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THE BEHAVIOURAL VARIANT OF AZLHEIMER DISEASE: A CLINICAL, NEUROPSYCHIATRIC AND IMAGING CHARACTERIZATION

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1. Introduction

1.1 Neurodegenerative diseases

Identifying the protagonist

Nowadays through the improvement and development of Medicine we are able to increase the years of life expectancy. Despite this prolongation, we are not able to guarantee the quality of these late years, threatened by varieties of morbidities and disabilities, that not only just impact on the single person but also weakens on the sanitary system and in general to the global economy.

One of the most common threats could be identified in neurological disorders, in particular in neurodegenerative diseases (NDDs). From the analysis of the Global Burden of Disease Study of 2021, all the neurological conditions contribute to 168 million Years Lived with Disability (YLDs) and 443 million Disability-adjusted life years (DALYs). Moreover analyzing each neurological disorder, it is possible to bring out a percentage increment of NDDs from 1990 to 2021, such as Alzheimer's disease (AD) and other dementias (+160,8 % in prevalence; +162,7 in YLDs; +168,7% in DALYs) and Parkinson's disease (PD) (+273,9% in prevalence; +271,2% in YLDs; + 161,8% in DALYs) [1].

NDDs are a complex heterogeneous group sharing the characteristic of progressive neuron loss, through different mechanisms, not balanced from the renewal of new ones. This provokes the damage and the impoverishment of brain circuits that phenomenologically results in brain function impairment [2-3].

The surface: clinical spectrum of NDDs

In clinical practice the NDDs are divided into different diseases based on the major leading symptoms that afflict the patient from the beginning of disease, although through the development of degeneration progress by the time, the number of symptoms increases and tends to overlap with other diseases.

The most common NDDs could start with:

- ➢ cognitive impairment (for example the loss of memory) such as in AD dementia
- ➢ changes in behavior and speech disorder such as Fronto-Temporal dementia
- ➢ motor symptoms, such as rigidity, tremor and bradykinesia in PD or muscle weakness and paralysis in Amyotrophic Lateral Sclerosis (ALS)
- ➢ mixture of changes in behavior and motor system such in Hungtinton's disease and Lewy's body dementia (LBD).

The core: what is hidden in

Under the surface of these diseases there are several genetic factors or biochemical pathways of damage that could be summarize in eight hallmarks, all interconnected: pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death [4].

The pathological protein aggregation is due to a gain-of-function of genes that encode the protein. This mechanism is provoked by mutations or by a repeat-associated non-ATG translation that induce the generation of aggregating dipeptide repeats from hexanucleotide repeat sequences [5-6]. Not only this aggregation of the protein in specific brain areas damaging neurons, but also this segregation from other areas, could be correlated with clinical dysfunction.

The tendency of propagation of that aggregation is defined as "prion-like", in order to distinguish from the true prion disease, a misfolded protein with extremely rapid propagation as primary pathogenetic mechanism [7].

The synaptic and neuronal network dysfunction could be considered an early stage that anticipates the loss of neurons. The well-functioning of the neuronal network and the regulation of neurotransmitters is supported by the homeostasis of intracellular calcium and energy provided by mitochondria [8].

The mitochondrial dysfunction leads to excessive calcium influx that provokes neuronal hyperexcitability, glutamate-mediated excitotoxicity, activation of calpain causing protein degradation, difficulties in eliminating and replacing neurotransmitters [9].

Other two important mechanisms for protein homeostasis include the ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP), which works also for synaptic functioning. The first is related to the degradation of marked proteins, whereas the second of protein aggregates and defective organelles, like damaged mitochondria. In both cases the target is linked to p62 [10-11]. The evidence of ALP is studied in mice knockout for gene autophagy related 7 (Atg7) and in lysosomal storage disorder due to recessive loss of function mutation [12-13] .

In the neurons there is a high protein turnover and transportation, especially through the axonal transport that connects the center (the body) where everything is built to the peripheral part (synapses) where it is used. The transport is allowed thanks to three types of polymeric chain: microtubules, microfilaments of actin and intermediate filaments. All three consist of what is called neuronal cytoskeleton. It is fundamental for the neurotransmission, stress response, architectural transformation and trophic signaling [14]. In many NDDs is found the aggregation of these proteins, through different pathways, such as the hyperphosphorylation of intermediate filaments. It becomes a liquid crystal aggregation released in cerebrospinal fluid (CSF), that could be detected also in the bloodstream at femtomolar concentrations [15].

Neurons, that are highly active and energy-demanding cells, rely on ATP produced in particular through oxidative phosphorylation in mitochondria. This process is fueled by glucose or lactate that is delivered directly from the bloodstream or indirectly through astrocytes. Defects in mitochondrial function lead to decreased ATP production, impairing essential high-energy processes in neurons, particularly at synapses. These processes include maintaining ion balance and calcium homeostasis, as well as ensuring the dynamics of the cytoskeleton and protein stability.

Mitochondrial dysfunction also increases oxidative stress by releasing free electrons that react with oxygen or nitrogen, resulting in damage to proteins, lipids, and nucleic acids through reactive oxygen species (ROS) [16-17].

DNA damage and defects in RNA metabolism play fundamental roles in various NDDs. Both the genome and transcriptome are vulnerable to damage from internal and external agents, like ROS. Such damage can lead to severe cellular events like mutagenesis, chromosome rearrangements, and interruptions in RNA transcription and DNA replication, all contributing to cell dysfunction and death. In order to contrast these negative effects, cells have developed repair mechanisms to maintain DNA and genome integrity. Similarly, complex systems are in place to manage RNA processing, including transcription, splicing, transport, degradation, and translation, as well as the production of regulatory non-coding RNAs. These systems involve multiple interactions with RNA-binding proteins and RNA molecules. Any disruptions in RNA metabolism can impact protein synthesis, lead to protein aggregation, and interfere with RNA interference mechanisms. Such defects can also affect RNA-driven processes and transport, potentially resulting in the formation of stress granules made up of ribonucleoproteins. Moreover, dysfunction in RNA metabolism may trigger repeat-associated non-ATG (RAN) translation, producing abnormal repeat proteins [18-19-20].

Neuroinflammation, characterized by microgliosis and astrogliosis, plays an important role in the spectrum of NDDs. This inflammatory response is not just a consequence but also a basic mechanism in the neurodegenerative process. Microglia, immune cells permanently staying in the brain, play different roles in sensing and responding to brain pathology. Their functions include clearing debris, producing inflammatory cytokines, and generating ROS. In NDDs, continuous activation of microglia due to unresolved stressors such as protein aggregates or mitochondrial dysfunction leads to chronic inflammation, contributing significantly to neurodegeneration. Different populations of microglia, such as disease-associated microglia or microglial neurodegenerative phenotype, can emerge during disease progression, each having distinct impacts on the brain's environment and adding to neuronal damage.

Astrocytes are crucial in maintaining neuronal health by regulating glutamate homeostasis. In NDDs, astrocytes become activated in response to neuronal damage and contribute to the inflammatory pathway by releasing cytokines and chemokines, and forming glial scars. This activation can exacerbate synaptic dysfunction and further drive the neurodegenerative process. Genetic studies have linked several genes involved in microglial and astrocytic functions to the risk and progression of NDDs. For example, mutations in TREM2 and variability in ApoE are associated with altered microglial responses and are risk factors for AD. These genes modulate the transition of microglia from a homeostatic state to a disease-associated state, influencing their ability to manage protein aggregates and neuronal damage [21-22-23]. Neurons entering in apoptosis expose phosphatidylserine as an "eat-me" signal, inducing phagocytosis by microglia, that exacerbate neuroinflammation and so neurodegeneration.

This link between protein aggregation, neuronal damage, and glial responses is what is under the complex mechanisms leading to neuronal cell death in NDDs. The fact that under the same pathologies there are several pathological mechanisms implicates that in future we could use therapies that act from different points.

1.2 Proteinopathies

The most common proteins that through their aggregation morphology and distribution in brain area cause each different NDDs are: amyloid β-peptide (Aβ), τ-protein (tau), α-synuclein (α-Syn), and TAR DNA-binding protein 43 (TDP 43) [24].

Aβ

Aβ peptides are produced through the sequential proteolysis of the amyloid precursor protein (APP) by β- and γ-secretases. Due to multiple cleavage sites for these enzymes, various lengths of Aβ peptides are generated, with Aβ40 and Aβ42 being the most common forms [25].

Aβ peptides, particularly Aβ42, have a high tendency to aggregate. Extracellular aggregation of Aβ in the brain parenchyma leads to the formation of amyloid plaques, which, along with neurofibrillary tangles (NFT) composed of hyperphosphorylated tau, constitute distinct pathological hallmarks of AD [26]. Additionally, Aβ can accumulate at cerebral blood vessels, a condition known as cerebral amyloid angiopathy (CAA). Parenchymal Aβ deposits are primarily composed of Aβ42 and Aβ43 peptides, while shorter variants from Aβ36 to Aβ41 are present in vascular deposits [27]. The function of Aβ in the brain is not fully understood, but recent research suggests its involvement in regulating synapse numbers and synaptic transmission in cultured human neurons. Several cleaning systems help prevent Aβ accumulation in the brain, including transport through the blood-brain barrier (BBB), cellular uptake and proteolysis, clearance through CSF, and the glymphatic pathway. Factors affecting normal Aβ clearance or increasing Aβ production can lead to its aggregation in the brain [28]. Mutations in genes presenilin-1 (PSEN1) and presenilin-2 (PSEN2), encoding subunits of γ-secretase, elevate Aβ42 production, increasing the risk of AD. Mutations in the APP gene have a more specific impact on pathology. Different mutations alter APP proteolysis, Aβ aggregation propensity, and affinity to clearance receptors. ApoE genotype also influences Aβ pathology, with ApoE4 being an AD risk factor and ApoE2 a CAA risk factor [29].

However, hereditary forms represent only a small fraction of AD cases, with most pathologies due to spontaneous Aβ aggregation. Misfolding of Aβ results in various amyloid strains. Aβ fibrils from human brains show significant differences between in vitro and ex vivo assemblies, as well as between sporadic AD, familial AD, and CAA [30]. Multiple Aβ polymorphs may coexist in the same biological sample, similar to tau protein aggregates. Brain parenchyma-derived fibrils from AD exhibit two identical S-shaped protofilaments, predominantly composed of Aβ42. Two types of fibrils are described, differing in the number and location of β-strands along the peptide chain: type I (5 β-strands) is predominant in sporadic AD, while type II (4 β-strands) is characteristic of familial AD and Aβ pathologies in other NDDs [31].

Familiar AD cases studied had mutations in PSEN1 or mutation V717F in APP, which did not affect the amino acid sequence of Aβ. Vascular deposit-derived fibrils show a C-shaped peptide fold, right-hand twisted protofilaments, and are predominantly formed by shorter forms Aβ36–Aβ40 with minimal Aβ42. They exhibit four β-strands along the peptide chain with a different localization compared to AD. CAA-derived fibrils can have one, two, or three protofibrils, representing different fibril architectures (types I, II, or III). These experiments confirm differences between in vitro and in vivo Aβ assemblies and heterogeneity of pathogenic Aβ conformations among AD variants and CAA [32]. Aβ aggregation is first observed at ages 11–20, with plaque frequency and distribution increasing with age; around 80% of autopsy cases show Aβ deposits at age 80. However, 20% of individuals up to age 100 do not develop amyloid plaques. Aβ plaques initially appear in the neocortex and then spread into further brain regions in a distinct hierarchical sequence [33].

Tau

Tau is a protein encoded by the MAPT gene, predominantly associated with neuronal microtubules. This gene, containing 16 exons, undergoes alternative splicing, resulting in different tau isoforms. Splicing of exon 10 leads to tau isoforms with either three or four microtubule-binding repeats (3R or 4R isoforms), and splicing at exons 2 and 3 results in isoforms with zero, one, or two N-terminal inserts. This creates six possible combinations (0N3R, 1N3R, 2N3R, 0N4R, 1N4R, and 2N4R) [34]. In tauopathies, tau proteins undergo various post-translational modifications (PTMs), destabilizing their interaction with microtubules and promoting self-aggregation. These PTMs include phosphorylation, ubiquitination, acetylation, and methylation. Such modifications are implicated in the morphological diversity of tau inclusions, their cellular localization, and are identifiable by specific staining techniques. For example, AD and primary age-related tauopathy (PART) feature inclusions of both 3R and 4R tau isoforms, while other diseases like progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and argyrophilic grain disease (AGD) are predominantly associated with 4R tau isoforms.

In contrast, Pick's disease (PiD) inclusions consist exclusively of 3R tau. Cryo-electron microscopy (cryo-EM) has been used to analyze the distinct structural conformations of tau protein aggregates specific to AD and Pick's Disease (PiD) [35]. In AD, tau fibrils consist of both 3R and 4R isoforms forming two types of C-shaped protofilaments. These structures feature different interfaces between protofilaments, with variations highlighted in symmetric paired helical and asymmetric straight fibrils. Notably, specific intermolecular interactions within the straight fibrils suggest potential sites for disease-specific antibody binding. In contrast, PiD tau fibrils are composed exclusively of 3R isoforms and exhibit a completely different J-shaped morphology. Two polymorphic forms were identified, with the majority being a narrow type formed by a single protofilament. The lack of a second microtubule-binding repeat in 3R isoforms, which is present in 4R isoforms, explains why 4R isoforms do not adopt the PiD-specific fold. These structural insights also shed light on the differential phosphorylation of tau in these diseases. For example, Ser262 is involved in the amyloid core of PiD fibrils, protecting it from phosphorylation, whereas in AD, it remains exposed and susceptible to modifications. The distinct conformations of tau in AD and PiD support the hypothesis that specific tau strains lead to different clinical manifestations of tauopathies, similar to prion strains [36].

The accumulation of abnormally phosphorylated tau protein is prevalent across the human population and can begin at an early age. A study examining 2,332 brains from individuals aged 1 to 100 years found that nearly all showed signs of tau pathology, with only 10 cases (mostly under the age of 10) displaying no abnormal tau phosphorylation. Signs of early tau aggregation, termed "pretangles," were observed as young as 6 years old. By age 40, most individuals exhibited some degree of tau pathology [37].

The combination of Aβ and tau

The interaction between Aβ and tau proteins results in the unique dual proteinopathy characteristic of AD, marked by the deposition of both proteins.

While tau pathology can occur independently of Aβ, as seen in primary age-related tauopathy (PART), in AD, Aβ plaques and NFT converge to form a distinct lesion known as neuritic plaque, combining intracellular tau inclusions with extracellular aggregated Aβ. Neuropathological evidence suggests that Aβ pathology is necessary for the spread of tau pathology beyond the medial temporal lobe, with tau pathology rarely exceeding NFT-Braak stage IV in the absence of Aβ, but reaching stages V/VI when Aβ pathology is present. Pathogenic mutations in genes such as APP, PSEN1, and PSEN2 lead to increased Aβ production and the development of familial AD, characterized by the accumulation of both Aβ and tau. Conversely, mutations in the MAPT gene lead to tauopathies but not AD. Crossbreeding transgenic mice with Aβ and tau pathology resulted in exacerbated tau pathology in offspring. Exogenous Aβ oligomers induced tau phosphorylation in an AD-specific manner and mis-sorting into dendrites in mouse primary cell culture, further indicating the role of Aβ pathology in tau pathology and AD development. The regions of interaction between tau and Aβ have been identified, with tau showing strong binding to specific regions of Aβ42. This interaction promotes tau phosphorylation by glycogen synthase kinase-3β (GSK-3β) and Aβ nucleation into aggregates. Phosphorylation of certain tau residues blocks Aβ42 binding, and complexes of tau and Aβ have been detected in AD brain tissues.

The interaction between Aβ and tau leads to specific post-translational modifications in tau, such as phosphorylation of Ser256 by GSK-3β in the Aβ-tau complex, diverting phosphorylated tau toward AD-specific amyloid conformation aggregation. This interaction and subsequent PTMs contribute to the convergence and exacerbation of tau and Aβ pathology in AD [38-39-40-41].

Alfa-sinucleina

Alpha-synuclein (α-Syn) is a protein encoded by the SNCA gene, composed of 140 amino acid residues. It is found in various neuronal compartments, and its function is not fully understood [42]. Certain regions of α-Syn, such as the lipid-binding domain and the central hydrophobic region (NAC), contribute to its aggregation propensity [43].

Aggregated α-Syn impairs various neuronal functions and is implicated in synucleinopathies, including Lewy body disease (LBD) and multiple system atrophy (MSA). In vitro, recombinant α-Syn can form oligomeric and fibrillar assemblies, adopting different conformations referred to as rod and twister polymorphs. These polymorphs exhibit distinct biochemical and functional properties and are associated with different disease presentations. Pathological α-Syn strains isolated from patients with PD, LDB, and MSA show differences in seeding activity, aggregate morphology, and pathogenicity [44]. Cryo-EM analysis revealed structural differences between in vitro and ex vivo α-Syn assemblies, with MSA-derived fibrils exhibiting twisted filaments and unique protofilament arrangements. In contrast, fibrils from PD, PDD, and LDB patients were mostly non-twisted and had a different folding pattern. The identification of disease-specific α-Syn conformations suggests that the nature of synucleinopathies is determined by specific strains of pathological α-Syn. These distinct conformations arise from different aggregation conditions in vitro or unique cellular environments in vivo [45-46-47-48].

TDP-43

TDP-43, a 43 kDa protein encoded by the TARDBP gene, plays a crucial role in regulating gene expression and RNA processing. It shuttles between the nucleus and cytoplasm and primarily exists in an oligomeric form, which prevents aggregation. However, disturbances in this equilibrium can lead to proteolytic cleavage of TDP-43, resulting in highly aggregation-prone fragments [49]. Discovered in 2006, TDP-43 was identified as a main component of inclusions in patients with frontotemporal lobar degeneration (FTLD) and ALS [50].

Post-translational modifications like phosphorylation, ubiquitination, and truncation can induce conformational changes in TDP-43, leading to cytoplasmic aggregation, which is cytotoxic and promotes neurodegeneration.

Recent studies have revealed the amyloidogenic nature of TDP-43, with fibrillar assemblies identified in ALS, FTLD, and AD patients. These fibrils, composed of TDP-43 glycine-rich domain (GRD) or full-length TDP-43, were structurally stable and shared epitopes with anti-amyloid oligomer-specific antibodies. TDP-43 inclusion bodies are pathological hallmarks of ALS and FTLD, with distinct progression patterns [51].

1.3 Alzheimer's dementia

AD is the most common NDD, the leading cause of cognitive impairment and dementia, and among the ten most common causes of death globally. AD prevalence is continuously increasing due to the progressive aging of the world's population since advanced age represents the most significant risk factor [52]. The National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines defined three AD phases: preclinical AD, characterized by pathologic brain changes without cognitive impact; mild cognitive impairment (MCI), showing mild neuropsychological impairment; dementia phase [53-54].

Considering the preclinical, prodromal (MCI), and overt dementia phases, it has been estimated that about one-fifth of people aged over fifty years live on the AD continuum [55].

Incidence

Estimates of dementia incidence vary significantly across different studies and are largely influenced by age. Generally, the incidence of dementia doubles every decade after the age of 60 [56]. For instance, in the Cardiovascular Health Study-Cognition Study (CHS-CS), out of 160 participants who were alive at age 93, only 19 were free from MCI or dementia [57].

The incidence and prevalence of dementia or AD show minimal differences between sexes, but in absolute terms, more females are affected than males, especially beyond the age of 85, largely due to their longer life expectancy. In 24 longitudinal studies, the age-specific incidence of dementia ranged from 5 per 1000 in individuals aged 65 to 70, to between 60 and 80 per 1000 in those aged 85 and older [58]. Specific study findings include:

- The CHS-CS, which tracked over 3000 adults initially free from dementia over five years, found incidence rates ranging from 32 per 1000 person-years in those aged 75 to 79 at the start, to 96 per 1000 person-years in those aged 85 or older, with little difference between sexes [59].
- A population-based study in Rotterdam in 2000 reported dementia incidence rates of 1 per 1000 for ages 60 to 69, 6.4 per 1000 for ages 70 to 79, and 26 per 1000 for ages 80 to 89 [60].

AD is also noted among younger adults with dementia, though fewer studies cover the population under 65 years old. In the UK, a study estimated the incidence of dementia at 54 per 100,000 person-years among individuals aged 30 to 65 years, with AD being the most common cause at 34%, followed by vascular dementia, frontotemporal dementia, LDB, alcohol-related dementia, and other causes [61]. Another study from England found the incidence of AD to be 4.2 cases per 100,000 person-years among individuals aged 45 to 64 [62].

Risk factor

Numerous genetic and environmental factors contribute to the risk of dementia, especially AD, with many of these factors being most influential during midlife. Studies have shown that having multiple vascular risk factors in midlife significantly increases the likelihood of amyloid deposition in the brain later in life, as evidenced by amyloid PET scans [63].

Addressing these vascular risk factors proactively during midlife is crucial for reducing the risk, progression, and severity of AD and other dementias [64]. It is estimated that up to one-third of AD cases globally could be linked to modifiable factors such as diabetes, midlife hypertension, and physical inactivity [65]. Main modifiable risk factors include:

- ➢ Hypertension: Midlife hypertension is consistently linked with an increased risk of dementia and AD. The mechanisms might involve arteriolosclerosis and fluctuations in blood pressure [66].
- ➢ Dyslipidemia: The relationship between cholesterol levels in midlife, particularly LDL-C, and AD risk is complex. Cholesterol in the brain is mostly produced locally and does not typically cross the BBB from peripheral sources unless the barrier is compromised [67].
- ➢ Cerebrovascular Disease: There's a frequent overlap between AD and cerebrovascular disease, contributing to forms of mixed dementia. Factors like reduced cerebral blood flow and white matter abnormalities can elevate AD risk and worsen cognitive outcomes in AD patients [68].
- ➢ Atherosclerosis: Indicators of atherosclerosis, such as carotid intima-media thickness and coronary artery calcification, have been linked with an increased risk of dementia and AD, potentially influenced by vascular brain diseases [69].
- ➢ Obesity and Diabetes: Midlife obesity and type 2 diabetes are associated with a heightened risk of AD [70].
- ➢ Lifestyle and Activity: Physical activity is strongly associated with reduced risks of cognitive decline and dementia, including AD [71].
- ➢ Brain Trauma: Severe brain trauma has been inconsistently linked with increased AD risk, with some evidence suggesting a causal relationship through increased brain amyloid shortly after injury [72].

- ➢ Medications: Some medications, like benzodiazepines and anticholinergics, have been associated with transient cognitive impairment in older adults [73].

The genetic basis of AD is more pronounced in the less common early-onset form, which is often due to mutations in specific genes like APP, PSEN1, and PSEN2. These mutations lead to changes in the production, aggregation, or clearance of Aβ protein, resulting in almost certain development of AD among carriers. For late-onset AD, genetic factors are more complex, with the APOE gene being a significant risk factor. Family history also plays a role, particularly if multiple first-degree relatives are affected by AD, significantly increasing the risk for other family members [74].

Clinical features and development

Memory impairment is typically the most prominent initial symptom of AD. Even if it isn't the primary concern reported, memory issues can usually be identified in most AD patients at their initial evaluation. As the disease progresses, impairments in other cognitive areas may emerge alongside or after memory problems develop.

The nature of memory impairment in AD is quite distinct, with declarative episodic memory—which involves recalling events that occurred at specific times and places—being significantly affected. This type of memory relies heavily on the hippocampus and other structures in the medial temporal lobe. In contrast, procedural memory and motor learning, which are supported by subcortical systems, generally remain intact until the later stages of the disease. Semantic memory, which includes knowledge of words and concepts, tends to deteriorate later and is tied to the neocortical regions of the temporal lobe, especially the anterior areas. Subtle difficulties with semantic memory can appear early on due to early involvement of the temporal lobe [75].

Episodic memory can be further categorized into immediate recall, such as remembering a phone number shortly after hearing it; recent memory, which involves recalling information once it's no longer in the immediate consciousness; and remote memory, pertaining to events from the more distant past. In early AD, recent memory is particularly affected due to impairments in the hippocampus and related medial temporal lobe structures. Immediate memory and long-consolidated memories, however, are usually preserved in the early stages. The typical early memory deficits in AD manifest as anterograde long-term episodic amnesia. This type of memory impairment is often described by patients and caregivers as problems with "short-term memory," though from a technical standpoint, the issues lie with the ability to form new long-term memories. Therefore, clinicians often use the term "recent memory impairment" to avoid confusion and more accurately describe the issue. Memory deficits in AD develop gradually and worsen over time, eventually including problems with semantic memory and immediate recall. Procedural memory impairments appear only in the later stages of the disease. Typically, memory is assessed by having patients learn and recall a list of words or objects immediately and after a short delay. A more severe and AD-specific memory deficit involves difficulty in recalling with cues or recognizing previously encountered items, indicating significant medial temporal lobe involvement. Clinicians should carefully evaluate both the patient's and an informant's reports of memory issues in daily life, considering that older individuals might not always accurately judge their memory performance and might also lack insight into their deficits, leading them to under-report or deny symptoms. Getting the perspective of someone close to the patient is crucial for a thorough assessment [76-77-78].

In the early stages of AD, changes in executive function and judgment/problem-solving abilities can range from subtle to significant.

Patients often do not fully recognize or report these changes themselves, making interviews with informants, typically family members, essential for an accurate diagnosis. It is common for those around the patient, including coworkers and family, to notice a decline in the patient's organization and motivation, with multitasking abilities being particularly affected. As AD progresses, patients typically find it increasingly difficult to complete tasks. A notable symptom of AD is anosognosia, or a reduced insight into one's own deficits, which varies from patient to patient. This often leads patients to underestimate their cognitive impairments and provide excuses when these deficits are highlighted. Consequently, it is usually family members who first notice and report cognitive problems to healthcare providers, not the patients themselves. This loss of insight tends to worsen alongside the progression of the disease and can be linked to behavioral changes. Patients with relatively intact insight may experience depression, while those with diminished awareness are more prone to agitation, disinhibition, and psychotic symptoms. The lack of awareness can also pose safety risks, as patients might attempt tasks that exceed their current capabilities, such as driving [79-80-81-82].

In patients with AD, impairments extend beyond memory to other cognitive domains. Visuospatial abilities can decline relatively early in the disease, whereas language deficits typically appear later as the condition progresses. These deficits gradually worsen over time. Occasionally, the most prominent early symptoms may include language difficulties, visuospatial issues, or even executive function impairments [54]. Behavioral and psychological symptoms are also common as AD progresses, especially in the middle and late stages. Initial symptoms can be subtle, such as apathy, withdrawal from social interactions, and irritability. Distinguishing between apathy and depression is crucial, as each has different treatment implications, though it can be challenging to diagnose depression in the context of dementia. Sometimes, empirically treating what is presumed to be depression may be considered a reasonable approach.

Management becomes more complicated with the onset of more severe behavioral problems such as agitation, aggression, wandering, and psychosis, including hallucinations, delusions, and misidentification syndromes. When such symptoms emerge, particularly if they develop suddenly or worsen quickly, it's important to rule out other potential causes like medical illnesses, medication side effects, or delirium [83]. Additional symptoms include:

- ➢ Apraxia: Dyspraxia, characterized by difficulty executing learned motor tasks, typically emerges later in the disease progression, following the onset of memory and language deficits. Initially, dyspraxia may be identified by asking the patient to perform ideomotor tasks, such as miming the use of tools (e.g., demonstrating how to use a comb). Clinical dyspraxia leads to progressive challenges with complex motor activities, followed by difficulties in dressing, eating with utensils, and other self-care tasks, significantly contributing to dependency in mid- to late-stage AD [84].
- ➢ Olfactory dysfunction: Changes in olfactory function are prevalent among AD patients and have been studied for diagnostic purposes. However, the predictive value of simple odor detection tests is limited, and standardized olfactory assessments face challenges, hindering widespread adoption. Additionally, olfactory dysfunction is not frequently reported by patients or their families. Nonetheless, it may augment patient classification beyond cognitive assessments alone [85].
- ➢ Sleep disturbances: AD patients commonly experience sleep disturbances, spending more time awake in bed and exhibiting more fragmented sleep compared to older adults without AD. These changes may occur early in the disease progression, even in cognitively normal individuals with evidence of Aβ deposition [86].

- ➢ Seizures: Seizures affect 10 to 20 percent of AD patients, typically occurring in later disease stages. Younger patients, including those with autosomal-dominant AD forms, may face a higher seizure risk, with seizures potentially manifesting early in the disease course. The predominant seizure type involves focal nonmotor symptoms with impaired awareness, often resembling medial temporal lobe onset (e.g., amnestic spells, unexplained emotions, metallic taste, rising epigastric sensation) [87].
- ➢ Motor signs: In the initial stages, AD patients typically exhibit a normal neurological examination except for cognitive deficits. While pyramidal and extrapyramidal motor signs, myoclonus, and seizures can occur in AD patients, these manifestations typically emerge in later disease stages. If such symptoms are evident in the early to middle stages, alternative diagnoses should be considered. Myoclonus may develop in some AD patients, particularly those with faster-than-usual decline. Additionally, primitive reflexes (e.g., grasp, snout reflexes) and incontinence are late-stage rather than early-stage features of AD [88].

AD progresses relentlessly, and its advancement can be tracked using mental status evaluations such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Clinical Dementia Rating (CDR) scale, and tools like the Functional Activities Questionnaire that assess daily functioning. Although the progression as measured by these instruments isn't always linear, studies indicate that patients typically experience an average decline of 3 to 3.5 points per year on the MMSE [89]. A smaller group (less than 10 percent) may experience a more rapid decline, dropping 5 to 6 points annually on the MMSE [90]. Patients diagnosed with AD at an older age (over 80 years) often exhibit a slower progression compared to those who are younger at onset [91].

On the other hand, the presence of early neuropsychiatric symptoms such as psychosis, agitation, and aggression is linked to a quicker progression [92]. The impact of neuropsychiatric symptoms on patients and caregivers is assessed using the Neuropsychiatric Inventory (NPI). Life expectancy following an AD diagnosis typically ranges from 8 to 10 years, although this can vary from 3 to 20 years depending on the severity of symptoms at diagnosis and the age at which symptoms first appear. Ultimately, individuals with AD usually face life-ending complications related to severe debilitation, such as dehydration, malnutrition, and infections [93].

Evaluation and diagnosis

AD should be considered in any older adult who shows a gradual onset and progressive worsening of memory along with impairment in at least one other cognitive domain that affects daily functioning. Conducting a thorough cognitive and general neurological examination is essential.

Clinicians should evaluate potential contributing factors to dementia such as medication side effects, depression, and metabolic imbalances or deficiencies. Many use standardized mental status scales to monitor the presence and progression of dementia. The MoCA is favored for its superior sensitivity in detecting executive and language dysfunction compared to other brief assessments like the MMSE. Normally, a MoCA score of 26 or above is considered normal, with adjustments made for educational level and other relevant norms. However, a diagnosis of dementia cannot be solely based on a low score from these assessments [94]. A comprehensive diagnostic evaluation includes a detailed history, ideally incorporating information from an informant such as a spouse or adult child, preferably interviewed separately from the patient. Employing validated questionnaires to assess the maintenance or decline of independent functioning, as well as the presence and type of neuropsychiatric symptoms, is crucial.

Additionally, cognitive symptom questionnaires can be beneficial. Formal neuropsychological testing offers a precise assessment of cognitive impairment and dementia under standardized conditions using demographically adjusted norms, particularly for detecting executive function impairments [95]. Neuropsychological assessments are valuable for several reasons:

- ➢ Establishing a baseline to monitor changes over time.
- ➢ Differentiating among various types of neurodegenerative dementias or between neurodegenerative dementia and other causes of cognitive impairment, such as cerebrovascular disease or depression.
- ➢ Evaluating competencies to inform decisions related to driving, financial management, and the level of supervision needed.
- ➢ Identifying potential for compensatory or rehabilitative interventions [96].

Brain imaging, especially magnetic resonance imaging (MRI), is recommended for evaluating patients with suspected AD. MRI helps identify possible alternative or additional causes of symptoms, such as cerebrovascular disease, other structural brain conditions (like chronic subdural hematoma, brain tumors, or normal pressure hydrocephalus), and patterns of brain atrophy indicative of frontotemporal dementia or other NDDs. Typical MRI findings in AD include generalized and focal brain atrophy and white matter changes. The most notable focal change in AD is the reduction in hippocampal volume or atrophy in the medial temporal lobe. However, since hippocampal volume decreases with normal aging, age-specific benchmarks are essential. While hippocampal atrophy supports an AD diagnosis in patients with typical symptoms, it alone does not significantly enhance diagnostic accuracy beyond clinical evaluation. Some research suggests that MRI characteristics might forecast the progression rate of AD and could eventually inform treatment choices.

Techniques like hippocampal volumetry, adjusted for age using standards from the Alzheimer Disease Neuroimaging Initiative, may predict the progression from MCI to dementia. Yet, these methods are not widely implemented or validated in clinical settings [97-98-99-100-101].

Functional brain imaging techniques such as 18-F fluorodeoxyglucose positron emission tomography (18F-FDG-PET) and single-photon emission computed tomography (SPECT) show specific areas of decreased metabolism (PET) and blood flow in AD, particularly in regions like the hippocampus, precuneus, and the lateral parietal and posterior temporal cortex. 18F-FDG-PET is particularly useful for distinguishing AD from frontotemporal dementia in cases with atypical symptoms and from non-neurodegenerative conditions such as depression. Currently, 18F-FDG-PET and SPECT are the main functional imaging methods available for clinical use [102-103-104].

The 18F-FDG-PET can reveal the cerebral areas where hypometabolism prevails, showing their extent and topography, thus allowing the assessment of the corresponding cognitive impairment, neuronal damage endophenotype, and associated clinical deficit [105]. Each type of dementia is associated with a specific regional distribution of neurodegeneration foci, and it is precisely the 18F-FDG-PET that highlights the hypometabolic pattern, thus aiding the physician in the diagnostic process [106]. Specifically, AD is characterized by hypometabolism involving temporal and parietal cortex, the posterior cingulate and the precuneus. In addition, the temporoparietal hypometabolic pattern is more severe in patients with early-onset Alzheimer's disease (EOAD) compared to those with late-onset disease (LOAD) due to the greater severity of the pathology and more significant clinical impairment [107]. There is a notable association between the topographic distribution of hypometabolism and the corresponding cognitive deficit, so 18F-FDG-PET can also help quantify the clinical impact of neurodegeneration and the stage of the disease [108].

Since 18F-FDG-PET can identify metabolic changes indicative of synaptic dysfunction that precede neuronal loss, it can detect signs of neurodegeneration before brain atrophy occurs [109], thus in the prodromal stage of dementia [110]. 18F-FDG-PET is of extreme importance in outlining disease progression and prognosis, particularly in predicting the conversion of MCI to dementia [111]. In individuals with MCI, the typical hypometabolic pattern involving the temporoparietal cortex predicts conversion to AD with an accuracy of over 90% [112]. Conversely, a normal 18F-FDG-PET scan excludes actual signs of neurodegeneration, especially when associated with clinical stability over several years of follow-up [113-114].

Based on this evidence, it is clear that regional neuronal dysfunction, revealed by hypometabolism in a brain area, represents a well-recognized marker indicative of NDDs [105]. The high prognostic value of 18F-FDG-PET is crucial for monitoring the disease by the physician and for choosing the best therapeutic approach. In summary, 18F-FDG-PET has a remarkable ability to highlight the typical temporoparietal hypometabolism pattern of AD already in the MCI condition, a high predictive value of the outcome, and a significant negative predictive role at the individual level.

The great potential of using 18F-FDG-PET to reveal neurodegenerative changes cannot hide some criticisms, especially in clinical settings where the use of quantification methods is not extremely common. The qualitative interpretation of brain metabolism maps and visual inspection significantly influence the sensitivity and specificity of 18F-FDG-PET: these values change according to the physicians' experience and the lack of an objective threshold between normal and pathological results [115]. In 2015, a systematic review of the Cochrane database collected and analyzed 14 studies (including a total of 421 participants) with the aim of determining the diagnostic accuracy of 18F-FDG-PET to predict progression to AD or other types of dementia in individuals with MCI.

The analysis concluded that there is no current evidence to support the routine use of 18F-FDG-PET in clinical practice in subjects with MCI. The result is related to the lack of defined pathological thresholds and the extreme variability of sensitivity and specificity values, which were nevertheless estimated at 76% and 82%, respectively [116]. A subsequent review aimed to clarify the role of 18F-FDG-PET in predicting AD in subjects with MCI compared to structural MRI and SPECT perfusion. Although both 18F-FDG-PET and MRI effectively predict AD in MCI conditions, the review highlighted the extreme variability in metrics, samples, and outcomes that produced discordant results [117]. Therefore, it is necessary to use standardized and validated quantification methods to provide reliable results in research studies and clinical settings; an example of a quantification technique is Statistical Parametric Mapping (SPM), which allows statistical comparison, based on individual voxels, of PET images from different patients or patients and normative data, thus providing the subject's cerebral hypometabolic pattern, which can be traced back to a degenerative disorder [118].

Amyloid PET imaging, using tracers like florbetapir F-18, flutemetamol F-18, and florbetaben F-18, measures the burden of amyloid plaques in the brain and aids in differentiating AD from other dementia causes. A significant study completed in December 2017 demonstrated that amyloid PET imaging markedly affects clinical management and diagnosis. These tracers are approved for qualitative assessment of Aβ plaque density in symptomatic dementia patients; a positive scan indicates amyloid pathology, but it doesn't exclude other coexisting pathologies. However, amyloid imaging is not recommended for patients who already meet the clinical criteria for probable AD with a typical age of onset, nor is it suitable for assessing dementia severity [119-120-121]. Research on tau PET imaging tracers, like flortaucipir F-18, which the FDA approved to assess NFT density, is ongoing. These tracers may provide better insights into AD progression and are more closely associated with clinical symptoms and brain atrophy than amyloid PET. However, flortaucipir F-18 is not effective for diagnosing non-AD tauopathies such as FTLD [122-123].

Several biomarkers have been extensively studied to understand the molecular and degenerative processes involved in AD, although they are not yet routinely used for diagnosis. Biomarkers are biological molecules found in blood, body fluids, or tissues that indicate normal or abnormal processes, conditions, or diseases. While not recommended for standard diagnosis, biomarker testing can enhance confidence in diagnosing AD, especially in cases of early-onset dementia or atypical presentations where distinguishing from other NDD like frontotemporal dementia (FTD) is challenging. Molecular biomarkers related to Aβ protein deposition include low levels of CSF Aβ42 or a decreased Aβ42:Aβ40 ratio and positive amyloid PET imaging using specific tracers. Biomarkers associated with tau deposition, a key component of neurofibrillary tangles, include elevated levels of total tau and phospho-tau in CSF and tau PET imaging with flortaucipir F-18.

Apart from molecular biomarkers, topographic or neurodegenerative biomarkers assess brain changes correlated with regional neuronal dysfunction and eventual neuronal death in AD. These include medial temporal lobe atrophy observed on MRI and reduced glucose metabolism in the temporoparietal regions detected by 18F-FDG-PET. While less specific than molecular biomarkers, topographic biomarkers better correlate with clinical symptoms. Combining multiple biomarkers rather than relying on individual tests improves predictive accuracy. Research criteria now incorporate these biomarkers to provide a biologically based diagnosis of AD, independent of clinical symptoms. The amyloid, tau, and neurodegeneration (ATN) framework integrates markers of neurodegeneration to aid in disease staging. Although promising, plasma biomarkers are not yet established in clinical practice. Reduced levels of APOE and APOE ε4 in plasma, along with various other plasma/serum and CSF proteins, have been investigated for their predictive value in AD and MCI. Ongoing research focuses on plasma biomarkers such as phospho-tau181 and phospho-tau217, which correlate strongly with CSF phospho-tau measures and amyloid and tau PET imaging.

Additionally, a plasma measure of β42/β40 ratio using specific assays has shown potential in detecting amyloid deposition [124-125-126].

Definitive diagnosis of AD requires histopathologic examination, which is rarely done in life, the diagnosis of AD in practice depends on the clinical criteria. Over the past 15 years, significant progress has been made in developing and making available in-vivo biomarkers for AD, understanding its natural history, and applying this knowledge to diagnostic research frameworks. The International Working Group (IWG) introduced the first revision to diagnostic criteria in 2007, proposing AD as a clinical-biological entity based on in-vivo biomarkers and specific clinical phenotypes. In 2010, the IWG established a lexicon for AD, including classifications for presymptomatic stages.

In 2011, NIA-AA criteria defined three preclinical stages based on the amyloid cascade hypothesis. In 2016, IWG and NIA-AA consensus expanded the classification to include preclinical AD diagnosed based on Aβ and tau positivity. In the 2018 NIA-AA framework, AD diagnosis centered around biomarker-defined disease status (ATN status), even in the absence of cognitive symptoms. These advancements have shifted AD diagnosis from the dementia stage to the prodromal stage and introduced the possibility of preclinical diagnosis, which is crucial for testing potential therapies for secondary prevention of AD. The diagnosis of AD is clinical–biological. It requires the presence of both a specific typical clinical phenotype of AD and biomarker evidence of AD pathology (amyloid-positive and tau-positive). The positivity of both amyloid and tau biomarkers is required for diagnose a probable AD because an amnestic phenotype with only amyloid or tau positivity is not specific to AD (diagnose of possible AD) and is seen in other NDDs with amyloid co-pathology [127].

Atypical presentation

The **posterior cortical atrophy** is a syndrome that manifests with progressive cortical visual impairment.

Patients are often first evaluated by optometrists or ophthalmologists for visual complaints, such as difficulty reading and driving. A diagnose requires three or more of the following early or presenting features:

- Space perception deficit
- Simultanagnosia (ie, the inability to integrate a visual scene despite adequate visual acuity to resolve individual elements)
- Object perception deficit
- Constructional dyspraxia
- Environmental agnosia
- Oculomotor apraxia (the inability to direct gaze accurately to a new target)
- Dressing apraxia
- Optic ataxia (the inability to reach accurately under visual guidance)
- Alexia
- Left/right disorientation
- Acalculia
- Limb apraxia
- Apperceptive prosopagnosia
- Agraphia
- Homonymous visual field defect
- Finger agnosia

Furthermore, there should be a notable preservation of anterograde memory function, speech, nonvisual language abilities, executive functions, and behavioral and personality traits. Neuroimaging typically reveals predominant atrophy, hypometabolism, or hypoperfusion in the occipitoparietal or occipitotemporal regions. Some individuals with a biparietal variant may exhibit dyspraxia and encounter challenges in performing basic bimanual tasks like dressing.

Additional early clinical indications may encompass visuospatial disorientation, dysgraphia, and language difficulties with deficits in semantic memory.

Both neuropathological examination and neuroimaging studies often reveal significant involvement of the bilateral parietal lobes [128-129-130].

Primary progressive aphasia (PPA) encompasses a diverse range of NDDs characterized by gradual language decline while memory and other cognitive functions remain relatively intact, particularly in the early stages. PPA is classified into three main variants based on the type of language impairment: nonfluent, semantic, and logopenic [131]. Typically, PPA is associated with FTLD rather than AD. However, a significant proportion, up to one-third, are later found to have AD upon autopsy. Among the variants, the logopenic variant is most commonly linked to AD. It is characterized by frequent word-finding pauses and paraphasic speech errors without significant grammar or comprehension deficits.

While AD pathology can also be present in nonfluent or semantic variants of PPA, it is less frequent. In cases of logopenic variant PPA, structural imaging often reveals predominant atrophy in the left posterior perisylvian or parietal regions. Functional imaging techniques such as 18F-FDG-PET or SPECT may demonstrate reduced metabolism or perfusion in these areas. Amyloid PET imaging may show elevated signal in approximately 85 percent of logopenic variant cases and around 20 percent of semantic and nonfluent variants, indicating AD pathology. However, it's essential to note that some cases may exhibit mixed pathologies, so amyloid PET results alone should not be considered diagnostic of AD [131-132-133].

The **behavioral variant of Alzheimer disease** (bvAD) represents another, rare variant of AD that is characterized by early and predominant behavioral deficits and personality changes caused by AD pathology. The bvAD clinical syndrome overlaps substantially with that of the behavioral variant of frontotemporal dementia (bvFTD) and approximately 10% to 40% of clinically diagnosed bvFTD cases have positive AD biomarkers and/or neuropathologically confirmed AD.

The latest research criteria in order to diagnose bvAD were made in 2022 by Ossenkoppele et al, and are the following [134-135].

The clinical syndrome is characterized by:

A) Early, persistent, predominant, and progressive change or exacerbation of at least 2 of 5 core behavioral features of the diagnostic criteria for behavioral variant frontotemporal dementia:

- ➢ Behavioral disinhibition (1 of the following symptoms must be present): socially inappropriate behavior; loss of manners or decorum; Impulsive, rash, or careless actions
- ➢ Apathy or inertia (1 of the following symptoms must be present): Apathy; Inertia
- ➢ Loss of empathy or sympathy (1 of the following symptoms must be present): diminished response to other people's needs and feelings; diminished social interest, interrelatedness, or personal warmth
- ➢ Perseverative, stereotyped, or compulsive or ritualistic behavior (1 of the following symptoms must be present): simple, repetitive movements; complex, compulsive, or ritualistic behaviors; stereotypy of speech
- ➢ Hyperorality and dietary changes (1 of the following symptoms must be present): altered food preferences; binge eating or increased consumption of alcohol or cigarettes; oral exploration or consumption of inedible objects

B) In addition, documented impairment in executive functions and/or episodic memory with relatively preserved language and visuospatial abilities.

Criteria for clinical bvAD are not met if the behavioral deficits are (better) accounted for by another concurrent (active) neurological (eg, LBD) or non neurological medical (eg, psychiatric) comorbidity, a known genetic variant associated with familial behavioral variant of frontotemporal dementia, or the use of medication.

Supportive features (not mandatory; categories A and B must be met):

- ➢ Presence of hallucinations and/or delusions.
- ➢ Alzheimer disease–specific (ie, temporoparietal pattern) and/or behavioral variant of frontotemporal dementia–specific neuroimaging features (ie, frontotemporal pattern) on magnetic resonance imaging, computed tomography, perfusion SPECT or 18F-FDG-PET.

For Possible bvAD: meets criteria for clinical bvAD and there is in vivo biomarker evidence for the presence of (1) Aβ pathology on amyloid PET and/or in CSF and/or (2) tau pathology in CSF and/or plasma.

For Probable bvAD: meets criteria for clinical bvAD or possible bvAD, with additional in vivo tau PET evidence for the presence of neocortical tau aggregates.

For Definite bvAD: meets criteria for clinical bvAD, possible bvAD, or probable bvAD, and presence of AD is established by:

- ➢ Histopathological indication of AD as the primary pathology on biopsy or at autopsy, or
- ➢ Presence of a known genetic variant associated with familial AD.

Therapy and future perspectives

Until now there is no specific treatment in order to heal or prevent AD.

The therapy clinically used at the moment is just to improve the cognitive symptoms and to delay the neurodegeneration. The first class of drug chosen are cholinesterase inhibitors (like donepezil, rivastigmine, galantamine), that increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft and provide modest symptomatic benefit in patients with AD [136]. In moderate-advanced AD is administered memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist having a neuroprotective function from glutamate esotoxicity [137]. A new hope for future therapy is arising thanks to the research and clinical trials related to active and passive immunotherapy for AD. The aim is to find a specific therapy for biomarkers that cause AD. Aducanumab has been one of the promising drugs, a monoclonal antibody against Aβ, that is prescribed in the USA. However after analysis it was shown that it has just reduced the level of biomarkers without a reduction of cognitive symptoms. This lack of efficacy could be due to the fact we still do not fully know the mechanism under NDDs [138].

All the effort to better under categorize the NDDs spectrum that is clinically viewed through biomarkers is in order to develop future therapeutic strategies directed to the core of the specific etiopathology.

2. Objectives

The bvAD represents an extremely rare variant of AD that is characterized by predominant behavioral disturbances, personality changes and executive deficits caused by AD pathology. The rarity of the variant and the clinical overlap with the behavioral variant of frontotemporal dementia, along with the frequent occurrence under the age of 65 years (early-onset AD), make it essential to recognize its clinical and prognostic features.

The study aims to in detail explore the characteristics of the rare bvAD. The main objectives are the following:

- ➢ identify the brain metabolism patterns, using the 18F-FDG-PET, in patients with clinical diagnosis of probable bvAD;
- ➢ define clinical, neuropsychological and neuropsychiatric characteristics at the baseline in patients with bvAD showing different hypometabolism patterns; analyze clinical, neuropsychological and neuropsychiatric characteristics at follow-up;
- ➢ evaluate the progression rate of the cognitive decline related to the brain hypometabolism pattern;
- ➢ identify a possible correlation between the metabolism pattern at the 18F-FDG-PET and clinical, neuropsychological and neuropsychiatric manifestations.

3. Methods

3.1 Participants

In this retrospective, longitudinal study, participants were recruited at the Centre for Dementia and Cognitive Disorders at Sant'Andrea Hospital, University of Piemonte Orientale, Vercelli, Italy. We selected 24 patients who have performed at 18F-FDG-PET from 2019 to 2023 based on defined inclusion and exclusion criteria.

The inclusion criteria were the following:

- ➢ diagnosis of probable bvAD based on the Research Criteria for bvAD made in 2022 [135];
- ➢ at least one MMSE performed at the first visit (baseline) and at the follow-up;
- ➢ baseline evaluation including neurological, neuropsychological and neuropsychiatric assessment and a follow-up visit including the same evaluation at least 6 months from baseline;
- ➢ 18F-FDG-PET performed within 6 months from the baseline visit.

The exclusion criteria were the following:

- ➢ lack of MMSE at the baseline and/or at the follow-up;
- ➢ lack of fundamental demographic data, like educational level, or follow-up assessment;
- ➢ story of active cancer, rheumatic disease or autoimmune, chronic infection or active hormone-therapy and/or chemotherapy;
- ➢ severe comorbidity not therapeutically controlled (like uncontrolled diabetes, severe renal failure) or primary psychiatric disorder.

3.2 Neuropsychological and neuropsychiatric evaluation

All the included patients were evaluated clinically and through cognitive, neuropsychological and neuropsychiatric tests described below.

Mini Mental State Examination (MMSE)

The global cognitive status was assessed with the MMSE, that is a quick and short assessment to explore the cognitive status and how it changes through the time. The test is composed of 22 items that quickly evaluate time and spatial orientation, verbal short and long term memory, attention, arithmetical calculation, oral denomination of objects ability, comprehension of sentences ability and constructive praxis. The final score, which is the sum of the score in each item, ranges between a minimum of 0 (maximum cognitive deficit) and 30 (no cognitive deficit). The most advantages of MMSE are the easy and short administration and the possibility to be used also in case of severe form of cognitive deterioration [139]. However, the MMSE lacks accuracy and it is not suitable for identifying specific cognitive deficits [140]. Despite these limitations, the MMSE can be fruitfully used to measure cognitive deterioration over time. In the current study, in order to analyze the progression of cognitive deterioration, due to the retrospective nature of the study, it was adopted a Progression Rate (PR) index, already used in other previous studies to evaluate the level of cognitive deterioration through the time in a population affected by MCI. The rate was obtained through the following formula: (Score MMSE at the baseline - Score MMSE at the follow-up) / years of follow-up. PR can be used to monitor the progression of cognitive deterioration, quantifying the number of points lost per year at the MMSE [141].

Neuropsychiatric Inventory (NPI)

The NPI is an inventory used to evaluate a variety of behavior disorders in patients with dementia in order to distinguish the frequency and severity of behavioral changes and their impact on the caregiver (evaluated as distress scores). This inventory is composed of 12 domains: delusions, hallucinations, agitation/aggressivity, depression/dysphoria, anxiety, euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, sleep behavior disorder, and eating disorder. Each domain consists of a specific screening item based on 7-8 questions performed if the caregiver answers positively at the beginning question. Each domain is evaluated in terms of the frequency and severity of behavior considered as the most aberrant or problematic in that domain. The questions are always related to the change after the onset of the disease and the patient's situation in the 4-6 weeks preceding the visit.

Regarding scoring, if the answer was positive to the screening question, it is asked to the caregiver to evaluate the frequency (F) and severity (S) of each symptom (on growing scales from 1 to 4 for frequency and from 1 to 3 for severity). For each scale corresponding to each behavioral domain, multiplying frequency per severity, a maximum score of 12 is obtained. The final score is obtained by summing all total scores for each domain to a maximum total final score of 144. The final total score of NPI is associated with the severity of dementia. The score of the distress (D) in each domain is between 0 and a maximum of 5 [142].

In the current study the NPI was used to evaluate the burden of neuropsychiatric symptoms at baseline and follow-up visits.

Neuropsychological battery test

All participants underwent a complete neuropsychological battery, both at baseline and follow-up, including the following tests.

- Digit Span Forward : analyze short-term verbal memory. The examiner reads in a loud voice a sequence of digits of length progressively increasing and then invites the patient to repeat each sequence of digits in the same order. The score obtained corresponds to the longest sequence of digits correctly repeated [143];
- Digit Span Backward: analyze short-term verbal memory. The examiner reads in a loud voice a sequence of digits of length progressively increasing and then invites the patient to repeat each sequence of digits in the reverse order. The score obtained corresponds to the longest sequence of digits correctly repeated [143];
- Rey's Auditory Verbal Learning test (RAVLT): analyze the short-term episodic memory. It evaluates the ability to learn a list of words read in loud voice from the examiner five times. In the Immediate Recall, at the end of each presentation the examiner asks the patient to repeat the largest number of words that have been read. The sum of the number of words correctly remembered from the patient after each presentation corresponds to the score of Immediate Recall (range between 0 and 75). In the Delayed Recall, after 15 minutes from the fifth presentation of words in the list, the examiner (without reading again in loud voice the list of words) asks the patient to remember the largest number of words previously read. The sum of the numbers of words correctly remembered after 15 minutes from the fifth presentation corresponds to the score of Delayed Recall (range between 0 and 15) [144];
- Raven's Progressive Matrices: it is an logic-deductive intelligence test based on visual material and without time limits. During the test, it is asked to the patient to indicate, from six possible alternatives, the missing element to a visual pattern (score between 0 and 36) [145];
- Rey-Osterrieth Complex Figure (ROCF): it is used to analyze fundamental aspects of mesic function, like short and long-term visuospatial memory, and constructional praxis. They are available in two shapes (A and B).

The patient has to copy at the beginning a complex geometrical figure, without a meaning, and after a break of 10 minutes, while it is possible to perform a verbal task, to recopy the figure just from the memory. Eventual constructive deficits emerged during the copy task. It is possible to make the delayed copy at a longer time interval (after 20, 30 or 45 minutes). The evaluation could consider three aspects: the time used to complete the task, the way of copy (how precede the patient during the task), the accuracy of the copy in each part of the figure [146];

- Trail Making Test (TMT): it evaluates split attention, visual-motor coordination, ability to conceptual setting, mental flexibility. It is extremely sensitive in revealing brain damage. The test is composed of two parts (A and B). The correct performance of part A required adequate visual elaboration capacity, number recognition, knowledge e reproduction of number sequences, motor speed. The correct performance of part B, in addition to previous abilities, needs cognitive flexibility and shifting ability in range. The difference of time between the two tasks (A and B) is also a rate of cognitive flexibility and shifting ability. In part A, the patient has to join with a line growing order 25 numbers circled and printed randomly on the sheet, while part B contains numbers and letters. The patient has to do simultaneously two tasks: connecting in growing and alternating order numbers and letters (like 1-A-2-B-3-C, etc…) and linking physically alternating numbers (from 1 to 13) and letters (from A to N). The examiner has to correct the patient after each mistake committed linking each item (without interrupting the time counting). The score is provided by time necessary to complete tasks A and B, and the gap time between the two tasks [147];
- Spinner's matrices: is used to analyze visual attention. It is composed of three number matrices where the patient has to tick with the pen the target number inside all the stimuli numbers: the first matrix has 1 target and 10 stimuli, the second 2 targets and 20 stimuli, the third 3 targets and 30

stimuli. On the top of the sheet is written the target number, line A is used by the examiner as an example for the task, line is used to check if the patient understands the task, while the test starts from line I. The total score is provided from the correct number ticked in each matrix in 45 seconds, considering omissions and/or mistakes. The maximum total score is 60 [148].

- Frontal Assessment Battery (FAB): this battery is used to evaluate the difference ability controlled by the frontal lobes. It is composed of 6 subtests for different abilities:
    1) semantic categorization through analogies: the patient has to conceptualize the link between two objects belonging to the same category (such as a banana and an orange). The range score is from 0, if not conceptualize none of the three relationships proposed, to a maximum of 3;
    2) cognitive flexibility through phonological verbal fluency: the patient has to say, in 60 seconds, as many words as he can starting with the letter "s". All grammar or semantic categories are accepted, except for proper names (name of person or city). The score assigned is: 3 if said more than 9 words, 2 between 6 and 9 words, 1 between 3 and 5 words, 0 less than 3 words;
    3) planning through motor sequence (Lurija Test): the examiner, sitting in front of patient, performs for three times Lurija's sequence "fist-cut-palm". Then the patient has to repeat the sequence, at the beginning simultaneously with the examiner and then alone. The score is: 3 if he performs correctly 6 consecutive times the sequence alone, 2 at least 3 times, 1 if he is able to perform the sequence only with the examiner, 0 neither with the examiner;

4) Sensibility to interference through the conflictual rules test: the patient has to reverse the motor program proposed by the examiner, like hit the table with the fist one time when the examiner hits two times, and hit two times when the examiner hits one time. The examiner performs the sequence 1-1-2-1-2-2-2-1-1-2. The score assigned is: 3 he performs without mistakes, 2 makes two mistakes, 1 more than two mistakes, 0 if hits the table like the examiner at least for 4 consecutive times;
5) Inhibition control through go/not to go test: the patient sometimes has to mimic the examiner, other times inhibits the motor program like hit the fist on the table one time when the examiner does it one time, and no hit when the examiner hits two times. The examiner performs the sequence 1-1-2-1-2-2-2-1-1-2. The score assigned is: 3 he performs without mistakes, 2 makes two mistakes, 1 more than two mistakes, 0 if hits the table like the examiner at least for 4 consecutive times;
6) environmental autonomy through inhibition of grasping behavior: the examiner, sitting in front of the patient, places the hands of the patient with palms up on his knees . Without saying anything or looking at the patient, the examiner brings his hands near to the hands of the patient, touches the palm and sees if the patient spontaneously grasps his hands. If the patient grasps the hand, the test is repeated but this time the examiner invites the patient not to grasp the hands. The score assigned is: 3 the patient does not grasp the hands, 2 if existates and asks what to do, 1 if the patient grasps without excitation, 0 grasps also when is invited not to do it.

The total score is obtained by summing the score of each subtest. The range of the score is between 0 and 18. A total score less than 13,48 is considered pathological [149];

- ➢ Phonological verbal fluency test: similarly to the subtest in the FAB, the patient has to say, in 60 seconds, as many words as he can starting with the letter “s”, “a” and “f”. The score is obtained by the total number of words said or the average during the three trials. It is very sensible to evaluate damage in the left hemisphere or in frontal lobes [150];
- ➢ Semantic verbal fluency test: the patient has to say, in 60 seconds, as many words as he can belonging to a specific category. Usually 3 or 4 categories are tested. General expression or circumlocutions are not considered. The score is obtained by the total number of words said or the average during the trials [150].

3.3 18F-FDG-PET

Brain 18F-FDG-PET acquisition was performed at the “Maggiore della Carità” University Hospital,Novara, Italy, following standardized procedures, in compliance with the European Association of Nuclear Medicine guidelines [151]. PET/CT images were acquired by the Philips Ingenuity TF 64 PET/CT (Philips Healthcare, Cleveland, OH, USA). Patients were fasted for at least six hours before radiopharmaceutical injection The blood glucose level was < 120 mg/dl. Static emission images were acquired 40–50 min after injecting 175–210 MBq of 18F-FDG via a venous cannula. The mean static acquisition scan duration was 10 min. PET images were reconstructed using a Time-Of-Flight (TOF), list mode, blob based, ordered subsets maximum likelihood expectation maximization algorithm (OSEM). Attenuation, scatter, random, detector normalization, isotope decay, system deadtime, and crystal timing corrections were applied.

The Statistical Parametric Mapping (SPM) 12 software, implemented in Matlab (MathWorks, Natick, MA, USA), was used for the image analysis.
We adopted the single-subject method, a standardized SPM procedure [152], allowing to obtain hypometabolism maps at the single subject level by a voxel-based comparison between the single patient scan and a large dataset of HC.

The procedure has been validated using different HC datasets for the single-subject estimation of brain metabolism [153]. In detail, each single-subject 18F-PET-FDG image is spatially normalized using a specific PET template, allowing an accurate estimation of metabolic abnormalities for single-subject analysis in the Montreal Neurological Institute-Hospital (MNI) space [115]. The warped image is smoothed with an isotropic 3D Gaussian kernel (FWHM: 8–8-8 mm), and global mean scaling is applied to each image to account for between-subject uptake variability. Then, the normalized and smoothed image is tested for relative brain hypometabolism by entering a SPM two-sample t-test in which the single-subject image is compared with a large 18F-FDG-PET dataset of HC, using age as a nuisance covariate. In the current study, we adopted the "Associazione Italiana Medicina Nucleare" (AIMN) 18F-FDG-PET HC dataset. The AIMN is a voluntary non-profit association promoting the application and development of the medical and biological use of the physical properties of the atomic nucleus. As previously described, we included n=125 HC from the dataset, aged between 20 and 84 years, characterized by normal global cognition [153]. The resulting SPM maps (t-maps) were thresholded at p-value < 0.05 family-wise error (FWE)-corrected for multiple comparisons (minimum cluster extent: 100 voxels). The single-subject method has been validated in clinical and research settings for differential diagnosis in several neurodegenerative conditions in both the symptomatic and preclinical stages of neurodegeneration. 18F-FDG-PET regional hypometabolism was extracted from regions of interest (ROIs) defined by using the automated anatomical labeling (AAL) atlas to extract ROIs and the toolbox REX to extract values from the hypometabolism maps [154].

3.4 Statistical analysis

All the statistical analyses were conducted using SPSS 25.0 version (Statistical Package for Social Science Software, IBM, Armonk, NY, USA).

The normality of the sample was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean and standard deviation (SD), while nominal variables were expressed as count and percentage (%).

Comparative analyses between groups identified based on belonging to different hypometabolism maps were performed using the Mann-Whitney test due to the non-normal distribution of the data. Comparisons between categorical variables were performed using the Chi-squared (χ^2) test. The variables examined and compared between the various groups included demographic (age, education, sex), neuropsychological (MMSE RAVLT RI and RD, Digit Span Forward and Backward, ROCF Copy and delayed copy, Raven's progressive matrices, TMT A and B, Spinner's matrices, FAB, Phonological and semantic verbal fluency test, all tests considered at baseline and follow-up), and neuropsychiatric (delusions FxS and D, hallucinations FxS and D, agitation FxS and D, depression FxS and D, anxiety FxG and D, euphoria FxS and D, apathy FxS and D, disinhibition FxS and D, irritability FxS and D, aberrant motor activity FxS and D, nocturnal behavior disorder FxS and D, eating disorder FxS and D, total score FxS and D, all both at baseline and follow-up) variables. The degree of cognitive decline over time was compared using the PR. To confirm statistical significance, considering multiple comparisons, Bonferroni correction was used. Regarding 18F-FDG-PET analysis, cerebral hypometabolism maps were obtained through voxel-based statistical comparison, using the SPM12 software, between the images of the included subjects and the images of 124 controls (t-test, significance threshold set at $p < 0.05$ for clusters containing at least 100 voxels). Finally, to test the presence of potential correlations between hypometabolism values and scores in neuropsychological and neuropsychiatric tests, Pearson correlations were conducted between the variables examined. All statistical results were considered significant with a p-value threshold of < 0.05.

3.5 Ethical aspects

The study was conducted according to the principles of the Declaration of Helsinki and received approval from the Intercompany Ethics Committee of Alessandria (approval code 14415/2023, approval date May 2023). Participants received comprehensive information regarding the study structure, procedures, objectives, and methods used. Patient data were anonymized and analyzed with the authorization of each participant.

4. Results

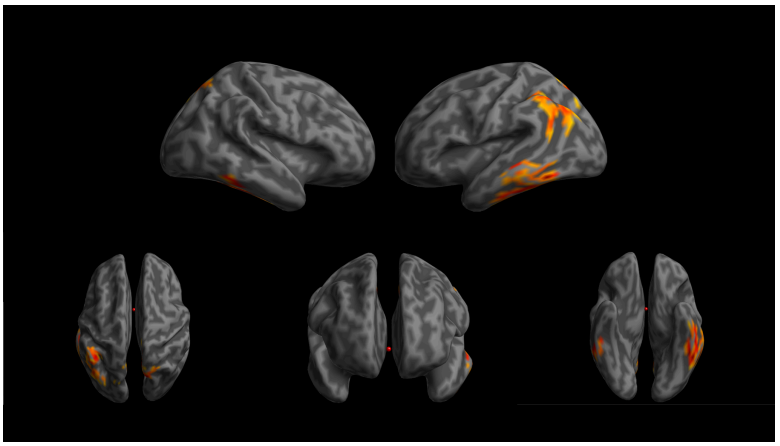
4.1 Classification based on brain hypometabolism through 18F-FDG-PET

The single-subject 18F-FDG-PET analysis revealed the presence of two main patterns of brain hypometabolism, characterized by some similarities and crucial peculiarities. In fact, considering the whole sample, n = 24 (100%) of participants showed brain metabolic abnormalities in temporo-parietal regions, while n = 14 (58%) showed brain hypometabolism involving both temporo-parietal and frontal regions. In order to explore clinical, neuropsychological and neuropsychiatric features related to the brain metabolism abnormalities, we classified subjects according to the main hypometabolic regions, in patients with solely temporo-parietal hypometabolism and patients with both temporo-parietal and frontotemporal hypometabolism. To provide a single-participant classification with an objective approach, we tested the group membership based on the adherence of the hypometabolism maps to predefined disease-specific anatomical templates, according to previously validated literature [111].

Thus, the rating of SPM maps allowed us to classify participants into two patterns:

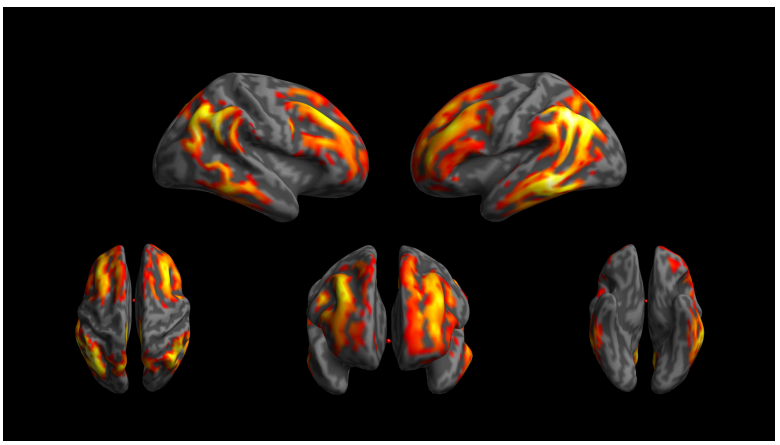
- temporoparietal hypometabolism pattern, namely TP-bvAD, that includes the following anatomical areas shown in figure 1:
    - inferior temporal gyrus;
    - precuneus;
    - inferior parietal gyrus;
    - angular gyrus;
    - superior temporal gyrus.

Figure 1



- hypometabolism in the fronto-temporal cortex, specifically frontal-like pattern, namely FT-bvAD, that includes the following anatomical areas shown in figure 2:
  - angular gyrus;
  - precuneus;
  - inferior, middle and superior temporal gyrus;
  - inferior, middle and superior frontal gyrus;
  - insula;
  - frontal inferior operculum.

Figure 2



4.2 Demographic, clinical and cognitive characteristics

The whole sample, composed by 24 bvAD patients, was divided into two groups based on the hypometabolism pattern revealed by the 18F-FDG-PET: n = 10 patients showed the TP-bvAD pattern and n = 14 patients showed the FT-bvAD group. The demographic, clinical and cognitive characteristics of the whole sample and the two groups are described in table 1.

Table 1

	Whole sample n = 24	TP-bvAD n = 10	FT-bvAD n = 14	p-values
Age (in years)	69,58 ± 8,54	70,60 ± 6,67	68,86 ± 6,67	0,841
Education	8,67 ± 3,66	9,10 ± 4,59	8,36 ± 4,59	0,796
Female	18 (75%)	8 (80%)	10 (71,43%)	0,914
Onset (in months)	22,75 ± 13,61	21,00 ± 10,48	24,00 ± 10,48	0,709
Follow-up (in months)	20,38 ± 8,65	19,00 ± 8,49	21,36 ± 8,49	0,585

Age, onset, and follow-up are perfectly comparable between the two groups. p-values refer to the comparison between TP-bvAD and FT-bvAD.

4.3 Cognitive, neuropsychological and neuropsychiatric features at the baseline

Cognitive and neuropsychological assessment

In table 2 is described the score at MMSE at the baseline for both groups. FT-bvAD group obtained a lower score in MMSE than TP-bvAD group, and it is statistically significant difference (p = 0,031).

In table 2 is also described each different score in different neuropsychological tests at the baseline for both groups. A part from TMT B, FT-bvAD group obtained a lower score in all neuropsychological tests than TP-bvAD group, with a statistically significant difference n Raven matrices (p = 0,016), TMT B (p = 0,48) and SVF test (p = 0,009).

Table 2

	Whole Sample	TP-bvAD	FT-bvAD	p-values
MMSE	19,50 ± 3,75	21,85 ± 2,75	17,81 ± 2,75	0,031
RAVLT RI	27,19 ± 6,51	30,24 ± 8,74	24,65 ± 8,74	0,107
RAVLT RD	3,78 ± 2,26	4,07 ± 2,76	3,53 ± 2,76	0,539
Digit Span F	4,31 ± 1,31	4,65 ± 0,68	4,09 ± 0,68	0,115
Digit Span B	2,89 ± 1,48	3,55 ± 1,56	2,44 ± 1,56	0,082
ROCF C	22,86 ± 9,77	26,4 ± 9,11	20,17 ± 9,11	0,169
ROCF R	7,25 ± 2,98	8,38 ± 3,26	5,90 ± 3,26	0,400
RAVEN matrices	25,43 ± 6,79	29,61 ± 2,81	22,39 ± 2,81	0.016
TMT A	96,18 ± 39,82	104,00 ± 113,28	89,67 ± 113,28	0,628
TMT B	210,50 ± 49,36	139,60 ± 78,02	261,14 ± 78,02	0,048
Spinner's test	28,29 ± 5,35	32,60 ± 12,09	22,91 ± 12,09	0,055
FAB	11,48 ± 3,22	12,34 ± 4,90	10,63 ± 4,90	0,505
PVF test	20,48 ± 8,00	23,29 ± 4,59	18,37 ± 4,59	0,095
SVF test	24,70 ± 8,59	31,05 ± 6,19	19,95 ± 6,19	0,009

Table 2 describes cognitive and neuropsychological characteristics. All scores are corrected by age and educational level. p-values refer to the comparison between TP-bvAD and FT-bvAD.

NPI

In table 3 is described the scores in each item in NPI and total score at the baseline for both groups. A part from Apathy Distress, FT-bvAD group obtain higher score in each item and in the total one than TP-bvAD group, showing a statistically significant difference in delusions FxS and D (p = 0,003 and p = 0,018), agitation FxS and D (both p = 0,003), motor disorder FxS and D (p = 0,004 and p = 0,012), sleep disorder FxS and D (p = 0,018 and p = 0,004), eating disorder FxS and D (p = 0,004 and p = 0,012), and total FxS and D (p = 0,000 and p = 0,003).

Table 3

	Whole Sample	TP-bvAD	FT-bvAD	p-values
Delusions FxS	1,52 ± 3,00	0,10 ± 0,30	2,62 ± 0,30	0,003
Delusions D	1,26 ± 1,75	0,30 ± 0,90	2,00 ± 0,90	0,018
Hallucinations FxS	0,78 ± 2,47	0,00 ± 0,00	1,38 ± 0,00	0,067
Hallucination D	0,78 ± 1,55	0,00 ± 0,00	1,38 ± 0,00	0,067
Agitation FxS	2,09 ± 3,56	0,10 ± 0,30	3,62 ± 0,30	0,003
Agitation D	1,17 ± 1,57	0,10 ± 0,30	2,00 ± 0,30	0,003
Depression FxS	3,52 ± 4,10	2,90 ± 2,07	4,00 ± 2,07	0,879
Depression D	1,74 ± 1,31	1,70 ± 1,00	1,77 ± 1,00	0,927
Anxiety FxS	3,87 ± 3,59	2,40 ± 1,91	5,00 ± 1,91	0,101
Anxiety D	2,17 ± 1,28	1,70 ± 1,10	2,54 ± 1,10	0,148
Euphoria FxS	0,48 ± 1,08	0,30 ± 0,90	0,62 ± 0,90	0,313
Euphoria D	0,39 ± 0,84	0,20 ± 0,60	0,54 ± 0,60	0,313
Apathy FxS	4,13 ± 4,70	3,10 ± 2,77	4,92 ± 2,77	0,410
Apathy D	2,17 ± 1,66	2,20 ± 1,72	2,15 ± 1,72	1,000
Disinhibition FxS	1,22 ± 3,47	0,10 ± 0,30	2,08 ± 0,30	0,208
Disinhibition D	0,70 ± 1,66	0,10 ± 0,30	1,15 ± 0,30	0,208

Irritability FxS	1,61 ± 2,29	0,80 ± 0,75	2,23 ± 0,75	0,232
Irritability D	1,43 ± 1,50	1,20 ± 1,47	1,62 ± 1,47	0,483
Motor disorder FxS	1,39 ± 2,68	0,00 ± 0,00	2,46 ± 0,00	0,004
Motor disorder D	0,83 ± 1,45	0,00 ± 0,00	1,46 ± 0,00	0,012
Sleep disorder FxS	1,74 ± 1,94	0,60 ± 1,20	2,62 ± 1,20	0,018
Sleep disorder D	1,22 ± 1,52	0,20 ± 0,40	2,00 ± 0,40	0,004
Eating disorder FxS	1,17 ± 2,84	0,00 ± 0,00	2,08 ± 0,00	0,004
Eating disorder D	0,61 ± 1,00	0,00 ± 0,00	1,08 ± 0,00	0,012
Total FxS	23,52 ± 14,70	10,40 ± 4,41	33,62 ± 4,41	0,000
Total D	14,57 ± 10,35	7,70 ± 2,87	19,85 ± 2,87	0,003

Table 3 shows neuropsychiatric scores in the whole sample and in the two hypometabolism groups. p-values refer to the comparison between TP-bvAD and FT-bvAD.

4.4 Correlation analysis

Regarding correlations between the cognitive features at the baseline and hypometabolism values, extracted by using 116 ROIs studied with the AAL atlas,, several correlations emerged. We included in the current description only strong correlations ($r > 0,7$). Regarding global cognitive status, an inverse statistically significant correlation emerged between MMSE and hypometabolism in the middle cingulum left ($r = -0,827$ and $p = 0,000$) and right ($r = -0,694$ and $p = 0,006$).

Regarding the neuropsychological features several inverse statistically significant correlations with hypometabolism values emerged, specifically between:

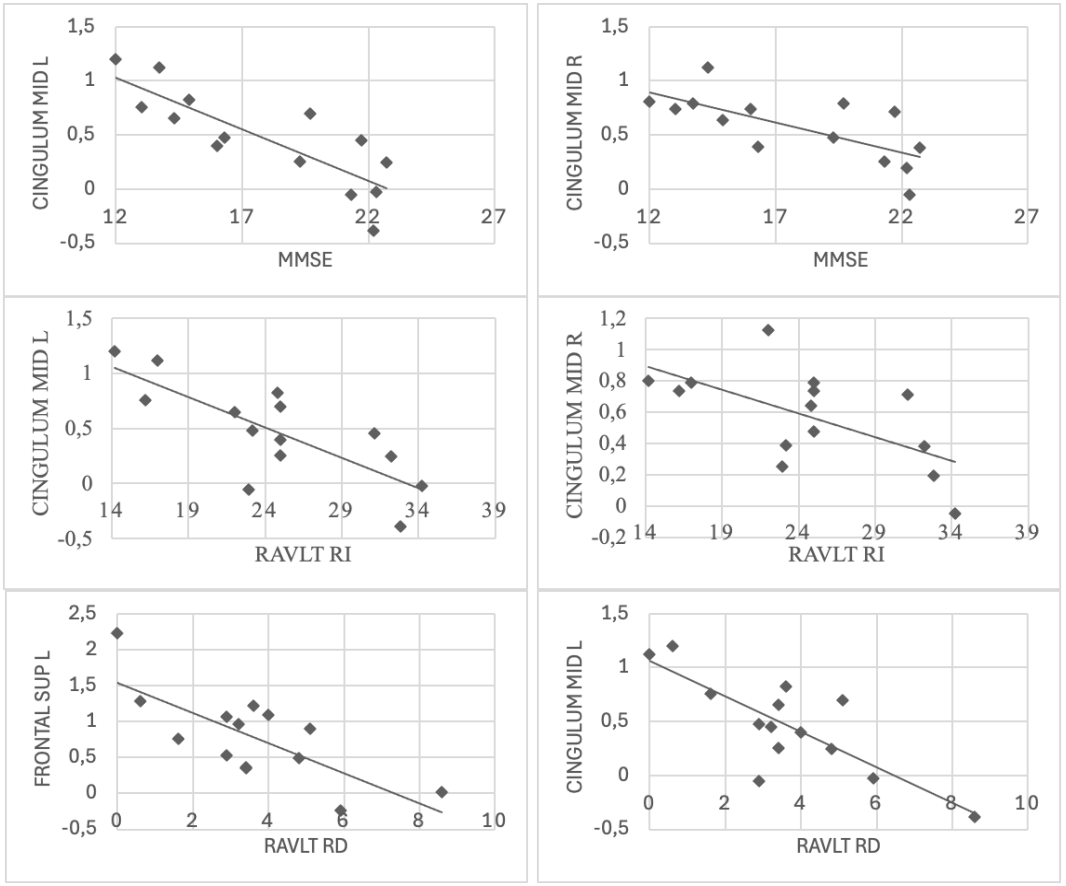
- RAVLT RI and middle cingulum left ($r = -0,771$ and $p = 0,001$) and right ($r = -0,619$ and $p = 0,018$);
- RAVLT RD and frontal superior gyrus left ($r = -0,749$ and $p = 0,002$), middle cingulum left ($r = -0,798$ and $p = 0,001$), and right ($r = -0,553$ and

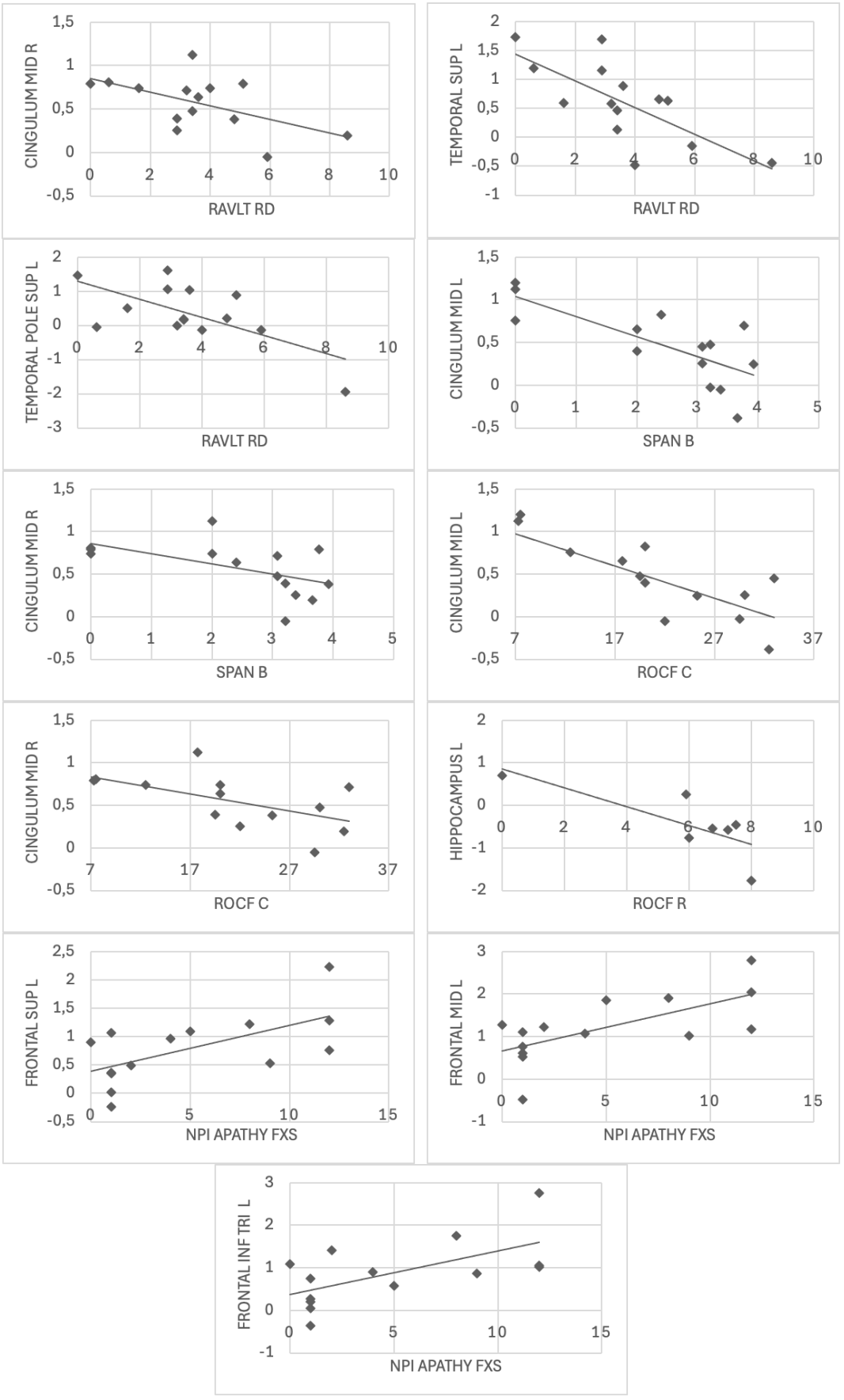
p = 0,40), superior temporal gyrus left (r = -0,695 and p = 0,006) and superior temporal pole left (r = -0,647 and p = 0,012);

- ➢ SPAN B and middle cingulum left (r = -0,754 and p = 0,002) and right (r = -0,538 and p = 0,047);
- ➢ ROCF C and middle cingulum left (r = -0,794 and p = 0,001) and right (r = -0,598 and p = 0,024);
- ➢ ROCF R and hippocampus left (r = - 0,767 and p = 0,044).

Regarding the neuropsychiatric features a direct statistically significant correlation emerged between apathy FxS and the hypometabolism value in the frontal superior left gyrus (r = 0,621 and p = 0,018), frontal middle left gyrus (r = 0,664 and p = 0,010) and frontal inferior triangularis part left (r = 0,617 and p = 0,019). All the statistically significant correlations found are represented in figure 1.

Figure 1: scatter plots of correlation analysis.




CINGULUM MID R
RAVLT RD
TEMPORAL SUP L
RAVLT RD
TEMPORAL POLE SUP L
RAVLT RD
CINGULUM MID L
SPAN B
CINGULUM MID R
SPAN B
CINGULUM MID L
ROCF C
CINGULUM MID R
ROCF C
HIPPOCAMPUS L
ROCF R
FRONTAL SUP L
NPI APATHY FXS
FRONTAL MID L
NPI APATHY FXS
FRONTAL INF TRI L
NPI APATHY FXS

Correlation analysis between cognitive and neuropsychological and neuropsychiatric scores, reported on the x axis, and regional hypometabolism within selected regions of interest, represented on the y axis (higher values indicating higher hypometabolism).

4.5 Cognitive, neuropsychological and neuropsychiatric features at follow-up

Cognitive and neuropsychological assessment

Table 4 describes the score at MMSE at the baseline for both groups. FT-bvAD group obtained a lower score in MMSE than TP-bvAD group, showing a statistically significant difference (p = 0,005).

Table 4 also describes each different score in different neuropsychological tests at follow-up for both groups. A part from TMT B, FT-bvAD group obtain a lower score in all neuropsychological tests than TP-bvAD group, showing a statistically significant difference in RAVLT RD (p = 0,025), SPAN F (p = 0,025), ROCF C (p = 0,030), Spinner's test (p = 0,004), and SVF (p = 0,002).

Table 4

	Whole Sample	TP-bvAD	FT-bvAD	p-values
MMSE	16,57 ± 3,43	19,57 ± 3,90	14,42 ± 3,90	0,005
RAVLT RI	20,11 ± 6,90	24,29 ± 7,76	16,63 ± 7,76	0,050
RAVLT RD	1,71 ± 1,68	2,51 ± 1,34	1,05 ± 1,34	0,025
Digit Span F	3,60 ± 1,43	4,40 ± 1,21	2,93 ± 1,21	0,025
Digit Span B	1,49 ± 1,40	2,00 ± 2,17	1,06 ± 2,17	0,228
ROCF C	17,18 ± 9,20	23,40 ± 9,78	12,00 ± 9,78	0,030
ROCF R	4,55 ± 2,60	5,03 ± 2,28	3,70 ± 2,28	0,364
RAVEN matrices	22,28 ± 6,79	24,14 ± 2,23	20,42 ± 2,23	0,421

TMT A	118,70 ± 27,62	130,50 ± 114,25	106,90 ± 114,25	0,393
TMT B	262,33 ± 0,00	232,20 ± 74,48	300,00 ± 74,48	0,413
Spinner's test	23,97 ± 6,60	30,47 ± 10,93	16,75 ± 10,93	0,004
FAB	10,86 ± 3,09	12,38 ± 3,38	9,34 ± 3,38	0,050
PVF test	17,07 ± 7,09	20,42 ± 8,57	14,28 ± 8,57	0,140
SVF test	20,03 ± 8,43	31,46 ± 4,32	14,83 ± 4,32	0,002

Table 4 shows the neuropsychological evaluation at follow-up. All scores are corrected by age and educational level. p-values refer to the comparison between TP-bvAD and FT-bvAD.

NPI

Table 5 lists the different scores in each item in NPI and total at follow-up for both groups. FT-bvAD group obtain higher score in all item and in the total one than TP-bvAD group, showing a statistically significant difference for delusions FxS and D (p = 0,012 and p = 0,018), agitation FxS and D (p = 0,030 and p = 0,018), anxiety FxS and D (p = 0,010 and p = 0,006), motor disorder (p = 0,005 and p = 0,018), sleep disorder FxS and D (p = 0,026 and p = 0,002), eating disorder FxS and D (p = 0,026 and p = 0,012), total FxS and D (p = 0,000 and p = 0,002).

Table 5

	Whole Sample	TP-bvAD	FT-bvAD	p-values
Delusions FxS	1,70 ± 3,08	0,20 ± 0,60	2,85 ± 0,60	0,012
Delusions D	1,26 ± 1,71	0,30 ± 0,90	2,00 ± 0,90	0,018
Hallucinations FxS	1,35 ± 3,17	0,10 ± 0,30	2,31 ± 0,30	0,057
Hallucination D	1,04 ±1,60	0,30 ± 0,90	1,62 ± 0,90	0,077
Agitation FxS	3,22 ± 4,31	1,10 ± 1,58	4,85 ± 1,58	0,030
Agitation D	1,83 ± 1,86	0,70 ± 0,90	2,69 ± 0,90	0,018
Depression FxS	3,43 ± 4,08	2,80 ±2,68	3,92 ± 2,68	0,832

Depression D	2,17 ± 1,69	1,80 ± 1,17	2,46 ± 1,17	0,522
Anxiety FxS	4,26 ± 2,79	2,50 ± 1,86	5,62 ± 1,86	0,010
Anxiety D	2,57 ± 1,19	1,70 ± 1,00	3,23 ± 1,00	0,006
Euphoria FxS	0,78 ± 1,41	0,50 ± 1,20	1,00 ± 1,20	0,313
Euphoria D	0,57 ± 0,97	0,30 ± 0,64	0,77 ± 0,64	0,284
Apathy FxS	4,13 ± 4,79	2,10 ± 1,97	5,69 ± 1,97	0,101
Apathy D	2,09 ± 1,65	1,60 ± 1,43	2,46 ± 1,43	0,232
Disinhibition FxS	1,61 ± 2,90	0,50 ± 0,67	2,46 ± 0,67	0,166
Disinhibition D	1,13 ± 1,64	0,50 ± 0,67	1,62 ± 0,67	0,232
Irritability FxS	2,17 ± 2,71	1,70 ± 1,62	2,54 ± 1,62	0,563
Irritability D	1,70 ± 1,62	1,60 ± 1,36	1,77 ± 1,36	0,879
Motor disorder FxS	1,26 ± 1,64	0,20 ± 0,40	2,08 ± 0,40	0,005
Motor disorder D	1,04 ± 1,49	0,20 ± 0,40	1,69 ± 0,40	0,018
Sleep disorder FxS	2,57 ± 1,60	1,50 ± 1,36	3,38 ± 1,36	0,026
Sleep disorder D	2,04 ± 1,05	1,10 ± 0,83	2,77 ± 0,83	0,002
Eating disorder FxS	0,74 ± 1,25	0,10 ± 0,30	1,23 ± 0,30	0,026
Eating disorder D	0,70 ± 1,12	0,00 ± 0,00	1,23 ± 0,00	0,012
Total FxS	27,22 ± 13,31	13,30 ± 5,85	37,92 ± 5,85	0,000
Total D	18,39 ± 9,05	10,10 ± 3,01	24,77 ± 3,01	0,002

Table 5 shows neuropsychiatric scores in the whole sample and in the two hypometabolism groups. p-values refer to the comparison between TP-bvAD and FT-bvAD.

4.6 Progression rate index of MMSE

In the whole sample the PR of MMSE was -1,61 ± 1,11 points per year, while in the two groups was:

- ➢ in TP-bvAD group -1,25 ± 2,00 points per year
- ➢ in FT-bvAD group -1,86 ± 2,00 points per year.

Although FT-bvAD lose more points per year, there was no statistically significant difference between the two groups in the PR ($p = 0,546$).

5. Discussion

In the current study we explored, in a large group of clinically and biomarkers characterized bvAD patients, the patterns of brain 18F-FDG-PET hypometabolism at the single-subject level, demonstrating the presence of two main patterns, corresponding to different clinical, neuropsychological and neuropsychiatric features. Specifically, a group of patients (TP-bvAD) showed the typical temporo-parietal hypometabolism pattern, such as in typical AD, and was characterized by widespread cognitive and neuropsychological deficits. On the other hand, the second group (FT-bvAD) showed, along with the typical involvement of temporo-parietal regions, a marked hypometabolism involving the fronto-temporal cortices; this latter group was characterized by a more pronounced alteration in almost all domains plus various neuropsychiatric disorders.

The main results of this work are based on the study of brain metabolism in a cohort of atypical AD. Brain 18F-FDG-PET is a crucial tool in revealing synaptic alterations and neuronal loss in several NDDs, including AD in typical and atypical variants. In particular, the semi-quantification analysis, based on the statistical voxel-based comparison between the subjects scan and a control group, using various methods, has shown in several works to be a reliable technique able to reveal hypometabolism regions better than visual analysis [116-155]. As a statistical parametric mapping method, we employed the single-subject analysis, a method initially developed at the San Raffaele Hospital [152] and subsequently adapted in the Neurology Unit and Nuclear Medicine of our Hospital [156]. The method has been validated using different scans, thus being particularly reliable in multicentre studies; in addition, several cohorts of controls have been used, demonstrating trustable results in several studies conducted in patients with different neurodegenerative diseases [153].

In our cohort of bvAD, we observed two main patterns of hypometabolism: the tempo-parietal TP (involving inferior temporal gyrus, precuneus, inferior parietal gyrus, angular gyrus, superior temporal gyrus) and the fronto-temporal FT (involving angular gyrus, precuneus, inferior and middle and superior temporal gyrus, inferior and middle and superior frontal gyrus, insula, frontal inferior operculum). The TP-bvAD group has hypometabolism in known areas involved in AD [112]. The FT-bvAD has hypometabolism in known areas involved in AD plus the fronto-temporal regions. The hypometabolism in frontal regions has been previously associated with neuropsychiatric disorders and worse performance in tests that evaluate attentional and executive functions [157-158]. In addition, few previous studies based on 18F-FDG-PET data investigated the burden of neuropsychiatric symptoms, as measured by the NPI, along the AD continuum.

In 2016, in the study conducted by Ballarini et al [157] three main neuropsychiatric symptoms in early onset AD (hyperactivity, anxiety, and apathy) were correlated with specific areas of hypometabolism. The hyperactivity was associated with hypometabolism in left insula, anterior cingulate gyrus, superior frontal gyrus, left temporal lobe (in a paralimbic structure that is involved in eliciting reactions to emotional stimuli [159]), right inferior frontal gyrus (which is associate with inhibitory action controlled [160]), left precentral sulcus (which has been specifically associated with aberrant motor behaviors in AD and FTD patients probably because of an impairment in motor planning abilities [161]). The anxiety was associated with superior frontal gyrus and anterior cingulate gyrus. These brain structures are involved in the appraisal (evaluation of what an internal/external stimulus means) and expression of negative emotions [162-163]. In particular, the anterior cingulate gyrus sends efferent projections to cortical and subcortical (including the amygdala) brain structures triggering visceromotor and emotional reactions to salience that may be a major source of anxiety [164]. The relationship between these findings and depressive symptoms were more controversial. The apathy, a negative neuropsychiatric symptom involving loss of interest and motivation as well as difficulty in engaging in activities [165], was associated with the bilateral middle orbitofrontal and middle frontal gyri.

These structures are involved in motivation and decision‑making [166-167] and, together with other frontal and subcortical structures (such as anterior cingulate gyrus, dorsolateral prefrontal cortices, caudate nucleus) were found hypometabolic in apathetic AD patients [168-169] .

In 2022, in the study conducted by Tondo et al [158] several neuropsychological and neuropsychiatric aspects in subjective cognitive decline, considered the preclinical AD phase, were correlated with specific areas of hypometabolism. The executive/visuomotor impairment was correlated with hypometabolism in the superior and the middle frontal gyri, lingual gyrus, cuneus, precuneus, and middle cingulate cortex, plus the caudate nuclei and thalamus, bilaterally. The memory impairment was correlated with hypometabolism in the precuneus, cuneus, superior and inferior parietal lobules, the posterior and middle cingulate cortices, and the superior and the middle frontal gyri. The visuospatial/constructional impairment was correlated with hypometabolism in the angular gyrus, the anterior and middle cingulate cortex, and the dorsolateral frontal cortex. Similarly, two neuropsychiatric factors, emerging from the subclassification of NPI scores, correlated primarily with fronto-temporal regional hypometabolism. Specifically, affective disturbances, including anxiety and depression, correlated with hypometabolism in orbitofrontal and cingulate cortex and insula, while hyperactive/psychotic disturbances, including agitation, irritability, euphoria, aberrant motor behavior, disinhibition, delusions, hallucinations, and nighttime sleep disturbances, correlated with hypometabolism in frontal, temporal, and parietal regions.

Regional patterns of decreased 18F-FDG‑PET signal is the result of both local pathology and long‑distance processes of deafferentation [170-171], capturing changes beyond MRI atrophy [172]. Moreover, neurodegeneration, as measured by 18F-FDG‑PET, strongly correlates with cognitive decline and is detectable even before clinical symptom onset [158-173]. Thus, 18F-FDG‑PET has been recognized as one of the most accurate biomarkers in predicting the possible progression from MCI to dementia, but also in recognizing those subjects remaining clinically stable over time [111-114-174].

Here, we used 18F-FDG-PET brain metabolism as biomarker of neurodegeneration and investigated the relationship with AD biological profiles. We distinguished two bvAD subtypes, based on 18F-FDG-PET hypometabolism features, with a distinguishable neuropsychological phenotype at baseline and different global cognitive status. We suggest that two specific patterns of brain hypometabolism, irrespective to other biomarker alterations, which were similar in the two groups leading to the AD spectrum, were able to identify subtypes representative of possibly diverse biological entities.

We studied the hypometabolism pattern in the rare bvAD. This is the first study employing the single-subject method in a bvAD cohort, while few other studies investigated the hypometabolism in the bvAD, considering the rarity of this condition.

In literature the results are very heterogeneous and so not conclusive, ranging from a predominantly temporoparietal hypometabolic pattern [175-176] to a mixed frontal and temporoparietal [177-179-180-182] or predominantly frontal [181], due to the small number of patients, that is the reason behind using our method [175-176-177-178-179-180-181-182-184].

Besides the study of brain metabolism, we explored the clinical, neuropsychological and neuropsychiatric correlates in the bvAD. Age, onset, and follow-up were perfectly comparable between the two groups identified by the brain hypometabolism pattern. Thus, all the statistically significant differences in cognitive, neuropsychological, neuropsychiatric aspects were not affected by these variables. As a group, the bvAD showed a moderate impairment of the global cognitive status after few years of symptoms onset (22,75 ± 13,61 months), with a MMSE of 19,5 ± 3,75 points. Regarding neuropsychological characteristics, the whole sample showed at baseline important deterioration in performance in attentional and executive tasks, including the TMT and Spinner's test. Lastly, regarding the neuropsychiatric profile in the whole sample, there was already at baseline a strong impact of depression, anxiety, and apathy - related symptoms, with corresponding marked impact on caregiver distress.

Previous studies examining the neuropsychological and neuropsychiatric features of bvAD showed various results [176-177 -179-180-183-184-185-186-187-188].

The classification based on the single-subject analysis allowed us to underline different neuropsychological and neuropsychiatric profiles. While the TP-bvAD confirmed in the neuropsychological assessment important impairment in executive function, in FT-bvAD there was a significantly higher deterioration in tests evaluating attention and logical reasoning (Spinner's test, and Raven's matrices). The significantly worse performances were confirmed also at the follow-up, with in addition a higher deterioration regarding memory, constructional praxis and language. Another important aspect is the fact that FT-bvAD has already a more deteriorated global cognitive status at baseline, confirmed by significantly worse MMSE scores also at the follow-up.

However, the PR index did not differ in the comparison between the two groups, likely due to the fact that the underlying disease (AD pathology) is the same, which evolves quite rapidly but appears not in uniform way based on the hypometabolic pattern.

Lastly, regarding the neuropsychiatric profiles, analyzing individually the two groups, the global impact of neuropsychiatric symptoms in the FT-bvAD is almost tripled when compared with TP-bvAD at the baseline, both on the patient and on the caregiver. This rate of neuropsychiatric burden is confirmed also at the follow-up. In detail, FT-bvAD showed at the baseline and follow-up a higher impact of neuropsychiatric disorders such as delusions, agitation, motor disorder, sleep disorder, and eating disorder. The higher burden of neuropsychiatric disturbances in FT-bvAD was correlated with the large hypometabolism in fronto-temporal cortices. Analyzing the specific domains, in FT-bvAD the apathy scores correlated with hypometabolism in dorsolateral prefrontal cortices.

As previously reported, frontal damage is correlated with impaired motivation and apathy, confirming that the neurodegenerative changes characteristics of the more severe subtype of the bvAD, involving extensively the frontal lobes, can be responsible for the high impact of neuropsychiatric disturbances in these patients [189-190].

6. Conclusion

The bvAD is a rare AD variant. In 2022, Ossenkoppele and Colleagues developed the diagnostic research criteria, which allows the precise identification of these patients. This AD subtype affects patients characterized by behavioural disturbances (like behavioural disinhibition, apathy or inertia, loss of empathy, preservative or stereotyped or compulsive or ritualistic behaviour, hyperorality or dietary change) and executive functions and/or episodic memory impairment. Considering the rarity of the variant, there is a need to explore its characteristics in depth as much as it is possible. In our study, starting from the cerebral metabolism classification, we demonstrated that in patients belonging to the bvAD variant there are different patterns and different neurodegeneration levels, which correspond to different neuropsychological and neuropsychiatric profiles. The precise clinical and biomarkers characterization of patients affected by a rare variant is particularly important in the future for the development of target therapies and personalized medicine, as patients with different clinical and biomarker profiles may benefit from different treatments. Specifically, we demonstrate that there are patients more prone to the frontal neurodegeneration, who develop neuropsychiatric disorders with challenging pharmacological management and needing closer monitoring. Lastly, the bvAD often involve young patients (early-onset dementia), with an average age under 75 years, and often in working age, entailing crucial social and economic repercussions. Thus, the confirmation of this data in a larger sample has important implications under the medical and social aspects.

7. References

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