathy has emerged as an independent

symptom with distinct underlying mechanisms, prompting some researchers to consider it an additional contributor to cognitive impairment (Van Dalen et al., 2018).

Malnutrition represents another modifiable risk factor, even when assessed through anthropometric and biological indicators. Inadequate nutritional intake in older adults is associated with muscle loss, weakness, mobility impairments, and compromised immune function (Ramsey et al., 2020). Specific measures, such as reduced calf circumference, higher total body fat, lower albumin levels, and lower vitamin D concentrations (though not Body Mass Index), have been linked to an increased prevalence of cognitive frailty (H. Kim et al., 2019). Consequently, nutritional assessment should be incorporated into cognitive risk evaluations, including the examination of alcohol consumption (Seesen et al., 2021). However, consensus on the optimal methods for assessing malnutrition in older adults and identifying the most predictive nutritional variables for cognitive frailty remains lacking (Pérez-Ros et al., 2020). Nevertheless, potential pathophysiological mechanisms through which nutrition may influence cognitive status have been proposed (Dominguez & Barbagallo, 2017). Nutrition can modulate immune system functioning, thereby affecting neuroinflammatory processes implicated in cognitive decline and neurodegeneration (Estrada & Contreras, 2019). In particular, omega-3 polyunsaturated fatty acids derived from fish have been identified as playing a protective role in brain health (Godos et al., 2020; Marventano et al., 2015). This may explain why adherence to a Mediterranean diet is associated with improvements in global cognitive functioning (Limongi et al., 2020), with phenolic acids and polyphenols potentially exerting additional beneficial effects (Caruso, Godos, et al., 2022).

A history of falls also constitutes a risk factor for cognitive frailty (Vatanabe et al., 2022). This association was confirmed by the China Health and Retirement Longitudinal Study (CHARLS), which, using a multi-state Markov model from

2011 to 2015, found that a history of falls was strongly associated with cognitive frailty in individuals with cognitive deficits, suggesting that fall prevention may serve as a strategy to mitigate the risk of developing cognitive frailty (M. Yuan et al., 2022). It is important to note, however, that falls often co-occur with various physical impairments. From this perspective, multimorbidity, including conditions such as hypertension and diabetes, may independently increase the risk of cognitive frailty (C. Wang et al., 2021), along with detrimental lifestyle factors such as smoking (X. Wang et al., 2022).

4. Neuropsychological functioning of cognitive frailty

When examining neuropsychological functioning, individuals with cognitive frailty demonstrate significant differences compared to robust older adults, those with physical frailty alone, and individuals with Mild Cognitive Impairment (MCI). Evidence from the Multidomain Alzheimer Disease Preventive Trial (MAPT), which included 1.617 participants, indicated that cognitive frailty is characterized by an amnestic multidomain MCI profile (Delrieu et al., 2016). Specifically, impairments were observed in memory, attention, and executive functioning, with deficits in executive functions notably more pronounced than in individuals with MCI who did not exhibit physical frailty. Processing speed, selective attention, and mental flexibility were particularly compromised, a finding consistent with other studies highlighting deficits in neurocognitive speed among cognitively frail individuals (Rolfson et al., 2013). Free recall and delayed free recall were also impaired in this population; however, performance improved with cueing, suggesting difficulties in employing autonomous retrieval strategies - a pattern typically associated with subcortical-frontal dementias. The pronounced neuropsychological deficits observed in individuals with cognitive frailty may be attributable to the interplay between cognitive and physical

impairments in the brain, as seen in conditions such as cerebrovascular disease and nigral neuronal loss (Buchman & Bennett, 2013).

Although the evidence regarding clinical differential diagnosis is mixed, several scholars have proposed that executive function impairments may serve as a key distinguishing feature of cognitive frailty, differentiating it from classical cognitive decline primarily driven by neurological etiologies (Bartoli et al., 2020).

An additional consideration involves identifying the onset of neuropsychological impairment within the context of physical frailty. Findings from the Toledo Study for Healthy Ageing, which examined 2.044 participants, demonstrated that more severe levels of physical frailty were associated with impairments across a greater number of cognitive domains, indicating a progressive decline in cognitive functioning as frailty severity increases (Rosado-Artalejo et al., 2017). Similar results were reported by Ginsberg et al., who identified specific deficits in executive functioning, working memory, and delayed recognition recall among cognitively frail individuals (Ginsberg et al., 2017). These findings emphasize the importance of the pre-frailty stage, characterized by the presence of only a few frailty criteria, as this phase offers the greatest potential for reversibility (Lorenzo-López et al., 2020). However, evidence regarding the neuropsychological functioning associated with the pre-frailty stage remains inconclusive. While some studies report no cognitive impairments during pre-frailty (Nishiguchi et al., 2015), others have identified a specific neuropsychological profile characterized by deficits in executive functions, immediate verbal and visual memory, and visuospatial functioning, despite the absence of global cognitive decline as measured by the Mini-Mental State Examination (Lorenzo-López et al., 2020). Notably, some researchers have also reported associations between pre-frailty and metacognitive dysfunction (particularly in action monitoring), as well as mood disturbances, including depression, apathy, and disinhibition. These findings support the hypothesis that

pre-frailty may be linked to dysfunction in the medial prefrontal-ventral striatal network, manifesting as impaired action monitoring, mood changes, and reduced awareness during instrumental activities of daily living (Amanzio et al., 2017).

Research examining the neuropsychological functioning of individuals with cognitive frailty also underscores the critical link between cognitive and motor abilities. For instance, Robertson et al. found a significant relationship between cognitive deficits, muscular weakness, and gait speed. Specifically, participants with slower gait exhibited poorer processing speed, attention, and executive functioning, while lower grip strength was also associated with deficits in executive functions (Robertson et al., 2014). These findings led the authors to conclude that "the etiology of frailty and cognitive decline may differ depending on which indicators of frailty are present" (p. 2122), reinforcing the validity of the cognitive frailty construct and related clinical profiles, such as motoric cognitive risk syndrome. The latter refers to older adults who present with slow gait and subjective cognitive complaints in the absence of dementia or significant mobility disability, and current evidence suggests that this condition may be associated with an elevated risk of developing dementia (Verghese et al., 2014).

5. Assessment tools for cognitive frailty

Assessing cognitive frailty presents several challenges that have only been partially addressed in the current literature.

The first challenge concerns the absence of a definitive consensus on the multidimensional nature of frailty itself. Frailty has been conceptualized as encompassing sociodemographic, physical, cognitive, psychological, nutritional, social, aging, and disease-related domains (Hoogendijk et al., 2014). This comprehensive perspective contrasts with the initial framework proposed by

Fried et al., who defined frailty based on the presence of three or more criteria among weight loss, exhaustion, weakness, low gait speed, and low physical activity in older adults (Fried et al., 2001). It also differs from Rockwood's bio-physiological perspective, which operationalized frailty as the ratio of current health deficits to the total number of potential deficits, although later iterations of this model began incorporating psychosocial indicators (Rockwood et al., 2005).

The second challenge pertains to the development of an assessment tool that comprehensively evaluates all relevant domains, with particular emphasis on cognitive deficits, while maintaining robust psychometric properties suitable for large-scale screening in community-dwelling populations (Huang & Lam, 2021). As early as 2008, cognitive impairment was identified as an independent prognostic factor that should be considered alongside the criteria proposed by Fried and colleagues (Rothman et al., 2008). Consequently, more recent tools have sought to incorporate cognitive domains into frailty assessments; however, the creation of a comprehensive yet practical tool remains an ongoing endeavor (Khezrian et al., 2017).

The rationale for developing specific tools for the assessment of cognitive frailty is further supported by methodological considerations. Evidence indicates that frailty levels can moderate the relationship between specific neuropsychological domains and overall cognitive functioning, suggesting that the "biological noise" associated with frailty can influence performance on cognitive assessments. This introduces the risk of bias when utilizing traditional neuropsychological assessment protocols in the context of frailty, highlighting the need for correction models for frailty similar to those currently used for age and education, or the development of dedicated cognitive frailty assessment tools (Canevelli et al., 2019). Furthermore, widely used cognitive screening tools, such as the Montreal

Cognitive Assessment, are not capable of reliably distinguishing between MCI and cognitive frailty (Xu et al., 2020).

Although cognitive assessments are increasingly included in frailty evaluation tools, the methods for operationalizing cognition within these assessments remain heterogeneous (Vella Azzopardi et al., 2018). For example, some researchers have augmented the Comprehensive Frailty Assessment Instrument (CFAI) - a self-report questionnaire with solid psychometric properties assessing physical, psychological, social, and environmental frailty (De Witte et al., 2013) - by incorporating additional items targeting cognitive status. This resulted in the CFAI-Plus, which includes a newly defined "cognitive domain" within its factorial structure and has demonstrated satisfactory psychometric performance (De Roeck et al., 2018). Other researchers have developed predictive models for cognitive frailty based on a range of measures, including educational background, cardiovascular conditions, gait speed, hand-grip strength, calf circumference, memory deficits, sarcopenia, and diabetes (Bai et al., 2023). Additionally, several instruments have been designed from the outset to measure multiple domains - namely, physical, emotional, cognitive, and comorbidity-related components. Examples include the Groningen Frailty Indicator (Steverink et al., 2001), the CaMos Frailty Index (Kennedy et al., 2014), the Multidimensional Frailty Score (Choi et al., 2015), the Care Partner-Derived Frailty Index based on the Comprehensive Geriatric Assessment (Goldstein et al., 2015), and the Frailty Index used in the Rotterdam Study (Schoufour et al., 2017).

Beyond psychometric strategies, emerging evidence points to the potential role of biomarkers in the assessment of cognitive frailty. For instance, elevated levels of tau protein and phosphorylated tau 181, lower levels of β-amyloid (Aβ)42 in cerebrospinal fluid, the presence of the apolipoprotein E (APOE) ε4 allele, elevated interleukin-6 and C-reactive protein, and indicators of sarcopenia have all been identified as potential early screening markers, detectable years before

symptom onset (Ruan et al., 2017). The role of microRNAs, such as miR-92a-5p and miR-532-5p, in cognitive frailty is also under investigation (Carini et al., 2021). In men, lower calf circumference has been found to be strongly associated with cognitive frailty (M. Kim et al., 2018). Additionally, gait performance assessed using single- and dual-task methodologies with wearable sensors - including parameters such as gait speed, unsteadiness, stride length, and double support - has shown promise as a biomarker for cognitive frailty in older adults (Zhou et al., 2022). Wearable devices have also demonstrated utility in monitoring related parameters, such as physical activity levels and sleep patterns, which have proven effective in assessing cognitive frailty (Razjouyan et al., 2020).

Recent empirical work has advanced tools for identifying potentially reversible cognitive frailty in community samples and has provided externally validated prediction models (nomograms) that combine motoric indicators (gait speed, grip strength) with cognitive and sociodemographic markers. These studies reinforce the conceptualization of cognitive frailty as a multidimensional and partly reversible condition amenable to targeted preventive interventions, and they supply candidate variables for inclusion in diagnostic algorithms and screening tools. Integrating such predictive models supports the translational potential of assessing cognitive frailty in routine geriatrics and community screening (Bai et al., 2023).

6. Supportive technology for cognitive frailty

Technologies are utilized not only as measurement tools but also as supportive interventions for individuals with cognitive frailty, in order to improve their autonomy. In recent years, a range of technological strategies has been implemented with the goal of enhancing the quality of life among this population

(X. Li et al., 2021). For example, mobile health (mHealth) interventions, including smartphone-assisted programs, have been shown to support cognitive functioning, reduce frailty, improve walking time, increase step count, and promote moderate-to-vigorous physical activity in older adults (Kwan et al., 2020). Additionally, various smart health management platforms have been developed to address the needs of individuals with cognitive frailty. The My Active and Healthy Ageing (My AHA) platform, for instance, delivers personalized physical exercise regimens, dietary interventions, and memory training activities informed by sensor-based monitoring (Rainero et al., 2021). Some researchers have introduced gamified cognitive training programs that engage older adults in dual-task fitness activities to enhance user interest and adherence (Liao et al., 2021). This approach has further evolved through the incorporation of virtual reality, with virtual motor-cognitive training demonstrating benefits in cognitive functioning among older adults with cognitive frailty by leveraging neuroplasticity (Oliveira et al., 2021; Bruni et al., 2022).

In recent years, several initiatives have received funding to facilitate the integration of Internet of Things (IoT) technologies into the daily lives of older adults, frequently employing support vector machine techniques and neural networks in conjunction with motion sensors. One notable example is the PHArA-ON (Pilots for Healthy and Active Ageing) project, which aims to develop integrated technological systems tailored to the preferences and needs of older individuals, including activities designed for cognitive stimulation (D'Onofrio et al., 2022). Many of these technological solutions have incorporated Human-Robot Interaction (HRI) using social robots capable of executing various collaborative tasks. However, the deployment of these systems has raised unresolved questions regarding platform usability and user acceptability (Søraa et al., 2023). Personality traits such as openness to experience have been found to influence interactions and performance in the context of social robotics (Rossi et al., 2018),

while factors such as anxiety, trust, and behavioral intentions have been linked to platform acceptance (Rossi et al., 2020).

This area of research is intrinsically connected to the attitudes of older adults toward technology use. Studies have shown that older adults with cognitive frailty are less likely to engage with digital interfaces or play games on their smartphones compared to robust individuals, with higher usage observed among males, younger adults, individuals with at least six years of formal education, and those with higher monthly household incomes (Md Fadzil et al., 2023). These findings were particularly salient during the COVID-19 pandemic, a period in which numerous activities - including learning, working, and leisure - transitioned to online formats for health and safety reasons, yielding both positive and negative outcomes (Pirrone et al., 2021). Barriers to technology adoption among older adults include financial limitations, visual impairments, low interest, and limited digital knowledge (Mohadis & Ali, 2014). Moreover, factors such as self-efficacy and digital literacy are critical for the successful implementation of technological interventions for older adults with cognitive frailty and Mild Cognitive Impairment (Van Houwelingen et al., 2018). Strategies such as providing assistance during sessions, issuing reminders, and delivering notifications have been identified as effective methods for enhancing user compliance (Vanoh et al., 2019).

Overall, while the implementation of technological interventions has the potential to enhance independent living, social engagement, perceived security, and overall quality of life among older adults with cognitive frailty, numerous psychosocial challenges remain that must be addressed to ensure the effective integration of these technologies into daily life (Md Fadzil et al., 2022).

7. Discussion

This narrative review sought to synthesize the current evidence regarding four critical domains associated with cognitive frailty, with the overarching objective of delineating future research directions by identifying areas that remain underexplored. While substantial literature exists on cognitive impairment and physical frailty, several topics require targeted investigation with a specific emphasis on cognitive frailty.

Regarding risk factors, the role of sex remains contentious. Although many researchers control for sex as a covariate in their analyses, it may, in fact, be linked to significant differences relevant to prevention and treatment strategies. This aligns with the emerging field of precision medicine, which considers sex differences as a fundamental variable in health research and practice (Ferretti et al., 2018). In the context of cognitive frailty, future studies could meaningfully examine sex-related differences in neural networks, hormonal profiles, biomarkers, and their respective contributions to cognitive and physical deterioration.

Among modifiable risk factors, apathy has emerged as a relevant construct. Defined as a reduction in motivation that cannot be attributed to diminished consciousness, cognitive deficits, or emotional distress, apathy can now be reliably measured using dedicated instruments (Furneri, Platania, et al., 2021). It is associated with poorer treatment outcomes, accelerated cognitive and functional decline, and higher mortality, and it shows a strong clinical association with dementia while exhibiting distinct neurobiological mechanisms (Furneri, Razza, et al., 2021). Consequently, investigating apathy as an independent risk factor across different stages of cognitive and physical impairment, including the exploration of pharmacological interventions already tested in other conditions such as depression, represents a promising research avenue (Guerrera et al., 2023).

Nutrition has also been a focal point of recent investigations, with several open challenges remaining. Evidence indicates an inverse relationship between cognitive impairment and the intake of total flavonoids, anthocyanins, flavones, flavan-3-ols, and flavonols, while findings regarding other polyphenols remain preliminary yet promising (Godos et al., 2023). This is particularly relevant for compounds such as quercetin, curcumin, carnosine/anserine, and tyrosol derived from extra virgin olive oil, which are currently under investigation at preclinical stages (Caruso et al., 2021; Caruso, Godos, et al., 2022; Caruso, Torrisi, et al., 2022). Additionally, elevated homocysteine levels, associated with low consumption of fruits and vegetables, have been linked to increased frequency and severity of cognitive impairment, neuropsychiatric symptoms, and functional decline (Lauriola et al., 2021). Further research examining specific nutrients, dietary patterns, and effective measurement strategies in older adults will be essential for advancing this field.

Another significant challenge involves the psychometric detection of cognitive frailty at early stages. As noted, the cognitive profile of the pre-frailty stage remains debated, and traditional cognitive screening tools, such as the Mini-Mental State Examination, may lack the sensitivity required for its detection in large-scale community screenings. This challenge encompasses both a neuropsychological issue - namely, the uncertainty regarding whether the pre-frailty stage predominantly affects memory or non-memory domains - and a psychometric challenge in developing targeted assessment tools accordingly (Lorenzo-López et al., 2020). Furthermore, the multidimensional nature of cognitive frailty necessitates detection strategies that extend beyond purely cognitive and physical measures.

In the context of large-scale screening and rehabilitation, the integration of supportive technologies into daily life remains a goal of ongoing research. However, technological implementation is often complicated by issues of user

acceptance and interface usability. As previously discussed, older adults experience greater difficulties with technology use compared to healthy controls, challenges that can become even more pronounced when interacting with platforms designed to support rather than burden users (Schmidt & Wahl, 2019). Within this context, the measurement and management of cognitive load in older adults has emerged as a critical variable in the design and implementation of technological interfaces (C. S. Lee & Hughes, 2019).

Finally, the relationship between cognitive frailty and cognitive reserve warrants further exploration. Cognitive reserve, which contributes to individual differences in cognitive resilience throughout aging, may serve as a protective factor against frailty and premature mortality (Zijlmans et al., 2021). However, the complexity of this relationship is compounded by the heterogeneous definitions and measurements of both cognitive frailty and cognitive reserve (Sardella et al., 2020). Future research should first address these methodological gaps and then work toward characterizing the connection between these constructs, moving beyond a pathology-focused perspective toward a health-oriented framework consistent with contemporary Health Psychology approaches (Castellano et al., 2020). This direction aligns with the World Health Organization's World Report on Ageing and Health, which emphasizes intrinsic capacity - all individual-level attributes contributing to healthy aging - and functional ability, defined as the combination of intrinsic capacity with physical and social environments (Beard et al., 2016). This framework underscores the importance of individual and contextual factors in achieving what older adults value during aging, prioritizing personal functioning over a purely disease-centered perspective. However, the operational definitions of intrinsic capacity and functional ability remain underdeveloped, representing an additional area for future research in gerontology and aging studies (Beard et al., 2022).

While the narrative synthesis highlights promising assessment strategies and candidate markers for cognitive frailty, several limitations should temper interpretation. The majority of cited validation studies are heterogeneous in operational definitions, sample composition (community vs clinic), and follow-up duration; as a result, effect estimates for predictive validity may not generalize across settings. In addition, cultural and normative differences in cognitive screening performance (education, language, regional norms) limit direct comparability and require local calibration of cut-offs. Potential confounding by multimorbidity and medication use is not consistently controlled across primary studies; therefore, the observed associations between motor indicators and cognitive measures could reflect shared vascular or systemic pathology rather than causal links. Future research should prioritize larger, multisite cohorts with harmonized case definitions and pre-specified analytic plans to better establish external validity and clinical utility of proposed frailty instruments.

8. Conclusion

Cognitive frailty represents a construct that seeks to bridge the traditional divide between physical and mental health by promoting a multidimensional perspective on healthy aging. Substantial theoretical and clinical evidence supports its validity, and its practical applications are progressively expanding within the field.

Nonetheless, this narrative review, which examined modifiable risk factors, neuropsychological functioning, assessment tools, and supportive technologies, indicates that further investigation is warranted across several areas. In some instances, it would be beneficial to expand research beyond isolated examinations of cognitive impairment and physical frailty to encompass the

broader framework of cognitive frailty. In other cases, entirely new research directions should be pursued to address existing gaps in the literature.

In conclusion, despite the inherent challenges in conceptualizing, preventing, measuring, and supporting cognitive frailty, this field holds considerable promise. Its complex, multidimensional framework aligns well with contemporary perspectives on health and aging, offering a more comprehensive approach to understanding and addressing the processes of deterioration in older adults.

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CHAPTER TWO

A network perspective on the relationship between apathy

and cognitive decline

Preface

This chapter investigates apathy as a multidimensional neuropsychiatric construct and its relationship with cognitive decline, adopting a network-based analytical framework to capture the complex interplay of behavioral, cognitive, emotional, and demographic factors. With this contribution, indeed, it is intended to explore the dynamic interaction of risk factors with the broader context of health features. By moving beyond traditional linear models, this approach aims to disentangle the specific components of apathy most strongly associated with functional and cognitive deterioration across the continuum from healthy aging to Mild Cognitive Impairment and early Alzheimer's Disease.

The chapter examines differential patterns of association and centrality of apathy-related symptoms within distinct cognitive profiles, thereby identifying potential early markers of pathological aging. Ultimately, the findings are intended to refine the conceptualization of apathy as a new risk factor for decline, support the development of more sensitive assessment tools, and inform targeted interventions based on Network Analysis to mitigate its impact on cognitive and functional trajectories in older adults.

1. Introduction

Apathy is characterized as a measurable reduction in goal-directed activity, marked by impairments in at least two of the following domains: behavior/cognition, emotion, and social engagement (Fahed & Steffens, 2021). To meet diagnostic criteria, such deficits must persist for a minimum duration of four weeks and must not be attributable to alternative medical, psychiatric, or environmental factors (Marin, 1991; P. Robert et al., 2009, 2018). Notably, apathy tends to increase with advancing age, both in cognitively healthy individuals and those with cognitive impairments (Guercio et al., 2015), and is frequently observed in the context of depressive disorders (Groeneweg-Koolhoven et al., 2017). Lower levels of educational attainment have been associated with elevated apathy (Brown et al., 2019), although evidence regarding sex differences in prevalence remains inconclusive (Groeneweg-Koolhoven et al., 2017). In clinical populations with cognitive impairment, apathy is a highly prevalent, enduring, and burdensome symptom, and has been strongly associated with increased mortality risk (van der Linde et al., 2017).

Apathy is considered a central non-cognitive symptom of Alzheimer's Disease (AD) (Landes et al., 2001, 2005), with robust associations to amyloid-β pathology (Johansson et al., 2020, 2022; Sun et al., 2021). Importantly, apathy contributes to cognitive and functional decline independently of depressive symptoms (Richard et al., 2012). It accounts for approximately 27% of the variance in instrumental activities of daily living and serves as a predictor of accelerated cognitive and functional deterioration (Boyle et al., 2003; Starkstein et al., 2006).

Emerging research and comprehensive reviews suggest that apathy may contribute to the risk of cognitive decline even within the general population, with a particularly strong association with executive function deficits (Fan et al., 2021). Among individuals with Mild Cognitive Impairment (MCI), higher levels of apathy have been shown to double the risk of progression to AD, independent of

comorbid depression (Ma, 2020; Richard et al., 2012; Van Dalen et al., 2018). Longitudinal studies further demonstrate that sustained apathy is predictive of rapid functional decline within one year in individuals diagnosed with AD, dementia with Lewy bodies, Huntington's Disease, or Parkinson's Disease (Andrews et al., 2021; Breitve et al., 2018; García-Ramos et al., 2010; Lechowski et al., 2009). In an effort to refine understanding, researchers have focused on specific components of apathy - such as diminished interest, reduced initiative, and emotional blunting - as key drivers of cognitive decline (Mulin et al., 2011).

For example, individuals exhibiting marked disinterest have been found to convert to AD at higher rates, even after controlling for demographic variables such as age, sex, and education (P. H. Robert et al., 2008). A decline in intellectual curiosity - manifested as reduced daily productivity and initiative - has likewise been associated with poorer cognitive outcomes (Montoya-Murillo et al., 2019). These findings align with more contemporary theoretical models of apathy, which conceptualize it as a misjudgment of available energetic resources for cognitive, emotional, and behavioral tasks (Husain & Roiser, 2018). Within this framework, effort-based decision making becomes a critical process for evaluating motivational deficits, encouraging a neurobiologically informed, transdiagnostic approach to the assessment and treatment of apathy using targeted tools (Ilardi et al., 2024). This perspective also helps to elucidate the strong relationship between apathetic symptomatology and underlying neuropathophysiological mechanisms.

Despite these advancements, substantial variability remains in how different components of apathy predict cognitive outcomes. This uncertainty is likely exacerbated by methodological limitations across studies, including small sample sizes, lack of longitudinal data, and insufficient comparison between cognitively impaired and unimpaired groups (Lechowski et al., 2005). Furthermore, the absence of a standardized classification of apathy impedes efforts to determine

which facets exert the greatest influence on cognitive trajectories (Bock et al., 2020). These limitations pose significant challenges for the development of preventative strategies, early diagnostic tools, and effective pharmacological interventions targeting apathy.

Given these challenges, it is essential to investigate the interactions among key variables across different stages of cognitive health in order to identify critical factors for monitoring, assessment, and intervention to promote healthy aging (Esposito et al., 2014). Network Analysis - a method designed to model the complex interplay of symptoms and their effects on health outcomes - offers a promising analytical framework for addressing this need (Platania et al., 2023; Sarti et al., 2024; Scarponi et al., 2023). For instance, van Wanrooij et al. applied this approach to examine the interconnections among apathy, depression, dementia, and functional disability, revealing significant associations between apathy, mood symptoms, and functional limitations. Their findings suggest that depression may mediate the relationship between apathy and subsequent dementia (Van Wanrooij et al., 2019).

The present study builds upon this body of work by comparing the network structures of individuals with healthy cognition, MCI, and varying stages of AD. Network Analyses were conducted on matched samples of older adults across these cognitive profiles, incorporating demographic variables (age, sex, education) and clinical indicators (global cognitive function, executive performance, depressive symptoms, apathy, comorbid conditions, medication use, and rehabilitation involvement). Special attention was given to apathy, which was examined at the item level using its psychometric measure, with the goal of identifying the most influential dimensions contributing to the overall network structure.

2. Materials and Methods

2.1 Participants

The study sample comprised 214 older adults, stratified into three distinct groups based on clinical diagnosis and cognitive status: an amnestic Mild Cognitive Impairment (MCI) group (n = 77; 54 females, 23 males; mean age = 75.53 ± 7.3 years), a mild Alzheimer's Disease (AD) group (n = 30; 19 females, 11 males; mean age = 76.33 ± 6.4 years), and a cognitively healthy Control group (n = 107; 78 females, 29 males; mean age = 74.06 ± 6.8 years).

Participants in the MCI and mild AD groups were consecutively recruited from a specialized public clinical service for cognitive disorders, the "U.O.S. Centro Alzheimer e Psicogeriatria", ASP3 Catania, Italy. All diagnoses were established on clinical rather than biological grounds and followed internationally recognized diagnostic criteria. Specifically, inclusion and exclusion procedures adhered to the protocols jointly proposed by the National Institute on Aging (NIA) and the Alzheimer's Association Workgroups for the diagnosis of amnestic MCI and probable AD.

The diagnosis of amnestic MCI was based on the following clinical criteria (Albert et al., 2011; Montine et al., 2012):

– Presence of cognitive concerns reflecting a decline, as reported by the individual, an informant, or a clinician;

– Objective evidence of impairment in one or more cognitive domains, typically memory;

– Preservation of functional independence in daily living activities;

– Absence of dementia.

For the clinical diagnosis of probable AD, the following criteria were applied (McKhann et al., 2011):

– Cognitive or behavioral symptoms that interfere with the ability to perform usual activities, represent a decline from prior levels of functioning, and are not attributable to delirium or major psychiatric disorders;

– Evidence of cognitive impairment obtained through clinical history and corroborated by informant reports and objective cognitive assessment;

– Impairment in at least two of the following areas: acquisition and recall of new information, reasoning and problem-solving, visuospatial skills, language functions, and personality or behavior;

– Insidious onset and documented progression of cognitive decline;

– Predominance of an amnestic presentation (the most frequent subtype), or a non-amnestic variant;

– Exclusion of alternative etiologies such as significant cerebrovascular disease, Lewy body dementia, frontotemporal dementia variants, and other neurological or systemic conditions or medications known to interfere with cognition.

All participants were administered the Italian standardized version of the Mini-Mental State Examination (MMSE) (Folstein et al., 1975; Magni et al., 1996) during their routine clinical appointments. The MMSE was used exclusively for initial screening purposes and to support the preliminary classification of participants into Control, MCI, and AD groups. These classifications were subsequently confirmed through a combination of clinical history and performance on a battery of neuropsychological tests, in line with the aforementioned diagnostic frameworks and national guidelines established by the Agenzia Italiana del Farmaco (AIFA) (AIFA, 2024).

Eligible participants were required to have an MMSE total score, adjusted for age and education, between 18 and 27 inclusive. Exclusion criteria included a recent history of cerebral ischemic events and the presence of psychotic disorders. Based on these criteria, 107 participants with amnestic MCI or mild AD were enrolled.

The Control group comprised 107 cognitively healthy volunteers who scored ≥ 28 on the MMSE. In accordance with DSM-5-TR (American Psychiatric Association, 2022), ICD-11 (World Health Organization, 2019), and national clinical guidelines, the classification of these individuals as cognitively unimpaired was supported by comprehensive assessment of their clinical history, neuropsychological performance, and preserved daily functioning. Information on the participants' autonomy in daily life was obtained both from the individual and a knowledgeable informant. Additionally, a score > 26 on the Montreal Cognitive Assessment (MoCA) was used as a conservative criterion to exclude preclinical cognitive decline. This cutoff was more stringent than other thresholds previously validated for the Italian population and was considered robust in differentiating healthy controls from individuals with MCI (Bosco et al., 2017; Ilardi et al., 2023).

All participants provided written informed consent prior to enrollment and underwent individual testing in a single session conducted by trained clinical psychologists with expertise in neurocognitive disorders. Ethical approval was obtained from the Internal Review Board of the Department of Educational Sciences (Section of Psychology) at the University of Catania (protocol Ierb-Edunict-2023.05.23/02). The final sample reflected a greater proportion of women than men, consistent with both national and international prevalence patterns in cognitive impairment and dementia (Huque et al., 2022).

2.2 Measures

All assessments were conducted individually by trained clinical psychologists with specific expertise in neurocognitive disorders. The neuropsychological battery and associated questionnaires were administered to all participants - namely, individuals with amnestic Mild Cognitive Impairment (MCI), patients with mild Alzheimer's Disease (AD), and cognitively healthy controls - under standardized conditions.

2.2.1 Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) (Folstein et al., 1975; Magni et al., 1996) is a widely adopted screening instrument for the evaluation of global cognitive functioning and the detection of cognitive impairment. It comprises a series of questions and tasks designed to assess multiple cognitive domains, including temporal and spatial orientation, immediate and delayed recall, attention and calculation, language abilities, and visuoconstructional praxis. The maximum score attainable is 30 points, with higher scores reflecting better cognitive functioning after adjusting for age and educational background.

2.2.2 Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005; Santangelo et al., 2015) serves as a rapid screening tool specifically designed to detect subtle cognitive decline, particularly in cases of MCI. It evaluates a broad range of cognitive domains, including attention, concentration, executive functions, memory, language, visuospatial skills, abstract reasoning, calculation, and orientation. The total score ranges from 0 to 30, with a normative cut-off of 26 generally indicating unimpaired cognition. However, in the present study, region-specific norms for the southern Italian population were applied, in recognition of cultural and demographic influences on test performance. Specifically, a MoCA

score ≤ 14 was considered indicative of probable AD, while a score ≤ 17 was used as the threshold for probable cognitive impairment (Bosco et al., 2017).

2.2.3 Frontal Assessment Battery (FAB)

The Frontal Assessment Battery (FAB) (Aiello et al., 2022) was employed to evaluate executive functioning associated with frontal lobe activity. This clinician-administered tool assesses conceptualization (e.g., through analogical reasoning), lexical fluency, motor programming (e.g., series of actions), sensitivity to interference, inhibitory control, and environmental autonomy. Each subtest is rated on a scale from 0 (failure) to 3 (optimal performance), and the total score is adjusted according to the participant's age and level of education.

2.2.4 Hamilton Depression Rating Scale (HDRS)

The Hamilton Depression Rating Scale (HDRS) (Fava et al., 1982) is a widely validated 21-item hetero-administered scale used to assess the severity of depressive symptoms. Scores are interpreted as follows: < 7 denotes an absence of depressive symptomatology; 8–17 indicates mild depression; 18–24 suggests moderate depression; and scores > 24 reflect severe depression.

2.2.5 Apathy Evaluation Scale – Clinician Version (AES-C)

Apathy was assessed using the clinician-rated version of the Apathy Evaluation Scale (AES-C) (Furneri et al., 2021; Marin, 1991), a standardized instrument composed of 18 items rated on a 4-point Likert scale. The items are categorized into behavioral (B), cognitive (C), and emotional (E) components, and are phrased with both positive and negative valence. The total score ranges from 18 to 72, with higher scores indicating greater apathy. Depending on the version used, the recommended clinical cut-off typically ranges between 39 and 41, although these thresholds may be considered somewhat conservative. In this study, the AES-C was administered following a semi-structured clinical interview

to ensure the accurate identification of apathetic symptoms, particularly in cases where comorbid depression was suspected.

2.2.6 Demographic and Clinical Variables

In addition to the aforementioned instruments, a series of demographic and clinical variables were collected and integrated into the network models for all participant groups. Common variables included biological sex, age, and years of education. For the MCI and mild AD groups, additional data were obtained regarding the presence of comorbid conditions, current pharmacological treatments, and participation in neurocognitive rehabilitation programs.

Among the MCI group, six individuals presented with comorbid depressive and/or anxiety disorders and were being treated with second-generation antidepressants (vortioxetine 5–10 mg/day or escitalopram 5–10 mg/day) for more than three months at the time of assessment. Furthermore, 26 out of 77 MCI participants were receiving low-dose cholinesterase inhibitors (donepezil 2.5–5 mg/day or rivastigmine transdermal patch 4.6 mg/day), administered for over three months. In contrast, the mild AD group was assessed prior to or at the very early stages of cholinesterase inhibitor therapy. Cognitive rehabilitation consisted of weekly sessions focused on stimulation of memory and executive functions. Clinical variables such as comorbidities, pharmacological treatment, and rehabilitation were treated as dichotomous categorical variables for the purposes of network analysis.

2.3 Network Model Rationale

Two distinct classes of network models were developed. The first consisted of generic models based on the total score of the Apathy Evaluation Scale. This approach enabled the integration of conventional statistical metrics with

network-based insights, with the goal of elucidating the relationships between apathy, cognitive variables, and demographic factors.

The second set of models involved a more granular approach, incorporating each AES-C item individually alongside all previously mentioned variables. This allowed for a finer-grained examination of the differential contributions of behavioral, cognitive, and emotional components of apathy in relation to cognitive decline. Although the cross-sectional design of the study precluded causal inference or longitudinal analysis, the network structure nonetheless permitted the identification of key variables potentially implicated at different stages of disease progression.

The accuracy of network estimation depends on sample size and regularization parameters; in small or heterogeneous samples, edge weights and community structures may become unstable. Moreover, network centrality indices describe statistical, not causal, importance of items. Therefore, the reported network configurations should be regarded as exploratory, requiring replication in larger independent datasets.

2.4 Statistical analyses

A series of quantitative statistical analyses were conducted to extract descriptive and inferential information from the study sample. Descriptive statistics, including means, standard deviations, and percentages, were computed to characterize the overall demographic and clinical profile of participants.

Subsequently, raw scores obtained from the three principal neuropsychological assessments - the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE), and the Frontal Assessment Battery (FAB) - as well as the total and item-level scores of the Apathy Evaluation Scale (AES-C), were compared across groups using independent samples t-tests. Importantly, the

decision to use raw (i.e., unadjusted) scores was guided by methodological considerations: age, sex, and years of education were already entered as independent variables in the statistical and network models. Adjusting scores for these variables in advance could have introduced multicollinearity, thereby distorting the statistical interpretation.

Additionally, a one-way Analysis of Variance (ANOVA) was performed to assess group differences where appropriate. Assumptions of normality and homogeneity of variance were tested using the Shapiro–Wilk and Levene's tests, respectively. A p-value > 0.05 in both cases indicated that the assumptions were met, thereby justifying the use of parametric tests. Correlational analyses were subsequently conducted to explore associations between the demographic, clinical, and neuropsychological variables.

Multiple regression analyses were then carried out within each group to assess whether overall apathy levels, as measured by the AES-C total score, could be predicted by the set of demographic and clinical covariates. To avoid multicollinearity effects inherent in the factorial structure of the AES-C, item-level scores were excluded from the regression models. Residuals were examined for normality and independence to determine the appropriateness of robust regression methods. Model selection was guided by the Akaike Information Criterion (AIC), and predictor effects were considered statistically significant at $p < 0.05$.

Finally, a clustering algorithm and Principal Component Analysis (PCA) were employed to investigate whether specific features - or their combinations - could effectively differentiate the three groups. All statistical analyses were conducted using IBM SPSS Statistics, Version 28.0 (SPSS Inc., Chicago, IL, USA) and RStudio (Version 4.3.2, 2023-10-10).

2.5 Network Analysis

To further explore the interrelationships among variables, network models were estimated for each group, resulting in a total of six models (two per group). The primary aim was to compare the structural characteristics of these networks both visually and analytically, focusing on differences in explained variance and the significance of inter-variable associations.

Each network was conceptualized as a Graphical Mixed Model (GMM), capable of handling both continuous and categorical variables through a parameterized joint probability density function (Sedgewick et al., 2016). This modeling approach enables the identification of direct associations - represented as edges - between nodes (variables), while partialling out the effects of all other variables in the system. The absence of an edge between two nodes implies conditional independence.

All networks were limited to pairwise interactions (k = 2), meaning that edges represent partial correlations between two variables, controlling for all others in the model. Different regularization techniques were employed depending on group size: LASSO (Least Absolute Shrinkage and Selection Operator) regularization was used for the control group to minimize potential spurious associations (Epskamp & Fried, 2018), while 10-fold cross-validation was applied to the MCI and mild AD groups due to smaller sample sizes. This cross-validation procedure partitions the dataset into 10 segments, iteratively using nine for model training and one for validation, thereby optimizing model generalizability while limiting false-positive associations (Jung & Hu, 2015).

Networks were visualized using the "qgraph" R package (Epskamp et al., 2012). Two distinct layout strategies were employed: a circular layout (layout = "circle") for models incorporating the AES-C total score, and a force-directed layout based on the Fruchterman-Reingold algorithm (layout = "spring") for models including

individual AES-C items (Fruchterman & Reingold, 1991). Node predictability metrics were calculated and displayed for each node. These reflect the extent to which each variable is explained by its directly connected neighbors. For continuous variables, this was quantified using R^2; for categorical variables, classification accuracy (CC) and normalized accuracy (nCC) were reported (Haslbeck & Waldorp, 2018).

Three centrality indices were computed to characterize each node's structural importance within the network:

- Strength Centrality (SC), representing the number and weight of a node's direct connections;

- Betweenness Centrality (BC), reflecting the extent to which a node lies on the shortest paths between other nodes;

- Expected Influence (EI), an index quantifying the overall influence - positive or negative - exerted by a node within the network (Robinaugh et al., 2016).

To assess the robustness and stability of the estimated network structures, nonparametric bootstrap analyses were performed using the "bootnet" package. A hypothetical sample size of n = 500 was simulated, and the resulting indices were correlated with those derived from the original dataset. Correlation coefficients exceeding 0.50 were considered indicative of acceptable model stability.

Finally, the estimated networks were converted into igraph objects (Csardi & Nepusz, 2006), allowing for the application of a community detection algorithm to investigate clustering structures within and between networks. Specifically, the "walktrap" algorithm (Pons & Latapy, 2006) was applied, which detects node clusters based on random walks across the network's edges. Several iterations with increasing step lengths were conducted, and the first stable solution for the

number of clusters was selected for interpretation. These subnetworks represent tightly interconnected variable groupings that may respond cohesively to alterations in the system's overall equilibrium.

3. Results

3.1 Descriptive and Inferential Analyses

A detailed summary of the demographic characteristics of the study sample is presented in Table 1. The sample size for the group diagnosed with mild Alzheimer's disease was consistent with the prevalence rates of the disorder within the Italian population (Istituto Superiore di Sanità, 2024). A significant trend was observed in educational attainment across the three groups: participants in the control group reported the highest mean years of education ($M = 10.29$, $SD = 5.8$), followed by those with Mild Cognitive Impairment (MCI), and the lowest educational levels were found in the group with mild Alzheimer's disease ($M = 6.87$, $SD = 4.2$). This difference was statistically significant ($p = 0.004$), indicating a progressive decline in educational background from controls to patients with more severe cognitive impairment.

Demographics	Control Group		Mild Cognitive Impairment		Mild Alzheimer's Disease	
	Sample	Percentage	Sample	Percentage	Sample	Percentage
Sample size	107	100	77	100	30	100
Females	78	72.9	54	70.1	19	63.3
Males	29	27.1	23	29.9	11	36.7
Mean Age	74.06 ± 6.8		75.53 ± 7.3		76.33 ± 6.4	
Years of Education						
- Mean Education	10.29 ± 5.7		8.56 ± 4.4		6.87 ± 4.2	
- Primary school	42	39.1	35	45.5	17	56.5
- Secondary school	14	13.1	18	23.4	7	23.4
- High School	22	20.5	15	19.5	4	13.3
- University and more	29	27.1	9	11.7	2	6.6
Comorbidity	0	0	19	24.7	9	30
Under Treatment	0	0	26	33.8	0	0
Doing Rehabilitation	0	0	45	58.4	22	73.3

Table 1. Demographic data of the samples[1]

Comorbid symptoms of anxiety and/or depression were reported in 24% of participants in the MCI group and in 30% of those with mild Alzheimer's disease. Furthermore, a substantial proportion of these participants were engaged in neurocognitive rehabilitation programs (58.4% of the MCI group and 73.3% of the mild AD group). Additionally, 33% of individuals in the MCI group were undergoing pharmacological treatment.

Tests of normality revealed that most variables in the MCI and mild AD groups deviated from a normal distribution. Consequently, non-parametric methods were applied. The Kruskal-Wallis ANOVA, followed by post-hoc comparisons, demonstrated statistically significant differences among the three groups across all the primary variables.

Group comparisons on neuropsychological assessments indicated highly significant differences in performance. Specifically, the Mini-Mental State Examination (MMSE) scores differed significantly between Control and MCI

[1] Taken from *Sarti, Varrasi, Guerrera, Platania, Furneri, Torre, Boccaccio, Rivi, Tascedda, Pirrone, Santagati, Blom, Castellano, Caraci (2025). Exploring apathy components and their relationship in cognitive decline: insights from a network cross-sectional study. BMC Psychology, 13, 129. https://doi.org/10.1186/s40359-024-02239-x*

groups ($F = 4.39$, $p < 0.0001$) and between MCI and mild AD groups ($F = 2.94$, $p < 0.0001$). Similarly, the Montreal Cognitive Assessment (MoCA) showed significant differences: Control vs. MCI ($F = 10.43$, $p < 0.0001$), and MCI vs. mild AD ($F = 4.77$, $p < 0.0001$). Frontal Assessment Battery (FAB) scores also differed significantly between Control and MCI participants ($F = 4.85$, $p < 0.0001$), while the difference between MCI and mild AD groups did not reach statistical significance ($F = 1.73$, $p = 0.059$).

The Hamilton Depression Rating Scale (HDRS) also revealed significant between-group differences. Participants in the MCI group exhibited HDRS scores 7.28 points higher than controls ($p < 0.0001$), and those in the mild AD group scored 2.39 points higher ($p = 0.034$). Similarly, scores on the Apathy Evaluation Scale (AES-C) were significantly elevated in the clinical groups, with MCI participants scoring 7.31 points higher and mild AD participants scoring 14.1 points higher than the control group ($p < 0.0001$ for both comparisons). These results are graphically depicted in Figure 1, which illustrates the relationship between MoCA scores and both apathy (AES-C) and depressive symptoms (HDRS) across all groups.

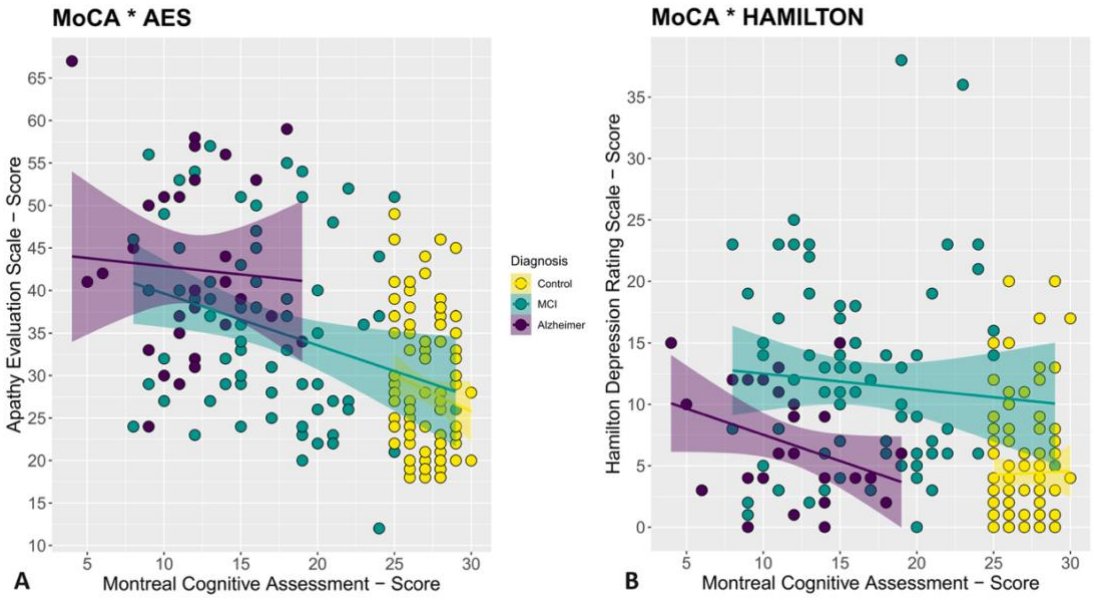

Figure 1. Part A is the representation of the three groups showing the relationship between apathy (x-axis) and cognitive decline using the MoCA test (y-axis). The size of the dots indicates a higher or lower score on the Hamilton scale (severity of depressive symptoms). The trend line is also shown for each of the groups[2]

Correlation analyses conducted on the entire sample confirmed existing literature linking apathy with neurocognitive deficits in Alzheimer-type dementias. The matrix of significant correlations is presented in Figure 2. The total score on the AES-C was negatively associated with global cognitive function and years of education, suggesting that higher apathy levels are related to more severe cognitive decline and lower educational attainment. Conversely, elevated AES-C scores were positively associated with diagnostic severity, presence of comorbid conditions, engagement in neurocognitive rehabilitation, use of pharmacological treatments, and higher HDRS scores.

[2] Taken from *Sarti, Varrasi, Guerrera, Platania, Furneri, Torre, Boccaccio, Rivi, Tascedda, Pirrone, Santagati, Blom, Castellano, Caraci (2025). Exploring apathy components and their relationship in cognitive decline: insights from a network cross-sectional study. BMC Psychology, 13, 129. https://doi.org/10.1186/s40359-024-02239-x*

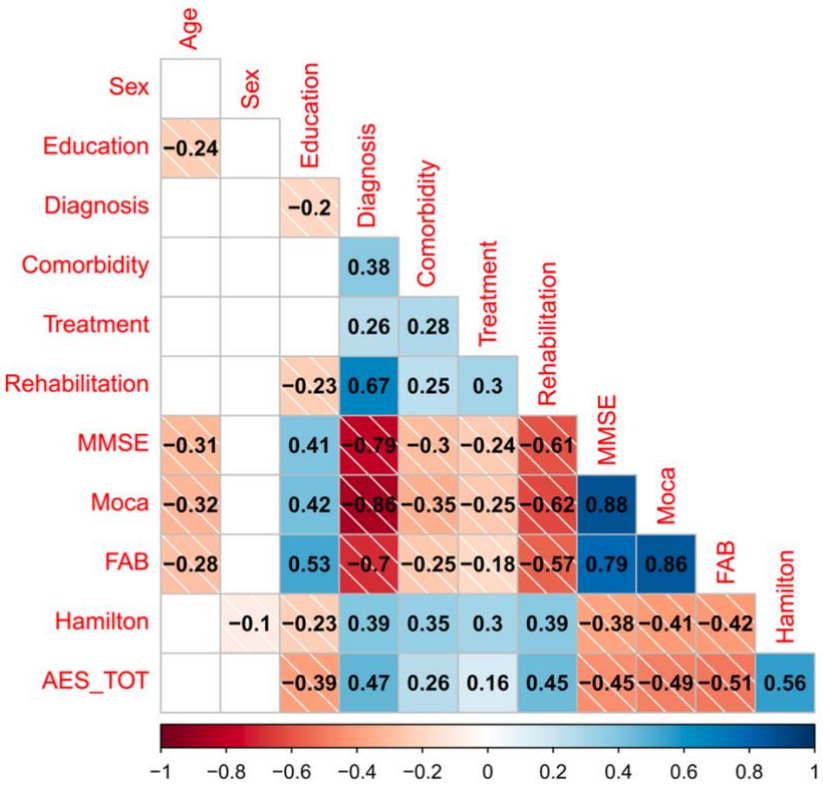

Figure 2. Spearman correlation tables of all sample. The absence of a circle in the grid indicates that the correlation is not statistically significant and was therefore not represented. Values tending towards dark red indicate negative correlations; values tending towards dark blue indicate a positive correlation. The specific value of the correlation is written inside every circle and that value is proportionate with the size of the circle[3]

When correlation analyses were stratified by clinical group (see Figure 3), further distinctions emerged. In both the Control and MCI groups, apathy was positively associated with depressive symptomatology and negatively associated with educational attainment and performance on the FAB, with the FAB score emerging as a particularly strong correlate of apathy compared to MoCA and MMSE. However, in the mild AD group, no significant correlations between apathy and the examined clinical or demographic variables were identified,

[3] Taken from *Sarti, Varrasi, Guerrera, Platania, Furneri, Torre, Boccaccio, Rivi, Tascedda, Pirrone, Santagati, Blom, Castellano, Caraci (2025). Exploring apathy components and their relationship in cognitive decline: insights from a network cross-sectional study. BMC Psychology, 13, 129. https://doi.org/10.1186/s40359-024-02239-x*

suggesting a potential dissociation of apathy symptomatology from other cognitive or affective features at this stage of disease progression.

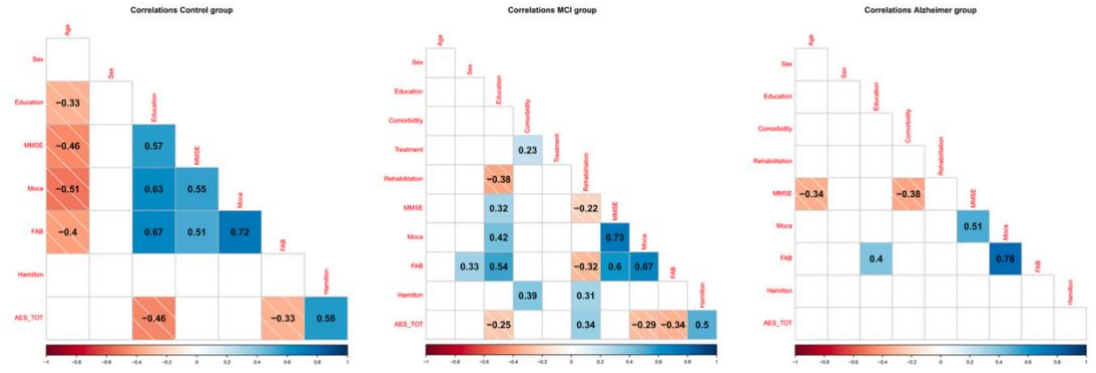

Figure 3. Spearman correlation tables dividing the three experimental groups. The absence of a circle in the grid indicates that the correlation is not statistically significant and was therefore not represented. Values tending towards dark red indicate negative correlations; values tending towards dark blue indicate a positive correlation. The specific value of the correlation is written inside every circle and that value is proportionate with the size of the circle[4]

Consistent with prior statistical findings, regression analysis was conducted using robust methods due to the non-normal distribution of residuals. All analyses were performed using the R statistical environment. Model selection was guided by Akaike's Information Criterion (AIC) to determine the best-fitting predictors of the Apathy construct for each clinical group.

In the Control group, the optimal regression model (AIC = 371.22) accounted for approximately 50% of the variance in apathy scores ($R^2 = 0.495$, $p < 0.001$). This model identified depressive symptomatology (Hamilton Depression Rating Scale), educational attainment, and global cognitive performance (MMSE) as significant predictors. In contrast, the MCI group model (AIC = 343.04) demonstrated a lower predictive capacity, explaining 26.3% of the variance (R^2 =

[4] Taken from *Sarti, Varrasi, Guerrera, Platania, Furneri, Torre, Boccaccio, Rivi, Tascedda, Pirrone, Santagati, Blom, Castellano, Caraci (2025). Exploring apathy components and their relationship in cognitive decline: insights from a network cross-sectional study. BMC Psychology, 13, 129. https://doi.org/10.1186/s40359-024-02239-x*

0.263, $p < 0.001$), with Hamilton scores, MMSE, and age emerging as significant contributors. The predictive accuracy of both models falls within an acceptable range in psychological research, as supported by prior literature (Ozili, 2022).

For the mild Alzheimer's disease group, however, the robust regression analysis failed to yield a statistically significant predictive model for apathy. To further explore this limitation, additional unsupervised machine learning techniques were employed exclusively within the mild AD cohort. Specifically, a k-means clustering approach did not yield a meaningful segmentation consistent with clinical groupings. Similarly, Principal Component Analysis (PCA) revealed considerable overlap among components, precluding the identification of distinct latent structures or unique apathy profiles within this subgroup.

Given these limitations, and the apparent inadequacy of traditional statistical and unsupervised approaches to capture the complexity of the apathy construct in the mild AD group, network analysis was employed to uncover the relational structure of apathy across the three diagnostic categories.

3.2 Network Analysis

Network analysis was conducted to further elucidate the structure of apathy as it relates to demographic and neurocognitive variables across the Control, MCI, and mild AD groups. The analysis incorporated item-level scores from the Apathy Evaluation Scale (AES-C) to avoid redundancy and mitigate the risk of spurious correlations, which may arise when including total scores.

As a preliminary step, three additional network models were constructed using a circular layout (Figure 4) to visualize general associations between demographic and cognitive variables. The network for the Control group (Figure 4, left panel) reproduced well-established associations documented in the literature: higher educational attainment was positively associated with global cognitive

functioning (MMSE, MoCA) and executive functioning (FAB), whereas age was inversely related to these cognitive scores particularly to MoCA and MMSE - while its association with the FAB was weaker.

In the MCI network, a notable shift in the structure of associations was observed. The FAB emerged as the only cognitive measure maintaining a positive relationship with educational level and, interestingly, also with male sex - suggesting that male participants exhibited higher performance, consistent with recent FAB standardization studies (Garofalo et al., 2021). Furthermore, while previous literature (Ilardi et al., 2022) has reported negative associations between apathy and educational level, in the present study this relationship was replicated only within the Control group.

Importantly, in the mild AD group, no significant pairwise associations were identified between AES-C items and any of the demographic or cognitive variables. This finding reinforces the results obtained in the regression analysis, further suggesting that the apathy construct in mild AD may not be linearly related to the variables assessed or may reflect greater clinical heterogeneity.

Following bootstrapping procedures, the Betweenness centrality index was found to be the least stable across all network models. Consequently, Strength Centrality and Expected Influence were adopted as more reliable indicators of node importance within each network. These metrics enabled a clearer interpretation of the structural role of each variable in relation to apathy and its interaction with the broader neurocognitive profile in each group.

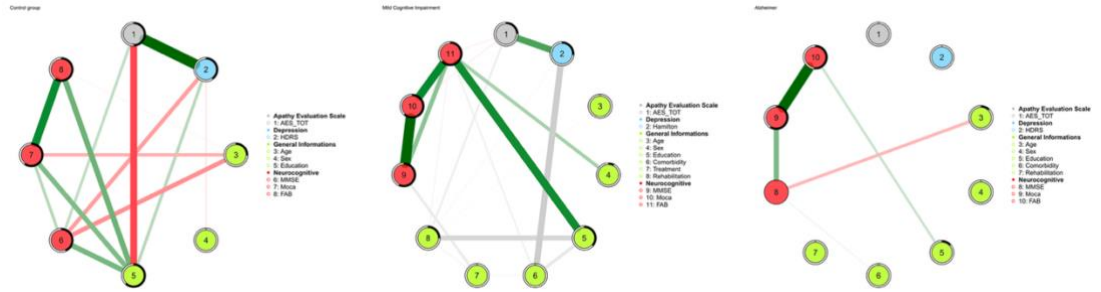

Figure 4. Network analysis of the three groups (Control on the left, MCI in the middle and mild Alzheimer on the right) keeping the Total Score of Apathy Evaluation Scale. Nodes represent the variables used to calculate the network model; Lines between nodes are the edges: partial correlations between variables (thicker the edge, greater the correlation value); green edges: positive correlations; red edges: negative correlations; black-colored edges: partial correlations between dichotomous and continuous variables. Predictability value was represented by a ring around each node. The blacker the ring, the more variance of the variable is explained by the other connected nodes[5]

3.3 Network Analysis by Diagnostic Group

3.3.1 Control Group

The network structure derived for the Control group (Figure 5) exhibited the highest density among the three cohorts, with a density index of 0.278 and a total of 77 edges. It also demonstrated the lowest modularity, as evidenced by the identification of only two clusters using the walktrap community detection algorithm. This structural configuration suggests a highly integrated and dynamic network, wherein perturbations - whether positive or negative - are likely to propagate swiftly due to the high level of interconnectivity. The limited clustering implies minimal compartmentalization, allowing for robust interaction between nodes through multiple concurrent pathways.

[5] Taken from *Sarti, Varrasi, Guerrera, Platania, Furneri, Torre, Boccaccio, Rivi, Tascedda, Pirrone, Santagati, Blom, Castellano, Caraci (2025). Exploring apathy components and their relationship in cognitive decline: insights from a network cross-sectional study. BMC Psychology, 13, 129. https://doi.org/10.1186/s40359-024-02239-x*

Graphically, the Apathy Evaluation Scale (AES-C) items (nodes 1–18) were predominantly localized on the right side of the network, while neurocognitive measures and demographic variables were positioned on the left. Centrality analyses revealed that the nodes with the highest Expected Influence (EI) were node 17 ("S/he has initiative", EI = 1), node 7 ("S/he approaches life with intensity", EI = 0.963), and node 13 ("Getting together with friends is important to him/her", EI = 0.885). Node 11 ("S/he is less concerned about her/his problems than s/he should be", EI = 0.830) and node 20 (Age) also emerged as important contributors to the overall network structure.

It is noteworthy that nodes 7 and 17, despite their centrality, do not share a direct edge and belong to separate clusters (Figure 5, part B), underscoring a degree of functional independence within the broader apathy construct. Additionally, node 19 (Hamilton Depression Rating Scale) exhibited minimal connectivity, suggesting that depressive symptoms have limited influence within the network of cognitively healthy individuals. This finding is consistent with prior statistical analyses, which highlighted a clear distinction between apathy and depression in this cohort.

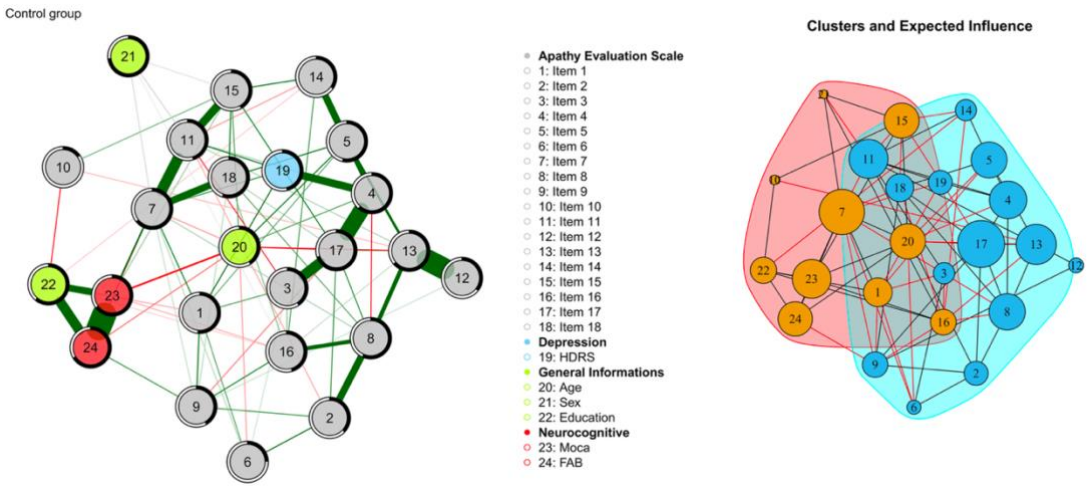

Figure 5. Part A: Network of the Control group. Nodes represent the variables used to calculate the network model; Lines between nodes are the edges: partial correlations between variables

(thicker the edge, greater the correlation value); green edges: positive correlations; red edges: negative correlations; black-colored edges: partial correlations between dichotomous and continuous variables. Predictability value was represented by a ring around each node. The blacker the ring, the more variance of the variable is explained by the other connected nodes. Part B: representation of the clusters identified through the walktrap algorithm. Black edges: intra-cluster connections; red edges: inter-cluster connections. The size of the nodes reflects the value of "Expected influence". The bigger the higher[6]

3.3.2 Mild Cognitive Impairment (MCI) Group

The network corresponding to the MCI group (Figure 6) was less densely connected than that of the Control group, with 65 edges and a density index of 0.185. The walktrap algorithm identified three distinct clusters, and one node - node 20 (Age) - was isolated, forming a singleton cluster (Figure 6, part B). The AES-C items remained relatively cohesive; however, their configuration was altered, likely due to the introduction of additional dichotomous clinical variables not present in the control model: Comorbidity (node 23), Pharmacological Treatment (node 24), and Neurocognitive Rehabilitation (node 25).

Neurocognitive variables (nodes 27–28) and the depression measure (node 19) remained peripheral, exerting limited influence on network dynamics. Notably, node 20 (Age), previously central in the Control group, lost its prominence and was effectively replaced by node 21 (Sex), which emerged as the most influential variable (EI = 1). Other nodes of high centrality included node 9 ("S/he spends time doing things that interest her/him", EI = 0.640), node 16 ("Getting things done during the day is important to her/him", Betweenness Centrality = 0.584), and node 17 ("S/he has initiative", EI = 0.592). These results suggest a shift in the

[6] Taken from *Sarti, Varrasi, Guerrera, Platania, Furneri, Torre, Boccaccio, Rivi, Tascedda, Pirrone, Santagati, Blom, Castellano, Caraci (2025). Exploring apathy components and their relationship in cognitive decline: insights from a network cross-sectional study. BMC Psychology, 13, 129. https://doi.org/10.1186/s40359-024-02239-x*

apathy construct's configuration in MCI, with a more prominent role for socio-demographic factors and specific behavioral indicators of goal-directed activity.

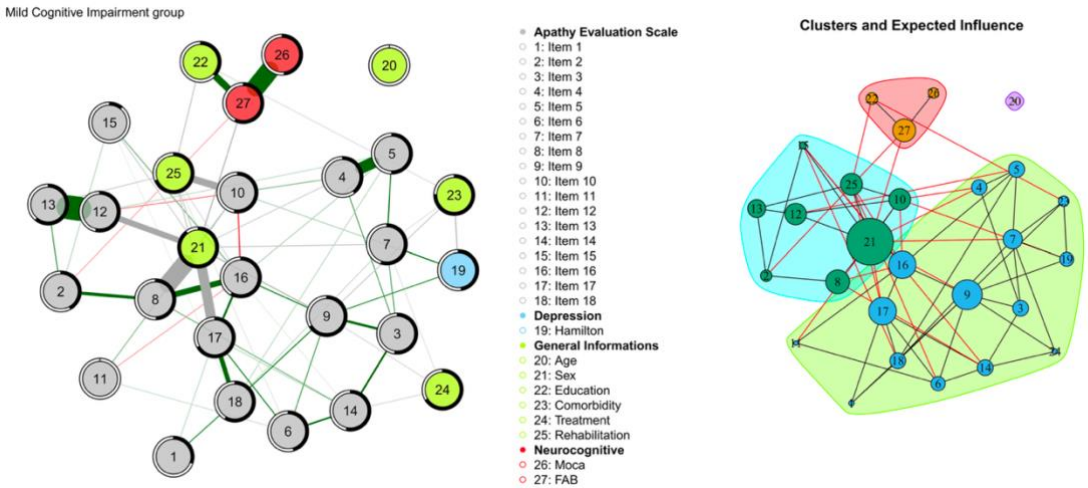

Figure 6. Part A: Network of the MCI group. Nodes represent the variables used to calculate the network model; Lines between nodes are the edges: partial correlations between variables (thicker the edge, greater the correlation value); green edges: positive correlations; red edges: negative correlations; black-colored edges: partial correlations between dichotomous and continuous variables. Predictability value was represented by a ring around each node. The blacker the ring, the more variance of the variable is explained by the other connected nodes. Part B: representation of the clusters identified through the walktrap algorithm. Black edges: intra-cluster connections; red edges: inter-cluster connections. The size of the nodes reflects the value of "Expected influence". The bigger the higher[7]

3.3.3 Mild Alzheimer's Disease Group

The network structure obtained for the mild Alzheimer's disease group (Figure 7) was the sparsest, comprising only 41 edges and presenting a density index of 0.126. The network appeared fragmented, with six distinct clusters identified, and a pronounced separation between AES-C items, demographic information,

[7] Taken from *Sarti, Varrasi, Guerrera, Platania, Furneri, Torre, Boccaccio, Rivi, Tascedda, Pirrone, Santagati, Blom, Castellano, Caraci (2025). Exploring apathy components and their relationship in cognitive decline: insights from a network cross-sectional study. BMC Psychology, 13, 129. https://doi.org/10.1186/s40359-024-02239-x*

and neurocognitive variables. This high degree of modularity suggests a diminished capacity for integrative functioning, possibly reflecting the neurodegenerative processes characterizing this clinical population.

Centrality analyses revealed that only two clusters - represented by light blue and red in Figure 7, part B - contained nodes with notable influence. Among these, node 23 (Comorbidity; EI = 1) and node 10 ("Someone has to tell her/him what to do each day", EI = 0.979) were the most influential. These nodes, along with node 24 (Rehabilitation), constituted a distinct cluster that encapsulated the construct of abulia, a core feature of cognitive apathy in Alzheimer's disease. Node 8 ("Seeing a job through to the end is important to her/him") was also linked within this cluster, reinforcing the pattern of diminished initiative and volitional behavior associated with advanced neurocognitive decline.

Additional AES-C items exhibiting high centrality included node 17 ("S/he has initiative"), node 16 ("Getting things done during the day is important to her/him"), node 1 ("S/he is interested in things") and again node 8. All of these items are representative of the cognitive dimension of apathy, further underscoring its predominance in this stage of the disease.

Of note, the betweenness centrality index proved highly unstable across the mild AD network, and was therefore not considered a reliable metric for interpreting nodal importance in this group. However, Expected Influence and Strength Centrality indices remained sufficiently robust to guide the analysis.

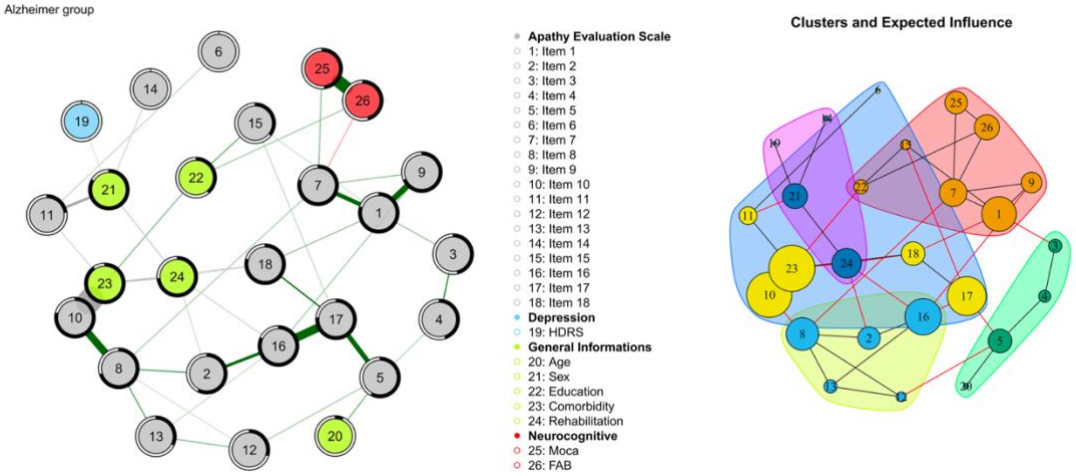

Figure 7. Part A: Network of the Mild Alzheimer group. Nodes represent the variables used to calculate the network model; Lines between nodes are the edges: partial correlations between variables (thicker the edge, greater the correlation value); green edges: positive correlations; red edges: negative correlations; black-colored edges: partial correlations between dichotomous and continuous variables. Predictability value was represented by a ring around each node. The blacker the ring, the more variance of the variable is explained by the other connected nodes. Part B: representation of the clusters identified through the walktrap algorithm. Black edges: intra-cluster connections; red edges: inter-cluster connections. The size of the nodes reflects the value of "Expected influence". The bigger the higher[8]

4. Discussion

The present study aimed to enhance our understanding of the interplay between apathy, neuropsychological symptoms, and demographic factors across different stages of cognitive decline, with a specific emphasis on the evolving role of apathy. Given the multifaceted nature of these constructs, a range of statistical

[8] Taken from *Sarti, Varrasi, Guerrera, Platania, Furneri, Torre, Boccaccio, Rivi, Tascedda, Pirrone, Santagati, Blom, Castellano, Caraci (2025). Exploring apathy components and their relationship in cognitive decline: insights from a network cross-sectional study. BMC Psychology, 13, 129. https://doi.org/10.1186/s40359-024-02239-x*

and network-based analyses were employed to uncover both overt and latent patterns within the data.

Initial analyses revealed that most variables within the MCI and mild AD cohorts were not normally distributed, a finding attributable both to the larger size of the control group and to the inherent symptomatic heterogeneity often observed in clinical populations. These observations further confirm that, as individuals transition toward Alzheimer's Disease, there is a concurrent increase in clinical severity - reflected in lower educational attainment, diminished cognitive test performance, and higher prevalence of comorbidities, depressive symptoms, and apathy.

Of particular note, individuals with MCI exhibited elevated depressive symptoms in comparison to those with mild AD, who conversely demonstrated more pronounced apathy. This pattern substantiates the conceptual and clinical distinction between depression and apathy in neurodegenerative disorders, reinforcing the necessity of their independent assessment and intervention. This differentiation is essential, given that symptoms of one condition may obscure or mimic those of the other (D'Iorio & Santangelo, 2022).

Interestingly, no statistically significant differences were found in executive functioning (as measured by the FAB) between the MCI and mild AD groups. The mean FAB score in the MCI cohort fell below the standard cutoff, suggesting a possible selection bias in the sample. This may have led to the inclusion of individuals presenting with non-amnestic MCI, who may not necessarily progress to AD. Nevertheless, executive dysfunction remains a pivotal symptom in disease progression and should be carefully monitored, given its close association with declining autonomy and increased risk of dementia onset (Junquera et al., 2020).

The linear increase in apathy severity observed across the three groups aligns with established models of clinical deterioration. However, when analyzed

independently, both the control and MCI groups exhibited similar apathy profiles, lending support to the hypothesis of a transitional "critical window" in which targeted psychosocial or pharmacological interventions may alter the trajectory of cognitive decline (Lissek & Suchan, 2021). In contrast, within the mild AD cohort, network cohesion deteriorated markedly, with no predictive patterns emerging from the data. Furthermore, automated variable clustering failed to isolate coherent behavioral structures, indicating that apathy in this group may reflect a disintegrated, less predictable construct.

To investigate these phenomena more comprehensively, a network analysis was conducted across the three groups. Initially, apathy was treated as a unidimensional construct, using total AES-C scores. Regression analyses, corroborated by network centrality measures, identified different predictors of apathy across stages: in the control group, significant predictors included depressive symptoms (HDRS), educational level, and MMSE scores; in the MCI group, predictors shifted to include HDRS, MMSE, and age; while in the mild AD group, no significant predictors were identified. These findings reveal a transition in the factors influencing apathy across the continuum of cognitive decline. Education, a modifiable factor, emerged as particularly salient in cognitively intact individuals, suggesting that it may serve a protective function against apathy onset. In contrast, age - a non-modifiable determinant - assumes greater influence in clinical populations, underscoring the progressive nature of apathy in neurodegeneration.

For cognitively healthy individuals, efforts to prevent or delay apathy should prioritize interventions targeting mood regulation, cognitive stimulation, and educational engagement. In those with early cognitive impairment, therapeutic focus may need to shift toward mood management and maintenance of goal-directed behaviors. Regardless of cognitive status, vigilance in detecting depressive symptoms remains critical.

Given the lack of predictive coherence in the mild AD group, subsequent network analyses focused on individual AES-C items. Among the three networks, the control group exhibited the highest density (Figure 5), with the fewest clusters - an indication of its integrative, non-compartmentalized nature. This high degree of interconnectedness among apathy subdomains, demographic features, and cognitive variables suggests a dynamic system capable of rapid adaptation and sensitive to both internal and external stimuli. The spatial clustering of AES-C items in proximity to neurocognitive and demographic variables underscores their mutual influence. These findings are consistent with prior evidence indicating a robust association between apathy and cognitive functioning, particularly intellectual curiosity in aging populations (Lanctôt et al., 2017; Montoya-Murillo et al., 2019).

In the Control group, the nodes exhibiting highest centrality included items related to initiative, learning, and vitality - spanning cognitive, behavioral, and emotional dimensions of apathy. Conversely, item 10 ("Someone has to tell me what to do each day") remained peripheral until becoming a central node in the mild AD network. This transition may represent the clinical emergence of abulia - a form of severe apathy frequently observed in Alzheimer's Disease (Kesserwani, 2021). Of note, item 10 was closely linked to comorbidity (node 23) and item 8 (goal-directed behavior), suggesting that environmental structuring - although intended to reduce burden on caregivers - may inadvertently exacerbate patient apathy by reducing opportunities for autonomous action (Wolfe et al., 2021).

In the MCI network (Figure 6), a reduction in density and increase in modularity were observed, reflecting diminished integration and adaptability. The incorporation of new binary variables - comorbidity, treatment, and rehabilitation - contributed to structural changes in the network. Age, previously central in the control group, lost its prominence and was supplanted by sex,

suggesting that biological and sociocultural sex-related factors may become increasingly influential during early cognitive decline. This finding supports the growing consensus that sex-specific profiles may serve as useful markers for early dementia risk stratification (Rosenberg et al., 2013; Stephan et al., 2010), ultimately facilitating more tailored clinical interventions.

In contrast, the network corresponding to mild AD (Figure 7) exhibited the lowest density and highest number of clusters, signifying fragmentation and reduced systemic coherence. The network displayed limited integrative capacity, potentially reflecting the neural and behavioral disorganization characteristic of this disease stage. Comorbidity emerged as the dominant influence, underscoring the importance of monitoring not only apathy but also co-occurring psychopathologies that may hinder rehabilitative efforts. Nonetheless, aspects of motivation and goal-directed behavior - such as initiative and life engagement - remained moderately influential, suggesting that these domains may still offer viable entry points for short-term intervention, such as the establishment of concrete daily goals.

A particularly compelling observation is the increasing number of network clusters across stages of cognitive decline, indicating a progressive compartmentalization of psychological and clinical information. Unlike the findings of Tosi et al. (Tosi et al., 2024), which suggested an evolution toward generality or non-specificity, the current study observed a parallel increase in both cluster specificity and reduction in density, suggesting that apathy becomes a more fragmented and individualized construct as disease severity increases. This phenomenon may stem from two principal factors: (1) the integration of medical, demographic, and treatment-related variables into the networks of clinically diagnosed participants (Ferguson, 2021, 2023), and (2) the growing clinical heterogeneity of apathy in Alzheimer's Disease, where it manifests with greater complexity than in MCI or healthy individuals.

This study is not without limitations. Chief among them is the cross-sectional design, which prevents the inference of temporal causality or the mapping of longitudinal symptom trajectories. Although this limitation was partially mitigated by analyzing three groups with progressively worsening cognitive status, future research would benefit from longitudinal follow-up of the same individuals to track intra-individual changes over time. Additionally, the relatively small sample size of the mild AD group may have limited the statistical power of some analyses. However, this constraint was addressed through robust methodological strategies, including bootstrap-based centrality stability testing and cross-validation of network models. These procedures ensured the reliability of the findings despite the limited sample size.

5. Conclusion

In conclusion, the present study highlights the pivotal role of apathy in the clinical continuum of cognitive impairment, enhancing our understanding of its complex interaction with clinical and demographic variables across healthy individuals, those with Mild Cognitive Impairment (MCI), and patients in the early stages of Alzheimer's Disease (AD). By employing Network Analysis, this research offers novel insights into the centrality of intrinsic factors - particularly initiative and interest - in shaping apathetic profiles. These factors were found to be especially salient in cognitively healthy individuals and those with MCI, and their relevance persists even in the context of mild AD. These findings provide empirical support for behavioral interventions designed to foster motivational engagement and preserve the autonomy of patients in daily activities, rather than prematurely withdrawing opportunities for self-directed functioning (Manera et al., 2020).

The observations within the MCI cohort further suggest that apathy may function as an early clinical marker for the transition to dementia. This underscores the

importance of future investigations into the potential for disease-modifying pharmacological interventions aimed at halting or delaying the progression from MCI to AD (Bogdan et al., 2020). However, the cross-sectional nature of this study limits causal inference regarding the temporal dynamics of these associations. To address this limitation, future longitudinal studies are needed to trace the evolution of apathy and related variables across the stages of cognitive decline.

Network Analysis also elucidated the differential contribution of specific symptoms to the broader construct of apathy, thereby offering a promising direction for refining psychometric tools. The identification of the most diagnostically informative items could lead to more efficient and targeted screening protocols, optimizing the trade-off between clinical utility, time constraints, and participant burden.

Furthermore, the findings emphasize the influence of demographic variables, particularly the emerging role of sex-related differences within the MCI group. This line of inquiry opens new avenues for understanding the heterogeneity of cognitive decline and may inform stratification strategies in future clinical trials. Specifically, sex-sensitive research could facilitate the identification of MCI subgroups with preclinical AD biomarkers, thereby refining participant selection for trials of disease-modifying therapies such as immunotherapy (Bradshaw & Georges, 2024; Ferretti et al., 2018). Future work integrating these findings with Network Intervention Analysis may further enable mapping of pharmacological effects across interconnected neurocognitive, affective, and environmental variables (Guerrera et al., 2023).

Lastly, it is imperative to deepen our understanding of the specific impact of apathy in the mild AD population prior to the initiation of cholinesterase inhibitor therapy, as originally planned within a subset of this study. Clarifying whether such pharmacological interventions influence apathetic symptoms remains a critical question, given that recent evidence has yielded inconclusive results

(Andrade, 2022; Steffens et al., 2022). Addressing this gap through dedicated, adequately powered trials will be essential to delineate effective treatment strategies for apathy in the context of AD.

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CHAPTER THREE

Exploratory Graph Analysis for refining the assessment of apathy

in cognitive decline

Preface

After exploring apathy as a potential risk factor in cognitive decline, this third chapter addresses its assessment by introducing and applying an innovative network-based methodology - Exploratory Graph Analysis (EGA) - to the clinician-rated Apathy Evaluation Scale (AES-C). Traditional latent-variable approaches, such as Exploratory Factor Analysis, have offered valuable insights into its dimensionality but remain limited in capturing the dynamic interrelationships among symptoms.

Within this framework, the chapter outlines how EGA, grounded in network psychometrics, overcomes these constraints by identifying empirically derived clusters of interrelated items without presupposing latent factors. The results reveal a four-factor structure that demonstrates superior psychometric performance, conceptual clarity, and model fit when compared to both Marin's original three-factor framework and a traditional EFA-derived model. These findings underscore the potential of EGA to refine the operationalization of apathy, yielding a dimensional structure that not only aligns with contemporary theoretical models but also enhances clinical interpretability and diagnostic precision.

1. Introduction

Apathy constitutes a prevalent and functionally impairing symptom across the spectrum of neurocognitive disorders, particularly in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) (Richard et al., 2012). Clinically, it is defined as a measurable reduction in goal-directed behavior, persisting for a minimum of four weeks and manifesting in at least two of the following domains: behavioral/cognitive, emotional, and social interaction (Fahed & Steffens, 2021). Importantly, apathy is recognized as a construct distinct from depression, insofar as it cannot be attributed to reduced levels of consciousness, generalized cognitive deterioration, or affective distress (Marin, 1991; Robert et al., 2009, 2018).

Contemporary research increasingly supports the conceptualization of apathy as a multidimensional syndrome. This view is substantiated by empirical findings across a range of neurological conditions, including Parkinson's disease (Pagonabarraga et al., 2015), multiple sclerosis (Raimo et al., 2016), and various forms of dementia (Leung et al., 2021). Within the context of AD and MCI, apathy has been consistently associated with accelerated cognitive decline (Breitve et al., 2018), diminished responsiveness to treatment (van Reekum, 2005), elevated mortality rates (Furneri, Razza, et al., 2021), and an increased risk of conversion to overt dementia (Van Dalen et al., 2018). Notably, only a fraction of the variance in apathy can be accounted for by cognitive or affective factors alone, reinforcing its status as an independent and multifaceted clinical entity (Sarti, Varrasi, et al., 2025). Recent investigations leveraging machine learning methodologies have further demonstrated that apathy contributes significantly to diagnostic classification across stages of cognitive decline, underscoring its clinical salience (Tascedda et al., 2024).

Given its complex phenomenology, there is a growing consensus that apathy should be examined through theoretical models capable of capturing its internal

heterogeneity (Furneri, Razza, et al., 2021). Among the most influential frameworks is the ABC model of apathy, which delineates three interrelated but distinct components: affective (emotional blunting or reduced responsiveness), behavioral (difficulty initiating goal-directed actions), and cognitive (diminished planning or engagement with tasks) (Levy & Dubois, 2006; Marin, 1991). This tripartite model reframes apathy not as a unitary syndrome with multiple expressions, but as a network of interacting yet non-redundant dimensions. Several psychometric instruments have been developed to operationalize this model. Among these, the Apathy Evaluation Scale (AES-C), originally developed by Marin and colleagues, remains one of the most established tools (Marin et al., 1991). The clinician-rated version (AES-C) has demonstrated solid psychometric properties across diverse populations and has recently been standardized in AD cohorts (Furneri, Platania, et al., 2021).

Historically, validation studies of the AES-C have relied on latent variable approaches such as Exploratory Factor Analysis (EFA), which presuppose that observable symptoms are manifestations of one or more underlying latent traits. However, this assumption has been increasingly challenged by both theoretical considerations and empirical findings (Nájera et al., 2023). For instance, emerging evidence suggests that the relative prominence of apathy components may vary across disease stages: cognitive apathy (abulia) appears more central in AD, whereas all three domains may carry equal weight in cognitively unimpaired individuals (Sarti, Varrasi, et al., 2025). Such dynamic patterns are not adequately captured by traditional factor-analytic methods.

In response to these limitations, network-based methodologies have been proposed. The network theory of psychopathology conceptualizes symptoms as interactive elements that may reinforce each other over time (Borsboom, 2017; Isvoranu et al., 2017). Within this framework, psychological syndromes are understood not as reflections of latent constructs, but as emergent phenomena

arising from complex interrelations among symptoms (Isvoranu et al., 2016). This paradigm has been successfully applied to a range of psychiatric and neurological conditions, including unipolar and bipolar depression (Guerrera et al., 2023; Platania et al., 2023; Sarti et al., 2024), schizophrenia (Sarti, Surbeck, et al., 2025; van Rooijen et al., 2017), and various neurodegenerative disorders (Goodwin et al., 2023; Grunden & Phillips, 2024).

Exploratory Graph Analysis (EGA) represents a novel and promising technique within the field of network psychometrics (H. F. Golino & Epskamp, 2017). Unlike EFA, EGA does not assume latent variables but instead uses partial correlation networks to identify clusters of items - interpreted as dimensions - based on their empirical co-occurrence patterns. The technique employs Gaussian Graphical Models, estimated through the graphical Least Absolute Shrinkage and Selection Operator (LASSO), and includes data-driven community detection algorithms to identify item groupings (Blondel et al., 2008; Epskamp et al., 2018). This data-driven approach minimizes researcher bias and enhances the interpretability of complex psychological constructs.

EGA offers several methodological advantages: it provides a visual representation of the relational structure among items, facilitates the identification of multidimensional constructs, and has demonstrated superior performance in determining the number of latent dimensions in both simulated and empirical datasets (Bell & O'Driscoll, 2018; H. Golino et al., 2019; H. F. Golino & Demetriou, 2017). Despite its potential, EGA has yet to be applied to the assessment of apathy, particularly within populations affected by MCI or AD.

In light of the theoretical complexity of apathy and the limitations inherent in traditional psychometric approaches, the present study aims to examine the dimensional structure of the AES-C through EGA. Furthermore, the findings will be compared with the original model proposed by Marin et al. and with factor solutions derived via EFA. This comparative analysis seeks to determine whether

network-based methodologies provide a more accurate and nuanced understanding of the multifaceted nature of apathy in the context of neurodegenerative disorders.

2. Materials and Methods

2.1 Participants

A total of 214 individuals were enrolled in the present study and stratified into two groups: a clinical group and a healthy control group. The clinical group comprised 107 patients (34 males, 73 females) recruited from the Alzheimer's and Psychogeriatric Unit (UOS) of the ASP3 DSM in Catania, Italy. Diagnostic classification adhered to the updated criteria established by the National Institute on Aging and the Alzheimer's Association for the identification of probable Alzheimer's disease (AD) and amnestic Mild Cognitive Impairment (MCI) due to AD (McKhann et al., 2011). Specifically, individuals with AD were diagnosed as "probable" cases based solely on clinical presentation in the absence of biomarker evidence, whereas the diagnosis of amnestic MCI was operationalized in accordance with Petersen's criteria (Petersen et al., 2014), emphasizing predominant single-domain memory deficits. The complete diagnostic criteria for both probable AD and amnestic MCI due to AD have been extensively described in previous literature (Albert et al., 2011; McKhann et al., 2011).

To assess general cognitive functioning, the Italian standardized version of the Mini-Mental State Examination (MMSE) was administered (Magni et al., 1996). Inclusion in the clinical group required an MMSE total score - adjusted for age and educational level - ranging from 18 (inclusive) to 28. The selection of the MMSE and corresponding thresholds was guided by the current recommendations for staging cognitive impairment issued by the Italian

Medicines Agency (AIFA, 2024). Of the 107 individuals in the clinical group, 77 were diagnosed with MCI due to AD and 30 with mild AD.

The control group was composed of 107 cognitively healthy individuals (29 males, 78 females), all of whom obtained MMSE scores equal to or greater than 28. The healthy status of these individuals was verified through comprehensive clinical interviews, cognitive assessments, and evaluations of daily functional autonomy, in accordance with the aforementioned national guidelines.

The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and its subsequent revisions. Ethical approval was granted by the Internal Review Board of the Department of Educational Sciences (Psychology Section), University of Catania (Protocol No. Ierb-Edunict-2023.05.23/02, approved on May 23, 2023). All research activities adhered to the ethical standards of the Italian Psychological Association (AIP) and relevant institutional regulations. Informed written consent for participation and publication of findings was obtained from all participants.

2.2 Materials

Neuropsychological evaluations were administered by licensed clinical psychologists in a standardized and controlled setting. The following instruments were employed for both the clinical and control groups:

- Apathy Evaluation Scale – Clinician Version (AES-C) (Marin et al., 1991): the AES-C is an 18-item clinician-administered instrument designed to measure apathy across behavioral (B), cognitive (C), and emotional (E) domains. Items are scored on a 4-point Likert scale, yielding a total score ranging from 18 to 72. Items are presented in both positive and negative formulations (indicated as "+" or "–"), with a predominance of positively worded items. Although patient self-report informs certain items, scoring is primarily based on the clinician's integrative

judgment following a semi-structured interview, thereby ensuring objective assessment of the patient's motivational state. In the present study, the scale was administered by trained clinicians to maximize diagnostic accuracy.

- Mini-Mental State Examination (MMSE) (Magni et al., 1996): the MMSE is a widely utilized screening tool for assessing global cognitive functioning. It evaluates multiple cognitive domains and yields a maximum score of 30. Scores are adjusted for age and educational level. The MMSE was selected as the primary screening measure in accordance with national clinical guidelines for staging cognitive deterioration.
- Montreal Cognitive Assessment (MoCA) (Santangelo et al., 2015): the MoCA is a multidimensional cognitive screening tool with heightened sensitivity to MCI. It provides a comprehensive evaluation of various cognitive domains. The maximum score is 30, with adjustments based on age and educational attainment. Region-specific normative data for Southern Italian elderly populations were applied in this study (Bosco et al., 2017).
- Frontal Assessment Battery (FAB) (Aiello et al., 2022): the FAB is a brief instrument designed to evaluate executive functions. It consists of six subtests examining conceptualization, mental flexibility, motor programming, interference sensitivity, inhibitory control, and environmental autonomy. The total score ranges from 0 to 18, with normative adjustments made for demographic variables.
- Hamilton Depression Rating Scale (HDRS) (HAMILTON, 1960): the HDRS is a semi-structured clinician-administered interview used to assess the severity of depressive symptoms. Interpretative thresholds are as follows: scores below 7 indicate an absence of depression; scores between 8 and 17 reflect mild depression; scores between 18 and 24 denote moderate depression; and scores above 24 suggest severe depression.

2.3 Statistical Analyses

All collected data from both clinical and control groups were subjected to quantitative analysis. Descriptive statistics, including means, standard deviations, and percentages, were calculated to summarize the demographic and psychometric characteristics of the sample.

Given the ordinal nature of the data obtained from the Apathy Evaluation Scale – Clinician version (AES-C), Spearman's rank-order correlations were employed to examine the relationships between variables. To investigate the underlying latent structure of the AES-C, Exploratory Graph Analysis (EGA) was performed using the EGA package in R (H. Golino et al., 2024). Since the initial descriptions of EGA, the methodological literature has matured: simulation studies and tutorials have evaluated EGA's performance relative to traditional factor-analytic techniques, while practical guidance and software implementations (e.g., the EGAnet framework) now provide bootstrapping and stability checks, multi-sample routines and explicit recommendations for reporting model estimation, community detection method, and robustness diagnostics. To align with current best practices, the present analyses applied EGA together with regularization, bootstrapped edge-weight stability, and sensitivity checks, and reported the community detection algorithm and seed parameters explicitly (Golino et al., 2019; Epskamp & Fried, 2018; EGAnet Development Team, 2025). The graphical least absolute shrinkage and selection operator (glasso) model was applied to reduce the risk of overfitting, while the walktrap community detection algorithm was utilized to optimize network modularity. The resulting network structure and dimensionality were visualized using the qgraph package. Centrality indices were computed to assess the relative influence of each item within the network structure.

Subsequently, the latent dimensions identified through EGA were subjected to Confirmatory Factor Analysis (CFA) to evaluate the adequacy of the proposed

structure. The CFA was conducted using the lavaan package in R, with the Weighted Least Squares Mean and Variance adjusted (WLSMV) estimator (Gomez et al., 2020; Li, 2016). This estimator was selected over the more commonly used Maximum Likelihood (ML) method, as WLSMV is more appropriate for categorical and ordinal data, and provides robust estimates in the presence of non-normal distributions.

Each model was fitted using the 'lavaan' package in R (Rosseel, 2012). Model fit was assessed using a combination of fit indices, including the chi-square statistic, Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), and Standardized Root Mean Square Residual (SRMR). Competing models were compared using the Satorra-Bentler chi-square difference test (Satorra & Bentler, 2010), enabling the selection of the best-fitting model. Internal consistency of the identified factors was subsequently evaluated through the calculation of Cronbach's alpha (Cronbach, 1951).

In addition, an Exploratory Factor Analysis (EFA) was conducted as a complementary approach to explore the underlying factor structure of the AES-C. Prior to conducting EFA, the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity were computed to ensure that the data met the assumptions for factor analysis (BARTLETT, 1950; Kaiser, 1974).

To assess measurement invariance across clinical subgroups, the EGA-derived model was further tested through a Multiple Group Confirmatory Factor Analysis (MGCFA), applied separately to the MCI and AD subsamples. CFA was again employed to evaluate the goodness of fit for the model within each subgroup.

Following this, Shapiro-Wilk tests were conducted to examine the distributional properties of the factor scores derived from the EGA model. Spearman's correlations were computed between the AES-C subscales and external

measures, including MMSE, MoCA, FAB, and HDRS, to assess convergent and discriminant validity.

Finally, non-parametric group comparisons were performed using the Kruskal-Wallis test to evaluate differences in AES-C subscale scores across the three participant groups (MCI, AD, and healthy controls). Where significant omnibus effects were observed, Dunn's post-hoc tests were conducted to identify specific between-group differences.

3. Results

A comprehensive overview of the demographic characteristics of the study sample, along with the mean scores of neuropsychological assessments stratified by group, is presented in Table 1.

Demographics	**Control Group**		**Mild Cognitive Impairment**		**Alzheimer's Disease**	
	Sample	**Percentage**	**Sample**	**Percentage**	**Sample**	**Percentage**
Sample size	107	100	77	100	30	100
Females	78	72.9	54	70.1	19	63.3
Males	29	27.1	23	29.9	11	36.7
Mean Age	74.06 (6.8)		75.53 (7.3)		76.33 (6.4)	
EDUCATION						
- Mean education	10.29 (5.7)		8.56 (4.4)		6.87 (4.2)	
- Primary school	42	39.1	35	45.5	17	56.5
- Secondary school	14	13.1	18	23.4	7	23.4
- High School	22	20.5	15	19.5	4	13.3
- University and more	29	27.1	9	11.7	2	6.6
NEUROPSYCHOLOGICAL ASSESSMENT						
- Mini-Mental State Examination	29.35 (0.84)		24.95 (3.42)		22.00 (2.92)	

- Montreal Cognitive Assessment	26.98 (1.38)	16.55 (4.80)	11.77 (3.51)
- Frontal Assessment Battery	15.56 (1.88)	10.7 (3.54)	8.97 (3.42)
- Hamilton Depression Rating Scale	4.37 (4.58)	11.66 (7.81)	6.67 (4.46)
- Apathy Evaluation Scale	25.42 (7.11)	32.32 (9.46)	38.23 (9.72)

Table 1. Demographic characteristics and neuropsychological test scores for the three diagnostic groups included in the study: cognitively healthy controls, individuals with Mild Cognitive Impairment, and patients with Alzheimer's Disease. For each group, the table reports sample size, gender distribution, mean age, and level of education (both as mean years and categorical levels). Neuropsychological measures include the Mini-Mental State Examination, Montreal Cognitive Assessment, Frontal Assessment Battery, Hamilton Depression Rating Scale, and Apathy Evaluation Scale – Clinician version. Values are presented as means with standard deviations in parentheses, or as absolute frequencies with corresponding percentages[1]

Exploratory Graph Analysis (EGA) revealed a four-factor structure underlying the Apathy Evaluation Scale – Clinician version (AES-C). The resulting network, depicted in Figure 1, delineates the following thematic groupings:

- Factor 1: Interests and Motivation (items 1, 3, 6, 7, 9, 10, 11, 15, 17, 18)
- Factor 2: Social Apathy (items 12, 13)
- Factor 3: Autonomy (items 2, 8, 14, 16)
- Factor 4: Novelty (items 4, 5)

[1] Taken from *Guerrera, Platania, Varrasi, Sarti, Boccaccio, Torre, Santagati, Furneri, Pirrone, Di Nuovo, Blom, Caraci, Castellano (2025). Investigating the multidimensional structure of apathy in cognitive decline: an exploratory network analysis of the Apathy Evaluation Scale. The American Journal of Geriatric Psychiatry. https://doi.org/10.1016/j.jagp.2025.07.010*

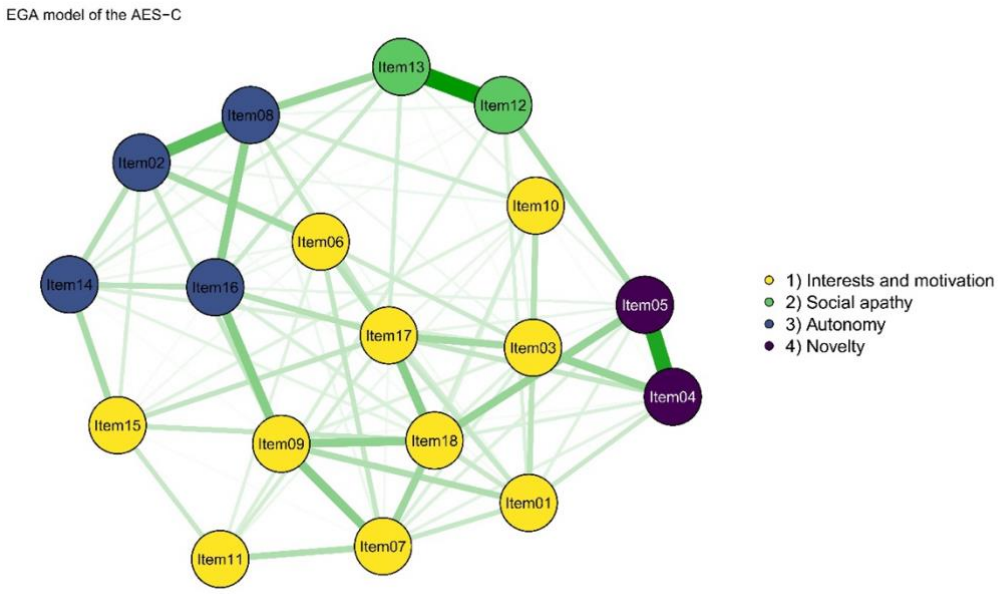

Figure 1. Exploratory Graph Analysis model of the Apathy Evaluation Scale – Clinician version. Each node represents one questionnaire item, while edges indicate positive Spearman partial correlations between items, with edge thickness corresponding to the strength of the association[2]

Edges between nodes in the network correspond to partial correlations, controlling for all other associations within the network. Notably, no negative edges were observed. Confirmatory Factor Analysis (CFA) conducted on the EGA-derived model demonstrated an excellent fit: $\chi^2(129) = 117.90$, $p = 0.749$; SRMR = 0.057; CFI (scaled) = 0.984; RMSEA (scaled) = 0.047; TLI (scaled) = 0.981. Internal consistency, as measured by Cronbach's alpha, was found to be satisfactory for all factors: Factor 1 = 0.87, Factor 2 = 0.80, Factor 3 = 0.74, and Factor 4 = 0.79. These indices collectively support the robustness and reliability of the proposed factorial solution.

[2] Taken from *Guerrera, Platania, Varrasi, Sarti, Boccaccio, Torre, Santagati, Furneri, Pirrone, Di Nuovo, Blom, Caraci, Castellano (2025). Investigating the multidimensional structure of apathy in cognitive decline: an exploratory network analysis of the Apathy Evaluation Scale. The American Journal of Geriatric Psychiatry. https://doi.org/10.1016/j.jagp.2025.07.010*

To further evaluate the factorial validity of the AES-C, an Exploratory Factor Analysis (EFA) was also conducted. Prior to analysis, data suitability was confirmed via the Kaiser-Meyer-Olkin (KMO) test, which yielded a sampling adequacy index of 0.91. Bartlett's test of sphericity was statistically significant (χ^2 = 1730.13, df = 153, p < 0.00001), supporting the appropriateness of factor analysis.

Parallel analysis indicated the retention of four factors. This initial four-factor EFA model accounted for 49% of the total variance (Factor 1: 24%, Factor 2: 12%, Factor 3: 7%, Factor 4: 7%). However, one of the extracted factors (Factor 4) consisted of a single item, rendering internal consistency assessment unfeasible. Item 10 failed to load exclusively onto any single factor and was consequently assigned to the factor with which it had the highest correlation (Factor 1).

A subsequent, more parsimonious EFA was conducted specifying a three-factor solution. In this alternative model, Items 10 and 11 again failed to demonstrate clear factor membership. As with the previous model, these items were assigned based on their highest item-factor correlations.

Confirmatory Factor Analyses were performed on both the three-factor EFA and the EGA-derived models. The EGA model, as previously reported, demonstrated excellent fit. In comparison, the EFA-based model exhibited slightly weaker fit indices: $\chi^2(132) = 156.30$, p = 0.073; SRMR = 0.066; CFI (scaled) = 0.974; RMSEA (scaled) = 0.060; TLI (scaled) = 0.969. The Satorra-Bentler scaled chi-square difference test confirmed the statistical superiority of the EGA model ($\Delta\chi^2(3) = 20.998$, p < 0.001). This was corroborated by lower Akaike (AIC) and Bayesian (BIC) Information Criteria for the EGA model (AIC = 8689.38; BIC = 8830.75) compared to the EFA model (AIC = 8736.89; BIC = 8868.16), further indicating improved parsimony and model adequacy.

In contrast, the original three-dimensional structure proposed by Marin et al. was also tested but demonstrated substantially poorer fit: $\chi^2(87) = 248.63$, $p < 0.001$; SRMR = 0.090; CFI (scaled) = 0.916; RMSEA (scaled) = 0.111; TLI (scaled) = 0.899. These indices, particularly RMSEA and SRMR, fall below acceptable thresholds, suggesting that the original model inadequately represents the latent structure of the current dataset. Consequently, the EGA-derived model was identified as the most appropriate and parsimonious representation of apathy dimensions in this sample.

To assess the generalizability of the EGA-based model across clinical subpopulations, CFA was conducted separately within the Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) groups. In the MCI group (n = 77), the model exhibited acceptable fit: $\chi^2(129) = 181.88$, $p = 0.002$; SRMR = 0.081; CFI = 0.895; RMSEA = 0.073; TLI = 0.875. Despite the significant chi-square - likely influenced by sample size - the remaining indices indicated a satisfactory fit. In contrast, model fit was weaker in the AD group (n = 30): $\chi^2(129) = 190.37$, $p < 0.001$; SRMR = 0.111; CFI = 0.789; RMSEA = 0.126; TLI = 0.750. These results must be interpreted cautiously, given the small sample size, which can disproportionately affect fit indices, particularly RMSEA and SRMR. Multigroup Confirmatory Factor Analysis (MGCFA) demonstrated configural and metric invariance, suggesting structural stability and equivalence of factor loadings across groups. Scalar invariance was only marginally supported ($p = 0.088$), indicating that group comparisons of latent means should be approached with caution. Nonetheless, the findings support the conceptual stability of the EGA-derived structure across varying stages of cognitive decline.

Convergent and discriminant validity of the AES-C subscales were examined via Spearman correlations with external measures, including MMSE, MoCA, FAB, and HDRS. As illustrated in Figure 2, subscales of the EGA-derived model exhibited negative correlations with cognitive performance (MMSE, MoCA, FAB) and

positive correlations with both diagnostic group status and depression severity (HDRS), consistent with previous literature. These results confirm the scale's sensitivity to cognitive decline while also affirming the conceptual distinction between apathy and depressive symptoms.

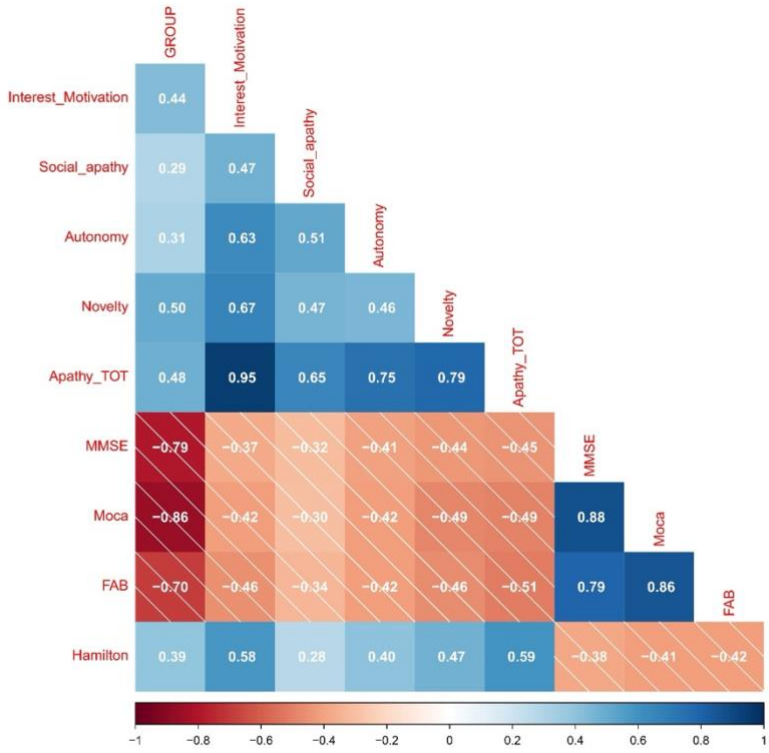

Figure 2. Spearman correlation matrix between the four EGA-derived subscales (Interests and motivation, Social apathy, Autonomy, Novelty) and the apathy evaluation scale total score, in relation to clinical and cognitive variables. These include the diagnostic group (categorical: 1 = Control, 2 = Mild Cognitive Impairment, 3 = Alzheimer's Disease), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), and Hamilton Depression Rating Scale (HDRS)[3]

[3] Taken from *Guerrera, Platania, Varrasi, Sarti, Boccaccio, Torre, Santagati, Furneri, Pirrone, Di Nuovo, Blom, Caraci, Castellano (2025). Investigating the multidimensional structure of apathy in cognitive decline: an exploratory network analysis of the Apathy Evaluation Scale. The American Journal of Geriatric Psychiatry. https://doi.org/10.1016/j.jagp.2025.07.010*

Non-parametric Kruskal-Wallis tests were conducted to evaluate group differences across AES-C subscales. Statistically significant differences emerged across all variables. Follow-up Dunn's post-hoc tests revealed that all pairwise comparisons between the control group (Group 1) and the clinical groups (Groups 2 and 3) were statistically significant. Comparisons between MCI and AD groups were significant for the Interests and Motivation and Novelty subscales. A summary of all pairwise comparisons and significance levels is provided in Figure 3, while group means, H statistics, and associated p-values are detailed in Table 2.

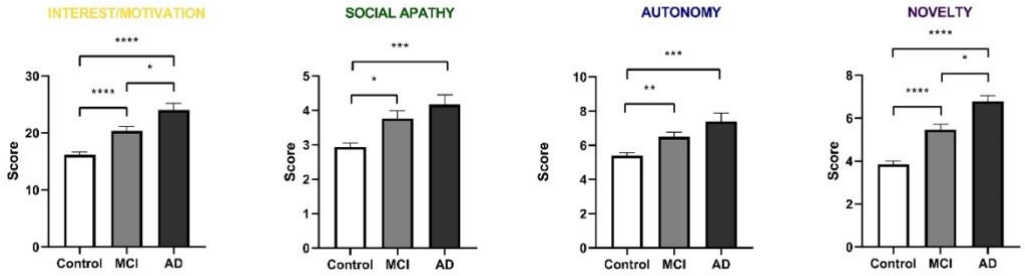

Figure 3: Multiple comparisons between the four-factor derived from the Exploratory graph analysis in the three study groups: control, MCI (mild cognitive impairment) and AD (Alzheimer's disease). The significance between the various groups was indicated according to the following scheme: $p < .05$ *; $p < .01$ **; $p < .001$ ***; $p < .0001$ ****. The colour of each title matches the group's colours in Figure 1[4]

EGA Factor	χ^2 (p)	Comparison	Mean difference	z	p-value
Interest and motivation	41.31 (<.0001)	Control vs MCI	-4.186	-40.61	<0,0001
		Control vs AD	-7.855	-74.08	<0,0001
		MCI vs AD	-3.669	-33.47	0.0356

[4] Taken from *Guerrera, Platania, Varrasi, Sarti, Boccaccio, Torre, Santagati, Furneri, Pirrone, Di Nuovo, Blom, Caraci, Castellano (2025). Investigating the multidimensional structure of apathy in cognitive decline: an exploratory network analysis of the Apathy Evaluation Scale. The American Journal of Geriatric Psychiatry. https://doi.org/10.1016/j.jagp.2025.07.010*

Social apathy	18.5 (<.0001)	Control vs MCI	-0.831	-23.5	0.0234
		Control vs AD	-1.232	-49.3	0.0002
		MCI vs AD	-0.4	-25.8	0.1289
Autonomy	20.7 (<0001)	Control vs MCI	-1.101	-28.2	0.0053
		Control vs AD	-2.007	-51.2	0.0001
		MCI vs AD	-0.906	-23	0.2321
Novelty	51.7 (<.0001)	Control vs MCI	-1.617	-46.2	<0,0001
		Control vs AD	-2.949	-84.2	<0,0001
		MCI vs AD	-1.332	-38	0.0115

Table 2. The table reports the results of Kruskal-Wallis tests (χ^2 and p-values) and Dunn's post-hoc pairwise comparisons (mean differences, z-scores, and adjusted p-values) for the four Exploratory graph analysis derived factors of the Apathy evaluation scale-Clinician version, across diagnostic groups: healthy subjects (control), mild cognitive impairment (MCI), and Alzheimer's disease (AD) patients[5]

4. Discussion

The present study aimed to apply Exploratory Graph Analysis (EGA) to the clinician-rated version of the Apathy Evaluation Scale (AES-C), with the objective of deriving an empirically grounded and clinically meaningful model of apathy. This novel, network-based methodology was compared with both the original three-factor model proposed by Marin et al. and an alternative structure derived through Exploratory Factor Analysis (EFA). The study particularly focused on populations affected by neurocognitive decline, including individuals with Mild

[5] Taken from *Guerrera, Platania, Varrasi, Sarti, Boccaccio, Torre, Santagati, Furneri, Pirrone, Di Nuovo, Blom, Caraci, Castellano (2025). Investigating the multidimensional structure of apathy in cognitive decline: an exploratory network analysis of the Apathy Evaluation Scale. The American Journal of Geriatric Psychiatry. https://doi.org/10.1016/j.jagp.2025.07.010*

Cognitive Impairment (MCI) and Alzheimer's Disease (AD), to assess the potential of EGA in capturing the multidimensional nature of apathy within these clinical contexts.

The EGA yielded a four-factor structure - Interest and Motivation, Social Apathy, Autonomy, and Novelty - which demonstrated superior model fit, parsimony, and psychometric properties when compared to both the EFA-derived solution and Marin's original model. In contrast to the EFA model, which revealed an unstable factor with weak item loadings, and to Marin's structure, which exhibited poor fit indices in the current clinical sample, the EGA model was characterized by high internal consistency, conceptual clarity, and robust statistical performance across subgroups. Importantly, each of the four emergent factors reflects core theoretical dimensions of apathy as a multidimensional construct. These findings support the utility of EGA in refining the operationalization of apathy and suggest that network-based methodologies may offer enhanced diagnostic and interpretative value in clinical assessment.

The multidimensional structure emerging from EGA aligns with a growing body of literature conceptualizing apathy as a heterogeneous syndrome encompassing cognitive, affective, behavioral, and social domains (Fahed & Steffens, 2021). Prior research has proposed various subtypes, such as executive dysfunction, emotional blunting, and behavioral inertia, each associated with distinct patterns of impairment in goal-directed behavior, social functioning, and cognitive engagement (Mortby et al., 2022). The present findings advance this framework by offering an empirically derived, clinically interpretable model that consolidates and refines these theoretical categories.

Specifically, the Interest and Motivation factor captures core motivational deficits and disturbances in goal-directed behavior that are central to apathy (Kotwal et al., 2024). The Autonomy factor reflects a diminished sense of self-agency and volition, which is particularly relevant given its implications for decision-making

and self-initiated action. Reduced autonomy frequently leads to greater functional dependence, underscoring its clinical relevance. The Novelty dimension highlights a decreased engagement in new or stimulating experiences - an aspect often overlooked but theoretically consistent with apathy's attenuation of exploratory behavior. Lastly, Social Apathy denotes a lack of interest in social interaction, reflecting the social withdrawal frequently observed in individuals with apathy. Collectively, these dimensions offer a nuanced framework capable of capturing the domain-specific impairments observed in clinical settings (Cheng et al., 2024; Njomboro & Lekhutlile, 2024).

When compared to recent models, the EGA-derived structure demonstrated stronger psychometric performance. For instance, the best-fitting model reported by Furneri et al. (Model 1) exhibited adequate but inferior fit indices (SRMR = 0.05; RMSEA = 0.064; CFI = 0.93; TLI = 0.92) relative to the present EGA solution. This comparison underscores the potential advantages of network-based approaches in psychometric modeling, particularly in capturing the complex and interconnected nature of neuropsychiatric syndromes such as apathy.

The EGA model also demonstrated satisfactory generalizability across clinical subpopulations. Despite minor reductions in fit indices within the MCI and AD groups, particularly with respect to SRMR, overall model performance remained within acceptable thresholds. Convergent and discriminant validity were supported by significant associations between EGA-derived subscales and independent cognitive and affective measures. Specifically, higher apathy scores were consistently associated with lower cognitive performance (MMSE, MoCA, FAB) and increased depressive symptomatology (HDRS), corroborating previous findings in the literature. Furthermore, apathy severity increased along the continuum of cognitive decline, with AD patients showing significantly greater

impairments than both controls and MCI individuals, especially on the Interest and Motivation and Novelty subscales.

These results suggest that certain dimensions of apathy may be particularly sensitive to disease progression. The fact that only the Interest and Motivation and Novelty factors differentiated AD from MCI patients indicates that these domains may serve as potential markers for the advancement of neurodegeneration (Bastin et al., 2019; Daffner et al., 1999). Such findings have implications for both diagnostic refinement and intervention design. For instance, patients with high scores on Novelty may benefit from behavioral activation interventions that promote engagement in novel experiences, whereas those with elevated Social Apathy may require social-based interventions aimed at enhancing interpersonal engagement. Moreover, this dimensional approach can aid clinicians in distinguishing primary apathy - characterized by intrinsic motivational deficits - from secondary forms of apathy arising in the context of depression or cognitive impairment (Kirkpatrick, 2014). Given the symptomatic overlap between these conditions, such differentiation is essential for improving diagnostic accuracy, guiding treatment decisions, and anticipating functional decline.

These findings are also consistent with recent network analyses, such as that conducted by Sarti et al. (Sarti, Surbeck, et al., 2025), which identified abulia and diminished initiative as central symptoms in AD, closely tied to reduced novelty-seeking behaviors - a domain captured robustly in the current model.

Despite the strengths of this study, several limitations should be acknowledged. First, the Social Apathy and Novelty dimensions were composed of only two items each. While internal consistency estimates were acceptable, and even Marin's original model included a domain (Emotional Apathy) with just two items, the limited number of items may constrain the breadth and stability of these

constructs. Future research should prioritize the development and validation of additional items to enrich these domains and enhance scale reliability.

Second, the clinical groups were uneven in size, with a notably smaller sample in the AD group compared to the MCI cohort. This imbalance may have reduced the statistical power of certain between-group comparisons and limited the generalizability of subgroup-specific findings. Future studies should aim for more balanced and adequately powered samples to validate and extend the current results.

Lastly, while the EGA-derived model exhibited strong fit across the overall and subgroup samples, slightly elevated SRMR values suggest that minor model misfit may still be present. Further model refinement and cross-validation in larger, demographically diverse populations are warranted to confirm the stability and applicability of the structure.

5. Conclusion

The application of EGA to the AES-C enabled a refined conceptualization of apathy, transcending a simplistic view of motivational deficit and revealing a multifaceted syndrome that impairs autonomy, novelty-seeking, social engagement, and intrinsic drive. This dimensional structure not only aligns with theoretical models but also offers clinically actionable insights, enhancing the assessment and treatment of apathy in neurodegenerative disorders. The model's robustness was supported through internal consistency, confirmatory factor analysis, and validity testing. Future research should aim to expand the item base for each domain and validate this structure across broader and more heterogeneous populations to solidify its utility in both clinical and research settings.

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CHAPTER FOUR

Assessing the clinical efficacy of cholinesterase inhibitors

and uncovering the predictors of therapeutic response

in mild Alzheimer's disease

Preface

This fourth chapter presents a longitudinal pilot study designed to address two interrelated challenges in the clinical management of mild Alzheimer's disease (AD): the selection of the most sensitive psychometric instruments for monitoring therapeutic efficacy, and the identification of affective risk factors that may shape cognitive outcomes.

By following patients over six- and nine-month intervals, the research examines not only the cognitive effects of pharmacological intervention but also the predictive role of baseline depressive symptoms on subsequent cognitive trajectories. This dual focus underscores the necessity of moving beyond a rigid and compartmentalized view of risk factors, where cognitive and affective domains are considered in isolation, toward a more integrated, multidimensional framework that recognizes their interaction in influencing therapeutic response.

On the one hand, this chapter offers evidence to guide the selection of outcome measures in pharmacological trials, highlighting the advantages of sensitive, domain-spanning instruments. On the other, it reinforces the importance of assessing and addressing affective symptoms, not merely as comorbid features but as potential modulators of treatment efficacy.

1. Introduction

Currently approved pharmacological treatments for Alzheimer's Disease (AD), including cholinesterase inhibitors (ChEIs), primarily offer symptomatic relief by decelerating the progression of cognitive decline (Howard et al., 2015). In this context, evaluating individual responses to ChEI therapy is essential to inform personalized treatment strategies. A recent meta-analysis (Knight et al., 2018) highlighted the widespread use of the Mini-Mental State Examination (MMSE) (Magni et al., 1996) as a primary tool for assessing the cognitive effects of ChEIs in dementia populations. However, the same study underscored the psychometric limitations of the MMSE, particularly its partial convergent validity and susceptibility to floor and ceiling effects (Knight et al., 2018). These findings highlight the necessity of incorporating additional assessment tools to more comprehensively evaluate the clinical efficacy of ChEI treatment in AD.

The Montreal Cognitive Assessment (MoCA) (Santangelo et al., 2015), for example, is a global cognitive screening instrument that has demonstrated superior sensitivity and specificity in detecting Mild Cognitive Impairment (MCI). Furthermore, the inclusion of measures targeting specific cognitive domains and neuropsychiatric symptoms - especially executive functions (Junquera et al., 2020) and affective disturbances such as depression (Platania et al., 2023) - may provide a more nuanced understanding of a patient's intrinsic functional capacity (López-Ortiz et al., 2024).

Within this clinical framework, emerging evidence focuses on the role of Major Depressive Disorder (MDD) as a relevant risk factor for both the onset and progression of AD (Herbert & Lucassen, 2016). Depression may contribute not only to the prodromal manifestations of dementia, but also to its overall clinical trajectory. On these grounds, depressive symptomatology might influence both disease onset, and the cognitive responsiveness to standard pharmacological treatments.

Therefore, the present pilot study aimed both to 1) compare the effectiveness of the MMSE, MoCA, Frontal Assessment Battery (FAB) (Appollonio et al., 2005), and Hamilton Depression Rating Scale (HDRS) (Fava et al., 1982) in capturing cognitive and affective changes associated with ChEI therapy in individuals with mild AD, and 2) to investigate the potential impact of baseline depressive symptoms on those patients' cognitive outcome to ChEIs.

To this end, a cohort of 33 patients was assessed at baseline (T0), prior to the initiation of pharmacological treatment, and at follow-up (T1) after either 6 months (Group 1) or 9 months (Group 2) of continuous drug administration.

2. Materials and Methods

2.1 Participants

The study sample comprised 33 individuals diagnosed with mild Alzheimer's Disease (AD), who were recruited from the U.O.S. Centro Alzheimer e Psicogeriatria, ASP3, in Catania, Italy. The diagnosis of probable AD was established in accordance with the criteria outlined by the National Institute on Aging and the Alzheimer's Association (NIA-AA) (McKhann et al., 2011). Inclusion criteria required an age- and education-adjusted Mini-Mental State Examination (MMSE) score ranging from 16 to 25, while exclusion criteria included the presence of comorbid neurological or psychiatric disorders that could confound cognitive performance.

Participants were stratified into two subgroups based on the duration of follow-up: Group 1 (n = 17) underwent neuropsychological assessment at baseline (T0) and after six months of ChEI treatment (T1); Group 2 (n = 16) was assessed at baseline (T0) and following nine months of treatment (T1). Demographic and clinical characteristics of the sample are presented in Table 1.

	No.	Age (Mean ± SD)	Years of Education (Mean ± SD)	Sex	
Group 1	17	76.29 ± 6.87	7.29 ± 3.39	*Females*	14
				Males	3
Group 2	16	76.38 ± 5.965	9.19 ± 5.72	*Females*	11
				Males	5

Table 1. Demographic characteristics of the samples[1]

2.2 Procedure

The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and adhered to the guidelines of the Italian Association of Psychology (AIP). Ethical approval was obtained from the Internal Review Board of the Department of Educational Sciences (Section of Psychology) at the University of Catania (protocol Ierb-Edunict-2023.05.23/02). All participants provided written informed consent prior to their inclusion in the study.

Neuropsychological assessments were administered by a trained neuropsychologist at two time points - prior to the initiation of pharmacological treatment (T0) and after 6 or 9 months of continuous therapy with cholinesterase inhibitors (T1). Each assessment session lasted approximately 20 minutes. All patients received either donepezil (10 mg/day) or rivastigmine transdermal

[1] Taken from: *Furneri, Varrasi, Guerrera, Platania, Torre, Boccaccio, Testa, Martelli, Privitera, Razza, Santagati, Di Nuovo, Pirrone, Castellano, Caraci, Monastero (2024). Combining Mini-Mental State Examination and Montreal Cognitive Assessment for assessing the clinical efficacy of cholinesterase inhibitors in mild Alzheimer's Disease: a pilot study. Aging Clinical and Experimental Research, 36(95). https://doi.org/10.1007/s40520-024-02744-4*

patch (9.5 mg/day) for the duration of the treatment period corresponding to their assigned group.

2.3 Measures

The psychometric battery administered at both T0 and T1 included the following standardized instruments, all in their validated Italian versions:

- Mini-Mental State Examination (MMSE) (Magni et al., 1996) – a widely used screening tool for global cognitive functioning;
- Montreal Cognitive Assessment (MoCA) (Santangelo et al., 2015) – a more sensitive measure of global cognition, particularly effective in detecting mild cognitive impairment;
- Frontal Assessment Battery (FAB) (Appollonio et al., 2005) – an instrument designed to evaluate executive functioning;
- Hamilton Depression Rating Scale (HDRS) (Fava et al., 1982) – employed to assess the severity of depressive symptoms.

2.4 Statistical Analyses

Given the modest sample size and the non-normal distribution of some variables, non-parametric statistical analyses were conducted using IBM SPSS Statistics, version 27. Between-group comparisons were performed using the Mann–Whitney U test, while within-subject changes from T0 to T1 were assessed using the Wilcoxon signed-rank test. Changes in cognitive and affective measures were analyzed separately for each group, corresponding to the 6- and 9-month treatment intervals. Cognitive and affective changes were operationalized as delta scores (Δ = T1 – T0) on the administered tests. Linear regression analyses were conducted to evaluate the predictive role of baseline depressive symptoms on cognitive outcomes, provided that model assumptions were met. Statistical

significance was defined as $p < 0.05$, and effect sizes were calculated to estimate the magnitude of observed differences.

3. Results

At baseline (T0), no statistically significant differences were observed between Group 1 and Group 2 with respect to global cognitive functioning, executive functioning, depressive symptoms, or educational attainment. Specifically, scores on the Mini-Mental State Examination (MMSE; $U = 126$, $p = 0.73$, $r_g = 0.07$), Montreal Cognitive Assessment (MoCA; $U = 132$, $p = 0.90$, $r_g = 0.02$), Frontal Assessment Battery (FAB; $U = 129$, $p = 0.81$, $r_g = 0.05$), and Hamilton Depression Rating Scale (HDRS; $U = 126$, $p = 0.73$, $r_g = 0.07$) did not differ significantly between the two groups. Similarly, the groups were comparable in terms of years of education ($U = 119$, $p = 0.51$, $r_g = 0.12$).

The impact of cholinesterase inhibitor treatment on cognitive and affective measures was then assessed separately for each group. In Group 1, which underwent evaluation after six months of treatment, within-group comparisons between T0 and T1 revealed no statistically significant changes in MMSE or FAB scores, indicating stability in global and executive cognitive performance over the treatment period (Table 2). Conversely, a statistically significant decline was observed in MoCA scores from T0 to T1, suggesting a reduction in overall cognitive efficiency despite pharmacological intervention. No significant changes were found in HDRS scores, indicating that ChEI treatment had no measurable effect on depressive symptoms in this group.

Measure	Baseline (T_0) Mean ± SD	6 months (T_1) Mean ± SD	Wilcoxon W	p	r_c
MMSE	20.42 ± 2.278	21.34 ± 3.291	20	0.143	-0.48
MoCA	16.47 ± 3.815	14.58 ± 4.634	75	0.042	0.64
FAB	10.65 ± 3.457	9.765 ± 3.413	88.5	0.11	0.47
HDRS	12.12 ± 7.999	10.47 ± 6.463	62.5	0.247	0.37

Table 2. Descriptive statistics and changes in Group 1[2]

In Group 2, assessed after nine months of ChEI therapy, statistically significant improvements were observed across all cognitive measures. Specifically, significant differences were found between T0 and T1 scores on the MMSE, MoCA, and FAB, with the MMSE showing the greatest level of significance, followed by the FAB and MoCA (Table 3). These results suggest a broader cognitive benefit of extended ChEI treatment in individuals with mild AD. As with Group 1, no significant differences were found in HDRS scores, indicating the absence of treatment effects on depressive symptoms in this cohort as well.

Measure	Baseline (T_0) Mean ± SD	9 months (T_1) Mean ± SD	Wilcoxon W	p	r_c
MMSE	20.47 ± 2.6	17.72 ± 2.241	136	< 0.001	1.0
MoCA	16.14 ± 3.3	12.94 ± 3.431	108	0.007	0.8
FAB	10.93 ± 2.718	8.363 ± 2.957	110	0.005	0.83
HDRS	12.94 ± 7.672	13.56 ± 10.88	61.5	0.755	-0.09

Table 3. Descriptive statistics and changes in Group 2[3]

[2] Taken from: *Furneri, Varrasi, Guerrera, Platania, Torre, Boccaccio, Testa, Martelli, Privitera, Razza, Santagati, Di Nuovo, Pirrone, Castellano, Caraci, Monastero (2024). Combining Mini-Mental State Examination and Montreal Cognitive Assessment for assessing the clinical efficacy of cholinesterase inhibitors in mild Alzheimer's Disease: a pilot study. Aging Clinical and Experimental Research, 36(95). https://doi.org/10.1007/s40520-024-02744-4*

[3] Taken from: *Furneri, Varrasi, Guerrera, Platania, Torre, Boccaccio, Testa, Martelli, Privitera, Razza, Santagati, Di Nuovo, Pirrone, Castellano, Caraci, Monastero (2024). Combining Mini-Mental State Examination and Montreal Cognitive Assessment for assessing the clinical efficacy of*

Linear regression analysis revealed that baseline HDRS scores significantly predicted cognitive response to ChEI treatment, but only at six months and only when cognitive functioning was assessed via the MoCA [$F(1,15) = 5.04$, $p < .05$; adjusted $R^2 = 0.20$]. Specifically, higher baseline depressive symptoms were associated with greater cognitive decline ($\beta = -0.50$, $t = -2.20$, $SE = 0.09$, $p < .05$).

4. Discussion

Despite the widespread use of cholinesterase inhibitors (ChEIs) in the clinical management of Alzheimer's Disease (AD), there remains a notable paucity of empirical data on the validity and sensitivity of alternative cognitive assessment tools - specifically the Montreal Cognitive Assessment (MoCA) and the Frontal Assessment Battery (FAB) - for monitoring pharmacological response (Ismail et al., 2020). Moreover, the role of well-established risk factors for cognitive deterioration towards drug response needs to be fully understood. In light of these gaps, the present pilot study aimed to examine the utility of MoCA and FAB in comparison to the Mini-Mental State Examination (MMSE) in detecting cognitive changes associated with ChEI treatment in patients with mild AD. Additionally, the study explored whether the Hamilton Depression Rating Scale (HDRS) could capture changes in affective symptoms following pharmacological intervention, and whether the severity of depressive symptoms could predict the cognitive response to ChEIs.

To ensure methodological robustness, preliminary analyses confirmed the equivalence of the two patient groups at baseline (T0) with respect to cognitive status, depressive symptomatology, and educational background.

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The analysis of data from Group 1, assessed at a 6-month follow-up, revealed no statistically significant changes in MMSE or FAB scores following ChEI administration. Interestingly, a significant decline in MoCA scores was observed, suggesting that this instrument may be more sensitive in detecting subtle cognitive changes - particularly early declines - than either the MMSE or the FAB (Boccardi et al., 2021; Limongi et al., 2019). This finding was reinforced by the results obtained from Group 2, assessed at a 9-month follow-up, which demonstrated statistically significant reductions in performance across all cognitive measures (MMSE, MoCA, and FAB). Notably, the MMSE exhibited the highest degree of statistical significance, followed by the FAB and MoCA. In both groups, HDRS scores remained unchanged, indicating that ChEI treatment did not appear to influence affective symptomatology over the short-to-intermediate term.

These findings are largely consistent with existing literature. For instance, Ciesielska et al. (Ciesielska et al., 2016) concluded that MoCA is superior to the MMSE in detecting mild cognitive impairment (MCI), a result supported by further studies highlighting MoCA's enhanced diagnostic accuracy not only for MCI but also for the early stages of AD (Aiello et al., 2022). Cecato et al. (Cecato et al., 2017), in a cross-sectional study of 136 elderly individuals, demonstrated that specific MoCA subtests (e.g., rhino naming, serial 7s, clock drawing, word recall, and orientation) effectively differentiated MCI from AD, supporting MoCA's broader diagnostic utility.

Moreover, the MoCA has been shown to be a sensitive tool for tracking subtle cognitive changes in various therapeutic contexts, including electroconvulsive therapy (Hebbrecht et al., 2020) and pharmacological treatment with second-generation antidepressants (Guerrera et al., 2023). The findings of the present study contribute to and extend this body of evidence, suggesting that MoCA may be particularly well-suited for evaluating cognitive response to ChEIs in patients

with mild AD, especially during the initial six months of treatment. One possible explanation for MoCA's superior sensitivity lies in its broader cognitive coverage, including executive functions, which are not comprehensively assessed by the MMSE and only partially captured by the FAB (De Roeck et al., 2019).

Additionally, the results suggest that depressive symptoms may not only co-occur with cognitive impairment but also modulate therapeutic response. This interplay between mood and cognitive domains points to the potential involvement of shared neurobiological mechanisms underlying both symptom clusters (dos Santos et al., 2024). Consequently, a more holistic assessment that integrates both cognitive and affective dimensions may enhance treatment planning and outcome prediction in individuals with mild AD.

Recent network-based investigations of neuropsychiatric symptoms in Alzheimer's disease and related disorders corroborate the importance of transdiagnostic symptom interactions (e.g., apathy, depression, sleep disturbance) and identify central/bridge symptoms that appear to influence both cognitive and functional trajectories. These analyses strengthen the rationale for treating apathy as a central, prognostically meaningful construct and justify the application of network metrics (centrality, bridge centrality) to detect intervention targets. In the same vein, longitudinal cohort and registry studies published in the last few years confirm that baseline affective burden (including depressive symptom severity) predicts adverse cognitive trajectories and treatment responsiveness, supporting the inclusion of HDRS-derived indices as moderators in pharmacological outcome models (Goodwin at al., 2023; Tosi et al., 2024).

The primary strength of this pilot study lies in its comparative design, evaluating multiple cognitive assessment tools over two distinct follow-up intervals. Nevertheless, several methodological limitations must be acknowledged. First, the relatively small sample size limits the generalizability of the findings and

reduces statistical power, particularly in detecting changes in depressive symptoms. Second, not all participants underwent comprehensive baseline neuropsychological assessment, thereby limiting the possibility of evaluating which specific cognitive domains were most effectively captured by MoCA relative to MMSE. Third, the relatively short follow-up periods may not adequately reflect long-term cognitive trajectories or delayed treatment effects. As such, favorable cognitive responses observed at 6 or 9 months may not persist over time, and potential adverse effects associated with prolonged ChEI use may remain undetected.

Furthermore, while diagnoses of probable AD were established according to standardized criteria, the possibility of residual confounding - such as medical comorbidities or concurrent pharmacological treatments - cannot be entirely excluded. Future research should incorporate larger samples, randomized controlled designs, and extended follow-up periods to more precisely evaluate the utility of MoCA and other tools in tracking treatment outcomes.

5. Conclusion

The results of this pilot study support the use of the Montreal Cognitive Assessment (MoCA) as a preferred tool for evaluating the cognitive effects of ChEI treatment in individuals with mild Alzheimer's Disease. The data suggest that MoCA may provide a more nuanced and sensitive measure of cognitive change than the MMSE or FAB, particularly during the initial stages of pharmacological intervention. Given the clinical importance of early detection and treatment in AD, the incorporation of MoCA as a standard outcome measure in future clinical trials appears both justified and beneficial. In clinical practice, the combined use of MMSE and MoCA may enhance diagnostic accuracy and facilitate more tailored therapeutic strategies, thereby potentially improving patient outcomes and

quality of life. Finally, the analysis of affective symptoms should be always included, as they seem to contribute to the overall cognitive outcome of pharmacological treatment.

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CHAPTER FIVE

Human and artificial support in cognitive load management: age differences across behavioral, subjective, and physiological measures

Preface

Following the preceding chapters - primarily focused on theoretical frameworks, prevention strategies, and clinical dimensions - this final chapter shifts the attention to the challenge of preserving daily autonomy through the support of emerging technologies. Rather than limiting the analysis to the construct of technological acceptability, it addresses a more complex and functionally relevant dimension: cognitive load, a pivotal factor in maintaining autonomy in aging.

Through a multimodal assessment combining objective performance metrics, subjective workload evaluations, and physiological indicators, the study compares independent task execution with human-assisted and robot-assisted support under varying cognitive demands. This approach moves beyond user preference to explore how different types of assistance interact with cognitive resources, potentially facilitating or hindering performance.

In doing so, the chapter bridges technological innovation and cognitive ergonomics, offering insights for designing adaptive, user-centered assistive solutions capable of supporting autonomy without imposing excessive mental demands - an essential step toward sustainable and meaningful aging.

1. Introduction

Independent living represents a central objective in the pursuit of active aging (Illario et al., 2016). Managing daily activities with appropriate support has garnered the attention of specialists across disciplines, particularly given the projected increase in the average age of the global population in the coming years (Vollset et al., 2024). This demographic shift will necessitate targeted interventions to foster a positive quality of life among older adults.

Advancements in technology have made significant contributions toward this goal. Intelligent systems can now be integrated into home environments, while embodied agents can be programmed to interact with users to achieve collaborative objectives (Di Nuovo et al., 2016). Within this context, Socially Assistive Robotics (SAR) specifically leverages human-robot interaction (HRI) to facilitate these tasks and promote daily autonomy (Karami et al., 2024). However, recent studies have demonstrated that enabling user communication with an artificial agent alone is insufficient to ensure effective interaction, particularly within vulnerable populations such as older adults. Several barriers, including platform acceptability, usability, and cognitive ergonomics, can hinder the successful adoption of these technologies (Luo et al., 2024; Nebe & Heimgärtner, 2024).

From the perspective of cognitive ergonomics, cognitive load (CL) emerges as a critical factor influencing the effectiveness of HRI (Rajavenkatanarayanan et al., 2020). Theoretically, CL is defined as the number of mental resources required to manage a given task (Orru & Longo, 2019). As these cognitive resources are inherently limited, individuals must allocate them strategically across a finite set of activities (Ghanbari et al., 2020).

Furthermore, CL is not a unitary construct but consists of distinct components: intrinsic, extraneous, and germane load. Intrinsic CL arises from the inherent

complexity of the task itself and is influenced by the volume of information that must be processed. Extraneous CL relates to the way information is presented and the presence of external distractions, both of which can be mitigated through effective task design and presentation. Germane cognitive load is associated with the learning processes that support schema development. Recent theoretical frameworks (Choi et al., 2014; Kalyuga, 2011) propose an integration of intrinsic and germane load, emphasizing intrinsic and extraneous load as the two primary dimensions of cognitive load theory (Korbach et al., 2018).

Multiple studies have indicated that older adults experience greater challenges in managing CL, which in turn affects their autonomy (MacPherson, 2019). This difficulty is likely attributable to age-related declines in cognitive functioning, leading to increased fatigue and difficulties in completing daily tasks (Montine et al., 2021). These challenges are also evident in the use of technology, where the additional processing demands of interacting with complex interfaces contribute to heightened CL (Bertolazzi et al., 2024; Schroeder et al., 2023). Importantly, older adults' attitudes toward advanced technologies are shaped not only by cultural and social factors but also by specific cognitive needs and the degree of customization available within technological systems (Ghorayeb et al., 2021). Failure to account for these needs risks imposing additional burdens on users, counteracting the original intent of simplifying their daily activities.

Therefore, it is essential to determine whether technological implementation increases users' cognitive load, to identify the specific features responsible for such increases, and to examine differences across age groups. Gaining these insights is crucial for designing adaptive interfaces that dynamically respond to users' cognitive needs. However, the current literature exhibits several limitations in addressing these issues.

First, assessing CL during technology use without a baseline comparison precludes the ability to draw reliable conclusions. It is thus necessary to design

studies that compare technology-supported performance with performance completed independently, enabling a clear evaluation of the advantages and disadvantages associated with technological aids. A seminal piece of work supporting this was proposed by Varrasi et al. (Varrasi et al., 2025). Additionally, demonstrating a positive impact of technology without including a condition involving human support lacks methodological rigor; multiple aid conditions should be tested for comprehensive analysis. Furthermore, hypothesizing user needs without conducting comparative analyses across different age groups limits the development of genuinely person-centered support systems, underscoring the need for stratified samples to facilitate between-group analyses and the identification of unique population profiles. Finally, the reliance on limited cognitive load measures constrains the validity of findings, emphasizing the importance of integrating multiple assessment methods.

Cognitive load can be evaluated using a range of objective, subjective, and physiological metrics, each offering distinct insights into the cognitive demands imposed on individuals. Objective metrics include performance-based measures such as accuracy, error rates, and task completion times, providing quantifiable indicators of cognitive effort (Korbach et al., 2017). Subjective metrics capture self-reported perceptions of mental workload, encompassing dimensions such as perceived effort, frustration, and mental demand (Ayres, 2017). Physiological metrics, including heart rate variability, pupil dilation, circulating cortisol concentrations, and electroencephalographic (EEG) activity, reflect physiological responses associated with cognitive effort and stress (Haapalainen et al., 2010). The integration of these assessment methods enables a comprehensive understanding of cognitive load, supporting the evaluation of task design and learning efficiency.

Given these considerations, the present study aims to address the aforementioned limitations in the literature. The primary objective is to examine

whether, and in what ways, human-robot interaction (HRI) and human-human interaction (HHI) can support the management of CL during a cognitive task, with particular attention to differences between adults and older adults. This general aim is further supported by the inclusion of a baseline condition in which participants complete the task independently, allowing for the assessment of the specific benefits and drawbacks of each type of support. Additionally, to ensure a comprehensive and valid assessment, the study employs multiple measures of CL, including objective, subjective, and physiological metrics.

2. Materials and Methods

2.1 Participants

The study sample comprised 60 adult volunteers, including 30 younger adults (13 males, 17 females; mean age = 34.8 ± 10.1 years) and 30 older adults (12 males, 18 females; mean age = 72.3 ± 5.49 years), with sex matching confirmed ($\chi^2(2) = 0.068$, $p = 0.793$). Younger adult participants were recruited from the student and staff population of Nottingham Trent University (Nottingham, United Kingdom), with eligibility defined as ages 18 to 65 years. Older adult participants consisted of community-dwelling individuals from the same urban area, matched by sex. All participants were screened to ensure they were in good health, as the study exclusively included healthy individuals.

2.2 Ethical considerations and tools

The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. Ethical approval was obtained from the Nottingham Trent University Board with reference number 729 in March 2024. All participants provided written informed consent prior to their inclusion in the study.

The cognitive task employed in this study was adapted from the B form of the Trail Making Test (TMT) (Bowie & Harvey, 2006). The TMT was selected over alternative cognitive measures due to its demand on multiple cognitive domains, including attention, visual search, executive functioning, and working memory. As such, it requires participants to engage multiple cognitive skills simultaneously, closely mirroring the complexity of everyday tasks.

Specifically, the task involved a 29.7 × 42 cm paper sheet displaying 52 randomly distributed circles (Figure 1). Half of the circles contained English letters (A-Z), while the remaining circles contained numbers (1-26). Seven parallel forms of the task, each with a different random arrangement of circles, were developed to correspond to the seven experimental conditions of the study. Objective performance was assessed through the number of correctly connected pairs and the time required to complete the task (in seconds).

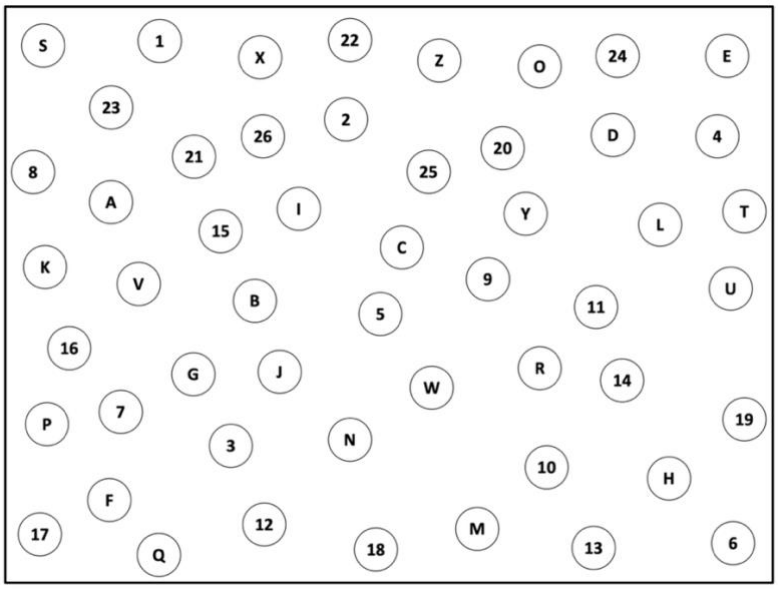

Figure 1. Example of the cognitive task sheet completed by the participants[1]

[1] Taken from *Varrasi, Vagnetti, Camp, Hough, Di Nuovo, Castellano, Magistro (2025). How human-robot interaction can influence task performance and perceived cognitive load at different support conditions. Information, 16(5), 374. https://doi.org/10.3390/info16050374*

As the supportive agent, the NAO 6 humanoid robot (United Robotics Group, Santa Monica, CA, USA) was utilized. This platform was selected due to its commercial availability and its capabilities aligned with the study's requirements, including speech production, speech recognition, and the ability to engage in social interactions. Previous research has identified NAO as a socially assistive robot that is generally well-received by older and vulnerable populations (Montine et al., 2021). The robot stands 58 cm tall and is capable of interacting using speech, gestures, and facial tracking. Programming was conducted using Choregraphe software (version 2.8.7) in conjunction with Python to facilitate interactive collaboration with participants in three of the seven study conditions.

The robot's behavior was structured using block-based visual programming with a node flow interface. Interaction commenced with the NAO tracking the participant's face to simulate eye contact, introducing itself, and delivering initial task instructions. Speech recognition was enabled to allow the robot to repeat instructions upon the participant's request during the initial interaction phase, which served as a vocal familiarization period adaptable to participant feedback. Following this initial phase, the NAO refrained from repeating instructions to avoid interfering with task performance, although speech recognition remained active to manage the pacing and turn-taking during interaction. The NAO advanced to subsequent task steps when the participant verbally indicated readiness using phrases such as "Okay" or "Done". A detailed flowchart of the interaction procedure is provided in Figure 2.

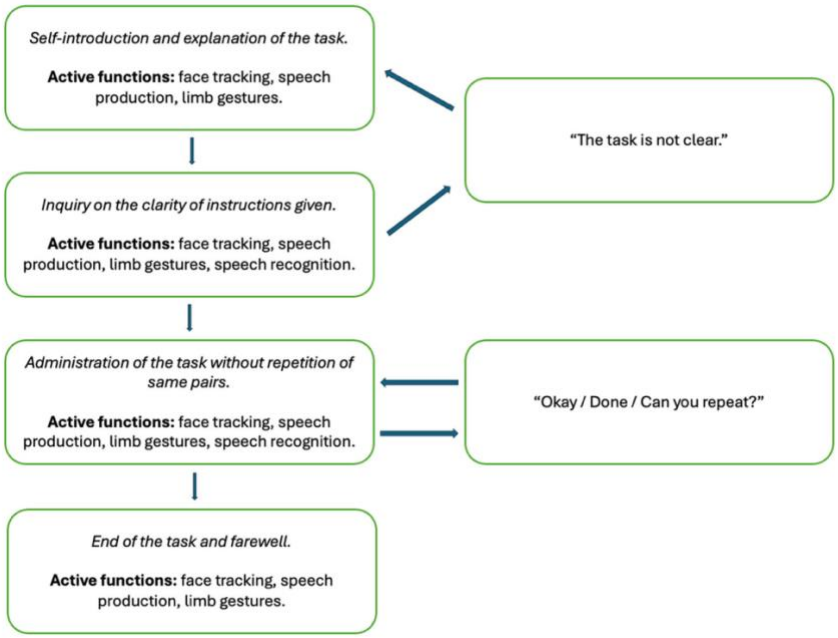

Figure 2. Flowchart of the interaction with the robot[2]

Perceived cognitive load (PCL) was assessed using the NASA Task Load Index (NASA-TLX) (Hart, 2006), a rapid, self-administered psychometric instrument evaluating six dimensions: Mental Demand, Physical Demand, Temporal Demand, Performance, Effort, and Frustration. Each dimension is rated on a 20-point scale, with higher scores reflecting greater perceived strain. The NASA-TLX was selected due to its strong psychometric properties and demonstrated superiority over alternative subjective workload measures (Devos et al., 2020), making it well-suited for assessing perceived cognitive load in this study.

In order to objectively measure the physiological stress response to the CL tasks, a saliva sample was taken immediately before and after each condition (i.e. robot-assisted and human-assisted conditions). Samples were collected utilizing a synthetic swab (Salivette® Cortisol, Sarstedt, Leicester, UK), asking the

[2] Taken from *Varrasi, Vagnetti, Camp, Hough, Di Nuovo, Castellano, Magistro (2025). How human-robot interaction can influence task performance and perceived cognitive load at different support conditions. Information, 16(5), 374. https://doi.org/10.3390/info16050374*

participant to slowly move the swab around their mouth for 2 minutes, following manufacturer guidance. After collection, all samples were kept on crushed ice during the entire period of testing, which did not exceed 45 minutes. Saliva samples were then centrifuged at 1,000 x *g* for 2 minutes (Espresso Microcentrifuge, Thermo Scientific, Loughborough, UK) and the supernatant was transferred into 1.5 mL aliquots in Eppendorf tubes (Eppendorf, Hamburg, Germany) and were stored at -80°C until further analysis. Quantitative determination of salivary cortisol concentrations was analyzed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Salimetrics, PA 16803, USA) following the manufacturer's recommended procedures.

2.3 Procedure

Each participant completed the experimental protocol individually across seven conditions: a baseline condition completed independently, three robot-assisted conditions at varying cognitive load levels (low, medium, and high), and three human-assisted conditions at corresponding cognitive load levels (low, medium, and high). The sequence of robot-assisted and human-assisted conditions was alternated and counterbalanced across participants to control for order effects. The entire session lasted approximately 30 minutes.

Following the provision of informed consent, participants were seated at a desk and presented with the first task sheet. In the baseline condition (first condition), participants were instructed to connect pairs of numbers and letters in reverse order (i.e., starting from the highest number and the last letter) as quickly as possible using a marker. This task was designed to induce cognitive load by engaging semantic memory, working memory, visual search, and processing speed. Specifically, participants were required to rapidly recall the reverse sequence of letters and numbers, maintain this information in working memory, and identify and connect the corresponding circles on the sheet.

During the three robot-assisted conditions, the NAO humanoid robot served as an interactive support agent (Figure 3). At the onset of each assisted condition, the robot greeted the participant, explained the task, and repeated the instructions upon request. Throughout the task, the robot verbally provided the pairs of circles to be connected, thereby reducing reliance on semantic memory and allowing participants to focus on visual search and motor execution. The robot waited for participants to complete each connection and to verbally confirm with "Okay" before announcing the next pair. To mitigate potential learning effects, the order of the pairs was randomized across trials. Cognitive load was manipulated as follows: in the low-load condition (second/fifth condition), the robot announced one pair at a time; in the medium-load condition (third/sixth condition), two to four pairs were provided at a time; and in the high-load condition (fourth/seventh condition), five to seven pairs were delivered simultaneously. The pairs were never repeated by the robot.

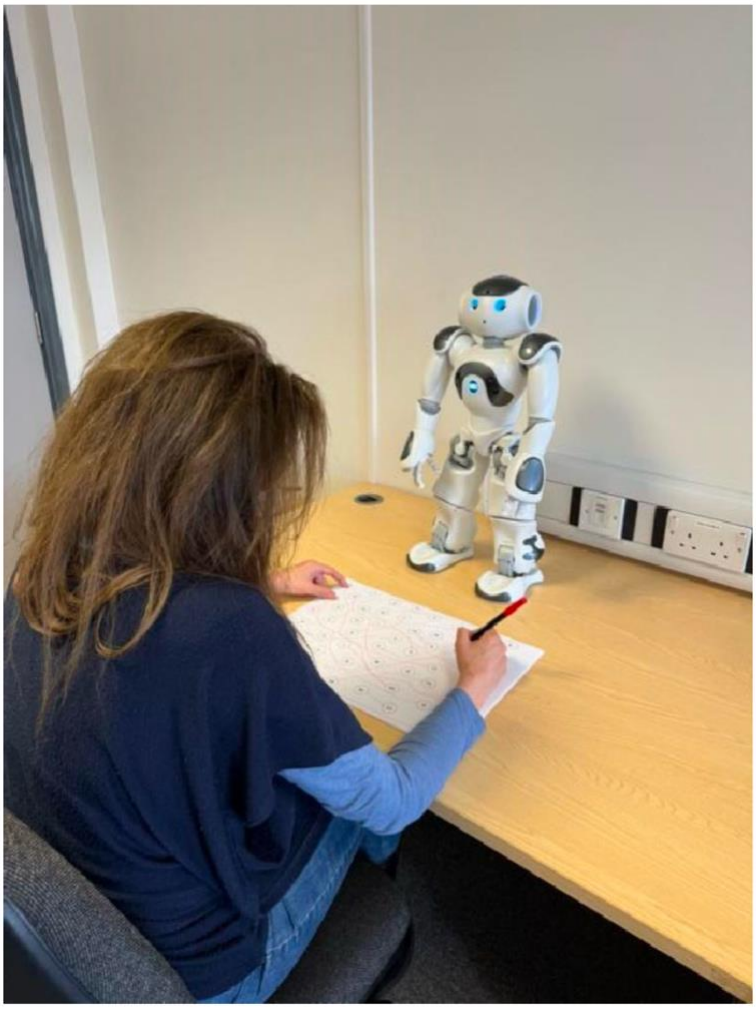

Figure 3. Setting of the robot-interactive task[3]

In the three human-assisted conditions, a human experimenter replicated the role of the robot, providing task instructions and verbal prompts under the same low, medium, and high cognitive load conditions, following the same structured methodology used in the robot-assisted conditions.

[3] Taken from *Varrasi, Vagnetti, Camp, Hough, Di Nuovo, Castellano, Magistro (2025). How human-robot interaction can influence task performance and perceived cognitive load at different support conditions. Information, 16(5), 374. https://doi.org/10.3390/info16050374*

At the conclusion of each condition - including the baseline, robot-assisted, and human-assisted tasks - participants completed the NASA Task Load Index (NASA-TLX) questionnaire to assess perceived cognitive load (PCL).

As detailed previously, saliva samples were collected at the beginning and end of both the robot-assisted and human-assisted conditions to measure physiological indicators of cognitive load, resulting in four samples per participant.

For data analysis, two independent experimenters evaluated task performance metrics across all conditions. Performance measures included accuracy (number of correctly connected pairs) and task completion time (in seconds). Perceived cognitive load was assessed using NASA-TLX scores. Physiological measure took into account cortisol levels pre- and post- each condition (robot vs human).

2.4 Statistical Analyses

Linear mixed-effects models were employed using restricted maximum likelihood estimation to analyze differences across outcome variables, including NASA-TLX scores, task performance measures, and cortisol responses. Participants were specified as random intercepts to account for individual variability in baseline performance and physiological measures.

A Type III ANOVA with Satterthwaite's approximation was utilized to evaluate the main effects and interactions of condition (robot-assisted vs human-assisted), cognitive load level (baseline, low, medium, high), and age group (older adults vs younger adults). Condition at varying cognitive load levels served as the within-subject factor, while age group functioned as the between-subject factor.

Post hoc analyses were conducted on estimated marginal means and mean differences (M_{dif}) to further investigate significant main effects and interactions, with Tukey's HSD correction applied to adjust for multiple comparisons. Consistent with the objectives of the study, particular emphasis was placed on

examining interactions between age group and experimental condition to elucidate differential patterns in cognitive load management and task performance across age cohorts.

3. Results

Means (M) and standard deviations (SD) of accuracy (number of pairs matched correctly), time (in seconds), and PCL across the seven conditions are displayed in Table 1.

Condition	Accuracy (M, SD)	Time (M, SD)	PCL (M, SD)
1. Alone: Baseline	23.4, 5.84	405, 116	49.2, 15.1
2. Robot: Low CL	24.4, 2.55	364, 141	40.9, 16.6
3. Robot: Medium CL	16, 4	342, 69.6	58.3, 15.2
4. Robot: High CL	9.03, 2.99	251, 56	66.2, 14
5. Human: Low CL	25.7, 0.65	332, 91.4	40.3, 15.3
6. Human: Medium CL	18.4, 3.16	362, 86.5	57.1, 13.4
7. Human: High CL	8.24, 2.28	246, 61.1	68.5, 12.3

Table 1. Means (M) and standard deviations (SD) of accuracy, time and PCL across conditions

Regarding performance, in terms of accuracy there was a significant effect between age group and condition ($F(1, 404.53) = 6.50$, $p = .011$) and between age group and cognitive load level ($F(3, 403.45) = 5.88$, $p < .001$). Post hoc analysis indicated older adults have less accuracy in the SAR condition compared to adults ($M_{dif} = 1.97$, $SE = 0.58$, $t(106) = 3.34$, $p = .001$, Figure 4a), and compared to the human condition ($M_{dif} = 1.54$, $SE = 0.43$, $t(403) = 3.57$, $p < .001$, Figure 4b). Additionally, they presented a significant lower accuracy, compared to adults, when the cognitive load level was medium ($M_{dif} = 2.75$, $SE = 0.73$, $t(219) = 3.75$, $p< .001$) or high ($M_{dif} = 1.64$, $SE = 0.73$, $t(219) = 2.23$, $p = .026$), which was not

reported for low levels (M_{dif} = 1.16, SE= 0.73, t(219) = 1.58, p = .115) and for the baseline task (M_{dif} = -0.80, SE = 0.73, t(217) = -1.09, p = .274, Figure 4c). There was also a significant interaction between condition and cognitive load level (F(1, 403.45) = 5.83, p < .001), where significant difference were found between robot and human condition at low (M_{dif} = 1.25, SE = 0.61, t(404) = 2.05, p = .040) and medium level (M_{dif} = 2.58, SE = 0.61, t(404) = 4.21, p < .001) for all the participants, however this was not indicated at high cognitive load levels (M_{dif} = -0.79, SE = 0.61, t(404) =-1.29, p = .19, Figure 4d).

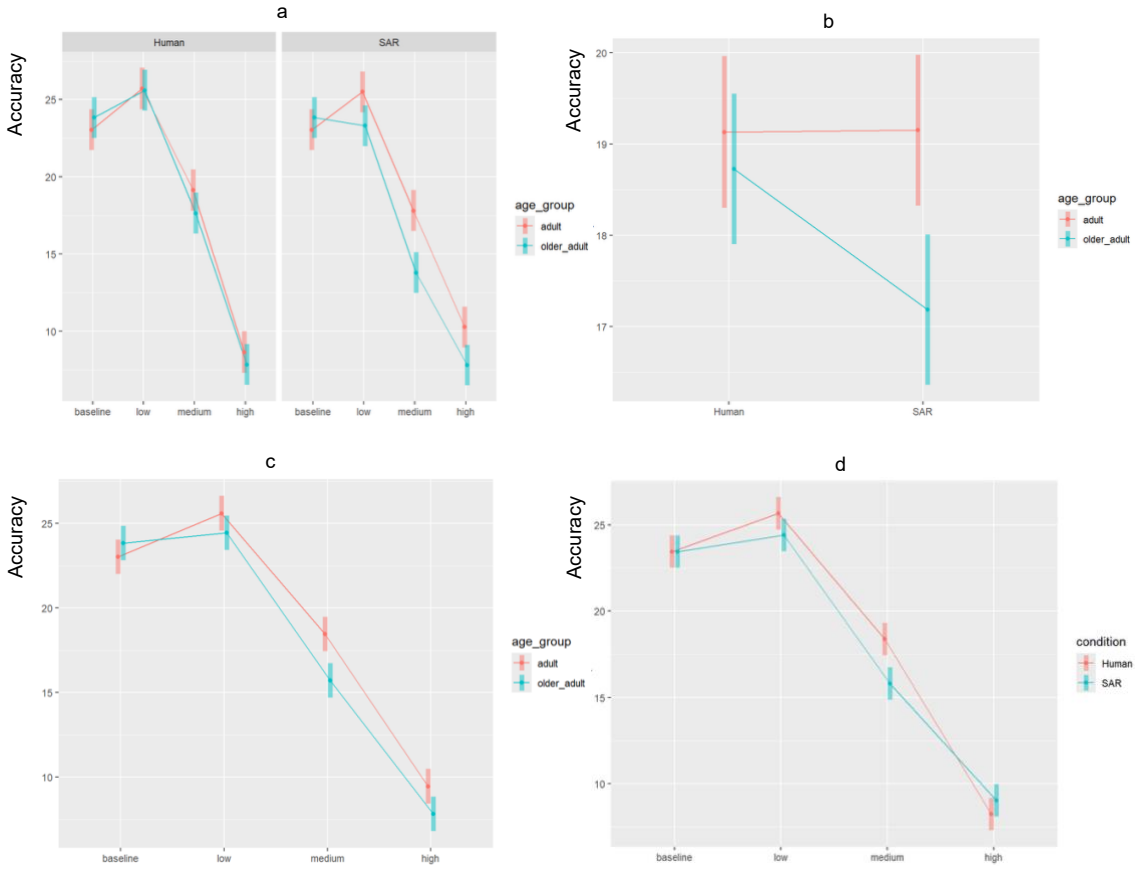

Figure 4. Older adults had a worse performance at SAR condition than adults (a) and than HHI (b). Lower accuracy was shown at increasing levels of CL respect to adults (c), while high CL was challenging for all participants independently from the interactive condition (d)

Regarding the time to complete the task, there was a significant effect between age group and cognitive load level (F(3, 402.85) = 23.73, p< .001). The post hoc

indicated that adults are faster than older adults at the baseline (M_{dif} = -123.73, SE = 18.70, t(114) = -6.62, p < .001) and at low (M_{dif} = -115.95, SE = 18.70, t(115) = -6.19, p < .001), and medium (M_{dif} = -75.16, SE = 18.70, t(115) = -4.01, p < .001) CL, while they perform in the same time at high cognitive load level (M_{dif} = 1.73, SE = 18.70, t(115) = 0.09, p = 0.92, Figure 5).

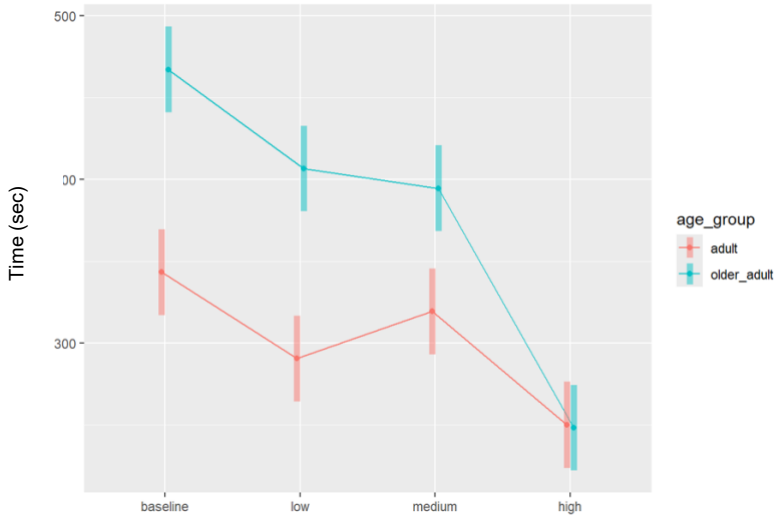

Figure 5. Adults were faster than older adults at the baseline, low CL, and medium CL

Results indicated significant interactions between age group and condition (F(1, 403.45) = 4.58 p = .032), and between age group and cognitive load level (F(3, 403.12) = 8.53, p < .001) on the NASA-TLX score. Regarding the interaction between age group and condition, post hoc indicated older adults have significant higher scores during the robot condition (mean = 576, SE = 2.13) compared to the human condition (mean= 54.3, SE = 2.13) with an estimated mean difference of -3.293 (SE = 1.16, t(403) = -2.83, p = .0049), while this was not indicated by adults (M_{dif} = 0.248, SE=1.18, t(404) = 0.211, p = .833), suggesting that older adults have a general higher cognitive load during the robot condition compared with the human condition (Figure 6a). Regarding the age group and cognitive load level interaction, post hoc indicates that older adults have significantly higher total scores at low cognitive load level compared (mean = 43.8, SE = 2.28)

to adults (mean = 37.2, SE = 2.29, M_{dif} = -6.63, SE = 3.23, t(89.0) = -2.05, p = .043), thus they perceive more cognitive load compared to adults when the cognitive load is low (Figure 6b).

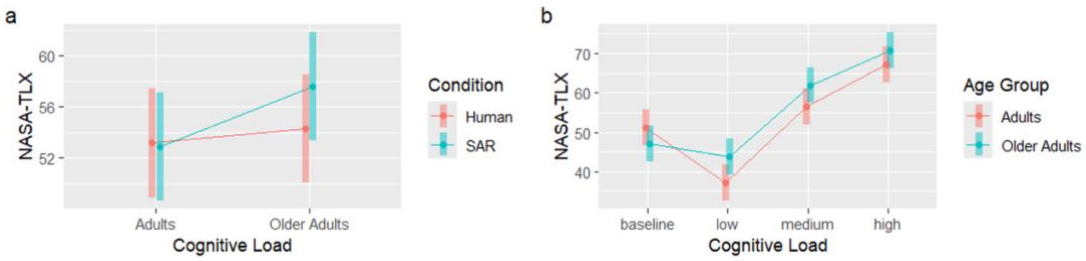

Figure 6. Older adults reported significantly higher overall cognitive load during the robot condition compared to the human condition. No significant condition differences were found for adults (a). Older adults perceived greater cognitive load than adults specifically under low cognitive load levels (b)

Regarding the physiological measure of cortisol, ANOVA revealed an interaction between age group, condition and time (pre vs post) (F(1, 156) = 5.16, p = .02). Considering the sample split by age group, older adults had a significant interaction between condition and time (F(1, 156) = 10.32, p = .001), while adults did not (F(1, 156) = 0.01, p = .9). Post hoc indicated (Figure 7) that older adults showed an increase in cortisol concentrations from baseline to post intervention during the SAR condition (M_{dif} = -5.65, SE = 1.31, t(156) = -4.31, p = .0002).

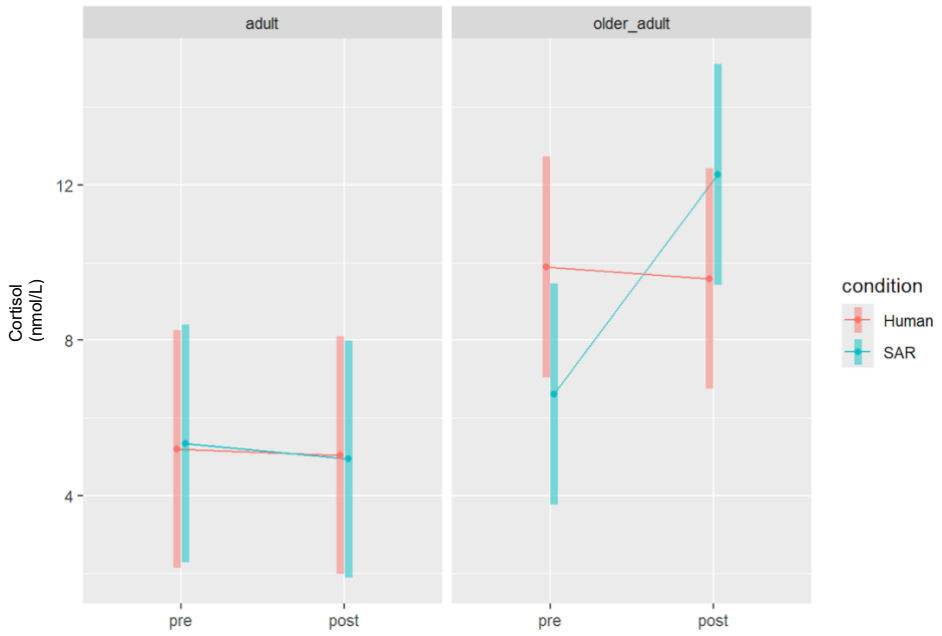

Figure 7. Cortisol concentrations (nmol/L) at pre- and post- HHI and SAR, divided by age groups. Older adults showed an increase of cortisol after the robot condition

4. Discussion

The present study sought to examine how human-human interaction (HHI) and human-robot interaction (HRI) support the management of cognitive load during task performance across younger and older adults, leveraging objective, subjective, and physiological measures. By including a baseline condition without assistance and systematically manipulating cognitive load levels, this investigation advances the literature on cognitive ergonomics in aging and technology-assisted contexts.

Consistent with prior findings indicating that aging is associated with reduced processing speed and working memory capacity (Park et al., 1996; Salthouse, 1996), older adults demonstrated lower accuracy and required more time to complete the task under conditions of increasing cognitive load. Notably, these

differences were most pronounced at medium and high cognitive load levels, supporting the theoretical framework that task complexity disproportionately impacts older adults due to age-related cognitive changes (Craik & Bialystok, 2006). Interestingly, at low cognitive load levels, accuracy differences between age groups diminished, suggesting that minimal support demands may align more closely with the preserved capacities of older adults, facilitating performance comparable to younger adults.

The interaction between assistance type and cognitive load level revealed that HHI was generally associated with higher accuracy compared to HRI, particularly under low and medium cognitive load levels. This finding aligns with research indicating that human support may better accommodate the nuanced needs of older adults through flexible, adaptive communication, thereby reducing extraneous cognitive load (Kushniruk & Patel, 2004). The lack of significant differences under high cognitive load conditions suggests a potential ceiling effect, wherein the cognitive demands of the task exceed the compensatory capacity provided by either form of assistance.

Subjective measures of perceived cognitive load, as assessed by NASA-TLX scores, revealed that older adults consistently reported higher cognitive load during HRI compared to HHI, particularly under low cognitive load conditions. This pattern suggests that even minimal interactions with robotic agents may impose additional extraneous cognitive load for older adults, potentially due to challenges in speech recognition interfaces, turn-taking, or the social-cognitive demands inherent in interpreting robotic behavior (Broadbent et al., 2009). Conversely, younger adults did not exhibit differences in perceived cognitive load across assistance types, indicating that HRI may be more seamlessly integrated by individuals with higher baseline cognitive flexibility and familiarity with technological systems (Czaja et al., 2006).

Physiologically, cortisol measures provided converging evidence of increased cognitive strain during HRI for older adults, with significant post-intervention increases observed in the SAR condition. This aligns with literature suggesting that older adults exhibit heightened physiological reactivity to task demands perceived as challenging or unfamiliar (Lupien et al., 2007). The absence of such an effect in younger adults further underscores the differential impact of HRI on cognitive stress across age groups, highlighting the importance of considering physiological indicators alongside subjective and objective measures to capture the multifaceted nature of cognitive load.

Collectively, these findings underscore the nuanced interplay between aging, cognitive load management, and the type of assistance provided during task performance. While robotic assistance offers potential for scalable and consistent support, its current implementation may inadvertently increase extraneous cognitive load for older adults, particularly in contexts requiring social-cognitive engagement. Human assistance, in contrast, appears to mitigate these challenges, facilitating better performance and lower perceived strain under comparable task demands.

The observed interaction patterns suggest that technological interventions aimed at supporting older adults should prioritize the reduction of extraneous cognitive load by simplifying robot interfaces, enhancing speech recognition reliability, and ensuring adaptive interaction pacing tailored to individual user needs. Moreover, leveraging multimodal support strategies, including visual cues or simplified verbal prompts, may help align HRI more closely with the cognitive profiles of older adults, enhancing usability and effectiveness.

Importantly, the inclusion of a baseline condition in this study allowed for a clear evaluation of the benefits and drawbacks associated with both human and robotic support. The findings demonstrate that while assistance generally improves performance over independent task completion, the type of assistance

and the complexity of the support provided are critical determinants of effectiveness, particularly for older adults.

Future research should explore longitudinal exposure to robotic systems to assess whether increased familiarity reduces the observed cognitive and physiological strain in older adults, potentially enhancing acceptability and effectiveness. Additionally, expanding physiological monitoring to include heart rate variability and EEG measures could provide further insights into the real-time cognitive dynamics associated with HRI and HHI across age groups.

In conclusion, this study provides critical evidence regarding the management of cognitive load in aging populations within assisted task contexts, emphasizing the importance of tailoring support strategies to individual cognitive capacities. While HRI holds promise for supporting aging-in-place initiatives, its implementation must be refined to ensure that it reduces rather than increases cognitive demands for older adults, thereby truly fostering autonomy and quality of life in the context of active aging.

5. Conclusion

The present study examined how human-human interaction (HHI) and human-robot interaction (HRI) support cognitive load management during task performance across younger and older adults, utilizing a comprehensive framework integrating objective, subjective, and physiological measures.

The findings demonstrated that while both HHI and HRI can enhance task performance relative to independent task completion, the nature and complexity of the support provided play a pivotal role in determining its effectiveness, particularly for older adults. HHI consistently facilitated higher accuracy and lower perceived cognitive load, while in contrast, HRI, despite its potential for

consistent and scalable support, was associated with increased perceived and physiological markers of cognitive load in older adults, particularly under low and medium cognitive load conditions.

In conclusion, this study contributes critical evidence supporting the development of adaptive, user-centered assistive technologies that effectively support cognitive load management across the adult lifespan. By emphasizing the need for tailored support strategies and comprehensive evaluation methods, this research advances the goal of fostering autonomy and enhancing quality of life for older adults within the framework of active aging.

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GENERAL CONCLUSION

The present dissertation set out to explore the multifaceted phenomenon of cognitive decline in aging, with a particular focus on its conceptualization, risk factors, psychometric approaches, clinical challenges, and technological interventions. From the outset, the general introduction has emphasized the urgent need to overcome the traditional dichotomy between physical and cognitive domains, advocating instead for an integrative framework to allow a healthy aging (European Commission, 2024; World Health Organization, 2017). The five chapters of this work have collectively sought to advance such a framework by combining theoretical insights, methodological innovation, and applied perspectives.

The construct of cognitive frailty has been introduced as a conceptual bridge linking physical and cognitive vulnerability in later life. By situating frailty within a multidomain model, it emerges as a useful category not only for research purposes but also as a clinical tool to identify individuals at risk before the onset of overt dementia (Dent et al., 2019; Ruan et al., 2015). Within this framework, apathy has been examined as a potentially modifiable risk factor. Network Analysis has made it possible to highlight the complex interplay of lifestyle and psychosocial variables in shaping trajectories of cognitive decline, reinforcing the notion that apathetic symptomatology may serve as an early marker of deterioration. The evidence suggests that specific interventions aimed at reducing apathy may significantly attenuate the risk of dementia (Livingston et al., 2024).

This perspective leads to the methodological and psychometric challenges involved in assessing apathy. Traditional statistical approaches have been critically evaluated in comparison with advanced modeling techniques, such as

Exploratory Graph Analysis, which proved useful in refining the understanding of the construct. In particular, the analysis identified a new four-factor structure within the AES-C, thereby opening avenues for improved diagnostic precision and prognostic accuracy. Building on this methodological foundation, attention has been directed to longitudinal research on the most sensitive psychometric tools for monitoring therapeutic response to pharmacological treatment in mild Alzheimer's disease. These investigations also considered how affective risk factors influence cognitive outcomes, calling for empirically based assessment protocols and a more integrated view of the multiple factors shaping patients' overall clinical conditions.

In parallel, the role of supportive technologies has been explored as a means of sustaining autonomy and quality of life among older adults with cognitive vulnerabilities. Assistive devices have been discussed as promising resources to promote independence within the framework of cognitive load, particularly through comparative analyses of different types of support, populations, and measurement strategies. Nevertheless, several challenges remain, including ethical considerations, accessibility, and usability issues, which must be addressed to ensure the effective and equitable implementation of such technologies (Vincek et al., 2024).

Taken together, the chapters of this dissertation converge toward the conclusion that an integrative, multidomain, and translational approach is essential for advancing the understanding, prevention, and management of cognitive decline. This perspective directly answers the call set forth in the introduction: to close the gap between theory and practice by combining conceptual innovation, psychometric rigor, and technological solutions.

Indeed, this dissertation aims to provide an innovative contribution to the existing body of literature by integrating multiple levels of analysis - epidemiological, clinical, neurobiological, and technological - within a

psychometric framework. While previous studies have often examined cognitive decline, neuropsychiatric symptoms, or technological supports as separate domains, this work emphasizes their interplay and explores how advanced psychometric approaches can capture such complexity. By linking the construct of apathy to cognitive trajectories, and by discussing the role of emerging digital tools in monitoring daily functioning, the thesis outlines a multidimensional model that moves beyond traditional descriptive accounts. In doing so, it highlights the potential of refined psychometric assessment not only to improve diagnostic accuracy and prognostic sensitivity, but also to inform the design of personalized interventions that bridge clinical care and technological innovation.

Strengths of the dissertation lie in:

- Conceptual breadth, achieved by bridging constructs of frailty, lifestyle, and technological support within an integrated framework of cognitive vulnerability;
- Methodological reflection on psychometrics, combined with a translational outlook that connects theoretical advances to preventive and rehabilitative strategies;
- Innovative integration of clinical and affective dimensions, highlighting apathy and related psychosocial factors as early markers and modulators of cognitive decline;
- Longitudinal and multidomain perspective, which validates psychometric tools over time while situating cognitive vulnerability within the dynamic interplay of biological, psychological, and environmental factors;
- Empirical examination of supportive technologies within a psychological framework, through comparative analyses of different conditions of support and diverse measurement strategies, thereby advancing both theoretical understanding and practical applications.

By weaving together multiple disciplines, the work contributes to a more comprehensive and forward-looking vision of aging research. The translational implications of this dissertation are consistent with recent policy priorities that call for integrating rehabilitation, assistive technologies and community-based prevention into health systems (WHO Rehabilitation 2030, WHO, 2023). Embedding psychometric innovations and network-informed screening into routine geriatric and primary-care pathways can facilitate earlier identification of reversible risk states (e.g., cognitive frailty) and help operationalize the Rehabilitation 2030 commitment to scale rehabilitation and supportive services globally.

Nevertheless, limitations must be acknowledged:

- The analyses remain largely (but not solely) cross-sectional;
- While advanced psychometric methods are discussed, their application to large-scale datasets remains prospective;
- Not all risk factors identified by Lacet Commission are explored dynamically altogether, as the present thesis analyzes only some of them;
- Given the rapidly evolving field of digital health technologies, the present work only preliminarily addresses their opportunities and uncertainties.

Future research directions should prioritize longitudinal, multimodal, and cross-cultural studies to better capture the complexity of cognitive decline across diverse populations, including a wide range of risk factors. Further integration of digital biomarkers, ecological momentary assessment, and AI-driven predictive analytics may offer new avenues for early detection and personalized intervention. Additionally, greater attention should be given to the ethical dimensions of technological implementation, ensuring that innovations enhance autonomy without reinforcing inequalities.

In conclusion, this dissertation underscores that the challenge of cognitive decline requires an integrated agenda combining theoretical, methodological, and applied perspectives. By advancing the dialogue between psychometrics, preventive strategies, and technological innovation, it aims to contribute to a more holistic, equitable, and sustainable vision of cognitive health in aging societies.

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