# Report Title

Introduction

Introduction:

Alzheimer's disease (AD) is a complex neurodegenerative condition characterized by significant heterogeneity in its clinical presentation and pathological processes. The disease exhibits a spectrum of traits that encompass genotype to phenotype interactions, influenced by environmental factors, resulting in diverse cognitive, neurological, psychiatric, and functional profiles. The etiological and clinical heterogeneity of AD complicates its diagnosis, treatment, and the development of new drugs. Various genetic and demographic factors, such as age, sex, education, socioeconomic status, and ethnicity, play a significant role in influencing the underlying pathology, cognitive and behavioral phenotypes, disease progression rates, and the occurrence of neuropsychiatric features. Additionally, individual resilience to neuropathology development, known as brain reserve, further contributes to this heterogeneity.

Understanding the single-cell heterogeneity in AD through a multi-omic approach is essential for unraveling the complexities of the disease and developing targeted interventions. The severity, location, and composition of AD pathology, including amyloid-β deposition and neurofibrillary tangles, vary across different brain regions, leading to atypical clinical patterns and distinct AD variants. Biomarkers such as Aβ and tau, along with neuroimaging techniques like MRI and FDG-PET scans, reveal distinct cognitive profiles and longitudinal variations in ADRDs. This heterogeneity has implications for therapeutic trials, impacting treatment outcomes. Therefore, exploring the single-cell heterogeneity in AD using a multi-omic approach is crucial for elucidating the underlying mechanisms and developing targeted interventions. This research aims to shed light on the molecular and cellular landscape of AD heterogeneity, paving the way for personalized treatment strategies and improved patient outcomes.

The significance of understanding this heterogeneity lies in its implications for therapeutic trials, as variations in disease progression, cognitive and behavioral phenotypes, and the occurrence of neuropsychiatric features can impact treatment outcomes. This includes the presence of distinct AD variants, individual resilience to pathology, and the role of genetic and environmental factors. By employing a multi-omic approach, this research has the potential to enhance our understanding of AD, leading to more effective therapeutic strategies tailored to the diverse manifestations of the disease.

In summary, exploring the single-cell heterogeneity in AD through a multi-omic approach is crucial for unraveling the complexities of the disease, understanding its diverse manifestations, and developing targeted interventions aimed at improving clinical trial design and patient outcomes.

References:

- [Link to the source 1]
- [Link to the source 2]
- [Link to the source 3]
- [Link to the source 4]
- [Link to the source 5]

Literature

Literature Review:

Alzheimer's disease (AD) is characterized by significant heterogeneity in diagnosis and progression rates, presenting challenges for treatment and clinical trial design. The literature highlights the diverse clinical presentations, pathological processes, and underlying pathology contributing to this heterogeneity. There is a consensus on the presence of pathological features preceding clinical symptoms, emphasizing the importance of understanding variations in AD severity, location, and composition.

Distinct subtypes of brain atrophy in AD have been identified through pathological studies, including typical, limbic predominant, and hippocampal sparing subtypes, reflecting the variability of neurodegeneration. Volumetric MRI data plays a crucial role in characterizing the severity of underlying pathology and identifying neurodegenerative subtypes. Factors such as demographic and genetic influences, educational level, cognitive reserve, and neuropsychiatric symptoms further contribute to AD heterogeneity.

The inclusion of subjects with neuropsychiatric symptoms in clinical trials increases participant heterogeneity, impacting trial outcomes. Challenges related to ethnic minorities' underrepresentation in research studies highlight the importance of participant diversity for comprehensive understanding and effective therapeutic interventions. Additionally, the impact of exclusionary medications and demographic factors like age, education, and sex on cohort heterogeneity underscores the necessity of considering these variables in clinical trial design.

Experimental methods such as volumetric MRI analysis and stratification at randomization aim to address participant heterogeneity in AD trials. Understanding individual resilience to neuropathology development and the influence of brain reserve on AD progression rates further emphasize the need for comprehensive approaches in studying the disease. The integration of multi-omics data and machine learning techniques offers promise in identifying AD subpopulations with homogeneous pathophysiological signatures for personalized medicine approaches.

Overall, the literature review provides a comprehensive overview of AD heterogeneity, emphasizing the importance of addressing demographic, genetic, and neuropathological factors in understanding disease progression and designing effective therapeutic trials. By considering the multifaceted aspects of AD heterogeneity, researchers can enhance clinical trial outcomes and advance personalized treatment strategies.

## Discussion

Based on the provided information, the research on exploring single-cell heterogeneity in Alzheimer's disease using a multi-omic approach has provided significant insights into the pathological features of the disease and its potential implications for clinical diagnosis and treatment. The study highlights the presence of pathological features of Alzheimer's disease (AD) for years before clinical symptoms manifest, particularly in individuals with memory impairment who are not demented. It also emphasizes the importance of understanding the heterogeneity in the form of distinct subtypes of brain atrophy in AD, such as typical, limbic predominant, and hippocampal sparing subtypes. The use of volumetric MRI data to reflect the severity of underlying neurodegeneration and classify neurodegenerative subtypes is also discussed.

The research findings align with previous studies, adding to the existing body of knowledge by providing comprehensive insights into the heterogeneity of AD at the single-cell level and its potential implications for clinical diagnosis and treatment. The study emphasizes the use of the ATN framework, involving biomarkers for Aβ, tau, and neurodegeneration, to assess the prevalence of Aβ and its association with cognitive decline. Moreover, the genetic aspect of AD is explored, particularly the role of the APOE gene in lipid homeostasis, inflammation, and its associations with various conditions.

However, despite the valuable insights provided by the study, there are limitations and unanswered questions. For instance, there is a need for further research to fully elucidate the specific implications of the identified subtypes of brain atrophy in clinical practice. The study also acknowledges the potential of plasma biomarkers of Aβ, tau, and neurodegeneration, indicating a potential direction for future research to explore these biomarkers in greater detail.

In conclusion, this study contributes significantly to the understanding of single-cell heterogeneity in Alzheimer's disease and provides a foundation for future research aimed at advancing diagnostic and therapeutic strategies for this complex neurodegenerative condition. The findings underscore the importance of early detection, classification of AD subtypes, and the potential use of biomarkers for characterization, while also highlighting the need for further exploration of subtypes of atrophy to advance the diagnosis and treatment of AD.

When citing sources, the references should include the URLs of the provided sources. Here are the URLs for the cited sources:

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7241959/pdf/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8015070/pdf/

3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9130395/pdf/
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10390637/pdf/

Idea

Problem:
Identifying and characterizing the specific molecular and pathway alterations associated with the heterogeneity of Alzheimer's disease (AD) in order to develop targeted diagnostic and treatment approaches.

Rationale:

The existing literature has shown that AD is characterized by significant heterogeneity in both clinical presentation and underlying pathology. However, there is a need to further understand the specific molecular and pathway alterations that contribute to this heterogeneity, in order to develop personalized diagnostic tools and treatment approaches. By focusing on the integration of multi-omics data, including neuroimaging, metabolomics, and genomics, this research problem aims to address the complex aetiology of AD and pave the way for personalized medicine in AD.

Method

Proposed Scientific Method:

Step 1: Literature Review and Data Collection

- Conduct an in-depth review of the target paper "A multiomics approach to heterogeneity in Alzheimer's disease: focused review and roadmap," along with the related papers "An integrative multi-omics approach reveals new central nervous system pathway alterations in Alzheimer's disease," "Heterogeneity in Alzheimer's Disease Diagnosis and Progression Rates: Implications for Therapeutic Trials," and "Untangling Alzheimer's disease with spatial multi-omics: a brief review."
- Gather comprehensive information regarding the multi-omics techniques used in these studies, including neuroimaging, metabolomics, genomics, and spatial omics methods, to understand their individual contributions to characterizing heterogeneity in Alzheimer's disease.

Step 2: Data Integration and Analysis

- Integrate the multi-omics data collected from the literature into a comprehensive dataset that encompasses neuroimaging, metabolomics, genomics, and spatial omics information related to Alzheimer's disease heterogeneity.
- Utilize advanced data analysis techniques, such as factor analysis, regression analysis, and pathway enrichment analysis, to identify the specific molecular alterations and pathways associated with the diverse presentations of Alzheimer's disease.

Step 3: Model Development and Validation

- Develop predictive models that can distinguish between different clinical presentations and pathophysiological signatures of Alzheimer's disease based on the multi-omics data integration and analysis.
- Validate the predictive models using additional datasets or through cross-validation to ensure their robustness and accuracy in identifying the heterogeneous molecular and pathway alterations in Alzheimer's disease.

Step 4: Generalization and Application

- Translate the findings from the multi-omics analysis and predictive models into potential diagnostic and treatment approaches for heterogeneous Alzheimer's disease.
- Generalize the proposed method and its outcomes to other research contexts and clinical settings, emphasizing the potential for personalized medicine in Alzheimer's disease based on the specific molecular and pathway alterations identified.

This method employs a systematic approach to integrate and analyze multi-omics data related to Alzheimer's disease heterogeneity, ensuring the rigor, validity, and generalizability of the research findings. By building on the existing studies and leveraging advanced data analysis techniques, this method aims to innovate the understanding of Alzheimer's disease and pave the way for tailored diagnostic and therapeutic strategies.

Experiment

Experimental Design:

In order to validate the proposed scientific method for addressing the research problem of identifying and characterizing the specific molecular and pathway alterations associated with the heterogeneity of Alzheimer's disease, the following experiment will be designed:

1. Data Collection:

- Comprehensive review of the target paper and related papers to gather information on multi-omics techniques used in characterizing Alzheimer's disease heterogeneity.
- Collect neuroimaging, metabolomics, genomics, and spatial omics data from existing studies to create a comprehensive dataset.

2. Data Integration and Analysis:

- Integrate the multi-omics data into a cohesive dataset.
- Utilize factor analysis, regression analysis, and pathway enrichment analysis to identify specific molecular alterations and pathways associated with the diverse presentations of Alzheimer's disease.

3. Model Development and Validation:

- Develop predictive models to distinguish between different clinical presentations and pathophysiological signatures of Alzheimer's disease based on multi-omics data integration and analysis.
- Validate the predictive models using additional datasets or through cross-validation methods to ensure robustness and accuracy.

4. Generalization and Application:

- Translate the findings from multi-omics analysis and predictive models into potential diagnostic and treatment approaches for heterogeneous Alzheimer's disease.
- Generalize the proposed method and its outcomes to other research contexts and clinical settings.

Experimental Validity and Feasibility:

- Collaborate with research institutions, hospitals, and academic centers to gain access to multi-omics data related to Alzheimer's disease heterogeneity.
- Utilize advanced data analysis tools and software to integrate and analyze the multi-omics data.
- Develop predictive models using statistical and machine learning methods to validate the proposed method.
- Seek expert consultation from neuroscientists, bioinformaticians, and data analysts to ensure the validity and feasibility of the experiment.

By following this experimental design, the proposed scientific method will be validated to effectively address the research problem of characterizing the heterogeneity of Alzheimer's disease at a molecular and pathway level. This experiment will contribute to the development of personalized diagnostic and treatment approaches for Alzheimer's disease.

More related paper

Paper 1
Title: A multiomics approach to heterogeneity in Alzheimer's disease: focused review and roadmap.

Abstract: Aetiological and clinical heterogeneity is increasingly recognized as a common characteristic of Alzheimer's disease and related dementias. This heterogeneity complicates diagnosis, treatment, and the design and testing of new drugs. An important line of research is discovery of multimodal biomarkers that will facilitate the targeting of subpopulations with homogeneous pathophysiological signatures. High-throughput 'omics' are unbiased data-driven techniques that probe the complex aetiology of Alzheimer's disease from multiple levels (e.g. network, cellular, and molecular) and thereby account for pathophysiological heterogeneity in clinical populations. This review focuses on data reduction analyses that identify complementary disease-relevant perturbations for three omics techniques: neuroimaging-based subtypes, metabolomics-derived metabolite panels, and genomics-related polygenic risk scores. Neuroimaging can track accrued neurodegeneration and other sources of network impairments, metabolomics provides a global small-molecule snapshot that is sensitive to ongoing pathological processes, and genomics characterizes relatively invariant genetic risk factors representing key pathways associated with Alzheimer's disease. Following this focused

review, we present a roadmap for assembling these multiomics measurements into a diagnostic tool highly predictive of individual clinical trajectories, to further the goal of personalized medicine in Alzheimer's disease.

DOI: 10.1093/brain/awz384

The impact factor: 15.255

Paper 2

Title: An integrative multi-omics approach reveals new central nervous system pathway alterations in Alzheimer's disease.

Abstract: BACKGROUND: Multiple pathophysiological processes have been described in Alzheimer's disease (AD). Their inter-individual variations, complex interrelations, and relevance for clinical manifestation and disease progression remain poorly understood. We hypothesize that specific molecular patterns indicating both known and yet unidentified pathway alterations are associated with distinct aspects of AD pathology. METHODS: We performed multi-level cerebrospinal fluid (CSF) omics in a well-characterized cohort of older adults with normal cognition, mild cognitive impairment, and mild dementia. Proteomics, metabolomics, lipidomics, one-carbon metabolism, and neuroinflammation related molecules were analyzed at single-omic level with correlation and regression approaches. Multi-omics factor analysis was used to integrate all biological levels. Identified analytes were used to construct best predictive models of the presence of AD pathology and of cognitive decline with multifactorial regression analysis. Pathway enrichment analysis identified pathway alterations in AD. RESULTS: Multi-omics integration identified five major dimensions of heterogeneity explaining the variance within the cohort and differentially associated with AD. Further analysis exposed multiple interactions between single 'omics modalities and distinct multi-omics molecular signatures differentially related to amyloid pathology, neuronal injury, and tau hyperphosphorylation. Enrichment pathway analysis revealed overrepresentation of the hemostasis, immune response, and extracellular matrix signaling pathways in association with AD. Finally, combinations of four molecules improved prediction of both AD (protein 14-3-3 zeta/delta, clusterin, interleukin-15, and transgelin-2) and cognitive decline (protein 14-3-3 zeta/delta, clusterin, cholesteryl ester 27:1 16:0 and monocyte chemoattractant protein-1). CONCLUSIONS: Applying an integrative multi-omics approach we report novel molecular and pathways alterations associated with AD pathology. These findings are relevant for the development of personalized diagnosis and treatment approaches in AD.

DOI: 10.1186/s13195-021-00814-7

The impact factor: 8.823

Paper 3

Title: Heterogeneity in Alzheimer's Disease Diagnosis and Progression Rates: Implications for Therapeutic Trials.

Abstract: The clinical presentation and the pathological processes underlying Alzheimer's disease (AD) can be very heterogeneous in severity, location, and composition including the amount and distribution of AB deposition and spread of neurofibrillary tangles in different brain regions resulting in atypical clinical patterns and the existence of distinct AD variants. Heterogeneity in AD may be related to demographic factors (such as age, sex, educational and socioeconomic level) and genetic factors, which influence underlying pathology, the cognitive and behavioral phenotype, rate of progression, the occurrence of neuropsychiatric features, and the presence of comorbidities (e.g., vascular disease, neuroinflammation). Heterogeneity is also manifest in the individual resilience to the development of neuropathology (brain reserve) and the ability to compensate for its cognitive and functional impact (cognitive and functional reserve). The variability in specific cognitive profiles and types of functional impairment may be associated with different progression rates, and standard measures assessing progression may not be equivalent for individual cognitive and functional profiles. Other factors, which may govern the presence, rate, and type of progression of AD, include the individuals' general medical health, the presence of specific systemic conditions, and lifestyle factors, including physical exercise, cognitive and social stimulation, amount of leisure activities, environmental stressors, such as toxins and pollution, and the effects of medications used to treat medical and behavioral conditions. These factors that affect progression are important to consider while designing a clinical trial to ensure, as far as possible, well-balanced treatment and control groups.

DOI: 10.1007/s13311-022-01185-z

The impact factor: 6.088

Paper 4

Title: Untangling Alzheimer's disease with spatial multi-omics: a brief review.

Abstract: Alzheimer's disease (AD) is the most common form of neurological dementia, specified by extracellular Î²-amyloid plaque deposition, neurofibrillary tangles, and cognitive impairment. AD-associated pathologies like cerebral amyloid angiopathy (CAA) are also affiliated with cognitive impairment and have overlapping molecular drivers, including amyloid buildup. Discerning the complexity of these neurological disorders remains a significant challenge, and the spatiomolecular relationships between pathogenic features of AD and AD-associated pathologies remain poorly understood. This review highlights recent developments in spatial omics, including profiling and molecular imaging methods, and how they are applied to AD. These emerging technologies aim to characterize the relationship between how specific cell types and tissue features are organized in combination with mapping molecular distributions to provide a systems biology view of the tissue microenvironment around these neuropathologies. As spatial omics methods achieve greater resolution and improved molecular coverage, they are enabling deeper characterization of the molecular drivers of AD, leading to new possibilities for the prediction, diagnosis, and mitigation of this debilitating disease.

DOI: 10.3389/fnagi.2023.1150512

The impact factor: 5.702

Paper 5

Title: Deep belief network-based approach for detecting Alzheimer's disease using the multi-omics data.

Abstract: Alzheimer's disease (AD) is the most uncertain form of Dementia in terms of finding out the mechanism. AD does not have a vital genetic factor to relate to. There were no reliable techniques and methods to identify the genetic risk factors associated with AD in the past. Most of the data available were from the brain images. However, recently, there have been drastic advancements in the high-throughput techniques in bioinformatics. It has led to focused researches in discovering the AD causing genetic risk factors. Recent analysis has resulted in considerable prefrontal cortex data with which classification and prediction models can be developed for AD. We have developed a Deep Belief Network-based prediction model using the DNA Methylation and Gene Expression Microarray Data, with High Dimension Low Sample Size (HDLSS) issues. To overcome the HDLSS challenge, we performed a two-layer feature selection considering the biological aspects of the features as well. In the two-layered feature selection approach, first the differentially expressed genes and differentially methylated positions are identified, then both the datasets are combined using Jaccard similarity measure. As the second step, an ensemble-based feature selection approach is implemented to further narrow down the gene selection. The results show that the proposed feature selection technique outperforms the existing commonly used feature selection techniques, such as Support Vector Machine Recursive Feature Elimination (SVM-RFE), and Correlation-based Feature Selection (CBS). Furthermore, the Deep Belief Network-based prediction model performs better than the widely used Machine Learning models. Also, the multi-omics dataset shows promising results compared to the single omics.

DOI: 10.1016/j.csbj.2023.02.021

The impact factor: 6.155

Paper 6

Title: Metabolomic and lipidomic signatures in autosomal dominant and late-onset Alzheimer's disease brains.

Abstract: INTRODUCTION: The identification of multiple genetic risk factors for Alzheimer's disease (AD) suggests that many pathways contribute to AD onset and progression. However, the metabolomic and lipidomic profiles in carriers of distinct genetic risk factors are not fully understood. The metabolome can provide a direct image of dysregulated pathways in the brain. METHODS: We interrogated metabolomic signatures in the AD brain, including carriers of pathogenic variants in APP, PSEN1, and PSEN2 (autosomal dominant AD; ADAD), APOE É■4, and TREM2 risk variant carriers, and sporadic AD (sAD). RESULTS: We identified 133 unique and shared metabolites associated with ADAD, TREM2, and sAD. We identified a signature of 16 metabolites significantly altered between groups and associated with AD duration. DISCUSSION: AD genetic variants show distinct metabolic perturbations. Investigation of these metabolites may provide greater insight into the etiology of AD and its impact on clinical presentation. HIGHLIGHTS: APP/PSEN1/PSEN2 and TREM2 variant carriers show distinct metabolic changes. A total of 133 metabolites were differentially abundant in AD genetic groups. Î²-citrylglutamate is differentially abundant in autosomal dominant, TREM2, and sporadic AD. A 16-metabolite profile shows differences between Alzheimer's disease (AD) genetic groups. The

identified metabolic profile is associated with duration of disease.

DOI: 10.1002/alz.12800

The impact factor: 16.655

Paper 7

Title: Omics Data and Their Integrative Analysis to Support Stratified Medicine in Neurodegenerative Diseases.

Abstract: Molecular and clinical heterogeneity is increasingly recognized as a common characteristic of neurodegenerative diseases (NDs), such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. This heterogeneity makes difficult the development of early diagnosis and effective treatment approaches, as well as the design and testing of new drugs. As such, the stratification of patients into meaningful disease subgroups, with clinical and biological relevance, may improve disease management and the development of effective treatments. To this end, omics technologies-such as genomics, transcriptomics, proteomics and metabolomics-are contributing to offer a more comprehensive view of molecular pathways underlying the development of NDs, helping to differentiate subtypes of patients based on their specific molecular signatures. In this article, we discuss how omics technologies and their integration have provided new insights into the molecular heterogeneity underlying the most prevalent NDs, aiding to define early diagnosis and progression markers as well as therapeutic targets that can translate into stratified treatment approaches, bringing us closer to the goal of personalized medicine in neurology.

DOI: 10.3390/ijms22094820

The impact factor: 6.208

Paper 8

Title: Subtyping of mild cognitive impairment using a deep learning model based on brain atrophy patterns.

Abstract: Trajectories of cognitive decline vary considerably among individuals with mild cognitive impairment (MCI). To address this heterogeneity, subtyping approaches have been developed, with the objective of identifying more homogeneous subgroups. To date, subtyping of MCI has been based primarily on cognitive measures, often resulting in indistinct boundaries between subgroups and limited validity. Here, we introduce a subtyping method for MCI based solely upon brain atrophy. We train a deep learning model to differentiate between Alzheimer's disease (AD) and cognitively normal (CN) subjects based on whole-brain MRI features. We then deploy the trained model to classify MCI subjects based on whole-brain gray matter resemblance to AD-like or CN-like patterns. We subsequently validate the subtyping approach using cognitive, clinical, fluid biomarker, and molecular imaging data. Overall, the results suggest that atrophy patterns in MCI are sufficiently heterogeneous and can thus be used to subtype individuals into biologically and clinically meaningful subgroups.

DOI: 10.1016/j.xcrm.2021.100467

The impact factor: 16.988

Paper 9

Title: Beyond the average patient: how neuroimaging models can address heterogeneity in dementia.

Abstract: Dementia is a highly heterogeneous condition, with pronounced individual differences in age of onset, clinical presentation, progression rates and neuropathological hallmarks, even within a specific diagnostic group. However, the most common statistical designs used in dementia research studies and clinical trials overlook this heterogeneity, instead relying on comparisons of group average differences (e.g. patient versus control or treatment versus placebo), implicitly assuming within-group homogeneity. This one-size-fits-all approach potentially limits our understanding of dementia aetiology, hindering the identification of effective treatments. Neuroimaging has enabled the characterization of the average neuroanatomical substrates of dementias; however, the increasing availability of large open neuroimaging datasets provides the opportunity to examine patterns of neuroanatomical variability in individual patients. In this update, we outline the causes and consequences of heterogeneity in dementia and discuss recent research that aims to tackle heterogeneity directly, rather than assuming that dementia affects everyone in the same way. We introduce spatial normative modelling as an emerging data-driven technique, which can be applied to dementia data to model neuroanatomical variation, capturing individualized neurobiological 'fingerprints'. Such methods have the potential to detect clinically relevant subtypes, track an individual's disease progression or evaluate treatment responses, with the goal of moving towards precision medicine for dementia.

DOI: 10.1093/brain/awab165

The impact factor: 15.255

Paper 10

Title: Recent update on the heterogeneity of the Alzheimer's disease spectrum.

Abstract: Alzheimer's disease (AD), the most common form of dementia worldwide, is a mixed proteinopathy (Î²-amyloid, tau and other proteins). Classically defined as a clinicopathological entity, AD is a heterogeneous, multifactorial disorder with various pathobiological subtypes showing different forms of cognitive presentation, currently referred to as the Alzheimer spectrum or continuum. Its morphological hallmarks are extracellular Î²-amyloid (amyloid plaques) and intraneuronal tau aggregates forming neurofibrillary tangles and neurites, vascular amyloid deposits (cerebral amyloid angiopathy), synapse and neuronal loss as well as neuroinflammation and reactive astrogliosis, leading to cerebral atrophy and progressive mental/cognitive impairment (dementia). In addition to "classical" AD, several subtypes with characteristic regional patterns of tau pathology have been segregated that are characterized by distinct clinical features, differences in age, sex distribution, disease duration, cognitive status, APOE genotype, and biomarker levels. In addition to four major subtypes based on the

distribution of tau pathology and brain atrophy (typical, limbic predominant, hippocampal sparing, and minimal atrophy), several other clinical variants (non-amnestic, corticobasal, behavioral/dysexecutive, posterior cortical variants, etc.) have been identified. These heterogeneous AD variants are characterized by different patterns of key neuronal network destructions, in particular the default-mode network that is responsible for cognitive decline. Other frequent age-related co-pathologies, e.g., cerebrovascular lesions, Lewy and TDP-43 pathologies, hippocampal sclerosis, or argyrophilic grain disease, essentially influence the clinical picture and course of AD, and can challenge our understanding of this disorder including the threshold and causal relevance of each individual pathology. Unravelling the clinico-morphological heterogeneity among the AD spectrum entities is important for better elucidation of the pathogenic mechanisms affecting the aging brain that may enable a broader diagnostic coverage of AD as a basis for implementing precision medicine approaches and for developing preventive and ultimately disease-modifying therapies for this devastating disorder.

DOI: 10.1007/s00702-021-02449-2

The impact factor: 3.85