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Dominique GOUILLY

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Thèse dirigée par
Jérémie PARIENTE et Patrice PERAN

Jury

M. David WALLON, Rapporteur
M. Michel BOTTLAENDER, Rapporteur
Mme Marie SARAZIN, Examinatrice
M. Julien DELRIEU, Examinateur
M. Jérémie PARIENTE, Directeur de thèse
M. Patrice PéRAN, Co-directeur de thèse

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Note : *Les articles insérés dans le texte contiennent également des figures et tableaux qui n'ont pas été indiqués ici. Les figures et tableaux supplémentaires de ces articles ont été placés à la suite du texte.*

Glossaire

$A\beta_{42}$: amyloïde-β 42, biomarqueur de la pathologie amyloïde cérébrale dans le liquide cérébrospinal

AINS : médicament anti-inflammatoire non-stéroïdien

CIC : Centre d'Investigation Clinique

CHU : Centre Hospitalier Universitaire

DMS 48 : 'delayed matching to sample test with 48 items', test d'évaluation de la mémoire visuelle

FDG : fluorodésoxyglucose, cible radiomarquée en imagerie TEP du métabolisme glucidique

IL : interleukine, médiateur des voies de signalisation de la neuro-inflammation

IRM : imagerie par résonnance magnétique

LCS : liquide cérébrospinal

MA : maladie d'Alzheimer

MAPK : 'mitogen activated protein kinase', famille de protéines des voies de la neuro-inflammation

MMS : 'mini-mental state examination', test d'efficience cognitive globale

RLRI 16 : test de rappel libre rappel indicé à 16 items, test d'évaluation de la mémoire verbale

SUV : 'standard uptake value', mesure semi-quantitative utilisée en imagerie TEP

TSPO : protéine translocatrice, cible radiomarquée en imagerie TEP de la neuro-inflammation

Tau-p : tau phosphorylé, biomarqueur de la pathologie tau cérébrale dans le liquide cérébrospinal

Tau-t : tau total, biomarqueur de la neurodégénérescence dans le liquide cérébrospinal

TEP : imagerie par tomographie par émission de positons

UMR : unité mixte de recherche

V : visite (exemples : v0, visite 0 ; v1, visite 1)

V.I.P : acronyme d'un projet de recherche signifiant 'VX-745 Inflammation PET scan'

Note : *Les articles insérés dans le texte contiennent également des abréviations qui n'ont pas été indiqués ici. Elles ont été indiquées au niveau des articles correspondants.*

Introduction générale

Les systèmes biologiques sont organisés à différents niveaux d'organisation (génétique, moléculaire, cellulaire, systémique, fonctionnement cognitif). L'étude de l'impact d'une pathologie sur cette organisation permet l'élaboration de stratégies diagnostiques et thérapeutiques.

Le système biologique de la maladie d'Alzheimer (MA) a été conceptualisée par l'hypothèse que la déposition cérébrale de peptides amyloïdes, qu'elle ait un déterminisme génétique ou stochastique, est le changement pathologique inaugural de la maladie (Selkoe and Hardy, 2016). La dyade formée avec la pathologie tau constitue les lésions pathognomoniques repris au fil de l'histoire de la MA (Knopman et al., 2019).

Cependant, cette hypothèse n'a pas été translatée en des thérapeutiques efficientes. Plusieurs avancées suggèrent l'intérêt de réviser cette conception de la MA. Premièrement, l'idée de la succession linéaire de changements pathologiques en cascade est de plus en plus questionnée (Chételat, 2013; Duyckaerts et al., 2015). Deuxièmement, de nouveaux facteurs de risque et de protection de la MA ont été découvert en épidémiologie et génétique (Kunkle et al., 2019; Livingston et al., 2020). Les relations entre ces facteurs et la physiopathologie de la MA sont mieux élucidées (Henstridge et al., 2019). Enfin, la contribution d'autres éléments conducteurs de la neurodégénérescence est élargi, notamment grâce à l'émergence de nouveaux biomarqueurs. C'est l'exemple de la neuroinflammation qui d'un épiphénomène physiopathologique devient une cible thérapeutique de nouvelle génération (Leng and Edison, 2021). La conception de la MA évolue ainsi vers la perspective plus complexe de pathologies multicellulaires (Scheltens et al., 2021).

Ces évolutions sont la base théorique des travaux de cette thèse, et sont présentées dans la section introductive suivante. Trois études seront ensuite développées portant sur les biomarqueurs du liquide cérébrospinal (LCS) et de neuroimagerie dans la MA. Ces travaux ont été focalisés sur la neuroinflammation. Enfin, une discussion portera sur ces études, et leur impact sur le développement thérapeutique de la MA.

Partie théorique

1. Introduction

1.1. Evolutions de la définition de la maladie d'Alzheimer

En 2018, une définition biologique de la MA est publiée par un groupe d'experts (National Institute of Aging - Alzheimer's Association, NIA-AA) (Jack et al., 2018). Il est proposé de pouvoir définir la MA uniquement par la présence de valeurs pathologiques aux biomarqueurs amyloïdes et tau. A la base de cette proposition, il y a l'idée de séparer la notion du syndrome de celle de la maladie d'Alzheimer. Depuis sa découverte, le syndrome a toujours fait partie des critères diagnostic de la MA en pratique clinique courante (Knopman et al., 2019). Cette définition nouvelle marque une rupture par la certitude de l'affirmation que la présence de la pathologie amyloïde est suffisante pour poser un diagnostic clinique (Jack and Vemuri, 2018). Cette affirmation est déroutante en particulier car la plupart des individus amyloïdes-négatifs ne développent pas de symptômes dans leur durée de vie (Dubois et al., 2018). Mais il est proposé par lesdits experts que le syndrome de la MA n'est ni sensible ni spécifique de la pathologie amyloïde, que cette pathologie a une fonction centrale dans la physiopathologie, et que s'affranchir du syndrome des patients permettra d'étudier la MA à des stades pré-symptomatiques, ce qui permettra peut-être des progrès en recherche thérapeutique (Jack et al., 2018; Jack and Vemuri, 2018; Jagust et al., 2019; Jagust, 2021).

Pour un autre groupe d'experts international (International Working Group, IWG), l'interprétation d'une valeur anormale à un biomarqueur amyloïde est pesée avec moins de certitudes. En 2021, ce groupe argumente une définition de la MA où l'interprétation des biomarqueurs amyloïdes est admise controversée entre un biomarqueur préclinique, ou un facteur de risque (Dubois et al., 2021). Dans ces critères, la place de la pathologie amyloïde n'est pas remise en question, mais plutôt l'interprétation des biomarqueurs de la MA qui est sujet à discussions (Dubois et al., 2021). Les limites d'une définition basée sur les biomarqueurs y sont clarifiées. Cette définition serait basée sur des critères cliniques et biologique, sous une forme assez similaire à ceux publiés précédemment (Dubois et al., 2014), applicables en pratique clinique courante et en recherche.

	NINCDS–ADRDA (1984)[2]	IWG (2007)[3]	IWG (2010)[4]	NIA–AA (2011)[5,6]	IWG (2014)[7]	IWG–AA (2016)[8]	NIA–AA (2018)[1]	IWG (2021)
Applicable settings	Research and clinical	Research	Research	Research and clinical	Research	Research	Research	Research and clinical
Clinical requirements	Dementia (memory changes and another cognitive impairment)	Amnestic syndrome of a hippocampal type	Amnestic syndrome of a hippocampal type, posterior cortical variant, logopenic variant, or behavioural–frontal variant	Mild cognitive impairment (amnestic or non-amnestic) or dementia	Amnestic syndrome of a hippocampal type, posterior cortical variant, logopenic variant, or behavioural–frontal variant	None	None	Amnestic variant, posterior cortical atrophy, logopenic variant primary progressive aphasia, behavioural or dysexecutive frontal variant, corticobasal syndrome, semantic and nonfluent variants of primary progressive aphasias*
Biological requirements	None	CSF biomarkers, MRI atrophy, ^{18}F-fluorodeoxyglucose PET hypometabolism, amyloid PET positive, or Alzheimer's disease autosomal dominant mutation	Pathophysiological markers: CSF changes (low CSF Aβ42, high phosphorylated tau, or high total tau) or amyloid PET positive	Amyloid β marker (CSF or PET) or marker of degeneration (CSF tau, phosphorylated tau, ^{18}F-fluorodeoxyglucose-PET, and T1-weighted MRI)	CSF amyloid β and tau or amyloid PET positive	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)

ADRDA=Alzheimer's Disease and Related Disorders Association (now the Alzheimer's Association) Work Group. IWG=International Working Group criteria. IWG–AA=International Working Group and Alzheimer's Association joint criteria. NIA–AA=US National Institute on Aging and Alzheimer's Association joint criteria. NINCDS=US National Institute of Neurological and Communicative Disorders and Stroke criteria.
*Cognitively unimpaired individuals are considered at-risk for Alzheimer's Disease.

Tableau 1 : Succession des critères diagnostic de la maladie d'Alzheimer (modifié de Dubois et al., 2021).

Les évolutions de ces critères donnent une place incontournable aux biomarqueurs dans le parcours de soin des patients (tableau 1). Les évolutions sur l'utilisation de ces biomarqueurs sont présentées dans la section suivante.

1.2. **Evolutions de l'utilisation des biomarqueurs**

Les biomarqueurs de la MA diffèrent selon la matrice d'où ils proviennent. En imagerie TEP, des traceurs spécifiques des pathologies amyloïde et tau sont disponibles, ainsi que du fluorodésoxyglucose (FDG) pour le métabolisme glucidique. Dans le liquide cérébrospinal (LCS), les valeurs d'amyloïde-β 42 ($A\beta_{42}$) ou le ratio $A\beta_{42/40}$ et le taux de tau-phosphorylé (tau-p) révèlent les pathologies amyloïdes et tau, respectivement. La neurodégénérescence peut être mesurée en IRM structurale ou bien par le taux de tau total (tau-t) dans le LCS. L'IRM permet aussi la recherche de co-pathologies cérébrovasculaires, et l'étude de la connectivité de réseaux avec des séquences d'acquisitions spécifiques.

Des biomarqueurs d'autres aspects physiopathologiques des maladies neurologiques ont émergé. Les taux de la neurogranine et de la chaîne légère des neurofilaments dans le LCS indiquent les dommages axonales et synaptiques qui précèdent la neurodégénérescence (Gaetani et al., 2019). La neuroinflammation peut aussi être étudiée dans le LCS par la mesure du taux d'interleukines (IL), cytokines, ou d'autres protéines spécifiques telles que le variant soluble de TREM2 exprimé par la microglie, ou YKL-40 exprimé par la microglie et les astrocytes (Baldacci et al., 2019; Morgan and Mielke, 2021). Des traceurs TEP sont aussi développés pour étudier ces processus, comme l'utilisation de traceurs TEP de la protéine 2A des vésicules synaptiques (SV2A) (Becker et al., 2020). Une des sections suivantes abordera le développement de l'imagerie TEP de la protéine translocatrice (TSPO) dans la MA. Le développement de biomarqueurs sanguins de la MA ne sera pas abordé dans ce manuscrit, bien qu'il s'agisse d'un axe massif de recherche en cours (Teunissen et al., 2022; Zetterberg, 2022). On voit aussi émerger des biomarqueurs des co-pathologies de la MA, notamment pour les α-synucléinopathies (Dauvilliers, 2021; Wang et al., 2021).

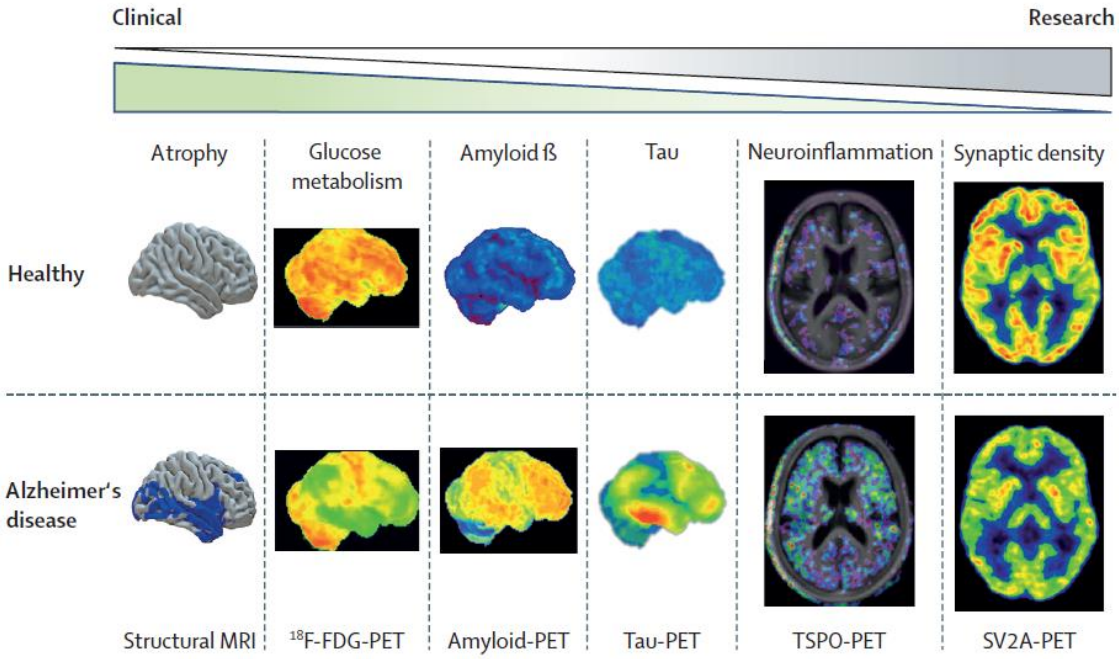

Figure 1 : Biomarqueurs de neuro-imagerie structurale et fonctionnelle en IRM ou TEP (modifiée de Chételat et al., 2020).

L'évolution de la définition de la MA a suscité des progrès dans la façon de les utiliser en pratique clinique et de recherche. On marque d'abord une distinction entre les biomarqueurs diagnostics (amyloïde et tau-p) et de progression de la maladie : dommages synaptiques, neuroinflammation, dégénérescence pour en citer quelques-uns.

On marque ensuite une distinction dans la façon d'utiliser les biomarqueurs en pratique clinique et de recherche (figure 1). Dans le premier cas, tout dépend du profil clinique avec lequel se présente le patient. Un groupe d'experts international a ainsi proposé un ordre d'emploi des biomarqueurs en fonction du profil clinique individuel pour donner une aide à l'orientation diagnostic (Chételat et al., 2020). Le lecteur pourra se référer à l'article de revue publié à ce sujet pour plus de détails.

Pour autant le profil clinique peut biaiser l'interprétation des biomarqueurs dans une pratique de recherche. Un schéma de classification des biomarqueurs de la MA a donc été proposé se voulant agnostique de ces aspects (Jack et al., 2016). Il s'agit du schéma AT(N) où A représente les biomarqueurs amyloïdes, T, ceux de la pathologie tau, et N, la neurodégénérescence (tableau 2).

Profil de biomarqueur	Interprétation	Continuum de la MA ?
A-T-N-	Biomarqueurs de la MA normaux	Non
A+T-N-	Changement pathologique de la MA	Oui
A+T+N-	MA	
A+T+N+		
A+T-N+	MA et changement pathologique concomitant suspecté de type non-MA	
A-T+N-	Changement pathologique de type non-MA	Non
A-T-N+		
A-T+N+		

Tableau 2 : Les huit profils AT(N) et leur interprétation dans le cadre d'une définition biologique de MA (inspiré de Hampel et al., 2021).

Il a récemment été proposé d'ajouter certains des biomarqueurs émergeant dans les bio-fluides à ce schéma (figure 2). Cela inclus les biomarqueurs des dommages axonales et synaptiques, des pathologies vasculaires, et de la neuroinflammation.

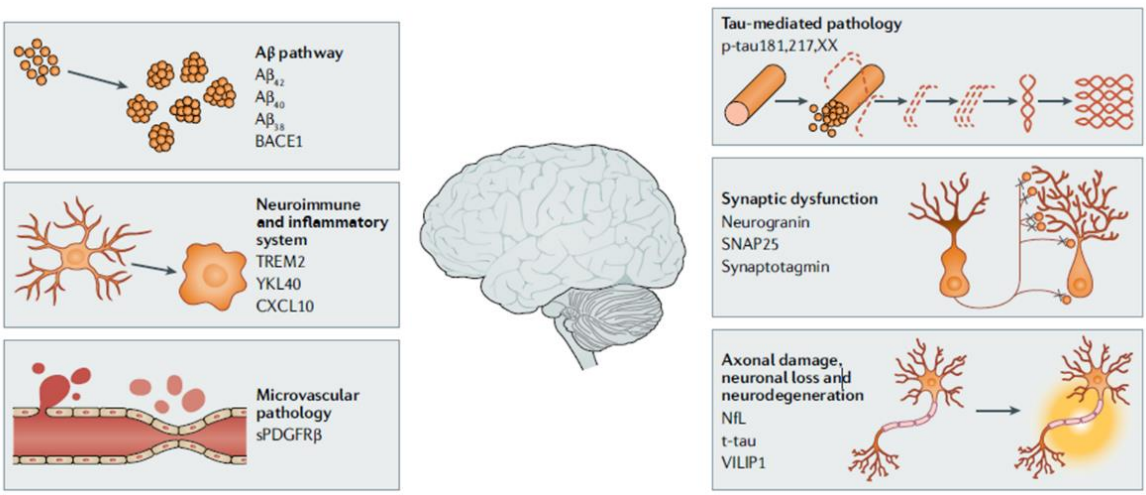

Figure 2 : Les évolutions du système AT(N) vers le système ATX(N) (modifiée de Hampel et al., 2021).

Le développement des biomarqueurs de la MA n'est pas au même niveau. La maturité de ce développement est évaluée sur cinq phases qui valident progressivement l'utilité clinique du biomarqueur (Frisoni et al., 2017). Cette utilité s'établit sur des facteurs relatifs à l'acquisition du biomarqueur (pré-analytique), à la méthode de quantification (analytique), et d'interprétation (post-analytique). Depuis une trentaine d'années, chaque biomarqueur a atteint une maturité de développement plus ou moins élevée. Dans la MA, l'atrophie en IRM structurale est au stade le plus avancé à ce jour (Frisoni et al., 2017; Ten Kate et al., 2017). Le lecteur pourra se référer à des articles de revue spécifiques à chaque biomarqueur pour plus de détails à propos de leur maturité de développement (Ashton et al., 2021; Cerami et al., 2017; Chiotis et al., 2017; Garibotto et al., 2017; Leuzy et al., 2021).

Des tentatives de standardisation internationale ont été élaborées pour rendre l'emploi des biomarqueurs plus précis et reproductible, parfois au point de permettre le remboursement des frais liés à leur utilisation dans certains pays (Frisoni et al., 2017). Des projets de standardisation sont en cours pour l'utilisation des biomarqueurs du LCS et d'imagerie TEP (Apostolova et al., 2016; Hampel et al., 2022; Hansson et al., 2021).

Il convient de mentionner que l'intérêt soulevé par l'utilisation des biomarqueurs influence le processus de leur développement. A titre d'exemple, le développement des biomarqueurs plasmatiques des pathologies amyloïde et tau a connu une extension plus rapide ces dernières années que d'autres biomarqueurs mentionnés ci-dessus (Ashton et al., 2021). La question de leur implémentation en pratique clinique est un enjeu actuel, notamment pour le diagnostic et la surveillance de thérapies anti-Alzheimer (Teunissen et al., 2022). Le processus pour rendre les biomarqueurs de la MA opérationnel est donc inégal, bien qu'un panel de plus en large de ces biomarqueurs soit disponible.

1.3. **Evolutions en physiopathologie**

1.3.1. **Faits introductifs**

La pathologie de la MA est caractérisée par la présence des lésions amyloïdes et tau. Les mécanismes par lesquels ces lésions induisent les symptômes ont été décrit par un effet en cascade initié par l'apparition des lésions amyloïdes (Selkoe and Hardy, 2016). Cette notion est profusément acceptée sur le plan physiopathologique, nosologique, et thérapeutique en termes de prévention et intervention. Bien qu'aucune preuve n'ait encore pu réfuter l'hypothèse d'un effet en cascade, plusieurs avancées récentes convergent pour modifier cette vision linéaire. J'ai écrit un article de revue pour essayer de donner un aperçu général de ces modèles émergeants. J'ai souhaité me focaliser sur les études récentes chez l'homme aux premiers stades de la forme sporadique de la MA.

Au cours de ces vingt dernières années, le système biologique de la MA a été exploré à différents niveaux d'organisation (génétique, moléculaire, cellulaire, réseaux cellulaires, fonctionnement cognitif). Les interactions entre ces niveaux, et l'arborescence de leur dysfonction a été révélée à des niveaux spatial et temporel. Elle soulève de profondes questions sur la dynamique des changements pathologiques de la MA, leurs associations aux facteurs de risque et de protection, ainsi que sur leur étiologie.

A ce jour, l'hétérogénéité biologique de la MA a été décrite à travers ses différents modes d'expression, en particulier sur l'hétérogénéité de la pathologie tau. Au niveau temporel, les études neuro-pathologiques ont montré que la pathologie tau était plus prévalente que la pathologie amyloïde, et qu'elle s'observe fréquemment en absence de celle-ci (Braak et al., 2011; Duyckaerts et al., 2015). Cette idée n'est forcément pas exclusive de la séquence mécanistique linéaire supposée dans la cascade amyloïde (figure 3). Cependant elle impose l'idée de modes d'interaction plus complexes, et pose la question poignante d'une étiologie différentielle.

La distribution spatiale des lésions amyloïde et tau suit une évolution hiérarchique et stéréotypée (Jagust, 2018). Comme l'avait mentionné C. Duyckaert et ses collègues, cette évolution suggère non seulement la dysfonction des mécanismes de clairance des lésions (Duyckaerts et al., 2015). Elle suggère que cette évolution est en partie indépendante du volume lésionnel. Il existerait donc une vulnérabilité cellulaire sélective et prédictive du pattern de neurodégénérescence (figure 3).

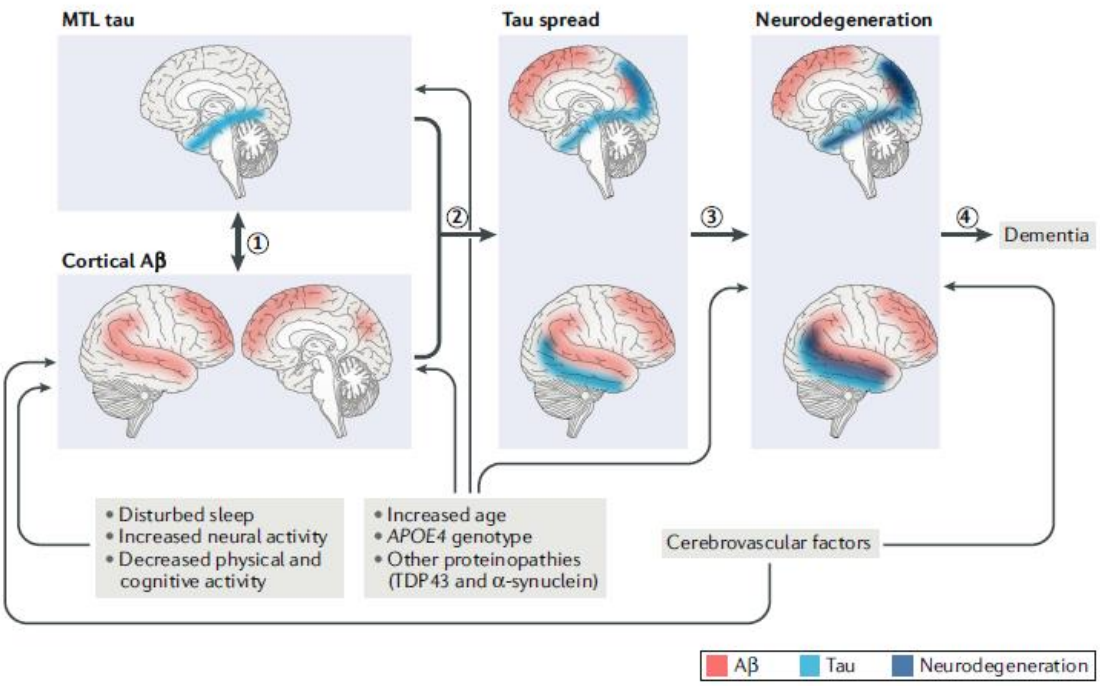

Figure 3 : Evolutions de la cascade physiopathologique de la maladie d'Alzheimer (modifiée de Jagust, 2018). Abréviations : Aβ, β-amyloïde ; MTL, lobe temporal médian.

Cette vulnérabilité a plusieurs vecteurs d'expression dans le contexte de la MA. Chez l'homme, les déterminants de la progression pathologique ont été décrit en épidémiologie, génétique, connectivité de réseaux, dans la fonction cérébrovasculaire, (neuro)-immunologie, ainsi que dans l'influence de pathologies surajoutées (Henstridge et al., 2019). La présence de changements pathologiques dans ces fonctions pourrait provenir des pathologies amyloïdes et tau. Cependant, l'arborescence de ces changements élargit la physiopathologie de la MA à une perspective multi-cellulaire (Scheltens et al., 2021). Dans ce contexte, la neuroinflammation prend une importance insoupçonnée. Elle serait un élément clé de la synergie des pathologies amyloïdes et tau, et ainsi une base biologique, peut-être donc déterminante, des facteurs de risque et de protection de la MA (Henstridge et al., 2019; Leng and Edison, 2021).

Au niveau spatial, différents patterns de distribution de la pathologie tau ont été révélé dans une étude rétrospective publiée en 2011 (Murray et al., 2011). Une sous-population présenterait une pathologie prédominante dans les régions limbiques, une autre aurait des lésions corticales épargnant l'hippocampe, et un troisième sous-type présenterait le pattern typique étendue entre les régions temporales et associatives. En dix ans, l'exploration des variations physiopathologiques entre ces sous-types apporte les débuts d'une base biologique à la variabilité clinique inter-individuelle de la MA (Ferreira et al., 2020). Il existerait des variations en termes de typicalité et de sévérité pathologique (figure 4). Ces éléments invitent à repenser l'hypothèse d'une causalité unique de la cascade amyloïde.

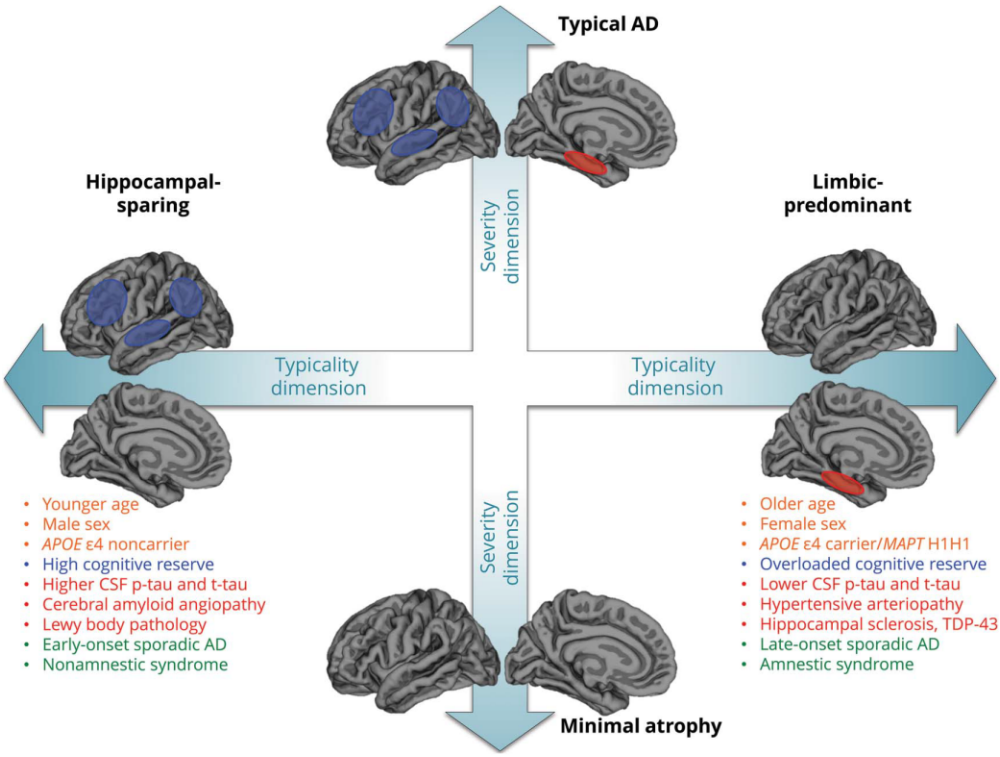

Figure 4 : Variabilité biologique de la maladie d'Alzheimer (modifiée de Ferreira et al., 2020). Abréviations : AD, Alzheimer's disease ; APOE, apolipoprotéine E ; CSF, liquide cérébrospinal ; MAPT, gène codant pour la protéine tau ; p-tau, tau phosphorylé ; -43 : TAR DNA- binding protein 43 t-tau, tau total ; TDP.

L'idée que la MA ne découle pas simplement de la pathologie amyloïde suggère que cette pathologie ne pourrait être qu'une partie de la réponse à la maladie plutôt que la maladie elle-même. Il est d'ailleurs remarquable que le rôle fonctionnel de l'accumulation de plaques amyloïdes soit encore incompris (Castellani et al., 2009). En outre, les résultats des interventions anti-amyloïdes restent en dessous des espoirs suscités par un modèle où cette pathologie provoquerait tous les autres changements en cascade (Avgerinos et al., 2021; Mo et al., 2017; Penninkilampi et al., 2017). La compréhension physiopathologique d'une maladie influence sa définition et sa thérapie. Circonscrire la MA à la pathologie amyloïde a donc plusieurs implications encore sujets à débat. Dans cet article de revue, j'ai voulu essayer d'établir une vue généralisée des éléments qui alimentent cette question.

Note : *Cet article a fait l'objet d'une soumission à une revue internationale. Il a été choisi de l'insérer dans le texte dans son format de soumission.*

1.3.2. **Article de revue de physiopathologie**

Beyond the amyloid cascade:

An update of Alzheimer's disease pathophysiology

Dominique Gouilly[a], Marie Rafiq[a, b], Leonor Nogueira[c], Anne-Sophie Salabert[a, d], Pierre Payoux[a, d, e], Patrice Péran[a], Jérémie Pariente[a, b, e]

a Toulouse Neuroimaging Center, Toulouse, France.

b Department of Cognitive Neurology, Epilepsy and Movement Disorders, CHU Toulouse Purpan, France.

c Department of Cell Biology and Cytology, CHU Toulouse Purpan, France.

d Department of Nuclear Medicine, CHU Toulouse Purpan, France.

e Center of Clinical Investigation, CHU Toulouse Purpan (CIC1436), France.

Abstract

Alzheimer's disease (AD) is a multi-etiology disease. The biological system of AD is associated with multidomain genetic, molecular, cellular, and network brain dysfunctions, interacting with central and peripheral immunity. These dysfunctions have been primarily conceptualized according to the assumption that amyloid deposition in the brain, whether from a stochastic or a genetic accident, is the upstream pathological change. However, the arborescence of AD pathological changes suggests that a single amyloid pathway might be too restrictive or inconsistent with a cascading effect. In this review, we discuss the recent human studies of late-onset AD pathophysiology in an attempt to establish a general updated view focusing on the early stages. Several factors highlight heterogenous multi-cellular pathological changes in AD, which seem to work in a self-amplifying manner with amyloid and tau pathologies. Neuroinflammation has an increasing importance as a major pathological driver, and perhaps as a convergent biological basis of aging, genetic, lifestyle and environmental risk factors.

Glossary

AD, Alzheimer's disease; APOE, apolipoprotein E; BBB, blood brain barrier; CBF, cerebral blood flow; CSF, cerebrospinal fluid; HI, healthy individuals; MRI, magnetic resonance imaging; PART, primary age-related tauopathy; PET, positron emission tomography; RCT, randomized controlled trials; SNAP, suspected non-Alzheimer's pathology.

1. Introduction

The biological systems are organized on different inter-related spatio-temporal scales (i.e., genetic, molecular, cellular, cellular network, cognitive functioning), which can be impacted by pathological changes at different levels. The hypothesis on Alzheimer's disease (AD) pathophysiology was primarily shaped by the brain biochemical pathway of amyloid production and cascade [1]. However, this has not yet been translated into effective therapeutics. Recent evidence indicates the need to refine this view of AD. First, increasing evidence questions the well-known sequential biomarker-based pathophysiological AD cascade [2]. This contributes to the emergence of new models of AD pathophysiology [3, 4]. Secondly, novel factors that influence the risk of developing AD have recently been discovered in epidemiology and genetics [5, 6]. Thirdly, the relationships of protective and risk factors with the pathophysiological mechanisms of AD are now beginning to be elucidated [7]. Finally, the contribution of other drivers of the neurodegenerative process besides amyloid peptides is increasingly being explored, especially regarding the role of immunity [8]. These advances have several implications regarding the pathophysiological conception of AD. In this review, we discuss these recent advances and their impact on AD therapeutic development.

2. Basic facts on Alzheimer's disease pathophysiology

AD currently refers to the disease associated with the pathological brain lesion dyad of amyloid plaques and neurofibrillary tangles [9, 10]. There are three subtypes of AD that share these pathological lesions but differ in terms of their genetic risk, pathophysiological mechanisms, and clinical characteristics. Rare autosomal dominant forms of AD (ADAD) (<5% of all cases) are caused by mutations in coding genes of amyloid metabolism (APP, PSEN1, PSEN2). The two other subtypes are considered sporadic in patients with early symptom onset, usually before 65 years, early-onset AD (EOAD), and those with late symptom onset after 65 years, late-onset AD (LOAD). EOAD might be associated with genetic recessive inheritance [11]. LOAD may be a multi-etiology disorder depending on genetic, environmental and lifestyle factors along with aging [12].

The pathobiological course of AD could be relatively similar in these subtypes. The aggregation of amyloid peptides is considered to be the initial pathological change, caused by an overproduction in ADAD, or by a clearance mechanisms dysfunction in EOAD and LOAD [13]. The presence of amyloid aggregates could be the driving force of the formation of intra-neuronal neurofibrillary tangles mainly composed of hyperphosphorylated tau (P-tau) proteins [14]. However, there is still some uncertainty about the mechanistic relationships between these two pathologies [15]. The amyloid pathology also induces neuroinflammation through molecular interactions with glial cells, and neurodegeneration through direct synaptic injuries [1, 16]. This cascade has been the most widely accepted view of AD pathophysiology since the 90's [17].

Neuroimaging biomarker studies in ADAD using positron emission tomography (PET) and magnetic resonance imaging (MRI), or cerebrospinal fluid (CSF) biomarkers have revealed that pathological changes precede the onset of symptoms: 20-22 years for amyloid deposition, 15-18 years for hypometabolism on PET, 10-13 years for the first signs of degeneration [18]. The progression of these lesions in the brain follow a specific and hierarchical pattern of distribution [19, 20]. Amyloid lesions are observed mainly in the neocortex, then in the hippocampus, the basal ganglia, the mesencephalon, and the cerebellum [20]. Tau deposits can be found in the entorhinal cortex alone, then in the hippocampus, and the neocortex [19]. However, there are differences between ADAD, EOAD and LOAD in terms of regional distribution, extent, and temporal trajectories of the pathological changes observed, which have been described in detail elsewhere [21, 22].

3. Refining the pathophysiological model of Alzheimer's disease

Biomarker studies demonstrate the well-known sequential cascade of AD pathological changes [2, 23]. This model was recently re-examined based on accumulated neuroimaging studies in a review article showing that most of the published studies appear to conform to the hypothetical model of Jack and colleagues [22]. This confirms the sequence of biomarker abnormalities seen in AD. However, there are several controversies and unresolved questions that challenge this linear conception of AD pathophysiological mechanisms. These notions are discussed in this section.

3.1. The relationship between amyloid and cognitive decline

The relationships between amyloid deposition and cognitive decline is complex in elderly healthy individuals (HI) with AD. The prevalence of amyloid-positive individuals increases with age, apolipoprotein E (APOE) 4 genotype, and the presence of cognitive impairment, and correspond to 30-40% of the individuals aged at least 70 years in neuropathological and biomarker studies [24–26]. Neuropathological studies show that the amyloid burden is similar between cognitively normal and AD patients [27, 28]. Furthermore, longitudinal PET studies show that the majority of asymptomatic amyloid-positive subjects (81-83%) remain cognitively stable after 2-6 years follow-up [29, 30]. Collectively, these results indicate that amyloid pathology is not directly related to cognitive decline, and confirms that most amyloid-positive individuals will not have cognitive impairment in their lifetime [31].

However, it would appear that cognitively normal amyloid-positive subjects may have a higher risk of cognitive decline than their counterparts [32, 33]. Cross-sectional studies are controversial on this notion, showing lower episodic memory among amyloid-positive cognitively normal individuals, although global cognitive efficiency appears to be preserved [34, 35]. Amyloid positivity is also associated with lower cognitive performances among MCI patients [35]. Furthermore, the risk for cognitive decline in amyloid-positive subjects appears to be highly variable according to gender, age, and disease state, ranging from 5 to 42% among cognitively normal subjects [31].

Biomarker studies show that the association of amyloid with cognitive decline could be 'dose-dependent' according to the presence of additional biomarker abnormalities, and the magnitude of the observed lesions [36–40]. For example, longitudinal cognitive decline is faster in amyloid-positive individuals carrying APOE4 [41], and among patients showing the highest amyloid burden [42]. Collectively these advances confirm that the relationship of amyloid with cognitive decline is weak and may vary at the individual level.

It should be noted that more complex factors such as educational level could modify resilience against age and AD-related cognitive decline at the individual level. These factors have been conceptualized in the notions of cognitive reserve and these derivatives [43, 44]. These might partly explain why some patients with the same pathological burden have distinct clinical states. Therefore, it was argued that detection of longitudinal decline in amyloid-positive HI depends on the follow-up time and the cohort characteristics [45]. This might explain why some studies have found no significant associations between amyloid positivity and cognitive decline.

3.2. The relationship between amyloid and tau

The mechanisms of interaction between amyloid and tau pathologies are not fully understood for several reasons. Firstly, neuropathological studies show that tau deposits are frequently observed in the absence of amyloid pathology in the brain of individuals of all ages, especially in HI without cognitive impairment [24, 46]. One autopsy study of elderly cognitively normal HI revealed 98% abnormal tau, but only 47% abnormal amyloid deposits [47]. The nosology of these cases showing tau pathology without amyloid deposits was first proposed to be apart from AD and related to normal aging under the nosology primary age-related tauopathy (PART) [48]. However, it was argued that no evidence strongly supports that PART and AD are a result of different processes [4], which suggests that PART might be a part of AD.

Secondly, a better understanding of the interactions between amyloid and tau have only just begun, both from a mechanistic and a biomarker perspective. Recent advances in the mechanisms of amyloid-tau interactions have recently been reviewed and strongly suggest that the synergy between both pathologies might be more detrimental that their independent effect, regardless of which pathology occurs first [15]. Biomarker studies in cognitively unimpaired subjects support this idea, which shows that amyloid burden is the best predictor of tau accumulation rates on PET [49], and that synergic amyloid and tau abnormalities in the neocortex are associated with cognitive decline, except for patients with localized tauopathy in common aged-related sites [50].

3.3. The biological heterogeneity of amyloid-positive individuals

The biological heterogeneity of amyloid-positive individuals has been increasingly explored in clinico-pathological or biomarker studies [51]. The heterogeneity was characterized in terms of typicality based on brain spatial distribution of a specific pathological pattern (e.g., tau distribution), and in terms of severity based on the magnitude of neurodegeneration. Three pathological subtypes have been described: limbic-predominant, hippocampal-sparing, and typical AD, typical AD exhibiting the classic tau distribution pattern from the limbic to associative regions [51–53]. MRI studies also described a fourth subtype with minimal atrophy [54]. The prevalence of typical AD is 55%, while the frequency of other subtypes ranges from 15-21% [51]. A meta-analysis showed clinical differences between these subtypes in terms of age at assessment and at symptoms onset, APOE genotype, gender, years of education, cognitive status, disease duration, and CSF biomarker levels [51]. These studies revealed unexpected biological heterogeneity among amyloid-patients with distinct profiles related to neurodegeneration and cognitive decline in different ways. This has implications for the conception of AD pathophysiology.

Furthermore, it becomes clear that both clinical and pathological progression of AD are more related to tauopathy and the degenerative process than to amyloid pathology [55, 56]. The spatial pattern of tau pathology on PET reflects different aspects of AD, including symptom focality and severity, disease progression, and overlap with hypometabolism on PET and atrophy on MRI [57, 58]. A recent tau PET study described four distinct spatio-temporal trajectories of tau pathology, replicating the limbic-predominant and hippocampal-sparing subtypes, while discovering additional posterior and lateral temporal patterns [59]. In this study, these subtypes presented distinct baseline and longitudinal outcomes. These recent studies reinforce the idea that AD might be an umbrella term for heterogenous pathological changes rather than a disease with a single amyloid-related prognosis.

3.4. What is the best model of Alzheimer's disease?

The notions presented in this section suggest that the linear and sequential view of the amyloid cascade might not be appropriate. The fact that tau tangle formation can precede the amyloid pathology suggests that tau deposition could be at least in part independent of amyloid pathology [60]. Braak and colleagues recently advanced the idea that tau pathology might be the initiating factor of AD [61]. Another hypothesis is that amyloid and tau pathologies have distinct etiologies, with both synergic and independent mechanisms at different spatio-temporal levels, and in interaction with other pathological mechanisms [15]. Finally, the biological heterogeneity inherent in AD may suggest that multiple biological factors drive or protect cellular susceptibility to neurodegeneration in AD. Current knowledge about these factors is discussed in the next sections.

4. Drivers and protectors of pathological progression

Recent advances extend the description of AD pathophysiology beyond neuronal dysfunctions [7]. This section discusses the multi-cellular pathologies that occur in AD and the relationships between these pathologies and the protective and risk factors of AD.

4.1. Lifestyle and environmental modifiers

Dementia and AD are associated with cardiovascular issues and an unhealthy lifestyle as risk factors: a lower educational level, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and infrequent social contact [62, 63]. Recent evidence indicates a role of excessive alcohol consumption, head injury, and air pollution [6, 62]. Many of these risk or protective factors are potentially modifiable, and it was estimated that the prevention of these factors might prevent or delay dementia in up to 35-40% of the cases [6, 63]. This might partly explain why the age-specific incidence of dementia has decreased in some high-income countries [64].

The first results of randomized controlled trials (RCT) that test whether multi-domain lifestyle interventions reduce the risk of developing AD and dementia showed cognitive benefits in HI at risk for cognitive decline and in AD patients [62]. For example, the FINGER trial showed 20-150% improvement in cognitive functions [65, 66]. The pathophysiological mechanisms underlying these results are complex. These approaches simultaneously target multiple pathways that might individually depend on the risk and protective factors present. Neuroinflammation might be a common biological basis that links several of these factors to AD pathological changes [67, 68]. For example, neuroinflammation influences the development of depression [69], and could be persistent up to 17 years after a traumatic brain injury [70]. Furthermore, recent studies show the interactions between peripheral and central immune dysregulation in AD [67] and that several aforementioned AD risk factors are associated with systemic inflammation [71, 72].

Observational studies report a reduction in the risk of developing AD with the long-term use of non-steroidal anti-inflammatory drugs, although this is not shown in RCTs [73]. Exposure to AD risk factors might create a chronic peripheral inflammatory environment that further drives or is permissive of AD pathological changes [67].

4.2. Aging

Recent reviews provided insights in aging pathophysiology, and how it can influence the course of AD [74, 75]. Aging brain cells are subject to genomic instability, epigenetic alterations, intercellular communication alterations, stem cell exhaustion, cellular senescence, mitochondrial dysfunction, deregulated nutrient sensing, loss of protein homeostasis and telomere attrition [74]. There is a large amount of evidence indicating that these aging-related changes promote and exacerbate AD pathological lesions, especially through neuroinflammatory mechanisms involving microglia and astrocytes [74, 75]. Cellular senescence in particular can be triggered by other aging-related changes in microglia, astrocytes, and neurons, and may contribute to AD pathological changes through the chronic secretion of pro-inflammatory molecules [75]. On the contrary, recent studies show that AD pathological changes are able to induce senescence in the human brain [76, 77]. These findings suggest that both aging and AD pathophysiology are able to trigger cellular senescence, which may correspond to a homeostatic mechanism to alleviate the pathological burden. However, the propagation and sustainment of neurotoxic proinflammatory secretions induced by this cellular state ultimately leads to aging-related proteinopathies, amyloid and tau synergy [15], and degeneration [75].

4.3. APOE

4.3.1. Advances in APOE genetics

The highest contribution of incompletely penetrant genes to AD still comes from APOE [78]. None of the three APOE isoforms (APOE2, APOE3, APOE4) is sufficient or required to develop AD but are rather associated with a dose-dependent increase in the risk of developing AD [25, 79]. Compared to APOE3 homozygotes, APOE2 homozygotes exhibit more than 40% risk reduction, an older age of onset and a reduced amyloid burden. This was confirmed in a recent study of 5,000 neuropathologically confirmed AD cases and controls [80]. Conversely, an earlier age of onset and a higher amyloid burden is observed among APOE4 heterozygotes with a 3-7-fold risk increase, and a 12-15-fold increase for APOE4 homozygotes [80–83]. However, the correlation of APOE polymorphism with clinical progression remains controversial [84, 85].

Furthermore a few APOE protective genetic modifiers have been recently described. The effect of APOE is dependent on ethnicity, with Hispanic and African American APOE ε4 carriers having a lower risk compared to Caucasian and Japanese APOE ε4 carriers [79, 86]. In addition, APOE protective modifiers include Klotho-vs heterozygosity [87], and other single nucleotide polymorphisms such as CASP7 (rs10553596) and SERPINA3 (rs4934-A/A) [88]. Besides, a single case of resistance to autosomal dominant AD was recently described. A 70-year-old PSEN1 carrier Colombian woman showed no evidence of cognitive impairment thirty years after the expected age of symptom onset [89]. Whole exome sequencing and in vitro analyses suggested that a rare APOE3 Christchurch homozygous mutation conferred resilience to AD through reduction of amyloid aggregation, and disruption of APOE binding to lipoprotein receptors and heparan sulfate proteoglycans [89]. These mechanisms probably explain why this patient exhibited a normal parietal glucose metabolism and a lower uptake of tau tracer on PET.

4.3.2. Advances in APOE pathophysiology

The conferred risk of APOE isoforms for AD has been attributed to direct interactions with amyloid peptides, and an isoform-dependent failed clearance ability [90, 91]. Neuropathological and PET studies confirmed that the genetic risk of APOE could be attributed to this effect in AD and cerebral amyloid angiopathy (CAA) [25, 26]. This might operate through receptor mediated interactions in neurons [92], astrocytes [93], endothelial cells, vascular smooth cells and pericytes [94].

Recent studies indicate that APOE may interact with other components of AD pathogenesis [95]. In fact, it has been suggested that APOE may have isoform-dependent effects with tau pathological burden [84]. However, PET studies are diverging in this respect, some indicating that the effect of APOE on tau pathology may be related to the effect of APOE on amyloid pathology [96, 97]. Direct interactions between APOE and P-tau seem unlikely [98].

Furthermore, APOE interactions probably occur with microglia, astrocytes, and cells of the neurovascular unit [95, 99]. The relationships between APOE and microglia can occur through interactions with the surface-receptor TREM2 (see section below). The effect of APOE on the blood brain barrier (BBB) is of major concern since APOE4 carriers have an increased risk of CAA [25]. It has also been demonstrated that APOE contributes to BBB permeability independently of amyloid in APOE4 carriers, inducing neuronal and synaptic degenerations and cognitive decline [100, 101]. A neuropathological study on subjects treated by amyloid immunotherapy showed that CAA was associated with increased vascular changes, and that APOE was involved in the removal of plaque and the transport of amyloid to the vasculature [102]. Besides, APOE4 carriers are also subject to amyloid-related imaging abnormalities on MRI after amyloid-immunotherapy (i.e., vasogenic edema, sulcal effusions, microhemorrhages and hemosiderin deposits) compared with APOE3 carriers [103]. These findings indicate that the biological basis of the association of APOE with AD may be related to multi-cellular pathological processes.

4.4. Advances in genetics

4.4.1. Novel genetic risk factors

LOAD is probably a complex polygenic disorder [12]. The genetic heritability of LOAD was estimated at 58-79%, and up to 90% in cases of EOAD (<65 years) [11, 104]. One study showed that 53% of the AD phenotypic variance could be explained by genetic factors [105].

Novel genetic risk factors with a smaller contribution to AD phenotypic variance than APOE were explored through genome-wide association studies (GWAS). GWAS test for the association of millions of genetic variants with a trait, generally with an allelic variation frequency >1% [106]. However, an elevated number of subjects is needed to reach genome-wide statistical significance ($P<5x10-8$ in European studies), resulting in a major collaborative effort, and the use of GWAS by proxy design (i.e., using parental history as a proxy to the phenotype of patients and controls) [107]. GWAS revealed 40 risk loci associated with AD in European GWAS according to a recent unified list. Of these, 24 have already been replicated [108]. Additional evidence from non-European GWAS found 50 risk loci associated with AD in another review [109]. It is noteworthy that half of these identified loci are protective and associated with a later age of symptom onset [109]. As it was estimated that known risk loci of AD only explain 30% of the total genetic variance [105], the number of AD risk loci is expected to increase [110].

The odds ratio of the 40 identified loci ranges from 0.80 to 5.15, suggesting a minor independent contribution to AD inheritability [108]. Therefore, it was suggested that their cumulative effect might be more relevant to predict the risk of AD. Based on the results of a previous meta-analysis [111], Escott-Price and colleagues developed a polygenic risk score incorporating age and gender with accuracy to distinguish AD patients from heathy individuals reaching 78-84% [112, 113]. Contrary to common variations, the cumulative effect of these risk loci was related to the clinical progression of AD, showing a rate of decline 23% faster in carriers of the rare variant of TREM2 [85, 114]. Collectively, these recent findings showed that a complex polygenic background contributes to the resistance or vulnerability to AD.

4.4.2. Functional genomics

The risk loci associated with AD are usually annotated with the name of nearest gene, or the strongest associated variant. However, variable evidence makes it possible to connect an identified loci to the variant causing the association, or to a gene or a function involved in a patho-mechanistic pathway of interest [108]. This is also challenging as most loci associated with AD lie in non-coding-regions [5, 78]. Based on recent functional genomic studies, APOE, CR1, BIN1, TREM2, CLU, SORL1, ADAM10, ABCA7, CD33, SPI1, and PILRA appear to be the causal genes in their respective loci [108].

Next-generation sequencing technologies such as whole genome and whole exome sequencing, allowed the identification of additional rare genetic variants associated with AD (population frequency <1%). Many of these rare variants were identified in the coding region of the loci of common genetic variants of AD, such as TREM2 [115, 116], ABI3 [115, 116], PLCG2 [115, 116], PILRA [117], ABCA7 [117], and SORL1 [118]. Many of these genes are also associated with EOAD [119].

Knowledge about the functions of these susceptibility genes highlights the importance of the immune system, lipid metabolism, and endocytosis in LOAD pathogenesis [120]. The over-representation of different biological pathways in the results of independent associations in GWAS confirms the major implication of the immune response pathway, and other pathways such as lipid metabolism regulation, endocytosis, protein ubiquitination, amyloid, APP and tau metabolism [5, 78, 121, 122]. These findings converge with epigenomic and transcriptomic studies showing the associations between AD risk variants and alterations in immune response gene expression [123–125]. Changes in molecular systems in elderly HI and patients with LOAD also highlighted the importance of innate immunity and amyloid pathways [126, 127]. It was suggested that common AD variants operate through a transcriptional and molecular network specific to the immune system [125].

Overall, these findings highlight the implication of non-neuronal dysfunctions in AD. The reader may refer to other comprehensive reviews for interpretation and limits of AD genomic studies [108, 120].

4.5. Network connectivity alterations

Cognitive functioning relies on the integrity of different brain areas assembled into networks. As recently reviewed, the pathophysiology of AD is associated with a disruption in structural and functional brain network connectivity [128]. Several factors indicate that amyloid deposition on PET accumulates in highly connected regions characterized as 'hubs', and in large areas of association cortex overlapping a set of regions active at rest, also known as the default-mode-network (DMN) [129, 130]. Amyloid-related DMN hypoconnectivity occurs in ADAD, EOAD, and LOAD, although in association with different genetic variants across these subtypes [128]. In LOAD, the earliest amyloid deposits are observed at the preclinical stage in the DMN, before plaque can be identified on PET, and before neurodegeneration and hypometabolism [131]. Other studies have also shown that amyloid deposition is associated with increased connectivity in anterior regions of the DMN, while posterior components of the DMN have loss of connectivity [132, 133]. Amyloid-driven DMN hypoconnectivity further extends to other brain networks as disease progresses, with disruption of connectivity within the DMN and between the DMN and other brain networks [131, 134, 135].

Furthermore, tau deposition has been associated with structural and functional connectivity disruption in AD [128]. This association, whether synergic or partly independent of amyloid, seems to be unspecific to any given network [136, 137]. Biomarker and preclinical studies suggest that cell-to-cell spreading of tau pathology occurs along structural connections and is facilitated by amyloidosis [128, 138]. One study showed that alterations in the hippocampal-cingulum bundle predict tau accumulation in the posterior cingulate cortex and episodic memory decline in amyloid-positive but not in amyloid-negative elderly HI [139]. These results confirm that specific networks can be facilitators of tau spreading from the medial temporal lobe to the posterior cingulate, preceding cognitive decline and the onset of AD.

The underlying mechanisms of network alterations in AD are subject to ongoing discussions. It was suggested that large highly-interconnected regions might be more vulnerable to the earliest AD pathological changes [140–142]. One explanation of this idea is the fact that brain networks have a high energetic demand [143, 144]. This is also consistent with the fact that neural activity is closely related to amyloid deposition [145, 146] and contributes to amyloid and tau synergy [15]. Furthermore, the regional pattern of gene expression might contribute to the different relationships of amyloid and tau with the spatial pattern of structural and functional connectivity alterations [128].

Network alterations may have an etiological role in LOAD. One interesting hypothesis is that the pattern of connectivity changes during the course of AD, with a cascading network failure [147]. In this model, hypoconnectivity of the posterior DMN is the starting event. It then shifts to other interconnected systems with increased connectivity in the anterior DMN, perhaps as a transient and compensatory phenomenon, preceding structural alterations, and cognitive decline. However, the origin of such a process is still debated. Studies show that network dysfunctions can be observed before amyloid deposition among elderly HI APOE4 carriers [148, 149], suggesting that network level alterations might drive molecular pathological changes. Other hypothesis includes an upstream influence of amyloid and tau aggregates, or another common factor that drives network level changes.

4.6. Cerebrovascular pathologies

Healthy cardiovascular function and blood vessels are needed for brain oxygen and glucose supply, auto-regulation of cerebral blood flow (CBF) in response to neuronal activity, and for the clearance of metabolic waste products [150]. AD is associated with cerebrovascular dysfunctions as indicated by epidemiological, pathological, biomarker, and experimental evidence [150–152]. However, whether this evidence is only associative in nature, or is a part of AD pathophysiology remains controversial [153, 154].

The vascular lesions frequently observed in AD include cortical micro infarcts, large and multiple infarcts, lacunas, atherosclerosis, arteriolosclerosis, hemorrhage, and CAA [155]. These cerebrovascular lesions are considered to increase cellular vulnerability to AD and neurodegeneration, and contribute to amyloid and tau synergy [15]. Studies of cerebrovascular dysfunctions in AD have been modelled in a recently updated two-hit scheme where amyloid-independent (hit 1) and amyloid-dependent (hit 2) interactions with neurovascular unit cells converge in blood vessel damages, and subsequently in a self-amplifying neurodegenerative process [151, 152]. The main vascular changes induced by AD are due to CBF dysregulation and reduction, BBB breakdown, and toxic accumulates. Amyloid-independent contributors of cerebrovascular pathologies include aging, lifestyle and environmental and genetic risk factors (APOE4, as mentioned in the previous section) [156].

Furthermore, recent multiple imaging biomarker studies show that CBF dysregulation and reduction develop early in AD. This seems to precedes gray matter atrophy, cognitive decline [151, 157, 158], and even before amyloid deposition, tau-mediated degeneration, and AD biomarker changes in the CSF as reported in one study [159]. CBF dysfunction is associated with APOE4 carriage and amyloid deposits [160]. A body of evidence suggests that the distribution and spread of hypoperfusion in the brain follows the pattern of amyloid deposition, gradually involving the precuneus, the cingulate gyrus, and the parieto-frontal and temporal regions [156]. This notion is consistent with experimental studies describing amyloid vasculo-toxic and vaso-constrictive properties [151]. However, the origin of hypoperfusion remains controversial in AD and might stem from inadequate blood supply in AD rather than a decreased metabolic demand [156, 161, 162]. Furthermore, it was argued that hypoperfusion can be caused by functional changes induced by amyloid pathology in the absence of structural alterations [156, 163, 164]. However, capillaries degeneration (i.e., pericytes) was also described dependently and independently of amyloid, and might be a partial explanation for CBF dysregulation [163, 165].

An obvious instance of the patho-mechanistic interactions between cerebrovascular and amyloid pathologies lies in CAA. CAA and AD have different clinico-pathological presentations, and neuronal injury mechanisms [166]. However, both seems to share impaired amyloid peptide clearance in the BBB which, whether or not a result of CBF dysfunction or amyloid pathogenicity, leads to a self-reinforcing cycle with increased amyloid peptide retention in vessels, and further CAA and AD progression [166]. This highlights the importance of vascular function in CAA and AD.

In addition, neuropathological and biomarker studies have demonstrated BBB permeability and breakdown in multiple brain regions from the early stages of AD [167]. The underlying mechanisms of BBB breakdown include degeneration of pericytes and endothelium which may or may not be dependent on amyloid and CAA [101, 168]. In AD, BBB dysfunction and breakdown leads to reduced CBF, and facilitates molecular transport defects, the entry of cells, pathogens, and blood-derived neurotoxic factors which together can lead to neuroinflammation and multiple degenerative pathways [167]. As the BBB undertakes a substantial part of amyloid peptide transport and clearance of [169], dysfunctions have major implication in AD research.

4.7. Co-pathologies

In LOAD, co-pathologies are more the norm than the exception [47, 170]. In addition to cerebrovascular pathologies, this mainly includes α-synucleinopathy, argyrophilic grain disease, TDP-43 proteinopathy, and hippocampal sclerosis. The prevalence of low or intermediate additional pathologies increases with age among individuals aged >60 [171]. Interestingly, most patients with EOAD might also present these co-pathologies, especially CAA or Lewy body disease [170]. Cognitive performances decrease proportionally with the number of these co-pathologies for both EOAD and LOAD, especially in APOE4 carriers, and independently of gender [170, 171]. One neuropathological study estimated that the risk to convert from MCI to dementia increases by 20 with an additional low or intermediate co-pathology [171].

This highlights the heterogeneity of pathological changes affecting AD patients. This also shows the substantial role of these changes on patients' clinical presentation, disease progression, and concerns for therapeutic interventions.

Whether or not these pathological changes are inherent in AD remains uncertain. This is illustrated by the sustained controversies about the concept of a suspected non-Alzheimer's pathology (SNAP). SNAP is a biomarker-based nosology describing the occurrence of neurodegeneration in amyloid-negative individuals irrespective of their clinical presentation [172]. SNAP is thought to result either from PART, cerebrovascular diseases, or other frequently AD co-pathologies. The pattern of neurodegeneration and clinical characteristics of patients with SNAP is quite similar to AD patients with and without cognitive impairment, although the prevalence of APOE4 carriers seems higher in AD than in SNAP [172–174]. The prognosis for patients with SNAP to develop MCI or dementia is worse than in HI. However, in patients with baseline cognitive impairment, the prognosis for SNAP is not always different from AD patients according to the number and magnitude of biomarker abnormalities, and the methodological considerations of biomarker use [172, 175]. Therefore, it was argued that no evidence allows separating SNAP from AD pathophysiology [3]. Subsequently, AD might be a multiparameter pathology of partly independent changes with an incremental risk for cognitive decline and not necessarily resulting from upstream linear influence of the amyloid pathology [3]. Therefore, whether SNAP is part of AD or not has major implications for AD diagnosis, research, and therapeutic development.

4.8. Neuroinflammation

4.8.1. Pathological mechanisms of central innate immunity

There is strong evidence that microglia and astroglia pathological changes contribute as much or more than amyloid and tangles to neuronal damages [176]. These advances were extensively discussed in specialized review articles [8, 68, 176, 177].

Studies reveal that the phenotypic changes of microglia and astroglia seem to evolve during aging and the pathological progression of AD with gradual transition from a homeostatic protective state and a disease-associated state [8]. These states are associated with distinct transcriptional, morphological, and functional features.

Transcriptomic studies highlight a reduction in genes involved in neuronal support and neuronal signaling, but an upregulation of pro-inflammatory genes [178]. However, the diversity of microglia transcriptomic response may vary between different regions, and might be related to the cellular vulnerability of age-related changes and neurodegeneration [179].

Morphological changes show a reduction of arborized area of immunosurveillance [180–182], and the appearance of dystrophic senescent pro-inflammatory cells [183, 184]. This may imply a loss of homeostatic functions by microglia and astroglia, which is significant as these cells have several pivotal roles in brain health. Loss of homeostatic function has been previously reviewed, and may include a contribution to cerebrovascular damage [151], aberrant neurotransmitter homeostasis [185], and loss of clearance ability of amyloid and tau deposits [186–189].

Not without import, functional changes of microglia and astroglia converge in the activation of signal-transduction pathways promoting a coordinated pro-inflammatory response between these cells. This advances through the secretion of pro-inflammatory neurotoxic mediators such as cytokines (IL-1β, IL-6, TNFα), chemokines (CXCL10), and the activation of immuno-regulators such as NF-κB, the NLRP3 inflammasome [177, 190].

These sustained secretions during the course of AD, and the synchronized dysfunction of astrocytes and microglia induce a basal inflammatory environment and several pathological changes including tau pathology induction [191], synaptic injuries, degeneration of neurons and oligodendrocytes [192–194], and the inhibition of neurogenesis [195]. Although anti-inflammatory cytokines are also part of AD, their contribution seems to be insufficient to resolve the inflammatory-related degenerative process.

The contribution of microglia and astrocytes to AD pathogenesis is similar to the egg and the chicken scenario. Microglial and astrocyte activation is triggered by interactions of microglia with amyloid and tau species, neuronal damage and proinflammatory mediators. Inversely, neuroinflammation can induce these pathologic changes [68, 196, 197]. Therefore, it was suggested that microglia and astroglia activation is an instrumental component of amyloid and tau synergy [15], and a driver of a self-amplifying pathological course [8]. Furthermore, although microglial activation was initially attributed to amyloid pathology, there is evidence that tau and neurodegeneration have the ability to drive microglial dysfunctions independently of amyloid [197]. Some experts even suggest that microglial activation might be directly involved in AD initiation [198].

4.8.2. TREM2

A major interest for the microglial receptor TREM2 (triggering receptor expressed on myeloid cells 2) emerged after the discovery of a strong genetic association with LOAD (odds =2.9-5.5) [199, 200]. TREM2 is involved in microglial metabolism, proliferation, and survival [201, 202]. Subsequent research into the patho-mechanistic role of TREM2 in AD revealed that TREM2 triggers microglial activation, pro-inflammatory cytokine production and promotes microglial survival in response to amyloid plaques and tau tangles [203]. Furthermore, TREM2 gene expression increases with amyloid load [204]. Studies show that TREM2 function involved the phagocytic clearance of soluble amyloid species and neuronal debris [205, 206], probably through isoform-dependent interactions with APOE, and amyloid peptides [207–209].

Recent preclinical studies show that TREM2 deficiency and the variant of TREM2 associated with AD are both associated with a strong amyloid-dependent microglial response impeding tau accumulation, spreading and atrophy [210, 211]. Overall, these results indicate that TREM2 could be an important mechanistic explanation of synergy between amyloid, tau and neuroinflammation [15, 212].

4.8.3. Advances in biomarkers of neuroinflammation

The current understanding of neuroinflammation is limited by the existence of major inter-species differences between human and animal model immunity [190, 213–215]. This section describes the main advances of the human biomarker studies of neuroinflammation in AD. The reader may refer to other reviews for the development and knowledge gap of immune biomarkers in AD [216–219].

4.8.3.1. Central immunity

Neuroinflammation has been increasingly studied in AD with fluidic biomarkers from CSF [218]. YKL-40 (chitinase-3-like protein 1) is secreted mainly by astrocytes during neuroinflammation. CSF levels of YKL-40 are increased in AD from the preclinical stage, and this is correlated with cognitive decline [220, 221]. The concentrations of other CSF biomarkers of neuroinflammation and cerebrovascular dysfunctions including YKL-40, IL-15, ICAM-1, VCAM-1, Flt-1 were increased in AD from the preclinical stage, and were correlated with CSF tau levels, cortical thinning on MRI, cognitive decline and conversion to AD dementia [222]. These results confirm the contribution of neuroinflammation in the clinical and patho-progression of AD.

Furthermore, PET imaging using tracers of the translocator protein (TSPO) was used to study neuroinflammation in AD [223]. Studies have shown that the neuroinflammation pattern parallels the spatio-temporal pattern of AD pathologic changes [8]. Cross-sectional examinations revealed that the association of amyloid with TSPO tracer are inconsistent, but show mostly positive correlations, especially among patients at the prodromal stage [224, 225].

Spatial association with tau pathology seems to be stronger than with amyloid [224, 226, 227], and exhibit distinct patterns between typical and atypical AD [226]. Longitudinal studies indicate different temporal dynamics, with resemblances and contradictions. Edison and colleagues described a stage-dependent model, with the first neuroprotective peak associated with a rising amyloid load and preserved cognitive abilities in MCI patients, followed by a later second peak along with the extension of tau pathology outside the median temporal regions associated with clinical worsening [8, 228, 229].

However, Sarazin and colleagues observed a high heterogeneity of neuroinflammatory profiles using [18F]-DPA714, with distinct clinical profiles and evolutive trajectories independently of disease stage [230]. In this study, the patients with low initial [18F]-DPA714 binding showed a subsequent longitudinal increase in neuroinflammation associated with disease and clinical worsening, while the patients with high initial binding exhibited longitudinal stability of neuroinflammation and a better clinical prognosis. The different signatures of neuroinflammation, neuroprotective or toxic, remain controversial. High TSPO tracer binding is generally associated with the lowest cognitive performances in cross-sectional and longitudinal studies, especially in the temporo-parietal regions [231–233], but the inverse association was also observed in patients with prodromal AD [225, 234]. The model by Sarazin and colleagues highlights the interesting idea that substantial heterogeneity of amyloid-positive individuals could be related to different neuroinflammatory endo-phenotype.

4.8.3.2. Peripheral and central immunity interactions

Several factors indicate that dysregulation of the central immune system in AD occurs in interaction with peripheral and adaptive immunity [67]. Systemic inflammation has been highly associated with AD [235, 236], even after taking account of cardiovascular risk factors [237]. In elderly amyloid-positive HI for instance, studies describe that a higher rate of peripheral pro-inflammatory markers corresponds to lower cognitive performances [238, 239]. However, a recent study indicated that higher rates of anti-inflammatory markers are associated with a slower rate of cognitive decline in elderly amyloid-positive HI [240].

These controversial results show that distinct peripheral inflammatory profiles could be associated with distinct clinical features from the early stages of AD. Nevertheless, the relationships between peripheral inflammatory markers and disease progression are not yet elucidated and might be different according to the clinical stage, the type of marker (pro/anti-inflammatory), and especially the timing and duration of exposure to various inflammatory events [67]. The interactions observed between peripheral and central immunity indicate a more significant role to exposure to various inflammatory conditions in AD pathogenesis than previously expected.

Emerging evidence indicates that the adaptive immune system may also play a role in AD [67]. There are increasing reports showing an alteration in T-cell activation, in the blood and CSF circulation, and brain infiltration in AD, with a plausible impact on the pathological progression [241, 242]. Gate and colleagues found an increase in a population of T-cell subtype in the blood of AD patients, negatively correlated with cognitive decline, and with 80% accuracy to predict AD severity [243]. In vitro analyses showed that these T-cells produced pro-inflammatory cytokine (interferon-γ) and was located in the perivascular space and in the vicinity of neurons and amyloid plaques [243]. Finally, Gate and colleagues found evidence of clonal expansion for these T-cells in the CSF of patients with AD. Further research is needed to explore which antigen is driving these mechanisms, and how it interacts with the innate response making some individuals more vulnerable to further insults and neurodegeneration [244].

From a mechanistic point of view, BBB dysfunctions and breakdown might be one of the bases of peripheral and central immune interactions, operating through brain stimulation by peripheral inflammatory markers, and infiltration of adaptive and peripheral innate immune cells [67, 167]. Another possible basis of peripheral and central immunity dysregulation is gut microbiota, through interaction across the gut-brain axis [245]. Gut microbiota regulates microglia [246, 247], astrocytes [248], and the interactions of these cells [249]. An accumulation of studies describes gut microbiota alterations in aging and AD, associated with peripheral inflammation [250–253]. Collectively, these data suggest that AD should be viewed as a systemic inflammatory disease involving changes in central and peripheral compartments [67].

5. The therapeutic pipeline of Alzheimer's disease

For the past twenty years, most pharmacological interventions in AD have been focused on the amyloid pathway [254]. However, results of these approaches are still mostly negative, even after efficient reduction of the amyloid burden [255–258]. Amyloid-related imaging abnormalities are systematically observed in these trials. Encouraging perspective on this hypothesis might be provided by the ongoing phase III donanemab [259] and aducanumab [260] trials.

The failure of anti-amyloid approaches has several implications in AD therapeutics research. One possibility is that an effective anti-amyloid treatment might be effective before the onset of symptoms, and before synergic interactions of amyloid with tau and other pathologies occur. However, the initial evidence from a preclinical anti-amyloid trial showed negative results in ADAD [261]. Lessons learned from this study have been implemented in another ongoing open-label extension of the gantenerumab prevention trial [261, 262].

Another possibility may be that amyloid is not the appropriate target to modify the course of AD. Next-generation targets include mainly tau or immune therapies [254]. Although, to date, most trials that investigate these pathways are negative [263, 264], interesting perspectives are being provided by an ongoing open-label extension trial of tau immunotherapy by semorinemab [265], and emergent microglia-targeting therapies [8]. Other emerging approaches include targeting APOE and aging pathophysiology [75, 95].

The arborescence of the pathological mechanisms of AD probably suggests that targeting a single pathway will be ultimately insufficient to modify the course of AD. To that extent, concomitant amyloid and tau therapies might be appropriate to address the synergic interactions of these pathologies [15]. Not the least, multi-domain prevention trials have proven to be an effective strategy. The forthcoming prevention trials are eagerly awaited [62], especially results of the world-wide extension of the FINGER trial [266, 267].

6. Perspectives: what is Alzheimer's disease?

The understanding of AD pathophysiology influences the definition of the disease and therapeutic research. LOAD is currently considered to be a multi-etiology disease in which the pathophysiology of amyloid and tau are at the core [9, 10]. This could induce an exclusive circular reasoning in the study of AD pathophysiology if amyloid and tau pathologies reflect only a part of the disease response rather than the disease per se. Such a misconception of AD might preclude the discovery of upstream pathological processes and effective therapeutics.

It is noteworthy that the functional significance of the presence of amyloid lesions remain unclear. Increasing evidence indicates that amyloid deposition does not have an exclusively a pathological role [268]. Several studies have revealed the striking fact that amyloid might be an effector of innate immunity, and that amyloid oligomerization could be part of an immune response pathway mediating pathogen entrapment and protecting against infection [269–272]. Building on these studies, Tanzi and colleagues described 'the antimicrobial protection hypothesis' of AD [271]. In this model, amyloid deposition is part of an early protective innate response to brain-invading pathogens, which becomes chronic in AD and drives a sustained neuroinflammatory response and a degenerative process [271]. The anti-microbial protection model of AD does not refute the amyloid cascade hypothesis as amyloid deposits are still considered to be neurotoxic. However, it shifts the AD pathophysiology from a set of abnormal stochastic accidents to a multi-domain dysregulated immune response. This idea is also consistent with the hypothesis that infection might contribute to the initiation of AD [273].

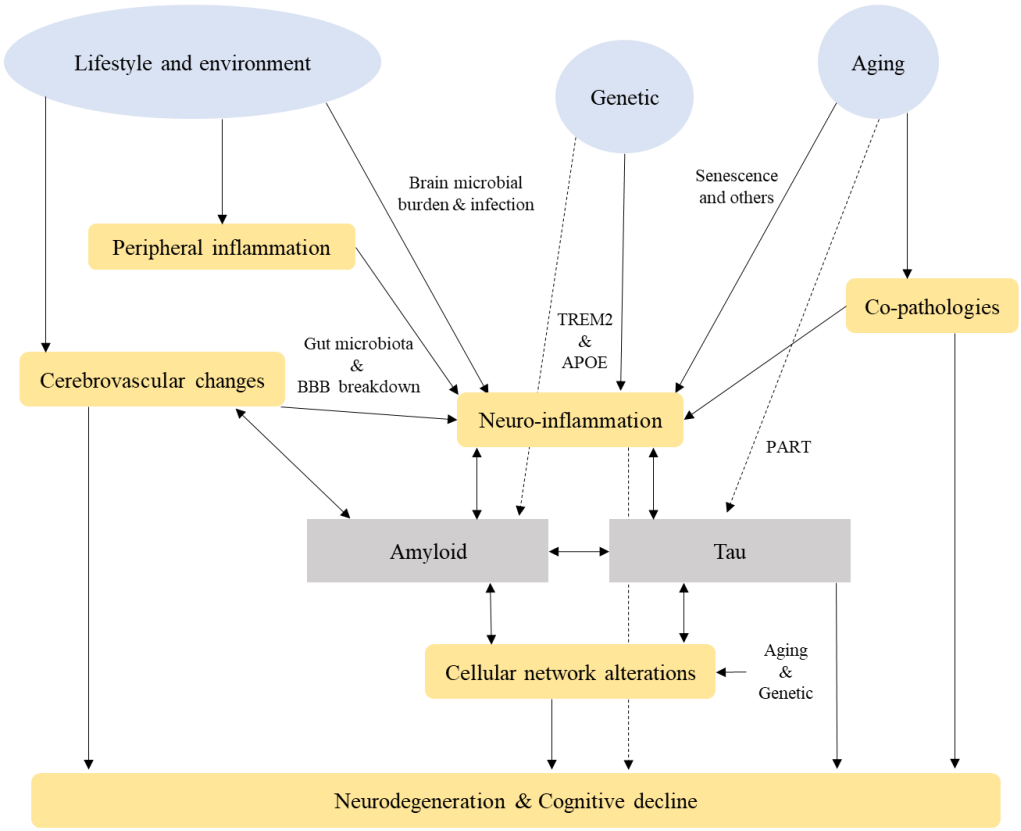

Figure 1: Alzheimer's related pathophysiology converges to neurodegeneration through multiple cellular pathways. Pathognomonic changes of AD (in gray squares) are considered to consist only of amyloid and tau pathologies. The pathological changes considered unspecific to AD are represented in yellow. Risk and protective factors, specified as aging, genetics, lifestyle and environmental are represented in blue circles.

Although neuroinflammation is not a specific feature of any neurological disease, the anti-microbial hypothesis suggests that neuroinflammation might be the etiology of AD. This idea has several implications for the definition of AD (Figure 1). First, if amyloid deposition is part of a protective immune response, this could explain why eradicating amyloid from the brain is not associated with major cognitive benefits [255]. As neuroinflammation is a heterogenous condition, this might also elucidate the failure of anti-amyloid or tau therapies if the neurodegenerative process was determined by upstream and partly independent processes. This might also explain why neurodegeneration can occur independently of amyloid in AD patients [3].

Secondly, this idea could explain why most amyloid-positive patients do not express cognitive impairment in their lifetime. In fact, it was observed that a reduced intensity of glial activation is one of the distinctive neuropathologic traits in cases of dementia and elderly cognitively unimpaired HI showing AD pathological changes [28]. Thirdly, it might explain the relationship between aging, genetic, and lifestyle risk factor and AD, since neuroinflammation is a convergent biological basis of these factors [7].

One hypothesis could be that heterogenous sources and responses of neuroinflammation may converge through multiple synergic pathways to AD and neurodegeneration. This heterogeneity of causes and responses of neuroinflammation might elucidate the failures of specific inflammatory treatments, while long-term exposure to anti-inflammatory drugs is protective against AD [73]. Further studies should address the heterogeneity of neuroinflammatory profiles in AD, and how this heterogeneity impacts the progression of AD.

7. Concluding remarks

The pathophysiology of AD remains centered on the pathological dyad of amyloid and tau brain lesions. However, there is a change in this conception towards a complex multi-cellular perspective. This shift has several lines of support, especially in the evidence of the immune mechanisms of AD.

Most disease model are wrong and the most useful definition of AD will be the one indicated by therapeutic efficacy. While the idea of eradicating amyloid and tau lesions from the brain currently falls short, integration of multiple cellular pathologies in the AD model is an encouraging perspective. Further research will be needed to elucidate the clinico-pathological heterogeneity of AD patients that is consistent with these advances, and the best associated therapeutic options.

References

Note : *L'ensemble des références de cet article de revue a été placé en annexe 1.*

1.4. **Evolutions en imagerie TEP scan de la neuroinflammation dans la maladie d'Alzheimer**

1.4.1. **Faits introductifs**

La neuroinflammation a un potentiel thérapeutique dans la MA (Leng and Edison, 2021). L'imagerie TEP de la protéine translocatrice (TSPO) a été le biomarqueur de neuroimagerie le plus employé pour étudier la neuroinflammation dans la MA. Cette section concerne les principales avancées liées à ce biomarqueur. Le lecteur pourra se référer à la section précédente pour comprendre la part de la neuroinflammation dans la physiopathologie de la MA, ainsi qu'à d'autres articles de revue pour les connaissances des autres biomarqueurs de la neuroinflammation dans les fluides (Molinuevo et al., 2018; Morgan and Mielke, 2021).

La problématique du développement des biomarqueurs de la neuroinflammation se situe dans la complexité de la relation entre le changement tissulaire et le changement dans la mesure du biomarqueur. Les biomarqueurs de progression, tel que le volume régional en IRM structural par exemple, indiquent une mesure de sévérité proportionelle aux changements pathologiques tissulaires. Pour les biomarqueurs de la neuroinflammation, un changement dans la mesure du biomarqueur peut reflèté un processus cellulaire de granularité plus fine. Par exemple, un changement dans le taux du variant soluble de TREM2 dans le LCS peut refléter la variation d'expression d'un récepteur de surface. C'est pourquoi il convient d'étudier la relation entre la mesure du biomarqueur de la neuro-inflammation et le changement tissulaire qui lui est associée pour comprendre comment interpréter l'impact tissulaire du changement mesuré (Morgan and Mielke, 2021). Cette considération est donc spécifique à chaque biomarqueur de la neuro-inflammation, et a des implications méthodologiques.

L'imagerie TEP de TSPO a souvent été désignée comme étant l'imagerie de l'activation microgliale (Venneti et al., 2006). Cependant cette appellation peut être considérée simpliste. En effet, en faisant des recherches, je me suis aperçu que la base biologique du signal TEP était incomprise. Il reste une incertitude sur la localisation cellulaire et le processus fonctionnel observé en TEP.

Plusieurs études indiquent la contribution d'autres types cellulaires au signal observé, en particulier celle de l'astroglie. De plus, la microglie et l'astroglie ont la particularité de préserver une plasticité fonctionnelle importante (Escartin et al., 2021; Murray et al., 2014; Ransohoff, 2016). On parle souvent du rôle de l'immunité comme étant protecteur ou toxique. Sans faire une trop grande disgression, il est nécessaire de préciser que ces rôles sont schématiques et simplifient la réalité. La variabilité des phénotypes de ces cellules est définie selon leur profil morphologique, transcriptomique, et fonctionnel (Arranz and De Strooper, 2019; Kettenmann et al., 2011). L'ensemble des potentialités qui en résulte est confondante pour interpréter le signal TEP de TSPO au niveau de connaissance actuel. On ne peut donc pas en réalité les comprendre par une dynamique polarisée en deux contraires opposés. Par exemple, des études expérimentales ont montré que les cellules microgliales pouvaient participer à la clairance des dépôts amyloïdes (Lee and Landreth, 2010), tandis qu'une étude récente a montré que ces cellules pouvaient propager ces dépôts (d'Errico et al., 2022). L'incertitude de la localisation cellulaire et du processus observé en imagerie TEP de TSPO a donc une implication sur l'interprétation des résultats de ces études. Cependant la vision simplifiée protecteur/toxique convient pour interpréter ce que montre l'imagerie TEP de TSPO. En effet, la fixation de traceur sur TSPO en TEP n'est pas spécifique d'un phénotype particulier de la microglie et de l'astroglie, ni d'une fonction particulière. Pour simplifier ce débat, il on parlera de rôle protecteur ou toxique de la neuroinflammation.

TSPO est une cible d'intérêt en TEP scan depuis 1984, avec comme traceur principal, le [^{11}C]-PK11195 (Camsonne et al., 1984). Cependant, plusieurs contraintes sont liées à l'utilisation de ce traceur tel qu'une faible spécificité et sensibilité de détection, ainsi qu'une faible durée de demi-vie (Chauveau et al., 2008). Ces contraintes provoquèrent le développement d'une seconde génération de traceurs tel que le [^{11}C]-PBR28 et le [^{18}F]-DPA714 (Cumming et al., 2018). En dépit des améliorations suscitées, l'emploi de ces nouveaux traceurs apporte de nouvelles contraintes méthodologiques pour la quantification. Ces contraintes sont liées dans l'ensemble à la biologie de TSPO (Turkheimer et al., 2015). Le lecteur pourra se référer à des revues spécialisées pour une description complète de ces aspects (Turkheimer et al., 2015; Wimberley et al., 2021).

Cependant il importe de citer qu'un polymorphisme génétique sur le gène de TSPO influence l'affinité de fixation des traceurs en TEP scan. Il s'agit d'un trait monogénique codominant qui est associé à une distribution trimodale des valeurs de fixation des traceurs de seconde génération (Kreisl et al., 2013; Owen et al., 2012, 2010). Il a ainsi été proposé de diviser la population en trois groupes selon ce polymorphisme : des sujets ayant une affinité de fixation haute (HAB), intermédiaire (MAB), ou faible (LAB).

Une autre contrainte méthodologique se situe dans l'expression cellulaire de TSPO. A l'exception des neurones, la plupart des cellules cérébrales expriment TSPO, notamment les cellules de l'unité neurovasculaire (Nutma et al., 2021). La méthode de quantification devra donc permettre d'isoler la part du signal relevant d'une fixation du traceur sur des cellules impliquées dans la neuroinflammation. Différentes stratégies ont été proposées pour cela en fonction des différentes méthodes de quantification. Cela a des implications importantes pour les méthodes utilisant une région de référence. Le lecteur peut se référer à des articles de revue spécialisés pour une description des avantages et des limites liées à l'emploi de chacune de ces méthodes (Turkheimer et al., 2015; Wimberley et al., 2021).

J'ai essayé de décrire les avancées des études en imagerie TEP de TSPO dans la MA dans un article de revue. Je me suis focalisé sur les études publiées depuis 2018 car de nombreux articles de revue étaient disponibles avant cette période. Globalement, ces études montrent que le rôle de la neuroinflammation est variable en fonction de paramètres multiples (figure 5). On comprend que le stade de la maladie influence le rôle de la neuroinflammation, en évoluant d'une activité protective vers un rôle toxique. On comprend également qu'il existe une variabilité inter-individuelle de l'intensité de la neuroinflammation à un stade donné. Dans la seconde partie de cette revue, j'ai choisi de discuter la compréhension actuelle de la base biologique de l'imagerie TEP de TSPO dans la MA.

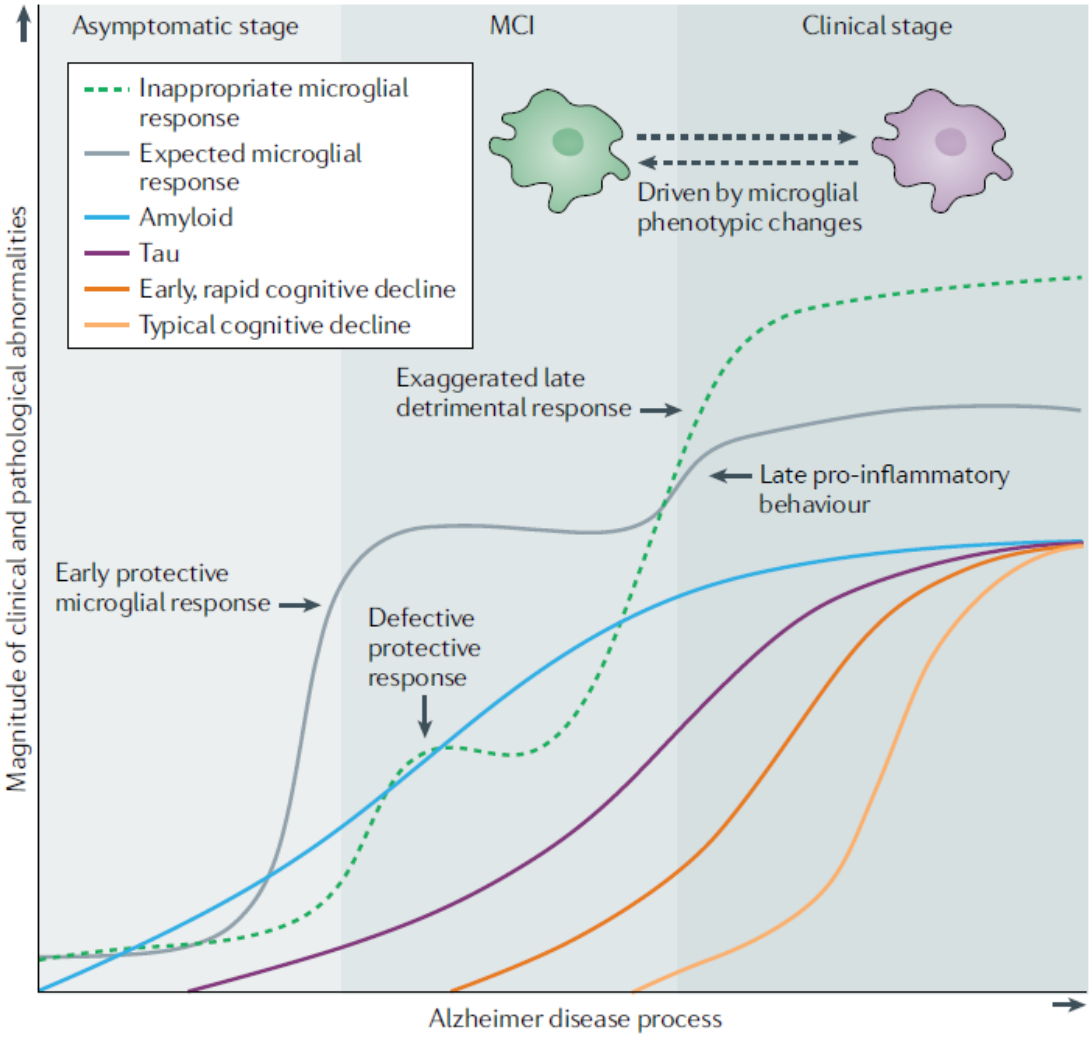

Figure 5 : Dynamique des changements de la neuro-inflammation dans la maladie d'Alzheimer (modifiée de Leng & Edison, 2021).

Note : *Cet article a fait l'objet d'une publication dans une revue internationale. Il a été choisi de l'insérer dans le texte dans son format de soumission. La référence de l'article est la suivante :*

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1.4.2. **Article de revue sur l'imagerie TEP de TSPO**

Neuroinflammation PET imaging of the translocator protein (TSPO) in Alzheimer's disease: an update

Dominique Gouilly[a], Laure Saint-Aubert[a], Maria-Joao Ribeiro[b,c,d], Anne-Sophie Salabert[a,e], Clovis Tauber[c], Patrice Péran[a], Nicolas Arlicot[c,d], Jérémie Pariente[a,f,g], Pierre Payoux[a,e].

a ToNIC, Toulouse NeuroImaging Center, Université de Toulouse, Inserm, UPS, France

b Department of Nuclear Medicine, CHU Tours, France

c UMR 1253, iBrain, Université de Tours, France

d Inserm CIC 1415, CHRU, Tours, France

e Department of Nuclear Medicine, CHU Toulouse Purpan, France.

f Department of Cognitive Neurology, Epilepsy and Movement Disorders, CHU Toulouse Purpan, France.

g Center of Clinical Investigations (CIC1436), CHU Toulouse Purpan, France

Abstract

Neuroinflammation is a significant contributor to Alzheimer's disease (AD). Until now, PET imaging of the translocator protein (TSPO) has been widely used to depict the neuroimmune endophenotype of AD. The aim of this review was to provide an update to the results from 2018 and to advance the characterization of the biological basis of TSPO imaging in AD by re-examining TSPO function and expression and the methodological aspects of interest. Although the biological basis of the TSPO PET signal is obviously related to microglia and astrocytes in AD, the observed process remains uncertain and might not be directly related to neuroinflammation. Further studies are required to re-examine the cellular significance underlying a variation in the PET signal in AD and how it can be impacted by a disease-modifying treatment.

Glossary

AD, Alzheimer's disease; CGM, cerebellar grey matter; HAB, high affinity binder; HI, healthy individuals; LAB, low affinity binder; MAB, mixed affinity binder; MCI, mild cognitive impairment; PET, positron emission tomography; SNP, single nucleotide polymorphism; TSPO, translocator protein.

1. Introduction

Neuroinflammation has an increasing importance in the pathophysiology of neurological disorders (Kreisl et al., 2020). In Alzheimer's disease (AD), neuroinflammation is an early pathomechanistic change that occurs concomitantly with the initiation of amyloid brain deposition decades before the onset of symptoms (Heneka et al., 2015). Preclinical studies have shown that the process of astrocyte and microglial activation becomes dysfunctional in AD, ultimately leading to neuronal damage (Arranz & De Strooper, 2019; Prokop et al., 2013). The discovery of genetic variants associated with AD pathogenesis has highlighted alterations in the innate immune system genes and pathways (Kunkle, 2019). These results have driven the development of biomarkers to improve our understanding of AD neuroimmune changes and to monitor the engagement of inflammatory treatments (Gyengesi & Münch, 2020; Hampel et al., 2020).

Neuroinflammation can be assessed in vivo using positron emission tomography (PET) and cerebrospinal fluid biomarkers (Morgan & Mielke, 2021). PET imaging has the advantage of providing a direct and spatially informative measurement of a selected protein in the brain. Although the development of PET tracers to explore neuroinflammation is rapidly evolving (Boche et al., 2019), the translocator protein (TSPO) remains the most common target used in neurological diseases (Kreisl et al., 2020). Clinical TSPO imaging recently provided substantial descriptions of the role of neuroinflammation in several neurological disorders, such as frontotemporal and Lewy body dementia, as well as semantic dementia (Kreisl et al., 2020; Palleis et al., 2021; Pascual et al., 2021). TSPO imaging is currently used in clinical phase two trials of anti-inflammatory compounds in AD as the primary endpoint (NCT03435861).

Several review articles have shown heterogenous results of TSPO imaging in AD and the challenges related to the interpretation of results (Chandra et al., 2019; Edison & Brooks, 2018; Lagarde et al., 2018). TSPO expression and function appears to be dependent on the etiopathogenic context (Nutma et al., 2021). However, the sources of variability that are specific to AD pathophysiology have yet to be defined, especially regarding the underlying cellular regulation of TSPO expression. The aim of this review was to provide an update to TSPO imaging results in AD and to revise the biological basis of the PET signal by re-examining TSPO function and expression and the methodological aspects of interest.

2. Basic facts about TSPO PET imaging

Several TSPO radiotracers have been used over the past two decades, such as [11C]-PK11195 and a second generation of compounds including [11C]-PBR28, [11C]-ER176, [18F]-GE-180, [18F]-GE-387, and [18F]-DPA714, among others (Cumming et al., 2018; Qiao et al., 2019). [11C]-PK11195 has been broadly used despite inappropriate physico-chemical properties like high non-specific binding, high plasma protein binding, and a short half-life (Chauveau et al., 2008). The second generation of compounds has improved binding affinity, sensibility, and specificity to subtle changes in TSPO density compared to [11C]-PK11195 (Boutin et al., 2013; Chauveau et al., 2009; Fujita, 2017). The reader may refer to the previous review for a systematic comparison of TSPO PET tracers in terms of their specificity and sensitivity to reveal neuroinflammation on PET, kinetic properties considering the different analysis methods, binding affinity and plasma metabolism (Cumming et al., 2018).

Furthermore, most of the methodological issues of TSPO imaging concern factors related to TSPO biology (Turkheimer et al., 2015). A single nucleotide polymorphism (SNP) rs6971 of a TSPO gene that affects the binding affinity of second-generation tracers results in three phenotypes of binding affinity indicated as low, high, and mixed affinity binders (LAB, MAB, and HAB, respectively) (Owen et al., 2012). The impact of SNP rs6971 depends on the tracer, which corresponds to approximatively 40%–50% variability in the distribution volume in healthy individuals (HIs) between MAB and HAB for [11C]-PBR28 and [18F]-DPA714 (Lavisse et al., 2015; Owen et al., 2014), while low affinity binders exhibit a TSPO affinity that is too low to distinguish elderly HIs from AD patients (Hamelin et al., 2016).

A recent neuropathological study showed that SNP rs6971 has no influence on tspo mRNA or TSPO expression level, the magnitude of astrocyte and microglial responses, cortical thickness, or AD neuropathological changes (Gui et al., 2020). Another study revealed that the three genotype categories are similar in terms of amyloid load and longitudinal cognitive decline in patients with mild cognitive impairment (MCI) and dementia, suggesting that the results from one category can be extrapolated to an entire AD cohort (Fan, Harold et al., 2015). Therefore, different results can be obtained among subjects with different SNP rs6971 but similar clinical characteristics, TSPO expression level, and equal neuroinflammation or AD-related pathology. When LAB cannot be excluded at screening, SNP rs6971 is usually added as a covariate for correlation analysis.

Another well-described characteristic of TSPO imaging is the ubiquitous brain expression of TSPO (Nutma et al., 2021) and especially a high endothelial expression (Betlazar et al., 2018). According to an estimation of a 3D reconstruction of histological data from the frontal lobe and the cerebellum, TSPO-positive vessels could represent 30% of total brain vascularization in cortical and white matter (Veronese et al., 2018). This has implications for the choice of quantification model and reference region. The reader may refer to recent articles for an overview of TSPO cellular expression (Nutma et al., 2021), the methodological implications of TSPO biology on quantification (Turkheimer et al., 2015), and the appropriate choice of quantification method (Wimberley et al., 2021; Schubert et al., 2021).

3. Results of clinical TSPO imaging in Alzheimer's disease: an update

The results of TSPO imaging in AD were widely reviewed up until 2018–2019 by several expert groups (Chandra et al., 2019; Edison & Brooks, 2018; Knezevic, 2018; Kreisl et al., 2020; Lagarde et al., 2018). The primary aim of this review was to provide an update to TSPO imaging results in AD since 2018. These recently published trans-sectional and longitudinal studies are listed in Table 1. The reader may refer to previous reviews for the results of studies published before 2018.

Table 1: Advances in human TSPO imaging studies in Alzheimer's disease since 2018

Subjects	TSPO tracer	Quantification method	SNP rs6971 management	Key findings	References
Trans-sectional studies					
6 patients with AD dementia, 20 patients with MCI	[^{11}C]-PK11195	Binding potential, SRTM, supervised cluster analysis	Not necessary	No correlation between inflammation level and tau burden on PET or MMSE scores in cases of high amyloid-β levels.	(Parbo et al., 2018)
11 patients with amnestic MCI, 14 HIs	[^{18}F]-FEPPA	(1) Distribution volume, 2TCM with arterial plasma input function. (2) SUVR using the cerebellum as a reference.	Only HAB included	No significant differences in [^{18}F]-FEPPA binding between MCI participants and HIs and no correlation of PET measurements with cognition. Positive correlation of [^{18}F]-FEPPA binding with amyloid load in the hippocampus in the amnestic MCI group.	(Knezevic et al.,2018)
16 patients with amnestic MCI, 16 patients with AD, 19 HIs	[^{11}C]-PBR28	Distribution volume, Logan graphical analysis with arterial plasma input function.	LAB excluded	Significant widespread clusters of positive correlation were observed between [^{11}C]-PBR28 binding and tau and amyloid deposits on PET.	(Dani et al.,2018)
16 amyloid-positive patients with amnestic MCI, 16 patients with progressive supranuclear palsy, 13 HIs	[^{11}C]-PK11195	Binding potential, SRTM, supervised cluster analysis.	Not necessary	[^{11}C]-PK11195 binding increased in patients with AD, in relation to both patients with progressive supranuclear palsy and HIs. [^{11}C]-PK11195 binding correlated with disease-specific cognitive impairment in the region specifically related to AD or to progressive supranuclear palsy.	(Passamonti et al.,2019)

37 patients with early stages of MCI, 18 HIs	[^{11}C]-PBR28	Distribution volume, Logan graphical analysis with arterial plasma input function.	LAB excluded	[^{11}C]-PBR28 binding positively correlated with gray matter volume in both amyloid-positive and -negative MCI. Higher hippocampal volume correlated with higher cortical [^{11}C]-PBR28 binding.	(Femminella et al., 2019)
20 amyloid-positive patients with AD dementia, 20 HIs	[^{11}C]-DPA-713	Binding potential, SRTM with a normalized mean time activity curve based on HIs as a reference input.	Not considered	Similar pattern of abnormal tau deposition and neuroinflammation on PET. Positive correlation observed in the parahippocampus.	(Terada et al., 2019)
30 amyloid-positive subjects, 27 amyloid-negative subjects, both stratified with cognitive status.	[^{11}C]-PBR28	SUVR using cerebellar gray matter as a reference.	LAB excluded	Increased neuroinflammation and tau pathology on PET associated with amyloid and cognitive status. [^{11}C]-PBR28 binding was independently associated with amyloid positivity and cognitive impairment.	(Zou et al., 2019)
27 amyloid-positive patients with MCI	[^{11}C]-PK11195	Binding potential, SRTM, supervised cluster analysis	Not necessary	Levels of brain inflammation inversely correlated with plasma neurofilament light levels and with mean diffusivity of water on MRI in overlapping regions.	(Parbo et al., 2020)
10 patients with dementia, 11 patients with amnestic MCI, 11 HIs	[^{18}F]-FEPPA	Distribution volume, 2TCM with and arterial plasma input function.	Only HAB included	Increased TSPO binding and serum IL-6 and IL-10 levels in AD and MCI compared to HIs, while serum levels of some fatty acids were modulated. No correlation of serum cytokines with neuroinflammation. A few serum fatty acid levels correlated with [^{18}F]-FEPPA binding.	(Cisbani et al., 2020)

25 amyloid-positive and 29 amyloid-negative elderly subjects without dementia	[^{11}C]-PBR28	(1) SUVR with respect to cerebellum gray matter. (2) Distribution volume ratio, Logan analysis within 30–70 min interval and the cerebellar cortex as a reference.	LAB excluded	[^{11}C]-PBR28 binding positively correlated with amyloid burden on PET only among amyloid-negative patients.	(Toppala et al., 2021)
29 amyloid-positive subjects, 25 amyloid-negative subjects, both stratified with cognitive status.	[^{11}C]-PBR28	SUVR with respect to cerebellar gray matter	LAB excluded	Olfactory identification deficits were associated with a higher tau and neuroinflammation load on PET and with higher cerebrospinal fluid concentrations of total tau and phosphorylated tau.	(Klein et al., 2021)
Longitudinal studies					
52 patients with prodromal AD (21 at follow-up), 17 amyloid-negative HIs (13 at follow-up, and 4 amyloid-positive).	[^{18}F]-DPA-714	SUVR with respect to cerebellar gray matter.	LAB excluded	High initial [^{18}F]-DPA-714 binding was correlated with a subsequent slight increase in microglial activation and a favorable clinical evolution, whereas the opposite profile was observed when initial [^{18}F]-DPA-714 binding was low, independently of disease severity at baseline.	(Hamelin et al., 2018)
12 patients with AD dementia, 14 amyloid-positive patients with MCI, 29 HIs	[^{11}C]-PK11195	Binding potential, SRTM, supervised cluster analysis, additional correction for endothelial binding.	Not necessary	Baseline markers for tau pathology, neuroinflammation, and atrophy in temporoparietal regions individually predicted cognitive decline. Multivariate and Bayesian analyses identified more tau pathology and increased neuroinflammation as the best predictors	(Malpetti et al., 2020)

				of cognitive decline without a significant influence of atrophy on MRI.	
43 patients with MCI	[^{11}C]-PK11195	Binding potential, SRTM, supervised cluster analysis.	Not necessary	In cases of MCI with a low/normal cortical amyloid load on PET that subsequently showed an increase in amyloid deposition over 2 years, [^{11}C]-PK11195 binding positively correlated with amyloid load. In cases of MCI with a high amyloid load at baseline, [^{11}C]-PK11195 binding declined over 2 years. In cases of MCI with both high amyloid and tau load on PET at baseline, a further rise in their tau tangle load over 2 years positively correlated with [^{11}C]-PK11195 binding.	(Ismail et al., 2020)
130 individuals across aging and AD clinical spectrum	[^{11}C]-PBR28	SUVR with respect to cerebellar gray matter.	Only HAB included	[^{11}C]-PBR28 binding correlated with CSF soluble TREM2 and showed regional distribution resembling TREM2 gene expression. [^{11}C]-PBR28 binding correlated to tau pathology on PET following Braak stages, and longitudinal tau spread depended more on baseline microglia network than tau network. The co-occurrence of amyloid, tau, and neuroinflammation abnormalities was the strongest predictor of cognitive symptoms.	(Pascoal et al., 2021)

Abbreviations: AD, Alzheimer's disease; HAB, high affinity binder; HI, healthy individual; IL, interleukin; LAB, low affinity binder; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standard uptake value ratio; SRTM, simple reference tissue model.

3.1. TSPO imaging and Alzheimer's pathological changes

Despite differences in the TSPO tracer, quantification methods, and inclusion criteria, a meta-analysis of 28 studies has shown an increase in TSPO levels in several neocortical regions in AD, especially in the frontotemporal cortex (Bradburn et al., 2019). However, there is a significant overlap in the TSPO levels on PET between HIs and AD patients, especially in the early stages of AD. The statistical significance is not always reached to differentiate these groups (Fan, Aman, et al., 2015; S. S. Golla et al., 2015; Gulyás et al., 2011; Knezevic et al., 2018; Kreisl et al., 2013; Schuitemaker et al., 2013; Wiley et al., 2009).

Recent trans-sectional studies have explored the relationship between TSPO imaging and other biomarkers, or neuropsychological measurements related to AD. Parbo and colleagues found that [11C]-PK11195 binding was increased in amyloid-positive patients with MCI and low tau pathology detected on PET (Parbo et al., 2018). This result was corroborated in another study that showed that [11C]-PBR28 binding was more strongly associated with amyloid than with tau deposits on PET in the absence of cognitive symptoms (Zou et al., 2020). Furthermore, this association seems to decrease during the course of the disease. On PET, a stronger association of [11C]-PBR28 with amyloid load was noted in MCI than in dementia, which is consistent with amyloid plateauing early in the course of AD, before the extension of tau pathology (Dani et al., 2018). However, other studies have shown inconsistent results regarding the correlation of neuroinflammation and amyloid load on PET with positive (Dani et al., 2018; Hamelin et al., 2016; Parbo et al., 2017), negative (Toppala et al., 2021; Yokokura et al., 2011), and no correlation (Okello et al., 2009; Wiley et al., 2009). The associations of the TSPO imaging pattern with tau seems less controversial. Three studies have revealed that [11C]-PBR28 binding seems more closely related to tau and glucose hypometabolism than amyloid abnormalities in typical and atypical (e.g., posterior cortical atrophy variant) AD phenotypes (Dani et al., 2018; Kreisl et al., 2017; Terada et al., 2019).

These results support the idea that an early glial response in the neocortex may have a transient neuroprotective role related to amyloid plaques that precedes the extension of tau pathology outside the medial temporal lobe. Another later detrimental response may be related to tau, hypometabolism, and neurodegeneration (Zou et al., 2020).

In a [11C]-PBR28 study, a closer topographic inspection revealed that tau, amyloid, and fluorodeoxyglucose PET abnormalities increase together as the disease progresses, in clusters that often target similar areas of the association cortex (Dani et al., 2018). A recent study on individuals across ages and different AD clinical stages showed that [11C]-PBR28 binding correlated with tau pathology on PET following Braak stages and that longitudinal tau propagation seemed to be dependent on the baseline microglial network (Pascoal et al., 2021). In this study, cognitive symptoms were better associated with the co-occurrence of abnormalities in amyloid, tau, and neuroinflammation rather than separated abnormalities on these processes. These studies support experimental studies showing that tau spread across Braak stages might be driven in part by neuroinflammation in a synergic way with amyloid (Busche & Hyman, 2020).

3.2. TSPO imaging and Alzheimer's disease progression

The protective or neurotoxic effect of neuroinflammation on disease progression is still being debated. Variable trajectories have been reported in longitudinal studies using TSPO imaging. The first model was developed using [11C]-PK11195 and described an early activation peak that precedes tau aggregation, associated with an increase in amyloid load and better cognitive abilities in patients (Fan et al., 2017; Ismail et al., 2020). A decrease and a later second activation peak is observed, associated with an increase in tau burden and clinical worsening over time (Fan et al., 2017; Ismail et al., 2020). These results support a stage-dependent model of neuroinflammation with a biphasic change, in accordance with trans-sectional TSPO PET studies and with neuropathological and mechanistic preclinical data (Leng & Edison, 2021).

However, one of the most controversial aspects of this model is the transient reduction in the TSPO PET signal during the conversion phase from prodromal AD to dementia. No longitudinal reduction of [18F]-DPA714 or [11C]-PBR28 binding was observed among AD patients with prodromal AD or dementia (Hamelin et al., 2018; Kreisl et al., 2016) and most trans-sectional studies have shown increased TSPO levels in patients with MCI and dementia (Bradburn et al., 2019).

Another model was developed using [18F]-DPA714. Hamelin and colleagues described early high stable [18F]-DPA714 binding associated with a better cognitive prognosis compared to patients with a low initial uptake, which is followed by an increase in longitudinal tracer binding in the temporoparietal regions associated with an increase in cortical atrophy and cognitive and functional worsening (Hamelin et al., 2018). This model supports the idea that neuroinflammation – reflected by TSPO imaging – may have both protective and detrimental signatures in AD. However, the results found by Hamelin and colleagues were not specific to a given disease stage, suggesting that neuroinflammation might differently influence disease progression between patients independently of disease stage. This notion is controversial with regards to the model of Edison and colleagues and introduces uncertainty on the predictive value of a high uptake of TSPO tracer at baseline for cognitive decline. The fact that elderly HIs showed low stable TSPO binding in longitudinal studies supports the idea of a disease-related temporospatial change in AD patients (Fan, Okello et al., 2015; Hamelin et al., 2018). A recent study using [11C]-PK11195 showed that an increase in tracer uptake at baseline predicts subsequent cognitive decline among AD patients with MCI or dementia (Malpetti et al., 2020), whereas, in another study, the patients with the highest [18F]-DPA714 uptake at baseline had the lowest cognitive decline (Hamelin et al., 2016). Therefore, the prognostic value of the AD-related signature of neuroinflammation with regards to cognitive decline remains to be clarified.

It is noteworthy that the two longitudinal models are not mutually exclusive to the extent that a longitudinal increase in TSPO tracer binding is generally associated with disease worsening, especially in the temporoparietal regions (Hamelin et al., 2018; Ismail et al., 2020; Kreisl et al., 2016). This notion is supported by trans-sectional studies showing that higher cognitive deficits are associated with higher ligand binding, especially in the temporoparietal regions (Bradburn et al., 2019). Hamelin and colleagues' model suggests the interesting notion that different neuroinflammation profiles might coexist in AD and could influence disease and clinical trajectories at the individual level. In two studies by Hamelin and colleagues, there was a substantial overlap in [18F]-DPA714 binding at baseline among the patients with rapid cognitive decline and those who remained stable at follow-up (Hamelin et al., 2016, 2018), perhaps indicating the inter-individual heterogeneity of AD neuroinflammatory profiles. Further studies are required to elucidate the extent to which the diversity of clinical trajectories seen in AD could be related to different neuroinflammation profiles.

Collectively, the recent results of clinical TSPO imaging provided more consistent descriptions of neuroinflammation in AD than previously (Edison & Brooks, 2018; Kreisl et al., 2020; Lagarde et al., 2018). However, one challenge of human TSPO imaging lies in interpreting the PET signal and explaining the variability between different studies. This will be the subject of the following sections.

4. The biological basis of TSPO PET imaging in Alzheimer's disease

4.1. Mechanistic lessons of preclinical TSPO studies

The interpretation of TSPO PET imaging is limited by the fact that the functional significance of TSPO expression is uncertain, especially in pathological conditions (Selvaraj & Stocco, 2015). TSPO appears to be a multifunctional protein involved in several homeostatic pathways that are highly dependent on the (patho-)biological context (Nutma et al., 2021) and has been the subject of several reviews (Gatliff & Campanella, 2015, 2016; Selvaraj & Stocco, 2015). The initial function of TSPO was described in cholesterol translocation into the mitochondrial matrix (Papadopoulos et al., 2006), which corresponds to the rate-limiting step for (neuro)steroidogenesis. The neuroprotective effects of the TSPO ligands PK11195 and Ro5-4864 in a mouse model of AD were assumed to be related to this function (Barron et al., 2013; Christensen & Pike, 2018). However, this interpretation remains unclear, as several studies have shown that steroidogenesis was unchanged in TSPO knock-out mice that were healthy or in models of multiple sclerosis (Banati et al., 2014; Daugherty et al., 2016; Tu et al., 2016). TSPO is involved in many other functions such as (1) cell proliferation and differentiation (Corsi et al., 2008), (2) apoptosis (Veenman & Gavish, 2012), (3) mitochondrial transition pore opening (Azarashvili et al., 2007), (4) heme biosynthesis (Rampon et al., 2009), (5) cell respiration and adenosine triphosphate production (Banati et al., 2014), (6) mitophagy and mitochondrial quality control (Gatliff & Campanella, 2015), and (7) immunomodulation (Choi et al., 2011). TSPO activity might occur at a crossroads between these functions in AD, perhaps in an attempt to alleviate the pathological changes (Jung, 2020).

Furthermore, the involvement of TSPO in the immune response is complex. TSPO gene expression is regulated by the protein kinase C epsilon and is mediated through a mitogen-activated protein kinase (MAPK)-dependent pathway (RAF1, MEK1/2, ERK1/2), suggesting interactions of TSPO with inflammatory pathways at a transcriptional level (Batarseh et al., 2008, 2010, 2012). Reactive oxygen species and pro-inflammatory mediators can stimulate TSPO transcription and expression (Kruczek et al., 2009; Trincavelli et al., 2002). Reciprocally, TSPO function appears to be related to immunomodulation (Choi et al., 2011; Gatliff & Campanella, 2015; J.-W. Lee et al., 2016) as well as the balance of reactive oxygen species, and pro- and anti-inflammatory cytokine production (Betlazar et al., 2020; Pozzo et al., 2019; Zeno et al., 2012). This strongly indicates the involvement of TSPO in immune processes. However, one study showed that TSPO loss-of-function was associated with unimpaired microglial activation, with no difference in the pattern of response after an axotomy of the facial nerve (Banati et al., 2014). In this study, TSPO knock-out mice had viable and normal phenotypes, while microglia cells showed decreased adenosine triphosphate production. Therefore, it was argued that TSPO might be involved in the neuroinflammatory response of glial cells through the regulation of adenosine triphosphate production, but not in direct neuro-glial interactions following pro-inflammatory stimulation (Banati et al., 2014). This hypothesis is supported by a growing body of evidence showing TSPO involvement in the mitochondrial metabolism and immunomodulation (Betlazar et al., 2020; Fu et al., 2020; Liu et al., 2017). If this hypothesis is confirmed, it might result in unpredictable associations of TSPO expression with neuroinflammation, as the underlying mechanisms of neuroglial interactions and microglial response cannot be distinguished in PET studies.

As TSPO function has been regularly studied using TSPO ligand PK11195 and Ro5-4864, it should be noted that the mechanism of action of these ligands may elicit off-target effects (Selvaraj & Stocco, 2015). For example, PK11195 has the potential to produce TSPO-independent effects, as was demonstrated for the induction of steroidogenesis (Tu et al., 2016) and apoptosis (Gonzalez-Polo et al., 2005). Therefore, TSPO function should be considered with caution to TSPO-specific and non-specific function and compensatory effects caused by the binding of these ligands.

4.2. Human TSPO cellular expression in Alzheimer's disease

Studies have shown that in the normal brain, basal TSPO expression is localized in astrocytes, resting and activated microglia, peripheral macrophages, and endothelial and muscular smooth cells in gray and white matter vessels of all sizes, including the capillaries (Cosenza-Nashat et al., 2009; Gui et al., 2020; Tournier et al., 2019, 2020; Veronese et al., 2018). Small arteries, arterioles, veins, and venules seem to express higher TSPO than capillaries (Veronese et al., 2018). TSPO expression has also been observed in certain types of neurons (Gui et al., 2020) but apparently not in oligodendrocytes (Cosenza-Nashat et al., 2009).

The results of neuropathological examinations of TSPO expression in AD are listed in Table 2. In autopsied AD patients, TSPO expression appeared to occur more in gray than white matter (Metaxas et al., 2019; Xu et al., 2019). However, a small increase in TSPO burden in white matter was observed in another study (Gui et al., 2020). TSPO expression has been observed in the vicinity of cortical □-amyloid plaques and in vessels affected by amyloid angiopathy (Cosenza-Nashat et al., 2009; Venneti et al., 2009). TSPO-positive peripheral infiltrating macrophages have also been observed (Cosenza-Nashat et al., 2009; Tomasi et al., 2008; Veronese et al., 2018). These studies clearly confirm that TSPO expression is not restricted to activated microglia in AD. However, a quantitative assessment of the different contributions of these cells to the TSPO PET pattern is still missing in AD.

Recent studies have shown the heterogeneity of microglia and astroglia phenotypes in terms of morphology, density, function, and transcriptomic profiles (Masuda et al., 2019; Tan et al., 2020). This heterogeneity goes beyond the simplified polarizing scheme of neuroprotective and neuro-toxic functions in AD (Escartin et al., 2021; Murray et al., 2014; Ransohoff, 2016). The fact that TSPO is expressed in different types of immune cells in healthy and AD brains without distinction of the role of these cells on PET could lead to confounding interpretations. This issue was recently addressed in a quantitative neuropathological study of patients with multiple sclerosis (Nutma et al., 2019).

TSPO overexpression was observed in human-leukocyte-antigen-DR cells in active lesions and in the rim of chronic active lesions, in a uniform manner across myeloid cells irrespective of their phenotype, and 25% of TSPO-positive cells were astrocytes in all lesion types (Nutma et al., 2019). In another recent histological study on small vessel disease, TSPO staining was observed in a subset of activated microglia (Wright et al., 2020), which indicates the possibility of TSPO-negative activated microglial cells. Although no study has yet investigated the contribution of different phenotypes of immune cells in AD, these findings reinforce the notion that TSPO expression might be neither sensitive nor specific to pro-inflammatory microglial cells depending on the etiopathogenic context.

A closer inspection provides understanding on how TSPO expression varies according to AD-related pathological changes. It was shown that specific TSPO ligand binding correlates with the presence of activated microglia but not with activated astrocytes in the brains of autopsied patients with AD and other neurological disorders (Venneti et al., 2008). Another study showed that TSPO was also correlated with activated astrocytes in the brains of AD patients, although to a lesser extent than activated microglia (Venneti et al., 2009). However, there is controversial evidence regarding TSPO upregulation in AD (Table 2). Recent quantitative neuropathological studies have highlighted no differences in TSPO expression between AD patients and HIs, with a substantial overlap between these groups in the frontal and temporal cortex, as well as in several brain regions (cerebellum, caudate, putamen, thalamus, substantia nigra, and the red nucleus) (Gui et al., 2020; Li et al., 2020; Xu et al., 2019). Gui and colleagues found no significant correlation of TSPO expression level with the immunoreactivity of reactive astrocytes or activated microglial in the temporal cortex of 22 AD patients (Gui et al., 2020). In this study, there was no correlation between tspo mRNA or TSPO levels and amyloid plaque burden, neurofibrillary tangles, or cortical thickness (Gui et al., 2020).

It is noteworthy that quantitative human tissue and neuropathological studies in other contexts besides AD have drawn similar conclusions. One study showed that pro-inflammatory stimulation using lipopolysaccharide produces no variation in tspo mRNA levels in primary microglia and macrophages, whereas it induces a decrease in tspo mRNA and binding site density in macrophages (Owen et al., 2017). Another study revealed that pro-inflammatory stimulation elicits a dose-dependent decrease in tspo mRNA and TSPO levels in the macrophages of patients with rheumatoid arthritis, whereas anti-inflammatory stimulation produces no change in TSPO levels (Narayan et al., 2017). These studies are concerning and seriously question the use of TSPO PET imaging as a biomarker of neuroinflammation in AD and other brain disorders. They provide evidence that a variation in TSPO expression might be determined neither by AD pathological changes nor by the microglia- or astrocyte-activation process. Moreover, these studies are obviously in conflict with preclinical data and might be explained by inter-species differences in TSPO regulation (see the following section).

The dissociation of postmortem and in vivo TSPO PET studies to show an increase in TSPO levels might stem from methodological concerns. From a mechanistic standpoint, TSPO function may be related to mitochondrial bioenergetics and immunomodulation (Betlazar et al., 2020). Unchanged TSPO levels in postmortem studies might reflect a decreased brain metabolism. Furthermore, immunostaining addresses different aspects of TSPO biology compared to PET and autoradiography (i.e., the total amount of proteins and the number of available binding sites, respectively). This might have influenced the results described above, for example, because of cell-specific micro-environmental differences and competition of TSPO radioligand binding with endogenous ligands (porphyrin and endozepine). Another possibility is that TSPO radiotracers might bind to different cells that express TSPO with dissimilar affinity. This could be further investigated using nuclear emulsion autoradiography on postmortem brain sections (Marquié et al., 2015).

Table 2: TSPO neuropathological studies in Alzheimer's disease

Brain samples	Brain regions	Key findings	References
12 AD patients, 10 elderly HIs.	Temporal cortex.	Increased [^{3}H]-R05-4864 binding in AD.	(Owen et al., 1983)
7 AD patients, 6 elderly HIs.	Frontal and temporal cortex.	Increased [^{11}C]-PK11195 binding in AD in the temporal but not in the frontal cortex.	(Diorio et al., 1991)
6 elderly HIs, 10 AD patients, and other patients with neurological diseases.	Frontal cortex.	Increased density of activated microglia and astrocytes in AD compared to HIs. Positive correlation of [^{3}H]-PK11195 and [^{3}H]-DAA1106 binding with microglial cell density but not with astrocyte density in all patients.	(Venneti et al., 2008)
3 young HIs, 3 elderly HIs, 3 AD patients	Frontal cortex.	Decreased TSPO expression in both elderly HIs and AD patients due to vascular fibrosis and to a lesser extent, because of endothelium damage.	(Tomasi et al., 2008)
9 AD patients, 4 HIs, and other patients with neurological diseases.	Temporal neocortex, hippocampus.	Widespread TSPO-positive cells in AD in the temporal neocortex, hippocampus, and adjacent brain regions. TSPO-positive cells within or around amyloid plaques and in vessels containing amyloid in AD.	(Cosenza-Nashat et al., 2009)
6 HIs, 5 AD patients.	Frontal cortex, cerebellum.	Increased [^{11}C]-PK11195 binding in the frontal cortex but not in the cerebellum. Increased activated microglial and astrocyte density in the frontal cortex. Correlation of [^{3}H]-PK11195 binding with microglial cell density and with astrocyte density, but to a lesser extent.	(Venneti et al., 2009)
7 elderly dementia-free subjects, 7 AD patients.	Middle frontal gyrus.	Increased [^{11}C]-PK11195 binding in gray matter. Positive correlation of [^{11}C]-PK11195 binding with tau burden, negative correlation with synaptic vesicle glycoprotein 2A (a synaptic density biomarker), and no correlation with amyloid burden.	(Metaxas et al., 2019)

8 elderly HIs, 7 AD patients, 5 cases with Lewy body disease.	Frontal cortex, striatum, thalamus, red nucleus, substantia nigra, caudate, putamen.	No increase in [^{3}H]-PK11195 and [^{3}H]-PBR28 binding in the frontal cortex, striatum, thalamus, or red nucleus, and reduction in TSPO density in the substantia nigra in AD and Lewy body dementia.	(Xu et al., 2019)
15 to 24 HIs, 20 to 24 AD patients.	Cerebral gray and white matter, frontal and temporal cortex, cerebellum.	Unchanged *tspo* mRNA and TSPO levels in AD patients and HIs. No correlation of TSPO cortical level with the activated microglia burden, reactive astrocytes, Aβ plaques, neurofibrillary tangles, or cortical thickness.	(Gui et al., 2020)
10 elderly HIs, 27 AD patients, 20 patients with Parkinson's disease, 10 patients with Lewy body disease.	Caudate, putamen.	Unchanged [^{3}H]-PBR28 binding in AD compared with elderly HIs in the caudate and the putamen, but increased binding compared to patients with Parkinson's disease and Lewy body disease. Positive correlation of [^{3}H]-PBR28 binding and tau density in the putamen.	(Li et al., 2020)
9 elderly HIs, 9 AD patients.	Frontal cortex.	Increased TSPO expression in astrocytes and microglia but not in endothelial cells, with an increase in microglial cell density but no difference in the radioactive concentration per cell.	(Tournier et al., 2020)
9 elderly HIs, 9 AD patients.	Temporal cortex.	Increased TSPO expression in microglia and astrocytes but not in endothelial cells, with an increase in the number of microglial cells but no difference in the radioactive concentration per cell.	(Tournier et al., 2020)

Abbreviations: AD, Alzheimer's disease; HI, healthy individual; TSPO, translocator protein.

4.3. Is TSPO regulated differently between species?

Preclinical studies in various pathological contexts have shown TSPO upregulation specifically in astrocytes, microglial cells, and peripheral infiltrating macrophages (Kuhlmann & Guilarte, 2000; Maeda et al., 2007), proportionate to the severity of lesions (Chen et al., 2004) and reflecting pro-inflammatory microglial phenotypes (Beckers et al., 2018; Pannell et al., 2020). TSPO expression has been colocalized with microglial cells and astrocytes in an AD mouse model (Ji et al., 2008), and it has been positively correlated with the longitudinal increase in the amyloid burden (Sérrière et al., 2015). The preclinical results from TSPO imaging in AD clearly support the idea that TSPO is an appropriate biomarker of neuroinflammation (Chaney et al., 2019; Sastre, 2018).

The idea that TSPO expression is increased in AD patients compared to HIs and that it correlates with the magnitude of neuroinflammation and other pathological changes has been extrapolated from preclinical animal studies. However, the evidence from human neuropathological examinations is weak (Table 2). This dissociation might be caused by inter-species differences in TSPO regulation in AD. One major concern in the understanding of microglial and astrocyte function in AD lies in inter-species divergences in terms of genetics, morphology, function, and pharmacology (Arranz & De Strooper, 2019; Bishop et al., 2010; Smith & Dragunow, 2014). With regards to this, Owen and colleagues have shown that pro-inflammatory stimulation elicits a nine-fold increase in tspo mRNA levels in rodent-derived macrophages and microglia, but unchanged tspo mRNA levels in human microglia and a decrease in tspo mRNA levels and binding site abundance in human macrophages (Owen et al., 2017). In an AD mouse model, another study showed an increase in TSPO expression in microglia and astrocytes with unchanged cell density, while an increase in TSPO expression was restricted to microglia and associated with an increase in microglial cell number in the temporal cortex of autopsied AD patients (Tournier et al., 2020). These studies highlight major inter-species differences in the cellular regulation of TSPO between rodents and autopsied AD patients.

They provide strong evidence that TSPO function should not be extrapolated from mice to humans. Further mechanistic studies on human tissue (e.g., 2D or 3D cultures, organs-on-chips technology) may be needed to confirm these ideas and explore the relationships between different types of cellular stress and TSPO pathobiology. Overall, the lack of functional redundancy in preclinical studies of TSPO function, along with the idea that TSPO regulation might be different in rodents and humans without reflecting neuroinflammation, might indicate that the precise function of TSPO in humans and AD is still unknown.

4.4. The pathophysiology of Alzheimer's disease and TSPO expression

The neuropathological changes of AD include deposition of tau and amyloid aggregates, cerebrovascular pathologies, dysfunction of the immune response, frequent co-pathologies, synaptic damage, and neurodegeneration (Henstridge et al., 2019). Considering that microglia and astrocytes are cells that are susceptible to brain pathologies, all these changes could affect the pattern of neuroinflammation in ways that are not always predictable. How these distinct pathological changes might induce interindividual variabilities in TSPO PET studies and influence how the results are interpreted is unclear.

There is strong evidence of an increase in the TSPO PET signal in AD in several brain regions (Bradburn et al., 2019), while neuropathological data are conflicting in terms of whether TSPO upregulation occurs in AD (Table 2). Therefore, which cellular process is observed by TSPO PET imaging in AD remains unclear. It can be hypothesized that an increase in ligand binding reflects a change in the number of binding sites within the cell or a change in the number of cells without variation in binding sites, or both. To address this issue, Tournier and colleagues developed a fluorescence-activated cell-sorting methodology to demonstrate that there is a significant increase in TSPO tracer binding in astrocytes and microglia, but not in endothelial cells, in the frontal and temporal cortex of autopsied AD patients (Tournier et al., 2019, 2020).

In two studies, the increase in TSPO expression in microglia and astrocytes was associated with an increase in microglial cell numbers with unchanged radioactivity per cell (Tournier et al., 2019, 2020). These findings suggest that TSPO expression may be an immune cell density marker in AD rather than reflecting the magnitude of neuroinflammation. However, this explanation seems unsatisfactory since the idea of increased glial cell numbers in AD is controversial. Postmortem human studies have shown an increase in glial cell proliferation markers in AD (Boekhoorn et al., 2006; Nagy et al., 1997; Wharton et al., 2005), which is consistent with the results of Tournier and colleagues. However, one neuropathological study of 40 AD patients and 32 HIs revealed a phenotype change in astrocytes and microglia in AD but a constant number of these cells over the clinical course of the disease (Serrano-Pozo et al., 2013). Another postmortem stereological study of 14 AD cases and 20 HIs showed no increase in the total number of neocortical glial cells in AD (Pelvig et al., 2003). These findings suggest that glial reactions in AD might occur due to the activation of resting cells rather than the generation of new glial cells. This is incompatible with TSPO PET studies, which have indicated increased TSPO ligand uptake (Bradburn et al., 2019). Although the basis of the TSPO PET signal is obviously related to microglia and astrocytes, the observed biological process cannot be delimited with the required precision at present. This also suggests that the impact of an anti-inflammatory intervention on TSPO PET imaging might be unpredictable. As mentioned above, the gap between neuropathological and in vivo TSPO PET studies might be explained by methodological aspects. For example, the observation of a constant number of glial cells and constant TSPO expression in AD might result from the cross-sectional nature of neuropathological investigations and be a consequence of a balance between cell death and proliferation.

The topography of AD brain lesions follows different trajectories according to disease stage and to the different subtypes of AD (e.g., monogenic or sporadic forms with early or late symptom onset) (Jagust, 2018), and the TSPO PET imaging pattern may also be dependent on the pathological context at a regional level.

Neuropathological studies have highlighted that microglial and astrocyte activation increases with the severity of neuritic plaques and neurofibrillary tangles, with variation according to the brain regions involved (Serrano-Pozo et al., 2011; Xiang et al., 2006). Similarly, in another postmortem brain study of HIs and patients with AD and Lewy body dementia showed significant inter-regional correlations of [11C]-PK11195 binding, with the significance levels varying according to the brain regions involved (Xu et al., 2019). It was suggested that distinct topographic and mechanistic relationships of microglia and astroglia with amyloid and tau pathology probably influence the observed pattern of TSPO imaging (Kreisl, 2017). For example, Parbo and colleagues observed that the clusters where the correlations of [11C]-PK11195 binding with amyloid deposits on PET occur are not necessarily colocalized with the highest neuroinflammatory signal (Parbo et al., 2017). However, the relationships of specific regional pathological changes with TSPO expression remain speculative if TSPO expression reflects glial cell density in AD without being directly related to neuroinflammation.

Furthermore, several studies have indicated a transition from homeostatic to disease-associated microglia phenotypes in the course of AD (Leng & Edison, 2021). Homeostatic and disease-associated microglia seem to be associated with distinct morphologic, transcriptomic, and functional roles in AD progression (Leng & Edison, 2021). These different states might also be regulated by spatial proximity and the type and stage of AD lesions. This might be an additional confounding factor in the interpretation of PET studies, for example, if tangle-associated microglia exhibit a pro-inflammatory phenotype in the medial temporal structures (Sanchez-Mejias et al., 2016), while plaque-associated microglia exert a neuroprotective role on amyloid clearance in other regions (Lee & Landreth, 2010). This regional heterogeneity of microglial and astrocyte response would be undistinguishable in TSPO PET studies and might induce an uncontrolled impact on the interpretation of the results, especially in the instance of pharmacological interventions that might be phenotype specific. This issue would be even more problematic in TSPO imaging studies where AD biomarkers are not used (Cagnin et al., 2001; Golla et al., 2015, 2016; Kreisl et al., 2013), as the absence of AD pathophysiology in the brain would certainly impact the immune response.

5. Methodological advances

There have been significant advances in the methodological understanding of TSPO PET imaging in recent years (Schubert et al., 2021; Wimberley et al., 2021). The reader may refer to previous reviews for aspects regarding TSPO tracers (Cumming et al., 2018) and a critical assessment of the advantages and drawbacks of each quantification method (Wimberley et al., 2021). This section will focus on advances in the management of vascular uptake and the choice of reference region in AD.

5.1. Endothelial activity

The cellular distribution of TSPO in a healthy brain or AD includes neurovascular cells (Gui et al., 2020). This creates a background signal unrelated to neuroinflammation. Therefore, the contribution of TSPO endothelial activity on binding quantification has gained interest. Studies have shown that the use of the two-tissue compartmental model (2TCM) with a supplementary compartment for irreversible vascular binding (2TCM-1k) shows a better fit with data compared to the 2TCM, as well as a three-fold reduction in the estimates, an improvement in the detection sensitivity of regional differences, and a decrease in inter-subject variability, all while preserving the differences due to SNP rs6971 (Rizzo et al., 2014, 2019; Wimberley et al., 2018). In HIs, the results of the 2TCM-1k were also more strongly correlated with tspo mRNA expression mapping from the Allen Human Brain Atlas (Rizzo et al., 2014; Veronese et al., 2018; Wimberley et al., 2018). These studies indicate the biological relevance of vascular TSPO modeling with the 2TCM-1k. After a displacement study of [11C]-PBR28 using XBD173 (a TSPO agonist), Veronese and colleagues showed that most kinetic changes in the 2TCM-1k were in specific and endothelial compartments, contrary to the 2TCM, for which changes were in the free and non-specifically bound tracer compartment (Veronese et al., 2018). This study demonstrates the unsuitability of 2TCM to describe the kinetics of TSPO tracer binding changes and that vascular modeling would improve the accuracy of binding quantification.

Furthermore, a comparison of vascular binding estimates of [11C]-PK11195 with previously published values for [11C]-PBR28 and [18F]-DPA714 revealed that vascular activity seems to be proportional to tracer affinity (Rizzo et al., 2019). As suggested by Turkheimer and colleagues (Turkheimer et al., 2015), this leads to the paradoxical notion that the higher the affinity for TSPO, the higher off-target binding will be. The strengths and limitations of vascular activity correction are discussed elsewhere (Wimberley et al., 2021).

Cerebrovascular pathologies are well documented in aging and AD and include blood-brain barrier dysfunctions or breakdown, cerebral blood flow dysregulation or reduction, and toxic accumulations (Banks et al., 2021; Kisler et al., 2017). However, the impact of these pathologies on TSPO expression remains unclear. A preliminary description by Tomasi and colleagues revealed decreased TSPO immunostaining in AD associated with vascular fibrosis compared to HIs (Tomasi et al., 2008). Therefore, vascular modeling might be useful to capture cerebrovascular changes and fibrosis in AD. However, other studies have revealed unchanged TSPO expression in the frontal and temporal cortex endothelium of autopsied AD patients compared to HIs (Tournier et al., 2019, 2020), which suggests that vascular modeling might not be appropriate. Further studies using vascular modeling with additional neuropathological examinations will be of particular interest to elucidate these results and assess how cerebrovascular changes affect TSPO radioligand binding in AD.

5.2. Choice of reference region

Full kinetic modeling of TSPO tracers has several limitations related to the estimations of TSPO tracer concentrations in blood vessels (i.e., arterial plasma input function) (Wimberley et al., 2021). Therefore, non-invasive reference region-based models are increasingly used and enable the correction of physiological TSPO expression between participants. Because of the cellular distribution of TSPO expression in the brain and the diffuse nature of AD pathological changes, there are ongoing debates on which region is most appropriate in AD.

While this section will focus on cerebellar gray matter (CGM) and supervised clustering algorithms (SCA), the choice of an appropriate quantification method and other alternative reference regions for AD are discussed elsewhere (Lagarde et al., 2018; Wimberley et al., 2021).

The CGM was mostly used as a reference in AD based on the following notions: (1) absence of early AD pathological changes (Braak & Braak, 1991; Thal et al., 2002), (2) low tracer activity, similar in elderly HIs and AD patients, not correlated with age, MMS scores or cortical volume (Hamelin et al., 2016; Lyoo et al., 2015), (3) no longitudinal changes in tracer activity among elderly HIs and AD patients (Hamelin et al., 2018), (4) strong correlations between the standard uptake value related to the CGM with dynamic estimates from the 2TCM or Logan graphical model (Hamelin et al., 2016; Lyoo et al., 2015), and (5) improvement in the sensitivity for the detection of regional differences and in the discriminative power between AD patients and HIs when compared to the 2TCM for [11C]-PBR28 (Lyoo et al., 2015). However, there is controversial evidence to consider. One postmortem study showed no difference in TSPO expression in the entire cerebellum of AD patients and HIs (Gui et al., 2020). However, in this study, TSPO expression levels in the cerebellum were heterogenous, and no upregulation of TSPO expression in cortical regions was observed in AD. Furthermore, the presence of neuroinflammation is unpredictable a priori and could stem from a local pathological change or a distal alteration in neocortical areas functionally connected with the CGM (Larner, 1997). While the cerebellum appears to be spared from AD pathological changes in the earliest stages (Braak & Braak, 1991; Thal et al., 2002), a few neuropathological studies have revealed the presence of amyloid angiopathy and diffuse amyloid plaques in the cerebellar cortex of AD patients with dementia, but not in non-demented subjects (Braak et al., 1989; Larner, 1997). Similarly, the cerebellum of demented patients with AD seems to be spared from insoluble tau proteins incorporated into paired helical filaments (Braak et al., 1989), though soluble tau was observed (Mukaetova-Ladinska et al., 1993).

Despite these results, evidence of glial activation in the cerebellum remains uncertain (Larner, 1997). Two neuropathological studies described clustered microglia around amyloid deposits in the cerebellum, but morphological features of activation were observed only in the vicinity of compact aggregates and not around diffuse deposits (Mattiace & Davies, 1990; Sasaki et al., 1997). These findings confirm the idea that microglial activation might occur in the CGM of AD patients, although apparently not in the early stages. This was corroborated in a recent meta-analysis showing an increase in TSPO tracer uptake in the entire cerebellum in AD and MCI patients compared with HIs, though this was not statistically significant in MCI patients (Bradburn et al., 2019). Another histological study revealed that vascular TSPO expression seems to be increased in cerebellar white matter compared to other brain regions (Veronese et al., 2018), which could explain why TSPO radioligand binding is increased when the entire cerebellum is considered instead of the CGM alone. Therefore, CGM might remain an acceptable pseudo-reference region in the early stages of AD but should be avoided for AD patients with dementia.

SCA are increasingly used in AD to bypass the incertitude regarding upregulation of TSPO in the targeted reference region. SCA consists in modeling the kinetics of each voxel as a linear combination of the kinetics of predefined classes and by defining the reference as the voxels with a significant contribution of a predefined reference region such as normal gray matter (Turkheimer et al., 2007) or CGM (García-Lorenzo et al., 2018). Therefore, SCA has the advantage of not requiring the definition of a reference region a priori. When compared to simple ratio methods, SCA showed improvements in terms of sensitivity, inter-subject variability and test re-test reproducibility for [18F]-DPA-714 (García-Lorenzo et al., 2018) and [11C]-PBR28 (Zanotti-Fregonara et al., 2019). Depending on the TSPO tracer, the use of SCA as a reference might be more suitable than GMC in AD (García-Lorenzo et al., 2018; Zanotti-Fregonara et al., 2019). A practical guide for implementing SCA and a comprehensive description of the strengths and limitations of this method were recently published (Schubert et al., 2021).

5.3. Perspective of methodological progress

The extent to which different image pre-processing steps affect image analyses in AD TSPO PET studies is unclear. For example, one [18F]-DPA-714 study showed a decrease in the result significance after partial volume correction (Golla et al., 2016). Inversely, [11C]-PBR28 studies showed that the results remain unchanged (Zou et al., 2020) or became even more significant after partial volume correction (Dani et al., 2018). Further studies are required to provide pre-processing guidelines in TSPO PET imaging by comparing different pipelines and corrections.

6. Conclusion

There is extensive development of clinical TSPO PET imaging in AD. Recent results are in line with the previous descriptions of the relationships of neuroinflammation visualized by TSPO PET and AD-related pathological changes and clinical progression. However, several aspects of TSPO pathobiology remain unclear and undermine the interpretation of TSPO PET imaging, especially the enigmatic TSPO function and uncertainty regarding the cellular regulation of TSPO during the course of AD. These limitations might also be impacted by specific effects of AD pathology or inter-species functional divergence. Further studies are needed to clarify the biological basis of TSPO PET imaging and confirm whether TSPO is an appropriate biomarker of neuroinflammation in AD.

References

Note : *L'ensemble des références de cet article de revue a été placé en annexe 2.*

1.5. **Evolutions des thérapeutiques**

1.5.1. **Evolutions d'accès aux thérapeutiques**

L'efficacité d'interventions thérapeutiques dépend de la cible, du stade de la maladie, de la conception de l'étude (type d'essai, critères d'éligibilité), et des paramètres de l'exposition. Dans la MA, on distingue les essais de préventions des essais menés à des stades où les patients expriment déjà des symptômes. C'est principalement ce deuxième cas de figure qui a été exploré. Et c'est principalement la pathologie amyloïde qui fut prise pour cible dans la MA (Cummings et al., 2021). Il convient de mentionner brièvement des évolutions importantes sur l'accès aux thérapies anti-Alzheimer car certaines de ces évolutions succèdent la soumission des articles de revues des sections précédentes.

On ne peut plus dire qu'aucun des essais anti-amyloïdes n'est positif depuis que l'aducanumab a été accepté sur le marché américain par la Food and Drug Administration (FDA) (Budd Haeberlein et al., 2022). Cependant, le refus de la mise sur le marché de ce composé en Europe par l'European Medical Agency (EMA) révèle le débat sur l'efficacité clinique de ces résultats (Alexander et al., 2021b; Knopman et al., 2021; Rabinovici, 2021a). Trois autres thérapies anti-amyloïdes sont prometteuses actuellement : le donanemab (Mintun et al., 2021), le lecanemab (https://www.alzforum.org/therapeutics/lecanemab), et le gantenerumab (Salloway et al., 2021). Après des résultats prometteurs en phase II, le donanemab et le lecanemab font l'objet d'une procédure d'acceptation accélérée de la FDA pour la mise sur le marché américain de ces composés avant la fin des études de phase III. Cette procédure avait été employée pour l'aducanumab.

Ces démarches est un sujet de débat en cours (https://www.alzforum.org/news/community-news/drilling-down-cms-aduhelm-decision-primer#comment-45456). L'intérêt pour la cascade amyloïde semble inextinguible, bien que la communauté scientifique soit divisée sur cette question. Certains experts actualisent régulièrement l'hypothèse amyloïde avec de nouvelles perspectives d'interventions (Frisoni et al., 2022; McDade et al., 2021).

La stratégie préventive est retenue en particulier (Sabbagh et al., 2022). Il s'agirait d'éradiquer la charge amyloïde cérébral à un stade précédant des interactions synergiques avec les pathologies tau et inflammatoires parmi d'autres. En pratique, cette idée est portée par l'étude du gantenerumab dans les formes monogéniques de MA (Rabinovici, 2021b).

L'accessibilité de nouvelles thérapies anti-amyloïdes suscite aussi des débats éthiques sans précédent (Liu and Howard, 2021). On peut citer en particularité l'inégalité géographique de l'accès à ces thérapies, économique aux endroits où il est disponible, ainsi que les difficultés liées à la gestion de leurs effets indésirables. La procédure d'acceptation de l'aducanumab et la précision des résultats apportés ont été critiquée également (Alexander et al., 2021a; Knopman et al., 2021; Liu et al., 2021).

Le manque d'efficacité des stratégies anti-amyloïde ou anti-tau entraina l'exploration d'autres pistes, bien que retenues de façon moins unanime jusqu'en 2022. Il s'agit de nouvelles stratégies ciblant les pathologies multi-cellulaires de la MA. Cette nouvelle génération d'essais anti-Alzheimer est plus complexe en termes de voix de signalisation, et d'impact physiopathologique. Le rationnel qui leur est associé a été décrit dans la section précédente. Mais l'évolution de l'accès à des essais thérapeutiques dans ce domaine est moins rapide que pour les thérapies anti-amyloïdes. Le lecteur peut donc se référer à la section précédente pour en avoir un bref aperçu. Un exemple représentatif de cette nouvelle génération de thérapie anti-Alzheimer est l'apparition de thérapies immunologiques. Cet exemple est développé dans la section suivante.

1.5.2. **Evolutions des thérapies immunologiques**

Les stratégies immunologiques sont une nouvelle perspective pour modifier la course de la MA. Les interventions peuvent avoir trois objectifs : (1) prévenir l'apparition de phénotypes immunitaires neurotoxiques, (2) moduler l'activité immunitaire pour favoriser une activité neuroprotectrice, (3) supprimer les propriétés pro-inflammatoires neurotoxiques de la neuroinflammation (Leng and Edison, 2021).

Le développement de ces approches n'est pas au même niveau. A ma connaissance, l'idée de prévenir l'apparition d'une activité immunitaire toxique relève encore de la théorie à ce jour. Mais il faut mentionner des progrès récents de la compréhension de la physiopathologie du vieillissement (Hou et al., 2019), en particulier dans les aspects se rapport à la neuroinflammation. Le lecteur peut se référer à des articles de revue récent à ce propos (Hou et al., 2019; Saez-Atienzar and Masliah, 2020). Il faut aussi mentionner les résultats prometteurs des interventions préventives sur le mode de vie, dont une part des voix de signalisation impactés sont liées à la neuroinflammation (Kivipelto et al., 2018). La deuxième idée est de moduler l'activité microgliale et astrogliale en favorisant les phénotypes immuns protecteurs. Ce type d'approche est actuellement à l'étude dans des essais de phase 2. On peut citer en particulier les interventions par injection d'IL-2, ou d'un agoniste de TREM2 (https://www.alzforum.org/news/conference-coverage/antibodies-against-microglial-receptors-trem2-and-cd33-head-trials). Il existe peu de résultats publiés de ce type d'approches en cours de développement.

L'idée de supprimer les propriétés pro-inflammatoires neurotoxiques de la neuroinflammation est la stratégie qui fut la plus étudiée. Pour autant la plupart des essais randomisés contrôlés d'anti-inflammatoires non-stéroïdiens (AINS) sont tous négatifs à ce jour (Meyer et al., 2019; Wang et al., 2015). Il convient de mentionner l'exception de la mise sur le marché chinois de l'oligomannate de sodium en 2019. Ce composé avait montré un bénéfice clinique en phase III, par un mécanisme de réduction de la neuroinflammation via le microbiote intestinal (Wang et al., 2019).

Il y a plusieurs leçons tirées des nombreux échecs des essais anti-inflammatoires. La physiopathologie immunitaire et les voix de signalisation multi-cellulaires associées sont mieux connues. Le développement de biomarqueurs de la neuroinflammation a aussi plusieurs implications. Il existe des différences inter-espèce importantes en termes de (neuro)immunité (Smith and Dragunow, 2014).

L'accès à plusieurs biomarqueurs de la neuroinflammation permet non seulement d'étayer les connaissances acquises sur les modèles animaux. Il permet de mieux comprendre l'impact d'une intervention anti-inflammatoire sur des processus moléculaires liés à ces interventions. Cela n'était pas le cas jusqu'alors. Les thérapies anti-inflammatoires négatives ont été évaluées par des critères non-spécifiques comme des mesures cognitives ou des biomarqueurs des pathologies amyloïde et tau (Meyer et al., 2019; Wang et al., 2015). L'utilisation de biomarqueurs de la neuroinflammation permettra de mieux comprendre l'engagement thérapeutique, et peut-être de rendre ces thérapies opérationnelles.

Pour donner un exemple, on peut mentionner l'inhibition de la protéine MAPK p38α ('mitogen activated protein kinase', en anglais). Le développement d'un inhibiteur de cette protéine est le travail principal de la firme pharmaceutique EIP Pharma (Boston, Massachusetts, Etats-Unis d'Amérique). La MAPK p38α est une protéine impliquée dans la production et la signalisation de médiateurs pro-inflammatoire neurotoxique (Corrêa and Eales, 2012; Munoz and Ammit, 2010). Son activité est associée aux pathologies neurodégénératives comme la MA, et la maladie à corps de Lewy. L'inhibiteur de la MAPK p38α a été nommé le neflamapimod. Son développement en est au stade de phase 2 dans la MA (Alam et al., 2017). Les résultats des essais précédents montraient un bénéfice clinique modéré et une diminution de la pathologie tau et des dommages synaptiques pour les patients recevant les plus fortes doses (Alam et al., 2017; Scheltens et al., 2018). La tolérance du neflamapimod semblait être correcte, également. Une étude de phase 2 du neflamapimod était en cours au CHU de Toulouse Purpan. Cette étude fait l'objet principal de cette thèse et de la section suivante.

Partie expérimentale

2. Partie expérimentale

2.1. Cohérence des biomarqueurs amyloïdes du liquide cérébrospinal

2.1.1. Faits introductifs

Il peut exister plusieurs biomarqueurs pour une même physiopathologie mais ils ne reflètent pas toujours le même processus. Être amyloïde positif peut donc avoir une signification différente selon le type de biomarqueur dont le résultat est pathologique. Cette notion est omise dans les critères de définition biologique de MA où l'emploi des biomarqueurs amyloïdes est interchangeable (Jack et al., 2018). Le TEP amyloïde montre la pathologie sous sa forme mature, c'est-à-dire de plaques agrégées (Ikonomovic et al., 2008). Les valeurs d'$A\beta_{42}$ et le ratio $A\beta_{42/40}$ reflètent le processus de déposition des peptides amyloïde indirectement par la diminution de leur concentration rejetée dans le LCS (Seppälä et al., 2012). Il est donc nécessaire de pouvoir considérer la possibilité de résultats incohérents entre ces biomarqueurs pour définir la MA uniquement sur leurs résultats.

Plusieurs études ont justement révélé des incohérences entre les résultats des biomarqueurs amyloïdes (Palmqvist et al., 2016; Reimand et al., 2020b, 2020a). La cohérence et du TEP amyloïde est moins bonne avec les valeurs de l'$A\beta_{42}$ que celle du ratio $A\beta_{42/40}$ (Hansson et al., 2019). Il a été montré que les cas TEP amyloïde/$A\beta_{42}$ discordants pouvaient être à un stade plus précoce de MA que les patients pour qui ces biomarqueurs sont concordants (Palmqvist et al., 2016). Cependant, d'autres études ont montré la présence de caractéristiques distinctives cliniques et biologiques (de Wilde et al., 2019; Reimand et al., 2020b), suggérant des différences de pronostic entre ces groupes. Il semble également que les incohérences des biomarqueurs amyloïdes peuvent coexister avec le statut neuropathologique (Reimand et al., 2020a). Dans ces études, la présence de cas discordants soulève la question de l'information suggérée par un statut amyloïde-positif (Fagan, 2015).

En octobre 2019, Camille Tisserand, interne de neurologie au CHU de Toulouse Purpan soutient une thèse sur l'intérêt d'utiliser le ratio $A\beta_{42/40}$ en pratique clinique courante sous la direction du professeur Jérémie Pariente. Elle dispose de données rétrospectives issues de pratique clinique courante du centre mémoire de Toulouse. Elle procéda à une analyse de la cohérence des valeurs de l'$A\beta_{42}$ et du ratio $A\beta_{42/40}$ dans la classification AT(N). On suppose ces biomarqueurs interchangeables dans les critères de définition biologique de MA (Jack et al., 2018). Bien que reflétant le même processus, l'utilisation du ratio $A\beta_{42/40}$ est plus précise pour le diagnostic et pronostic de MA, tout en étant moins sensible aux facteurs pré-analytiques (Hansson et al., 2019). Cependant, aucune n'étude n'avait considéré la possibilité de leur incohérence dans la perspective d'un diagnostic biologique de MA, aucune étude n'avait fait une évaluation quantitative de leur cohérence en pratique clinique, aucune étude n'avait étudié l'intérêt du ratio $A\beta_{42/40}$ sans l'influence des caractéristiques cliniques des patients recrutés.

J'ai pu travailler avec Camille Tisserand pour reproduire les analyses qu'elle avait effectuées sur une population plus grande. Dans ce projet J'eu l'opportunité d'être encadré par le docteur Leonor Nogueira, médecin biologiste à l'Institut Fédératif de Biologie du CHU de Toulouse Purpan, et responsable du dosage des biomarqueurs des maladies neurodégénératives. Nous avons porté nos analyses sur les résultats des ponctions lombaires (PL) effectuées entre janvier 2016 et août 2019 au département de neurologie du CHU. D'un point de vue statistique, la question de l'agréement de deux biomarqueurs équivaut à celle de la cohérence de deux tests diagnostic en statistique. Je me suis appuyé en particulier sur les travaux de A.R. Feinstein décrivant les notions basiques de sensibilités, spécificités, précision, valeurs prédictives (Feinstein, 1975; Ransohoff and Feinstein, 1978; Sackett and Haynes, 2002).

Note : *Cet article a fait l'objet d'une courte publication dans une revue internationale. Il a été choisi de l'insérer dans le texte dans son format de soumission. La référence de l'article est la suivante :*

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2.1.2. **Taking the A train?**

Taking the A train? Limited consistency of Aβ42 and the Aβ42/40 ratio in the AT(N) classification

Dominique Gouilly[a], Camille Tisserand[b], Leonor Nogueira[c], Laura Saint-Lary[d], Vanessa Rousseau[d], Marie Benaiteau[b], Marie Rafiq[b], Jasmine Carlier[b], Emilie Milongo-Rigal[b], Jean-Christophe Pagès[c], Jérémie Pariente[a, b].

a Toulouse Neuroimaging Center, Toulouse, France.

b Department of Cognitive Neurology, Epilepsy and Movement Disorders, CHU Toulouse Purpan, France.

c Department of Cell Biology and Cytology, CHU Toulouse Purpan, France.

d Center of Clinical Investigation, CHU Toulouse Purpan (CIC1436), France.

Note : *Le tableau supplémentaire de cet article a été placé à la suite du texte.*

Abstract

The consistency of cerebrospinal fluid $A\beta_{42/40}$ ratio and $A\beta_{42}$ has not been assessed in the AT(N) classification system. We analyzed the classification changes of the dichotomized amyloid status (A+/A-) in 363 patients tested for Alzheimer's disease biomarkers after $A\beta_{42}$ was superseded by the $A\beta_{42/40}$ ratio. The consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio was very low. Notably, the proportions of "false" A+T- patients were considerable (74-91%) and corresponded mostly to patients not clinically diagnosed with Alzheimer's disease. Our results suggest that the interchangeability of $A\beta_{42/40}$ ratio and $A\beta_{42}$ is limited for classifying patients in clinical setting using the AT(N) scheme.

Glossary

AD, Alzheimer's disease; $A\beta_{42}$, amyloid-β 42; CSF, cerebrospinal fluid; P-tau, phosphorylated tau; NPV, negative predictive value; PPV, positive predictive value; 95%-CI, 95% confidence interval.

1. Background

In 2018, the US National Institute on Aging and the Alzheimer's Association proposed a biological definition and diagnosis of Alzheimer's disease (AD) based on abnormal amyloid and phosphorylated tau (P-tau) biomarkers [1]. It was suggested that neuroimaging and cerebrospinal fluid (CSF) biomarkers can be compiled in the AT(N) classification system with A meaning amyloid (A), T tauopathy, and (N) neurodegeneration [1]. In these guidelines, CSF amyloid-β 42 ($A\beta_{42}$) and the $A\beta_{42/40}$ ratio are considered interchangeable to establish entry in the AD continuum. However, the $A\beta_{42/40}$ ratio is recognized as a better amyloid biomarker than $A\beta_{42}$ alone [2], and shows less sensitivity to non-AD-related pathologic changes and pre-analytic factors [2, 3], and superior accuracy for the prognosis and diagnosis of AD [4]. It is therefore of major interest to assess the consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio. Although the AT(N) system was not designed for clinical practice [1], we analyzed the classification changes after $A\beta_{42}$ was superseded by the $A\beta_{42/40}$ ratio.

2. Method

We recruited all patients who had a CSF sample collected by lumbar puncture during a routine workup of cognitive decline between January 2015 and August 2019 at the Neurology Department of the Toulouse Memory Clinic (France). All subjects with subjective or mild cognitive impairment and dementia were included. Exclusion criteria were: (1) unavailable $A\beta_{42}$, Aβ40, P-tau, or tau biomarkers; (2) lumbar puncture performed for other indications besides AD biomarker analysis; (3) tau>1200 pg/mL associated with acute vascular events, traumatic brain injury or status epilepticus. Only one result per subject was considered. Diagnosis was established as: "AD", "Non-AD", or "Other" using international and validated criteria after the clinician was informed of the biomarker results, including the $A\beta_{42/40}$ ratio when possible. Non-AD patients included all other neurodegenerative diseases besides AD (frontotemporal lobar degeneration, Lewy body disease, Parkinson's disease, Creutzfeldt-Jacob's disease, etc.). Other included all other conditions besides neurodegenerative diseases (psychiatric disease, cerebrovascular pathology, epilepsy, encephalopathy, etc.).

All patients gave their informed consent, and the study was approved by the French National Commission for Informatics and Liberties (CNIL number: 2206723v0). CSF samples were collected in polypropylene tubes (Greiner bio-one), centrifuged immediately after their receipt (3500g, 10mn, 4°C), aliquoted, and frozen at -20°C until assayed (<2 weeks). $A\beta_{42}$, Aβ40, P-tau and tau were measured using commercial assays (INNOTEST, Fujeribo, Ghent, Belgium) according to the manufacturer's procedures. Intra-assay variability was controlled according to manufacturer's recommendations. The laboratory also participated in the external quality control program by the Alzheimer's Association. AD biomarker profiles were specified for each patient by applying the AT(N) classification system [1] using cutoff values recommended by the manufacturer and used in previous publications [5]: A+ was defined as $A\beta_{42}$<500 pg/mL and T+ as P-tau>60 pg/mL. (N) was not included in the analyses as non-specific to AD [1]. Up until December 2018, Aβ40 dosing was performed only for patients with A+T- and A-T+ profiles as previous reports had failed to show the clinical utility of using the $A\beta_{42/40}$ ratio when $A\beta_{42}$ and P-tau are congruent [5]. Starting in January 2019, Aβ40 dosing was performed systematically following recent recommendations [4]. Patients were assigned to two groups according to these periods: one cohort referred to as patients with selective $A\beta_{42/40}$ ratio evaluation (i.e., samples from 2015-2018), and one cohort referred to as patients with systematic $A\beta_{42/40}$ ratio evaluation (i.e., samples from 2019). An $A\beta_{42/40}$ ratio <0.05 was considered abnormal [5]. When the $A\beta_{42/40}$ ratio and $A\beta_{42}$ values were congruent, we used the $A\beta_{42/40}$ ratio as reference to classify patients as "true" A+ or "true" A-. For example, for "true" A+ patients, both $A\beta_{42}$ value and $A\beta_{42/40}$ ratio were abnormal. When $A\beta_{42}$ values and $A\beta_{42/40}$ ratio were incongruent, $A\beta_{42/40}$ ratio was used as the reference to classify patients as "false" A+ or "false" A-. For example, a "false" A- patient had a normal $A\beta_{42}$ value and an abnormal $A\beta_{42/40}$ ratio. To ensure that the results of reclassification does not depend on the cutoffs, we applied a +/- 10% interval margin to exclude borderline patients, and we reanalyzed the consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio using different cutoffs with A+ redefined as $A\beta_{42}$<700 pg/mL or $A\beta_{42/40}$<0.06.

Rates of classification changes were expressed as percentages and the corresponding 95% confidence interval (95%-CI) using the Wilson or binomial approach. The accuracy of $A\beta_{42}$ prediction was estimated by positive and negative predictive values (PPV and NPV). The consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio was assessed using Cohen's Kappa index (k) for an agreement analysis, and the McNemar test to estimate the significance of discordance rates. Comparisons of demographics and biomarker values were performed between patients who shared the same amyloid status with $A\beta_{42}$ but different $A\beta_{42/40}$ ratio classifications (for example "true" and "false" A+T-). We used the non-parametric Mann-Whitney U test for quantitative variables, and chi-squared or Fisher's tests for qualitative variables. Statistical analyses were performed on R v.1.4., with significance set at $p<0.05$, two-tailed.

3. Results

Of 1266 patients, 903 (71.3%) were excluded, mostly because of lack of Aβ40 dosing, while 363 (28.7%) were included (Figure 1). Of these patients, 242 patients were assigned to the cohort with selective $A\beta_{42/40}$ evaluation including 202 A+T- and 40 A-T+ patients. The cohort with systematic $A\beta_{42/40}$ evaluation comprised 121 patients including 43 A-T-, 44 A+T-, 22 A+T+ and 12 A-T+ individuals (Supplementary Table 1). After $A\beta_{42}$ was superseded by the $A\beta_{42/40}$ ratio, in the cohort with selective $A\beta_{42/40}$ evaluation, we observed classification changes of 149/202 A+T- patients to "false" A+T- (73.8%; 95%-CI=[67.3–79.3]), and 13/40 A-T+ patients to "false" A-T+ (32.5%; 95%-CI=[20.1–48]). For these patients, the consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio was at chance level (k=-0.03; $p>0.05$; 95-CI=[-0.09–0.04]). The predictive accuracy of $A\beta_{42}$ was low (PPV=26.2%; NPV=67.5%) and discordant rates were significant ($p<0.01$; Figure 2A). In the cohort with systematic $A\beta_{42/40}$ evaluation, we observed classification changes of 1/43 A-T- patients to "false" A-T- (2.3%; 95%-CI= [0.001–12.3]), 40/44 A+T- patients to "false" A+T- (90.9%; 95%-CI= [78.8–96.4]), 7/22 A+T+ to "false" A+T+ (31.8%; 95%-CI= [16.4–52.7]), and 3/12 A-T+ patients to "false" A-T+ (25%; 95%-CI= [5.5–57.2]). For this cohort, the consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio was moderate (k=0.2; $p<0.01$; 95-CI= [0.08–0.33]).

The predictive accuracy of $A\beta_{42}$ was low (PPV=28.8%; NPV=92.7%) and discordant rates were significant ($p<0.01$; Figure 2B). When we applied a +/-10% interval margin around the cutoffs to exclude borderline patients, the consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio was still at chance level in the cohort with selective $A\beta_{42/40}$ evaluation (Cohen's kappa; k=-0.002; $p>0.05$; 95-CI=[-0.07–0.07]; PPV=22.2%; NPV=77.4%; McNemar test; $p<0.01$). In the cohort with systematic $A\beta_{42/40}$ evaluation the consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio was still moderate (Cohen's kappa; k=0.27; $p<0.01$; 95-CI=[0.13–0.41]; PPV=29.2%; NPV=97.8%; McNemar test; $p<0.01$). When we used different cut-off values for $A\beta_{42}$ (700 pg/mL), and the $A\beta_{42/40}$ ratio (0.06), and a +/-10% interval margin, the consistency of both markers remained unchanged in the cohort with selective $A\beta_{42/40}$ evaluation (Cohen's kappa; k=0.05; $p<0.05$; 95-CI=[0.01–0.1]; PPV=36.8%; NPV=90.9%; McNemar test; $p<0.01$) and the cohort with systematic $A\beta_{42/40}$ evaluation (Cohen's kappa; k=0.23; $p<0.01$; 95-CI=[0.12–0.34]; PPV=38.8%; NPV=100%; McNemar test; $p<0.01$).

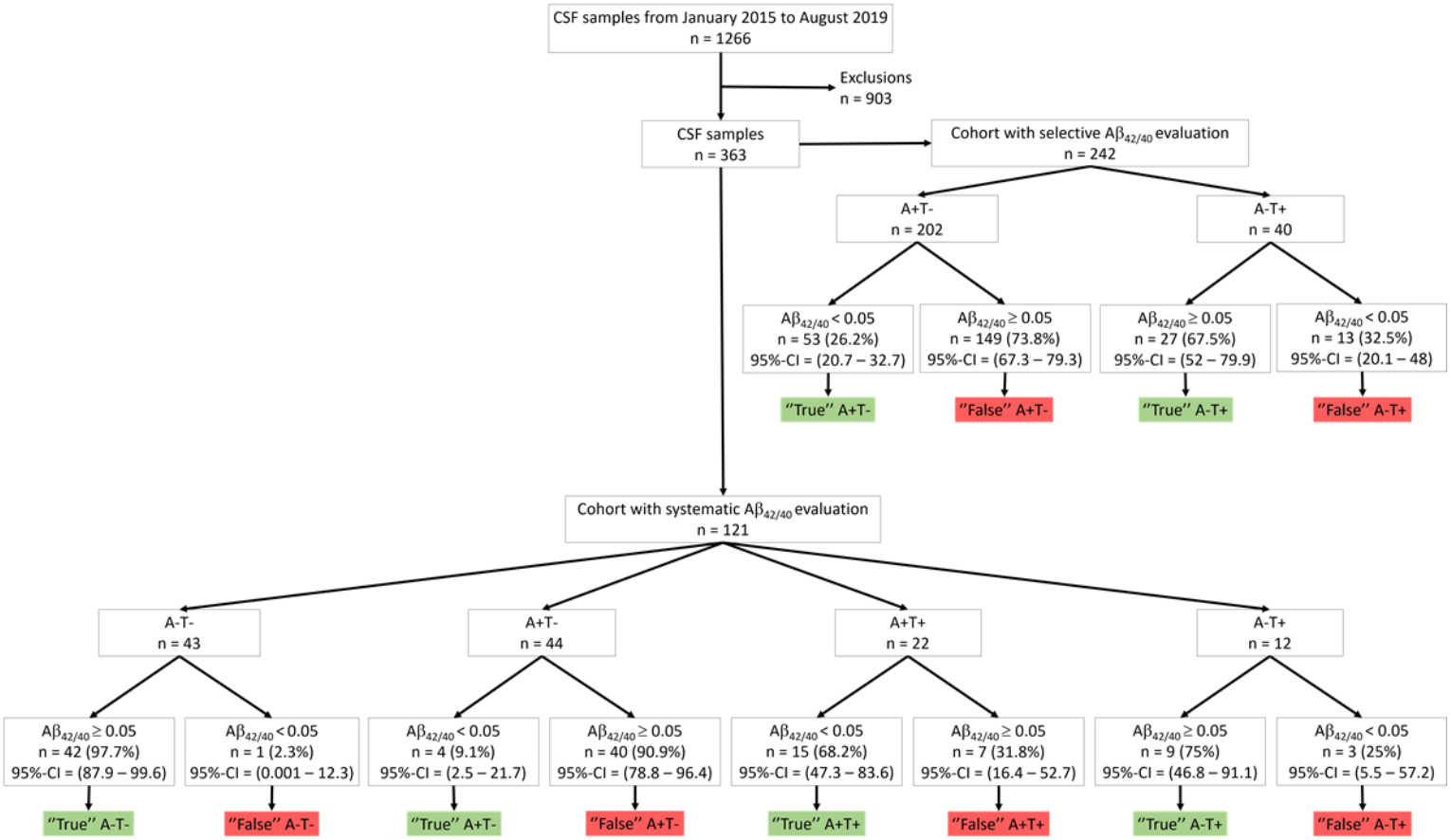

Figure 1. Flow chart of cerebrospinal fluid samples inclusion and classification.

CSF biomarker profiles were determined according to the AT(N) classification system [1]: A+ correspond to $A\beta_{42}$<500 pg/mL and T+ to P-tau>60 pg/mL.

Abbreviations: $A\beta_{42}$, amyloid-β 42; CSF, cerebrospinal fluid, P-tau, phosphorylated tau on threonine 181; 95%-CI, 95% confidence interval.

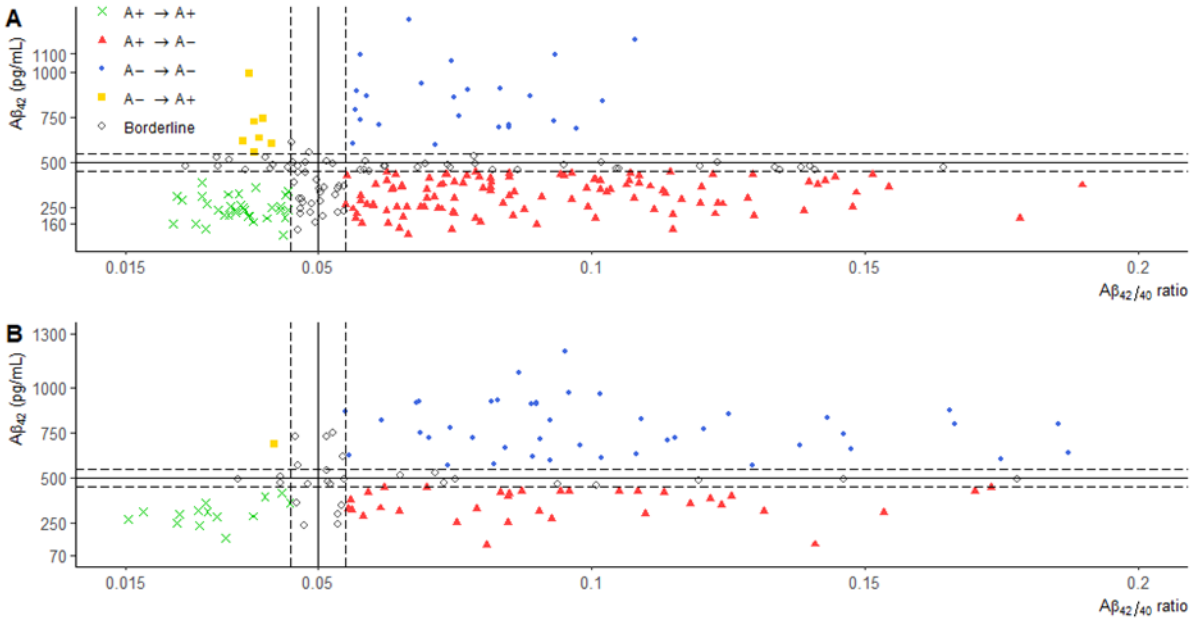

Figure 2. Scatter plot of cerebrospinal fluid $A\beta_{42}$ values and $A\beta_{42/40}$ ratio. One point represents one CSF sample for each patient in the cohort with selective $A\beta_{42/40}$ ratio evaluation only for patients with A+T- and A-T+ profiles (A), or from the cohort with systematic $A\beta_{42/40}$ ratio evaluation (B). The vertical and horizontal lines represent the $A\beta_{42/40}$ ratio (0.05) and the $A\beta_{42}$ (500 pg/mL) cutoff values. Dashed lines represent a +/- 10% interval margin around the cutoffs. Amyloid status was determined according to the AT(N) classification system [1]: A+ corresponds to CSF $A\beta_{42}$ < 500 pg/mL or $A\beta_{42/40}$ ratio < 0.05. The consistency between the dichotomized biomarker values resulted in "true" amyloid positive (A+ → A+) for cases with $A\beta_{42}$ < 500 and $A\beta_{42/40}$ < 0.05 or "true" amyloid negative (A- → A-) for cases with $A\beta_{42}$ ≥ 500 and $A\beta_{42/40}$ ≥ 0.05. Incongruent amyloid biomarker values resulted in "false" amyloid positive (A+ → A-) for cases with $A\beta_{42}$ < 500 and $A\beta_{42/40}$ ≥ 0.05 or "false" amyloid negative (A- → A+) for cases with $A\beta_{42}$ ≥ 500 and $A\beta_{42/40}$ < 0.05.

Abbreviations: $A\beta_{42}$, amyloid-β 42; CSF, cerebrospinal fluid.

The subgroups of patients resulting from the reclassification were compared when the number of patients per subgroup was superior to 5 (Table 1). As expected, significant differences between amyloid biomarker levels were observed. “False” A+T+ patients had lower P-tau, and tau values compared to “true” A+T+ patients ($p<0.01$). In the cohort with selective $A\beta_{42/40}$ evaluation, “false” A+T- patients also had lower P-tau, and tau values compared to “true” A+T- patients ($p<0.01$). Finally, for this cohort, we observed an increased proportion of patients with AD diagnosis, and a decreased proportion of patients with other neurodegenerative diseases and other conditions among “true” A+T- and “false” A-T+ compared to “false” A+T- and “true” A-T+ respectively ($p<0.05$).

Table 1. Comparison of the subgroups of patients resulting from amyloid status reclassification.

Group	Cohort with systematic $A\beta_{42/40}$ evaluation								Cohort with selective $A\beta_{42/40}$ evaluation			
Biomarker profile	"True" A-T-	"False" A-T-	"True" A+T-	"False" A+T-	"True" A+T+	"False" A+T+	"True" A-T+	"False" A-T+	"True" A+T-	"False" A+T-	"True" A-T+	"False" A-T+
Demographics												
n	42	1	4	40	15	7	9	3	53	149	27	13
Age (years), mean (SD)	66.9 (10.9)	50	73 (6.7)	70.7 (9.2)	73.7 (8.3)	73.3 (8.8)	70.9 (6.4)	78.7 (4.9)	73.5 (7.3)	72.3 (10.3)	73 (9.1)	78.5 (6.1)
Gender (female), n (%)	16 (38%)	1 (100%)	1 (25%)	14 (35%)	11 (73%)	3 (43%)	7 (78%)	3 (100%)	24 (45%)	64 (43%)	17 (63%)	7 (54%)
Diagnostic categories, n (%)												
AD	0	0	1 (25%)	1 (3%)	12 (80%)	3 (43%)	1 (11%)	3 (100%)	29 (55%)	13 (9%) *	4 (15%)	12 (92%) *
Non-AD	18 (43%)	0	1 (25%)	24 (60%)	2 (13%)	2 (29%)	5 (56%)	0	16 (30%)	73 (49%) *	15 (56%)	1 (8%) *
Other	24 (57%)	1 (100%)	2 (50%)	15 (38%)	1 (7%)	2 (29%)	3 (33%)	0	8 (15%)	63 (42%) *	8 (30%)	0 *
CSF biomarker values, median [IQR]												
$A\beta_{42}$ (pg/mL)	750 [660 - 865]	731	414 [344 - 466]	421 [314 - 452]	311 [260 - 361]	331 [303 - 356]	728 [539 - 923]	572 [538 - 631]	265 [217 - 364]	361 [260 - 432] *	789 [695 - 904]	607 [529 - 635] *
$A\beta_{40}$ (pg/mL)	6985	15920	8740	4078	10280	5397	10445	12337	6760	3924	10874	15166
	[5424 - 10244]		[7784 - 9950]	[2962 - 5176]	[8641 - 12104]	[4718 - 6252] *	[8842 - 12635]	[11989 - 14350]	[5544 - 9558]	[2879 - 5227] *	[8366 - 13134]	[13505 - 17019] *
$A\beta_{42/40}$ ratio	0.094	0.046	0.045	0.093	0.03	0.058	0.069	0.043	0.041	0.082	0.075	0.039
	[0.082 – 0.136]		[0.042 – 0.047]	[0.075 – 0.12]	[0.026 – 0.038]	[0.056 – 0.06] *	[0.056 – 0.093]	[0.043 – 0.045]	[0.034 – 0.046]	[0.065 – 0.112] *	[0.059 – 0.085]	[0.037 – 0.042] *
P-tau (pg/mL)	43 [38 - 50]	35	51 [45 - 53]	34 [28 - 48]	108 [97 - 123]	68 [67 - 87] *	72 [70 - 92]	73 [71 – 122]	49 [40 – 54]	32 [24 – 42] *	76 [71 – 89]	88 [70 – 106]
Tau (pg/mL)	250 [198 - 303]	188	293 [242 - 340]	222 [162 - 289]	854 [727 - 891]	479 [429 - 575] *	515 [498 - 712]	604 [574 - 772]	294 [250 - 361]	196 [137 - 273] *	511 [457 - 648]	609 [460 - 682]

Abbreviations: $A\beta_{42}$, amyloid β 42; CSF, cerebrospinal fluid; IQR, interquartile range; P-tau, phosphorylated tau on threonine 181; SD, standard-deviation.

CSF profiles were determined according to the AT(N) classification system [1]: A+ corresponds to abnormal $A\beta_{42}$ < 500 pg/mL, T+ corresponds to P-tau > 60 pg/mL. Non-parametric Mann-Whitney *U* test and chi-squared test or Fisher's test were used to compare subgroups of patients who share the same amyloid status with $A\beta_{42}$ but different $A\beta_{42/40}$ ratio classifications ("true" and "false" A+T- for example). Comparisons were made only when the number of individuals per subgroup was superior to 5. Statistical analyses were performed on R v.1.4., with significance set at $p < 0.05$, two-tailed.

4. Discussion

There is increasing evidence from clinical practice of issues related to a purely biological definition of AD [6]. The issue of the interchangeability of biomarkers related to the same pathophysiology was recently addressed in the AT(N) classification system [7, 8]. Our study shows considerable classification differences between $A\beta_{42}$ and the $A\beta_{42/40}$ ratio. However, one limitation is the absence of a standard reference, and this precludes ascertaining of which patient is ultimately misclassified. As we found significant differences in Aβ40 concentrations between the subgroups resulting from the reclassification, interindividual variabilities in amyloid processing might have caused classification errors when $A\beta_{42}$ alone was used in the AT(N) scheme. The high rates of classification changes observed, especially those for A+T- patients, might also be due to the heterogeneity of the population. Most "false A+T-" patients did not have AD according to the clinician's diagnosis, which suggests that the use of $A\beta_{42}$ alone might produce classification errors concerning other brain pathologies in the AT(N) scheme [2, 9]. We observed 14 "false" A+T- patients clinically diagnosed with AD (Table 1). These might be cases of false-negative $A\beta_{42/40}$ ratio or P-tau value (half of these patients had borderline values), or diagnostic errors. Another less likely hypothesis is that a few of these patients might have been tested at an early disease stage, before positivity on both $A\beta_{42}$ and the $A\beta_{42/40}$ ratio would have been detectable [10, 11]. Furthermore, we observed that most of the "true" A-T+ patients had non-AD degenerative diseases, and most of the "false" A-T+ patients had AD according to clinician's diagnosis. These observations are consistent with a recent study showing that frontotemporal lobar degeneration was probably the main cause of "true" A-T+ patients [12]. Therefore, in our study, "false" A-T+ patients might be misclassified. We found only one "false" A-T- patient, which confirms the idea that almost no patients exhibit negative CSF $A\beta_{42}$ and positive amyloid PET [2, 7-11, 13-15]. A recent study showed that positivity in both $A\beta_{42}$ and PET amyloid biomarkers is not invariably associated with AD at autopsy [9]. Further investigations of our results are warranted in an autopsy confirmed AD population.

Previous studies have reported that patients with discordant $A\beta_{42}$ and amyloid PET results have distinct profiles and trajectories in terms of APOEε4 carriage, amyloid and tau deposition, and cognitive decline [13, 14]. Other studies have shown that these patients are subject to diagnostic reclassification [13, 15], and that the major reason for requesting an amyloid PET scan after performing CSF biomarkers was the discrepancies between the primary clinical diagnosis and CSF results [15]. As the $A\beta_{42/40}$ ratio is a better amyloid marker than $A\beta_{42}$ alone [4], our results suggest that the $A\beta_{42/40}$ ratio might help to avoid an additional PET scan for complex clinical cases. However, previous studies have shown that the use of $A\beta_{42/40}$ ratio did not influence clinician's diagnosis when $A\beta_{42}$ and P-tau are congruent [5]. As we did not assess clinician's diagnostic changes after $A\beta_{42}$ was superseded by $A\beta_{42/40}$ ratio, the consistency of $A\beta_{42/40}$ ratio results and clinician's diagnosis might be artificially improved. The clinical relevance of our findings remains to be established in terms of diagnostic and evolutive trajectories.

The different operationalizations of the AT(N) system are impacted by biomarker selection, dichotomization, and population characteristics [7, 8]. The patients included in our study were heterogenous as exemplified by the small proportion of AD patients. The cohort with systematic $A\beta_{42/40}$ evaluation should be considered as representative of everyday clinical practice for neurological consultations. One limitation is the exclusion of A+T+ and A-T- patients in the cohort with selective $A\beta_{42/40}$ evaluation. There were few of these patients in our study, and the proportion of misclassifications among A+T+ and A-T- patients may be different with a larger population. Another concern is the choice of threshold values. However, there was no change in our results after excluding borderline patients and after retesting the analyses with different cut-off values. Besides, it has been shown that cut-off modifications for biomarkers related to the same pathophysiology did not improve their consistency [7]. Therefore, it seems unlikely that the choice of threshold values significantly influenced our analyses.

In conclusion, our results suggest that the $A\beta_{42/40}$ ratio is not interchangeable with $A\beta_{42}$ to delimit amyloid pathology in clinical practice using the AT(N) classification system.

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References:

Note : *L'ensemble des références de cet article de revue a été placé en annexe 3.*

Supplementary Table 1. Demographics and CSF AD biomarkers of the population studied.

Characteristics	Cohort with systematic $A\beta_{42/40}$ evaluation	Cohort with selective $A\beta_{42/40}$ evaluation
Demographics		
n	121	242
Age (years), mean (SD)	70 (9.8)	73 (9.5)
Gender (female), n (%)	56 (46%)	112 (46%)
Diagnostic categories, n (%)		
AD	21 (17%)	58 (24%)
Non-AD	52 (43%)	105 (43%)
Other	48 (40%)	79 (33%)
CSF biomarker profiles, n (%)		
A-T-	43 (36%)	0
A+T-	44 (36%)	202 (83%)
A+T+	22 (18%)	0
A-T+	12 (10%)	40 (17%)
CSF biomarker values, median [IQR]		
$A\beta_{42}$ (pg/mL)	487 [356 – 722]	369 [255 – 471]
$A\beta_{40}$ (pg/mL)	6608 [4545 – 10156]	5219 [3428 – 7782]
$A\beta_{42/40}$ ratio	0.082 [0.054 – 0.109]	0.069 [0.048 – 0.096]
P-tau (pg/mL)	47 [36 – 66]	42 [29 – 55]
Tau (pg/mL)	279 [199 – 515]	257 [167 – 374]

Abbreviations: AD, Alzheimer's disease; $A\beta_{42}$, amyloid-β 42; CSF, cerebrospinal fluid; IQR, interquartile range; P-tau, phosphorylated tau on threonine 181; SD, standard-deviation.

The AT(N) classification system [1] was used to define CSF biomarker profiles: A+ corresponds to $A\beta_{42}$ < 500 pg/mL, and T+ to P-tau > 60 pg/mL.

2.2. **Le projet VIP**

2.2.1. **Le concept de l'étude**

Les années 2012-2015 sont marquées d'une série d'échecs d'essais anti-amyloïdes (Doody et al., 2014; Salloway et al., 2014). Dans le même temps l'intérêt d'interventions immunologiques grandit (Heneka et al., 2015). Il s'agirait de diminuer les pathologies amyloïdes et tau indirectement, en modifiant l'interactions du système immunitaire cérébral avec ces pathologies. La voie de signalisation de la MAPK p38α a ce potentiel thérapeutique (abordé en introduction). La firme EIP Pharma a exploré ce potentiel en développant un inhibiteur de cette protéine sous le nom de neflamapimod (VX-745). Le neflamapimod est un AINS dont le développement en est actuellement au stade de la phase 2 dans la MA (Alam et al., 2017).

Il est courant d'utiliser des critères de jugement biologiques dans les essais de phase 2 pour évaluer l'engagement thérapeutique. Le développement de biomarqueurs de la neuroinflammation est récent, tant en imagerie TEP scan que dans le LCS. L'inhibition de la voie de la MAPK p38α a un effet sur la pathologie tau et les dommages synaptiques (Alam et al., 2017; Scheltens et al., 2018). Elle semble avoir aussi avoir un effet sur la pathologie amyloïde et la cognition aux plus fortes doses de médicament reçues. Mais aucune étude n'a évalué l'effet du neflamapimod sur la neuroinflammation. Comprendre l'effet de ces thérapies avec des biomarqueurs de la neuroinflammation permettrait de décomposer le mode d'action des composés à l'étude, c'est-à-dire délimiter les processus moléculaires sur lesquels l'engagement thérapeutique s'opère, ainsi que les relations avec les autres caractéristiques cliniques et biologiques de la MA.

L'ensemble des interventions immunologiques ont été évaluées sur la progression de la MA directement, sans mesurer leur effet sur la neuroinflammation (Meyer et al., 2019; Wang et al., 2015). Cependant l'emploi des biomarqueurs de la neuroinflammation a révélé la complexité des changements immunitaires dans la MA. Cette complexité résulte du stade de la maladie, de la vulnérabilité individuelle à la neuroinflammation, et de la variété des processus neuro-immunitaires. L'utilisation de biomarqueurs de la neuro-inflammation permettrait également de comprendre l'impact de la variabilité des profils neuro-inflammatoires sur la réponse théprapeutique.

C'est sur ce rationnel que se base le projet V.I.P dont l'acronyme résume les idées. Il s'agit d'une étude de phase 2 du **V**X-754 (le neflamapimod) sur l'**I**nflammation cérébrale mesurée en imagerie **P**ET (TEP) de TSPO. Les critères secondaires de jugement seraient les performances neuropsychologiques des patients, ainsi que des mesures volumétriques en IRM structural. VIP serait une étude randomisée contre placébo et avec un suivi d'une durée de trois mois. Cette étude aurait donc pour objectif de tester si le neflamapimod diminue la neuroinflammation sur une courte durée d'exposition, du moins plus courte que la durée classique de ce type d'essai. L'objectif secondaire serait de tester si l'effet observée sur la neuroinflammation est associé à un bénéfice sur les critères secondaires de progression de la MA.

La question du choix de la fenêtre thérapeutique est capitale pour mettre en place VIP. Il y a un intérêt évident à recruter des patients aux premiers stades symptomatiques pour intervenir à un stade où la pathologie est encore débutante. Cette idée pourrait être néanmoins être débattue dans le cas d'une thérapie anti-inflammatoire. Les études sur les biomarqueurs en imagerie TEP de TSPO ont montré que l'inflammation semble être protectrice aux stades de déficits cognitifs légers (Leng and Edison, 2021). Mais ces preuves sont de nature associative. La MAPK p38α intervient dans la production de médiateurs pro-inflammatoire neurotoxiques. Son inhibition à un stade où l'inflammation est initialement protectrice et évolue vers une activité cellulaires pro-inflammatoire pourrait être une fenêtre thérapeutique adaptée car elle correspondrait au moment où les interactions amyloïde/tau/inflammations deviennent synergiques. Pour tester cette hypothèse, les patients furent recrutés avec des déficits cognitifs léger dans VIP.

2.2.2. **Le protocole de l'étude et sa réalisation**

L'étude V.I.P est un projet soutenu par la Fondation Alzheimer et la Fondation de l'Avenir (Paris, France). La réalisation du protocole comprenait les mêmes examens réalisés à la visite d'inclusion (v0) et à la visite de sortie d'étude, trois mois plus tard (v3) (figure 6). Tous ces examens étaient passés entre le Centre d'Investigation Clinique (CIC 1436) du CHU de Toulouse Purpan, la plateforme IRM de l'UMR 1214, et le département de médecine nucléaire du CHU de Toulouse Purpan : un bilan clinique complet, une PL, une prise de sang, un examen neuropsychologique, et un examen d'imagerie IRM et TEP scan. L'administration de ces examens a été approuvée par un comité éthique (Comité de protection des personnes, CPP) et par l'Agence Nationale de Sureté du Médicament (ANSM).

Les recrutements de l'étude eurent lieu entre octobre 2018 et juin 2021. La progression de ces recrutements fut ralentie par plusieurs incidents dont certains sont classiques dans la réalisation des essais cliniques. Il y eu par exemple des difficultés de planification des examens d'imagerie TEP, dont la radio-synthèse du traceur de TSPO, le [^{18}F]-DPA-714, était effectuée au CHU de Toulouse Purpan. D'autres incidents furent moins triviaux, en particulier l'interruption temporaire de l'étude en raison de la crise sanitaire de mars 2020. Ces incidents entrainaient des retards et des difficultés de reprogrammation. Il s'agissait d'une organisation complexe en raison du temps entre les différents examens, et la prise du traitement.

Figure 6 : Protocole du projet V.I.P.

Abréviation : v, visite.

2.2.3. **Mon travail dans VIP**

Le lecteur peut se référer à la section introductive qui décrit les connaissances que j'ai dû acquérir pour travailler sur VIP. Cette section décrit mon apport à la réalisation du projet.

Mon travail a consisté au receuil et à l'analyse des résultats de VIP. Ce travail a été initié dans le cadre d'un stage de recherche en deuxième année de master recherche en neuropsychologie et neurosciences cliniques. Ce stage était sous la direction de Jérémie Pariente et Laura Guerrier à l'UMR 1214. C'est leur soutien durant ce stage qui me permis d'accéder à la poursuite de cette activité dans le cadre de cette thèse.

J'ai consacré une partie importante de ma thèse au recueil des résultats cliniques et neuropsychologiques de VIP. J'ai été accueilli CIC du CHU de Toulouse Purpan pour faire cette recension. Johanne Germain, attachée de recherche clinique coordinatrice de l'étude, me consacra un temps important pour me permettre de comprendre l'organisation du projet. Elsa Bertrand et Marie Goubeaud, psychologues spécialisées en neuropsychologie me consacrèrent un temps considérable pour m'aider à comprendre les bilans qu'elles avaient administrés en totalité. J'ai également assisté à certains de ces bilans. J'ai pu ainsi établir une base de données qui serait exploitable pour des analyses futures.

L'analyse des données de VIP reposait sur l'établissement d'une méthode de quantification de l'imagerie de TSPO en TEP scan, ce qui dura un an et demi sous la guidance de Patrice Péran et Pierre Payoux à l'UMR 1214. En février 2020, je mis en place un groupe de travail sur l'imagerie TEP scan de TSPO. Les réunions de ce groupe étaient réalisées en visoconférence sur des thématiques de méthodologie ou physiopathologie. Je m'occupais de la programmation des réunions. Entre février 2020 et mars 2022, il y eu neuf séances rassemblant 20 à 30 participants pour 17 intervenants au total, et quelques interventions internationnales.

Au court du recrutement de VIP, j'ai eu l'opportunité de travailler avec le professeur Stein Silva et Benjamine Sarton, du service d'anesthésie et réanimation du CHU de Toulouse Purpan. J'ai passé beaucoup de temps avec Benjamine Sarton pour réfléchir à la mise en application de la méthode de traitement de l'imagerie TEP de TSPO.

En parrallèle, des analyses intermédiaires des résultats de l'étude VIP furent réalisées par Mélissa Villatte, et Maëva Fisher, sur un effectif de 13 et 18 patients, respectivement. Ces analyses étaient réalisées dans le cadre d'un stage de recherche du même master que j'avais fait. J'ai pu aider Mélissa Villatte et Maëva Fisher à conduire ces analyses qui nous informaient sur les résultats de l'étude.

2.2.4. **La variabilité clinique et neuropsychologique des profils de neuroinflammation**

2.2.4.1. **Faits introductifs**

Le développement de l'imagerie de TSPO en TEP est à un stade où il reste plusieurs incertitudes dans son utilisation. Une vue d'ensemble en a été donnée en introduction dans la section dédiée. Ces incertitudes se situent (1) dans la relation entre la mesure faite en TEP et les autres biomarqueurs et mesures neuropsychologiques de la MA, (2) le choix de la méthode de quantification, et (3) la relation entre la mesure du niveau de TSPO en TEP et le type changement tissulaire qui lui est associé.

L'imagerie de TSPO en TEP mesure une activité immunitaire pouvant être protective ou toxique. La mesure du niveau de TSPO en TEP est indissociable de ces activités. L'ensemble des connaissances sur le rôle de la neuroinflammation en imagerie de TSPO en TEP est donc de nature associative car on ne peut pas directement interpréter le métabolisme que l'on visualise. On a ainsi montré que la neuroinflammation – visualisée en imagerie TEP de TSPO – a une activité neuroprotectrice aux premiers stades de la MA (Hamelin et al., 2016). Cette activité deviendrait progressivement neurotoxique au cours de l'évolution de la maladie (Leng and Edison, 2021). Mais la relation entre l'imagerie de TSPO en TEP et les performances neuropsychologiques est incertaine aux premiers stades de la MA. Dans les études transversales, on recense des corrélations positives (Hamelin et al., 2016), négatives (Bradburn et al., 2019), ou encore non significatives (Knezevic et al., 2018; Parbo et al., 2018). Les études longitudinales montrent que les patients ayant une forte inflammation pourrait avoir un déclin cognitif plus rapide (Malpetti et al., 2020) ou au contraire plus lent que les autres (Hamelin et al., 2016). Il a aussi été suggéré que différents profils en imagerie de TSPO seraient associés à différentes trajectoires évolutives indépendamment du stade de la maladie (Hamelin et al., 2018). La variabilité des profils cliniques associés aux profils de neuroinflammation est donc encore débattue dans la MA.

Pour VIP, ce type d'incertitude est problématique. Les patients de l'étude VIP sont aux premiers stades de la maladie (MMS >20/30). On ne connaît donc pas d'emblée la relation entre la mesure faite en TEP et les performances neuropsychologiques des patients. Mais le type d'activité immunitaire que l'on visualise en TEP, protective ou toxique c'est-à-dire, est déduit par associations aux caractéristiques cliniques de la MA. De plus, la méconnaissance du type d'activité cellulaire visualisée par l'examen TEP des patients de VIP pourrait compromettre l'interprétation des résultats du traitement. Je vais faire une brève disgression pour essayer de le montrer.

L'effet biologique du neflamapimod est connue pour être bénéfique dans la MA, comme cela a été décrit dans une section dédiée en introduction. Mais il n'est pas certain que l'on puisse observer ce bénéfice en imagerie de TSPO. La mesure du niveau de TSPO en TEP est probablement dissociée du processus biologique impacté par le neflamapimod. Il est donc possible de ne pas voir le bénéfice du traitement en imagerie de TSPO malgré un engagement thérapeutique efficient. Par exemple, si les patients de l'étude VIP dont la neuroinflammation en TEP est la plus forte ont aussi les meilleures capacités cognitives, on pourrait en conclure que la mesure de TSPO faite en TEP reflète une activité immunitaire neuroprotectrice. On pourrait alors s'attendre à ce que la prise du traitement n'ait pas d'effet visible en TEP puisque le neflamapimod inhibe une activité pro-inflammatoire neurotoxique. Dans ce cas, il pourrait peut-être y avoir un bénéfice clinique pour les patients traités qui soit indépendant de la mesure de TSPO en TEP. La réciproque est également possible. Si les patients de l'étude VIP dont la neuroinflammation en TEP est la plus forte ont aussi les capacités cognitives les plus basses, on pourrait conclure la mesure de TSPO faite en TEP reflète une activité immunitaire neurotoxique. On pourrait alors s'attendre à ce que la prise du traitement ait un effet visible sur la mesure du niveau de TSPO en TEP, tout en étant probablement associé à un bénéfice clinique. Dans ces exemples, c'est l'association des caractéristiques cliniques avec la mesure du niveau de TSPO en TEP qui permet de comprendre l'effet du traitement sur le résultat du TEP. A mon sens, il est donc possible que les résultats de VIP soient difficilement interprétables si cette association n'est pas établie au préalable.

Il était donc nécessaire de faire une étude pour élucider la relation entre l'imagerie de TSPO en TEP et les caractéristiques cliniques des patients de l'étude VIP. Cette étude serait préalable à celle de l'effet du neflamapimod. Il s'agirait d'une étude ancillaire transversale basée sur les données de la v0, avant la prise du traitement. Une telle étude permettrait d'apporter des connaissances supplémentaires sur les liens entre l'imagerie de TSPO en TEP et la cognition aux premiers stades de la MA. Elle permettrait aussi de mieux comprendre les résultats de l'effet du traitement pour l'étude VIP. Les principaux aspects méthodologiques de cette étude se rapportent donc aux mesures des caractéristiques cliniques et de l'imagerie de TSPO en TEP.

En ce qui concerne les caractéristiques cliniques, on observe souvent que le score MMS est la seule évaluation utilisée dans les études en imagerie TEP de TSPO (Bradburn et al., 2019). Cela pourrait poser problème aux premiers stades de la MA. Le score MMS est une mesure de l'efficience cognitive globale. La variabilité inter-individuelle des capacités cognitives est donc masquée par cette évaluation. De plus il est possible d'avoir un score non pathologique au MMS tout en ayant des déficits cognitifs focalisés si ces déficits influencent peu l'efficience cognitive globale. C'est justement le cas des premiers stades de la MA où les premiers déficits ne sont pas détectables par des évaluations standards, initialement (Weston et al., 2018). C'est aussi la conséquence des limites de précision, sensibilité et spécificité des évaluations standards en général.

Pour remédier aux limites d'emploi du MMS, les patients de l'étude VIP ont effectué une évaluation cognitive multi-domaine. Cette évaluation avait pour originalité d'inclure des tests de l'oubli accéléré à long-termes. Des études dans l'épilepsie du lobe temporal et la forme monogénique de MA ont montré que les déficits de mémoire à très long-termes précèdent ceux de la mémoire immédiate (Lemesle et al., 2021; Weston et al., 2018).

Dans VIP, les examens de la v0 et le bilan neuropsychologique étaient réalisés sur deux journées espacées d'une semaine. L'évaluation de l'oubli accéléré à long-termes était effectuée lors de la deuxième journée, c'est-à-dire sept jours après l'encodage.

Il a été décidé de procéder de deux formes d'évaluations différentes. La première consistait à un rappel des tests de rappel libre rappel indicé à 16 items (RLRI 16) et du DMS 48 ('delayed matching-to-sample' test, en anglais) dont l'encodage avait été fait sept jours plus tôt. La deuxième était une évaluation de la rétention de la première session du bilan neuropsychologique en tant que tel, c'est-à-dire évaluer le souvenir du patient d'un évènement partagé avec la psychologue spécialisée en neuropsychologie sept jours plus tôt (Lemesle et al., 2017).

Cette première session a été organisée pour que des évènements soient intercalés insidieusement au cours de la passation des tests, sans que le patient en soit informé. C'est la rétention de ces évènements qui serait évaluée. Il s'agissait d'une organisation minutieuse pour que la réalisation de la première session et son évaluation au cours de la deuxième session soient reproductibles. L'intérêt de cette procédure est qu'elle permettrait une évaluation de la mémoire autobiographique à un niveau de granularité plus fin que des évaluations standards (Lemesle et al., 2017). Une telle évaluation nécessiterait une recontextualisation du souvenir dans sa dimension spatiale, temporelle, et substantielle. Cette évaluation a été développée par Béatrice Lemesle,psychologue spécialisée en neuropsychologie, à partir de ses travaux précédant dans l'épilepsie du lobe temporal (Lemesle et al., 2021, 2017). Le lecteur pourra s'y référer pour plus de détails sur le rationnel sur lequel s'est construit ce test original. Ainsi l'exhaustivité et la précision de l'évaluation neuropsychologique de VIP permettrait de remédier aux limites sans doute induites par l'utilisation du MMS ou d'autres évaluations neuropsychologique classiques aux premiers stades de la MA.

L'autre aspect méthodologique de cette étude concerne le choix de méthode de quantification pour l'imagerie de TSPO. Ces méthodes ont été détaillées dans des articles de revue de Federico Turkheimer et ses collègues (Turkheimer et al., 2015; Wimberley et al., 2021). Le lecteur peut se référer à ces articles pour en avoir un tour d'horizon. La réflexion que nous avons eu est une adaptation de ces idées au contexte de VIP.

Les méthodes quantitatives standards en TEP dépendent de la réalisation de prélèvements artériels effectués au cours de l'examen. Ces prélèvements permettent d'établir la fraction du traceur susceptible de pénétrer le tissu cérébral par la mesure de la fraction du traceur non liée à des composants du plasma. Une mesure exacte de la concentration tissulaire du traceur fixé sur TSPO est ensuite déduite par l'utilisation de modèles de quantification cinétiques. Ces modèles diffèrent selon les hypothèses ou les connaissances dont on dispose sur le métabolisme cérébral du traceur à l'étude. Cependant, il y a plusieurs inconvénients à l'utilisation de ces prélèvements artériels dans le cas des traceurs de TSPO. La fraction plasmatique libre des traceurs de TSPO est très faible à cause d'une fixation importante sur les composants du sang, et pouvant être influencé par des changements immunitaires à la périphérie (Turkheimer et al., 2015). Cela peut intruidre une variabilité dans les estimations de la fraction plasmatique. De plus ces prélèvements sont invasifs et désagréables pour les patients, nécessite une méthode d'estimation fiable et réalisée par des experts tout en rajoutant des couts supplémentaires. C'est pour ces raisons que l'acquisition TEP pour VIP a été conçue en envisageant des méthodes de quantification non-invasives.

Les méthodes non-invasives consistent généralement à estimer la fixation d'une région d'intérêt par rapport à celle d'une région de référence. Une région de référence est définie par l'absence d'expression de la cible (TSPO), l'absence de changement d'expression de la cible en condition pathologique, et une proportion équivalente d'activité non-spécifique ('non-displaceable binding', en anglais). Cela est problématique car ça n'est entièrement le cas pour aucune région cérébrale. En effet, l'expression de TSPO est ubiquitaire et aucune région n'est dépourvue de son expression (Nutma et al., 2021). Cela est également problématique car la neuroinflammation est un processus biologique susceptible à tout type de changement pathologique, et ne peut donc pas être prédit systématiquement avec certitude, comme s'il s'agissait d'un processus ayant un pattern spatial stéréotypé, par exemple comme c'est le cas pour les pathologies amyloïde et tau. Pour ces raisons, il est mention de région de 'pseudo-référence'. Dans cette thèse, la mention de région de référence sera utilisée par simplicité.

La mesure d'un ratio simple de la fixation du traceur relative à celle d'une région de référence a plusieurs intérêts en imagerie TEP de TSPO. Cette mesure peut se baser sur la conversion de l'activité radioactive mesurée lors de l'acquisition TEP en une valeur standard ('standard uptake value', ou SUV en anglais). Cette conversion permet la prise en compte du poids et de la dose de traceur injectée. Il s'agit alors d'une estimation semi-quantitative dans le sens où la fixation n'est pas mesurée de façon exacte mais proportionnelle à celle de la région de référence (SUV ratio en anglais, ou SUVR). La MA est connue pour être associée à des changement de perfusion cérébrale, ou à des changements pathologiques sanguins à la périphérie (Bettcher et al., 2021; Kisler et al., 2017). L'influence de ces changements est moindre dans l'utilisation la SUVR que les méthodes de quantifications exactes. De plus l'utilisation de la SUVR permet une réduction de l'influence de la présence de métabolites, ainsi que de l'influence de la variabilité causée par les changements diurnes du niveau de TSPO, et par le phénotype d'affinité de TSPO entre des sujets de phénotypes d'affinité différents.

Néanmoins, l'utilisation de la SUVR requiert le choix d'un intervalle de temps approprié pour la mesurer. Il est nécessaire qu'il y ait une stabilité de la SUVR sur l'intervalle de temps choisi. Si ça n'est pas le cas, la SUVR montrera vraisemblablement un processus pharmacocinétique comme l'absorption tissulaire du traceur, ou bien sa clairance par exemple. Si la fixation du traceur est à l'équilibre, la SUVR montrera vraisemblablement le processus biologique étudié, c'est-à-dire dans le contexte de cette étude, la fixation du DPA sur TSPO au cours de la neuroinflammation.

Michel Bottlaender et ses collègues montrèrent plus tard que la phase d'équilibre du DPA était situé entre 60 et 90 minutes après l'injection chez le sujet sain et que cet interval pouvait être exploité dans une analyse de SUVR chez les patients ayant une MA (Hamelin et al., 2016; Lavisse et al., 2015). Cependant, pour l'étude VIP, nous avons opté de faire une acquisition continue de 60 minutes après l'injection du DPA sans prélèvements artériels. Au moment de la conception de VIP, il était nécessaire de procéder à une acquisition dynamique pour explorer la cinétique du DPA et les différentes manières de procéder à sa quantification. Le choix d'arrêter l'acquisition à 60 minutes permettait de limiter la durée d'examen. Ces modalités d'acquisition permettent donc un compromis entre le confort des patients, et l'intérêt scientifique de ces explorations.

Note : *Cet article a fait l'objet d'une soumission à une revue internationale. Il a été choisi de l'insérer dans le texte dans son format de soumission.*

2.2.4.2. **Etude 1 de VIP**

Clinical and neuropsychological variability of neuro-inflammatory PET profiles in early Alzheimer's disease

Dominique Gouilly[1], Anne-Sophie Salabert[1, 2], Elsa Bertrand[3], Marie Goubeaud[3], Hélène Catala[3], Johanne Germain[3], Nadéra Ainaoui[3], Marie Rafiq[1, 4], Marie Benaiteau[4], Jasmine Carlier[4], Leonor Nogueira[5], Mélanie Planton[4], Anne Hitzel[2], Déborah Méligne[1], Benjamine Sarton[1, 6], Stein Silva[1, 6], Béatrice Lemesle[4], Pierre Payoux[1, 2], Claire Thalamas[3], Patrice Péran*[1] and Jérémie Pariente*[1, 3, 4].

1. Toulouse Neuroimaging Center, UMR 1214, Inserm/UPS, Toulouse, France.

2. Department of Nuclear Medicine, CHU Toulouse Purpan, Toulouse, France.

3. Center of Clinical Investigation, CHU Toulouse Purpan (CIC 1436), Toulouse, France.

4. Department of Cognitive Neurology, Epilepsy and Movement Disorders, CHU Toulouse Purpan, Toulouse, France.

5. Laboratory of Cell Biology and Cytology, CHU Toulouse Purpan, Toulouse, France.

6. Critical Care Unit, CHU Toulouse Purpan, Toulouse, France.

Note : *Les figures et tableaux supplémentaires de cet article ainsi que le glossaire ont été placés à la suite du texte.*

Abstract

Objective: To elucidate the relationship between neuroinflammation and neuropsychological measurements in the first stages of Alzheimer's disease (AD).

Methods: Patients with clinical and biological evidence of early AD were recruited. PET imaging of the translocator protein (TSPO) was used as proxy for brain neuroinflammation. We performed a standard uptake value ratio (SUVR) analysis using the cerebellar cortex or the whole brain as a (pseudo)reference region. In addition, we performed a comprehensive neuropsychological evaluation including an assessment of accelerated long-term forgetting. An analysis of the correlation was used between neuropsychological measurements and voxel-wise, regional, and whole brain SUVR values, adjusted for age and affinity phenotype of TSPO.

Results: AD patients (n=33) had a higher regional uptake than healthy age-unmatched individuals (n=16). High inter-individual heterogeneity of the intensity of neuroinflammation was observed, while the inter-regional variance depended on the reference region. No significant correlation was observed between neuropsychological performance and SUVR values among AD patients. Some patients with similar PET inflammatory profiles had opposite neuropsychological presentations, while some patients with an opposite neuropsychological presentation exhibited similar PET inflammatory profiles.

Conclusion: Neuroinflammation PET profiles highly differ among patients with early AD. Further studies are needed to understand how this individual variability impacts the course of AD.

1. Introduction

Neuroinflammation influences the course of Alzheimer's disease (AD)[1]. Most PET imaging studies of the translocator protein (TSPO) have been consistent with the notion of a transient neuroprotective immune response at the early stages of the disease[2–4]. However, the relationship between cognitive performances and TSPO PET imaging remains controversial. Cross-sectional studies have shown positive[3], negative[5] and no correlation[4,6] in AD patients with mild cognitive impairment (MCI). Longitudinal studies have shown that an increased in neuroinflammation at baseline is associated with either a better[3] or worse[7] cognitive prognosis.

One explanation for these contradictory findings could be that variability in neuroinflammation is inherent to the early stages of AD. In fact, it has been shown that distinct neuroinflammatory profiles are associated with differences in AD progression depending on the patient rather than the disease stage[8]. The inter-individual variability of neuroinflammation might reflect distinct dynamic pathophysiological mechanisms related to AD and individual vulnerability to neuroinflammation.

Another explanation could be related to methodological concerns. The low magnitude of cognitive deficits in early AD might preclude the observation of a consistent correlation with neuroinflammation on PET. Most TSPO PET studies have used the mini-mental state examination (MMS) as proxy for cognitive staging[5]. However, the use of tests that assess a finer granularity of neuropsychological impairment could be more appropriate in the early stages of AD.

Furthermore, quantification of TSPO PET imaging is challenging because of the biology of TSPO[9]. Simple ratio methods such as the standard uptake value ratio (SUVR) have been shown to be of interest in AD[2,3,8]. However, debates on the most appropriate choice of reference region are ongoing, especially because there is no brain region deprived of TSPO expression[9]. It would be useful to assess whether the choice of reference region impact the correlation with cognition in early AD.

To elucidate these issues, we performed a cross-sectional study using TSPO PET imaging as proxy of neuroinflammation in early AD.

2. Method

2.1. Standard Protocol Approvals, Registrations, and Patient Consents

This study was ancillary to a phase II trial (NCT03435861) on the effect of a non-steroidal anti-inflammatory drug (neflamapimod, EIP Pharma, Boston, MA, USA) in early AD. This trial was approved by the French Ethics Comity "Comité de Protection des Personnes Sud-Est 1" (reference number: 2017-78), and by the French Drug Safety and Health Products Agency (reference number: MEDAECNAT-2018-01-0034). Only pre-treatment data were analyzed in this study.

We also recruited healthy individuals (HIs) as controls for the neuroimaging assessments. These subjects were enrolled in a study at the Toulouse University Hospital (France) related to brain network disruption in coma (NCT03482115), which was approved by the French Ethics Comity "Comité de Protection des Personnes Sud Méditerranée 5" (reference number: 17-032), and by the French Drug Safety and Health Products Agency (reference number: MEDSANAT-2018-07-00110).

All the participants were willing and able to give their informed consent.

2.2. Participants

Patients were recruited at the Neurology Department Memory Clinic of the Toulouse University Hospital (France). The inclusion criteria were age ranging from 50-90 years, amnestic MCI with MMS>20/30, and CSF biomarker evidence of AD[10]. The exclusion criteria were: (1) evidence of significant co-pathology including another neurodegenerative disease, psychiatric disorder or an inflammatory condition, (2) ongoing anti-inflammatory treatment or recent (<30 days) medication changes with a potential to impact cognition, (3) a recent (<6 months) history of alcohol or illicit drug abuse, (4) the inability (for any reason) to undergo MRI, PET scan, or lumbar puncture.

The HIs were age-unmatched and ages ranged from 18 to 75 years. The exclusion criteria were threefold: (1) evidence of any neurological or psychiatric disorders, or any inflammatory condition, (2) ongoing anti-inflammatory treatment, (3) the inability (for any reason) to undergo MRI or PET scan.

2.3. Neurological and neuropsychological assessments

AD patients underwent a neurological examination and a comprehensive neuropsychological battery of tests on two days within a week of each other (mean= 7 days ±3). Cognitive functions were assessed using the MMS; the free and cued selective reminding test (FCSRT); the delayed-to-matching sample 48 (DMS48) test; the Rey-Osterrieth Complex figure (ROCF) test; forward and backward digit span from the Wechsler Adult Intelligence Scale fourth edition (WAIS IV); the frontal assessment battery (FAB); the trail making test A and B (TMT); the Go/No Go test; the phasic alertness test from the Test of Attentional Performance battery; a measurement of reaction time in neutral condition from the phasic alertness test was used as an assessment of processing speed; the codes from the WAIS IV; two minutes phonemic (p) and categorical (animal) verbal fluency; a test of denomination from the French GREMOTS battery; a test of identical figures identification for gnosis from the French PEGV battery; and the Mahieux's battery of gestural praxis. In addition, behavioral assessment included the State-Trait Anxiety Inventory scale (Stai-y) and the Beck's depression inventory. All these tests and the assessment techniques we used are detailed elsewhere[11].

Furthermore, it was shown that accelerated long-term forgetting pre-dated the objective multi-domain memory impairment of patients with temporal lobe epilepsy or autosomal dominant AD[12,13]. Our team has developed sensitive long-term memory assessment for patients with a subjective memory complaint and temporal lobe epilepsy[12,14]. In one previous study, these patients were tested with recall at three weeks of the FCSRT and a new test called Epireal designed to assess anterograde autobiographical memory[12]. Here, we adapted Epireal to 'Mareal' as a new test of autobiographic memory in AD (Supplementary Figure 1). The structure of Mareal is composed of height mini-events that are incidentally interleaved during the first session of the neuropsychological assessment. Each participant was asked to recall the memory of these mini-events one week later (details on Mareal scoring are shown in Supplementary Table 1). In addition, we performed a 7-day delayed recall of the FCSRT.

For one patient, the second part of the neuropsychological assessment was performed three weeks after the first session because of COVID-19 infection was suspected. For this patient, the accelerated long-term forgetting assessment was performed on day 7 by videoconference. Furthermore, because of cognitive impairment, fatigue, or technical issues, a few patients did not perform one of the neuropsychological tests. This included one patient for the FCSRT immediate and 20-minutes recall, three for the ROCF, one for the gnosis test, two for the Go/No Go test, nine for the TMT, three for the WAIS IV codes, and one for the denomination test. When these tests were used in statistical analyses, the values for these patients were not considered.

2.4. Lumbar puncture

CSF samples were collected as previously described[15]. AD biomarker values were measured using either ELISA (INNOTEST) or the Lumipulse G1200 system (Fujeribo, Ghent, Belgium) according to the manufacturer's procedures. For the samples quantified by ELISA, abnormal values were defined as amyloid-β 42 ($A\beta_{42}$) <500 pg/mL or $A\beta_{42/40}$ ratio <0.05, phosphorylated-tau >60 pg/mL, total-tau >450 pg/mL, according to the cutoff values recommended by the manufacturer, internal data and in the literature[15,16]. For the sample quantified with the Lumipulse, abnormal values were defined as $A\beta_{42}$ <600 pg/mL, or $A\beta_{42/40}$ ratio <0.07, phosphorylated-tau >60 pg/mL, total-tau >450 pg/mL, according to the cutoff values recommended by the manufacturer, and internal data.

2.5. APOE and TSPO genotype

Blood samples were drawn to characterize APOE and TSPO genotypes. Based on the rs6971 polymorphism within the TSPO gene, all subjects were classified as high (HAB), mixed (MAB) or low affinity binders (LAB). The LAB patients were excluded from further analyses.

2.6. Neuroimaging acquisition

2.6.1. Magnetic resonance imaging

For each subject, an encephalic MRI acquisition was performed on a 3T MRI scanner (Philips Achieva dStream, 32-channel head coil) at the INSERM/UPS Tonic technical platform. A 3D-T1-weighted, a fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI) were acquired.

For a descriptive analysis, white matter hyperintensities (WMH) were visually assessed on axial FLAIR images by a trained rater (MP) on the 9-point Fazekas' rating scale[17]. In addition, the SWI images were reviewed by the same rater to assess the presence of strictly lobar or deep cerebral microbleeds and the presence of focal or disseminated cortical superficial siderosis. Patients were classified as having possible or probable cerebral amyloid angiopathy (CAA) according to the modified Boston criteria[18]. The patients with both lobar and infra-tentorial or deep microbleeds were classified as having mixed angiopathy. The patients with no microbleeds were classified as having 'absent' cerebrovascular co-pathology. One patient had one infra-tentorial microbleed and was classified as having 'absent' cerebrovascular co-pathology for compliancy. In addition, two patients had severe artefacts on their SWI images and could not be classified.

2.6.2. TSPO PET imaging

For each subject, an encephalic PET scanner was performed on a hybrid PET/CT tomograph (Siemens Biograph TruePoint 6.0) within a week of the MRI scan (mean= 8 days ±5) except for one patient for whom the second examination was performed three weeks later because COVID-19 infection was suspected. The CT scan was performed to correct for tissue attenuation before intravenous injection of [^{18}F]-DPA-714. The PET examination was acquired in list mode over 60 minutes following intravenous injection (3.5MBq/kg; AD patients: mean= 241MBq ±46; HIs: 233 ±57). All corrections (attenuation, radioactive decay, random, scatter coincidences, and a partial volume correction) were incorporated in an iterative OSEM reconstruction using 3 iterations and 21 subsets. The dynamic data were reconstructed into 32 time-frames (6x10s; 8x30s; 5x1min; 5x2min; 8x5min).

2.7. Neuroimaging analysis

2.7.1. SUVR analysis of TSPO PET imaging

The use of the SUVR method is non-invasive and more comfortable for the participants than a method requiring arterial sampling, and seems to increase quantification sensitivity compared to full kinetic modelling, and have a high test retest reliability for TSPO PET imaging in AD[3,9,19,20]. In this study, we performed a 50-60-minute SUVR analysis. The time stability analysis of this interval is shown in Supplementary Figure 2. However, TSPO is expressed in all brain regions, and the absence of neuroinflammation from the reference region cannot be predicted with certitude. Although the cerebellar cortex was already used as a (pseudo)reference region in early AD[3,8], significant uptake was already observed in the cerebellum[5]. Therefore, in addition to an initial analysis using the cerebellar cortex as a (pseudo)reference, we also used the whole brain (WB) as a second (pseudo)reference region in all analyses.

2.7.1.1. Regional analysis

Denoised and inhomogeneity bias corrected T1-weighted MRI scans were segmented and spatially normalized (Geodesic Shooting registration) on the standard Montreal Neurological Institute space using the CAT12 toolbox[21] on SPM12 implemented on MATLAB (v2019b.; Mathworks.inc). Smoothing was applied using a Gaussian filter with 8mm full-width at half-maximum.

Reconstructed PET images were realigned and corrected for subject motion using an averaged image as reference. Mean SUV parametric images were calculated on the 50-60-minute interval post injection using the subject's weight and [^{18}F]-DPA-714 injected dose. CT scans were co-registered on the T1-weighted MRI images. The transformation thereby derived was applied to the SUV PET images to co-register them on the corresponding T1-weighted images. This allowed to use the signal of the skull on the CT and MRI scans to perform a more accurate co-registration of the PET images. All the co-registrations were performed using a normalized mutual information algorithm. A binary inclusive mask of pooled gray and white matter segment at $p>0.5$ was applied as an atrophy correction.

The automated anatomical labeling (AAL3) atlas[22] was deformed to each subject's MRI native space with the inverse deformation field used for T1-weighted image spatial normalization on CAT12. Mean SUV values were then extracted on the following bilateral ROIs using the PETPVE12 toolbox on SPM12[23]: frontal, orbitofrontal, temporal, parietal, precuneus, occipital, anterior cingulate, medium cingulate, posterior cingulate, thalamus, insula, pallidum, striatum, and cerebellar cortex. The WB was defined as the entire remaining regions after atrophy correction. In addition, we defined a temporal meta-ROI including the bilateral hippocampus, parahippocampal cortex, amygdala, and the fusiform gyrus. Finally, we calculated the SUVR using the mean SUV from the cerebellar cortex or WB as a (pseudo)reference.

2.7.1.2. Voxel-wise analysis

SUV PET images co-registered on T1-weighted MRI scans were spatially normalized with the deformation field used for spatial normalization of T1-weighted images on CAT12. An inclusive binary brain mask of pooled gray and white matter was applied on spatially normalized images. Voxel-wise calculation of the SUVR was performed using the mean SUV of the cerebellar cortex or the WB. Smoothing was applied using a Gaussian filter with 6mm full-width at half-maximum.

AD patients and HIs were compared using an unpaired two-sample t-test, adjusted for TSPO genotype and age. Multiple linear regressions were performed with the following neuropsychological measurements: the total score on the MMS; Mareal, 7-day free and total recall scores; FCSRT, 7-day free and total recall scores, 20-minutes total recall and immediate total recall scores; DMS48, one-hour delayed recall score; ROCF, 5-minutes delayed recall score; forward and backward digit span; the total score on the FAB battery; the Go/No Go test, median reaction time; scores on categorical (animal) and phonemic (p) verbal fluency; phasic alertness index from the phasic alertness test; and the mean reaction time in neutral condition from the phasic alertness test as a processing speed assessment. All regressions were adjusted for age and TSPO genotype, and significance was set at $p<0.05$, family-wise error (FWE) corrected, using a threshold k of 20 minimum-activated voxels.

For Go/No Go, processing speed and phasic alertness tests, we used the number of incorrect responses as an additional covariate. In all voxel-wise analyses, when no results were observed at $p<0.05$, FWE corrected, significance was set at $p<0.001$, FWE uncorrected, and $k=20$.

2.8. Statistical analysis

Univariate non-parametric tests were used for comparisons. The Mann-Whitney, Chi2 or Fisher's test were used when appropriate. We performed linear regressions of the regional SUVR for neuropsychological measurements, adjusted for TSPO genotype and age. We used the same neuropsychological measurements mentioned above, with the SUVR of functionally related regions for these measurements. This included the WB, temporal, temporal meta-ROI, and frontal regions. For Go/No Go, processing speed and phasic alertness tests, we added the number of incorrect responses as an additional covariate. In addition, A Spearman's correlation matrix was constructed using the regional SUVR. In all analyses, significance was set at $p<0.05$, two-tailed, with Holm's correction for multiple testing when appropriate. All analyses were performed on R software (v1.4.).

3. Results

3.1. Inclusion summary

We recruited 34 patients 33 of whom were clinically-diagnosed with MCI due to AD. One patient had normal $A\beta_{42}$ and $A\beta_{42/40}$ ratio values and was therefore excluded from further analyses (table 1). The neuropsychological results are indicated in table 2. In addition, we recruited 19 HIs. Two had aberrant [^{18}F]-DPA-714 PET imaging on the visual reading (Supplementary Figure 3). The regional SUVR values of these subjects were higher than for all the AD patients when the cerebellar cortex was used as a reference (data not shown). We found no explanatory medical information for these results. Therefore, these subjects were excluded from further analyses. Compared to AD patients, the remaining HIs were unmatched for age (AD patients: mean= 68±7.5; min=53; max=82; HIs: mean=40±19.2; min=20; max=75; $p<0.01$) but were matched for gender ($p>0.05$). Regarding TSPO genotype analysis, we obtained four LAB AD patients and one LAB HI who were excluded from further analyses. The proportion of HAB/MAB was equivalent between AD (48%/39%) patients and HIs (47%/47%).

Table 1: Demographics of clinically diagnosed AD patients.

Demographics	AD patients n = 33
Age, mean (standard-deviation)	68 (7.5)
Gender, female, n (%)	15 (45%)
TSPO genotype, n (%)	16 HAB (48%) 13 MAB (39%) 4 LAB (12%)
Education, years, mean (standard-deviation)	13.4 (3)
Familial history of AD, n (%)	17 (52%)
Anti-AD treatment, n (%)	18 None (55%) 1 Donepezil (3%) 1 Memantine (3%) 13 Rivastigmine (39%)
Time from diagnosis (months), median [IQR]	9 [2-16]
APOE, n (%)	2 E2/E4 (6%) 11 E3/E3 (33%) 15 E3/E4 (45%) 5 E4/E4 (15%)
Cerebrovascular co-pathology, n (%)	19 Absent (58%) 3 Possible CAA (9%) 5 Probable CAA (15%) 5 Mixed angiopathy (15%)
Fazekas' WMH score (/9), median [IQR]	5 [3-7]

The presence of cerebrovascular co-pathology was described after reviewing patients' SWI MRI sequence. Diagnosis for CAA was based on consensus diagnostic criteria[18]. The presence of WMH was visually assessed on axial FLAIR images on the 9-point Fazekas' rating scale[17].

Abreviations: APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery; HAB, high affinity binder; IQR, inter-quantile range; LAB, low affinity binder; MAB, mixed affinity binder; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging; TSPO, translocator protein; WMH, white matter hypersensitivity.

Table 2: Neuropsychological profiles of clinically diagnosed AD patients.

Clinical and neuropsychological assessments, mean (SD)	**AD patients** n = 33
MMS score (/30)	24.3 (3.1)
Long-term forgetting	
Mareal, 7-day free recall (/39)	3.7 (2.7)
Mareal, 7-day total recall (/39)	15.3 (5.4)
FCSRT, 7-day free recall (/16)	1.7 (2.8)
FCSRT, 7-day total recall (/16)	6.5 (5)
Anterograde episodic memory	
FCSRT, 20-minute delayed recall (/16)	10.7 (4.4)
FCSRT, immediate total recall (/48)	33.1 (11.8)
DMS48, one-hour delayed recall (/48)	42.7 (5.2)
ROCF, 5-minutes delayed recall (/36)	7.5 (5.7)
Working memory	
Forward digit span	5.5 (1.3)
Backward digit span	3.8 (1)
Executive functioning	
FAB (/18)	14.1 (2.2)
Phonemic (p) verbal fluency, initiation	20.8 (7.7)
Categorial (animal) verbal fluency, initiation	17.2 (8.3)
TMT B – A, time (s), flexibility	121 (93.4)
Go/No Go, median reaction time (ms) [mean number of false responses], inhibition	467 (84) [3.1]
Attention and processing speed	
TMT A, time (s)	67.5 (38.7)
The codes, WAIS IV (/53)	36.9 (17.8)
Processing speed, reaction time (ms) [mean number of false responses]	371 (132) [2.1]
Phasic alertness, reaction time index [mean number of false responses]	-0.04 (0.15) [8.5]
Instrumental	
Language - Denomination (/36)	31 (6.5)
Gnosis – Test of identical figures (/10)	8.8 (1.9)
Praxis - Gestural praxis (/23)	20.5 (2.7)
Behavioral assessment	
Stai-Y anxiety scale (/80)	43.7 (9.3)
Beck's depression inventory (/39)	4 (2.2)

Mareal is a new test designed to assess anterograde autobiographical memory (details are shown in Supplementary Figure 1) adapted from an assessment of accelerated long-term forgetting in temporal lobe epilepsy[12]. Values are presented as the mean (SD). The number of false responses was indicated for the Go/No Go, processing speed and phasic alertness testing.

DMS48, delayed matching-to-sample 48; FAB, frontal assessment battery; FCSRT, free and cued selective reminding test; MMS, Mini-mental state examination; ROCF, Rey-Osterrieth Complex figure; SD, standard-deviation; Stai-y, State-Trait Anxiety Inventory scale; TMT, trail making test, WAIS IV, Wechsler Adult Intelligence Scale fourth edition.

3.2. [^{18}F]-DPA-714 uptake

In voxel-wise analysis, we observed significant differences between AD patients and HIs widely distributed across several brain regions, using both the cerebellar cortex and the WB as a reference ($p<0.001$; uncorrected; Supplementary Figure 4). With FWE correction, no significant difference was observed between AD patients and HIs, using the cerebellar cortex or WB as a reference ($p<0.05$; corrected).

In the regional analysis, we first compared AD patients to HIs irrespectively of the TSPO genotype. When the cerebellar cortex was used as a reference, we observed a higher uptake in the frontal, orbitofrontal, temporal, temporal meta-ROI, parietal, precuneus and occipital regions for AD patients ($p<0.05$; corrected; figure 1A). When the WB was used as a reference, we found fewer regional differences in the frontal, and temporal regions in favor of AD patients ($p<0.05$; corrected; figure 1B). In addition, we observed a lower uptake in the striatum of AD patients using the WB as a reference ($p<0.01$; corrected).

We then compared HAB AD patients to HAB HIs. We observed a higher uptake in the temporal cortex of HAB patients using the cerebellar cortex or the WB as a reference ($p<0.05$; corrected). When the cerebellar cortex was used as a reference to compare MAB AD patients to MAB HIs, we observed a higher uptake in the WB, the frontal, orbitofrontal, temporal, temporal meta-ROI, precuneus and anterior cingulate regions of MAB patients ($p<0.05$; corrected). When the WB was used as a reference, we found fewer regional differences, with a higher uptake in the frontal and temporal regions of MAB patients, and a lower uptake in the cerebellar cortex ($p<0.05$; corrected).

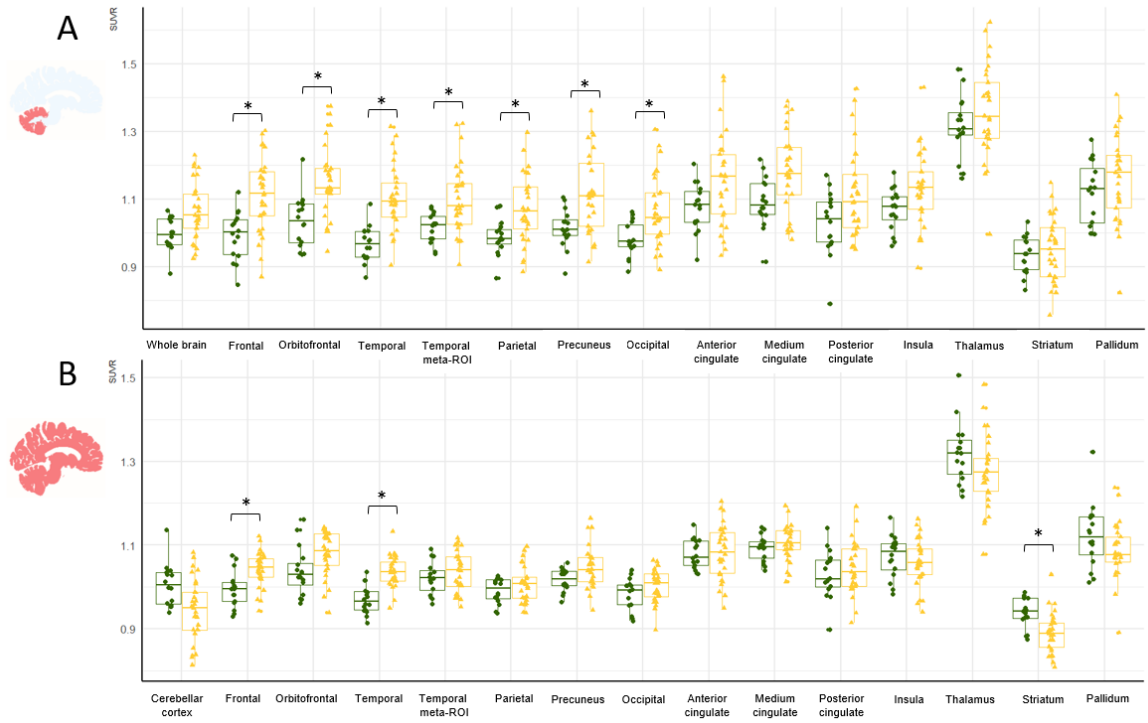


Figure 1: Regional SUVR among AD patients and HIs.

Figures 1A and 1B represent SUVR values using the cerebellar cortex or the whole brain as a reference, for each respective group. Regional SUVR of AD patients (in yellow triangles) was compared to HIs (in green circles) using the Mann-Whitney test, with significance set at 0.05, with Holm's correction for multiple comparisons, two-tailed.

*: $p<0.05$

Abreviations: HIs, healthy individuals; ROI, region of interest; SUVR, standard uptake value ratio.

3.3. Correlations with neuropsychological scores

3.3.1. Voxel-wise analysis

We performed voxel-wise linear regression of the SUVR and several neuropsychological measurements as detailed above. No significant results were found with correction for multiple comparisons (FWE) using either the cerebellar cortex or the WB as a reference (adjusted for TSPO genotype and age). With a more permissive statistical threshold, we observed several positive and negative correlations ($p<0.001$; uncorrected; adjusted for TSPO genotype and age; Supplementary Table 2). Both positive and negative correlations were frequently observed for the same test.

3.3.2. Regional analysis

We performed the same regression analysis using the regional SUVR. No significant results corrected for multiple comparison were found using either the cerebellar cortex or WB as a reference (adjusted for TSPO genotype and age; figure 2). With a more permissive threshold and using the WB as a reference, we observed three negative correlations of the temporal meta-ROI SUVR with the FCSRT total recall ($p=0.04$; uncorrected; T value= -2.1; β= -0.002; 95%-CI= [-0.003 - -0.0001]; adjusted R^2=29%); FCSRT 7-day total recall ($p=0.01$; uncorrected; T value= -2.7; β= -0.004; 95%-CI= [-0.007 - -0.001]; adjusted R^2=38%); and the FCSRT 20-minutes total recall ($p<0.01$; uncorrected; T value= -3; β= -0.005; 95%-CI= [-0.009 - -0.002]; adjusted R^2=38%).

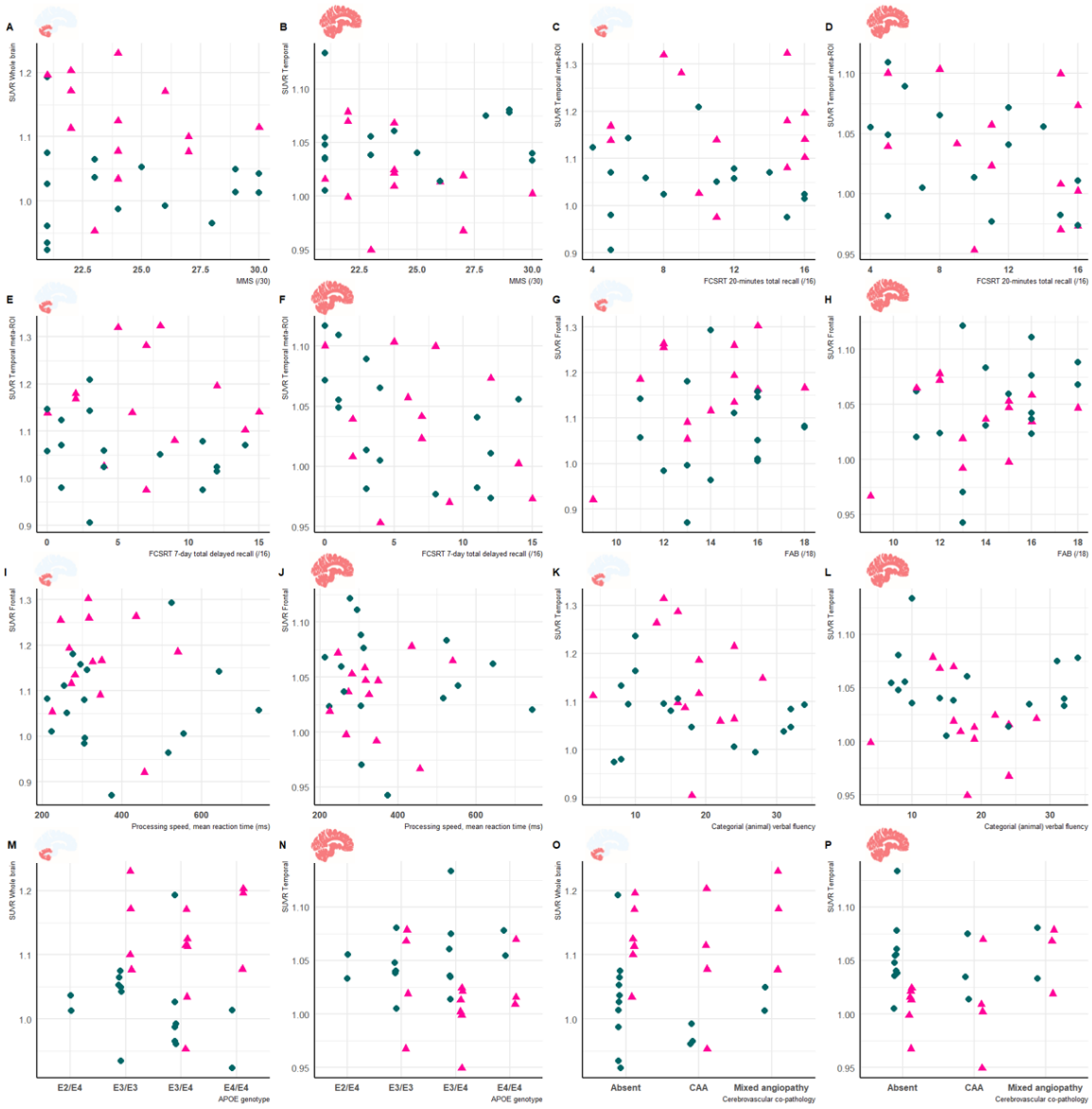


Figure 2: Clinical and neuropsychological variability of neuroinflammatory PET profiles in early AD.

HAB are represented in green circles, and MAB in pink triangles. None of these correlations were significant using linear regression model analyses adjusted for TSPO genotype and age, significance set at $p<0.05$, with Holm's correction for multiple correlations. The presence and type of cerebrovascular co-pathology was described after reviewing patients' SWI MRI sequence. A diagnosis of CAA was based on consensus diagnostic criteria[18]. Patients with both lobar and deep microbleeds were classified as having mixed angiopathy. Collectively, these figures show that neuroinflammation does not appear to be related to neuropsychological performances, cerebrovascular co-pathology, or APOE genotype in our cohort of patients with early AD.

3.4. [^{18}F]-DPA-714 uptake heterogeneity

Strong inter-individual differences of [^{18}F]-DPA-714 PET images were observed on visual reading. This heterogeneity appeared to be lower among HIs than AD patients (Supplementary Figure 5). As was the case with the correlation analyses, the observed neuroinflammatory PET profiles appeared not to be predictable of patients' clinical profiles, and vice versa (table 3). For example, two patients with a similar clinical presentation could have opposite neuroinflammatory PET profiles. Similarly, two patients with opposite clinical presentations could have similar neuroinflammatory PET profiles.

To understand the absence of correlation between [^{18}F]-DPA-714 SUVR and neuropsychological measurements, we performed a topographical analysis of [^{18}F]-DPA-714 uptake. We observed a strong positive uniform co-variance of [^{18}F]-DPA-714 SUVR values between all regions using the cerebellar cortex but not with the WB as a reference (figure 3A and 3B). In addition, we constructed a matrix of regional z-values using the HIs as controls (HAB and MAB together). We observed a strong regional heterogeneity both at the inter and the intra-individual level, especially when using the WB as a reference (figure 3C and 3D). The highest uptake was observed in the fronto-temporal regions, whereas the lowest uptake was observed in the striatum and pallidum. Collectively, these results show that [^{18}F]-DPA-714 uptake is not uniform in terms of regional intensity, while uniformity in terms of regional co-variance depends on the reference region.

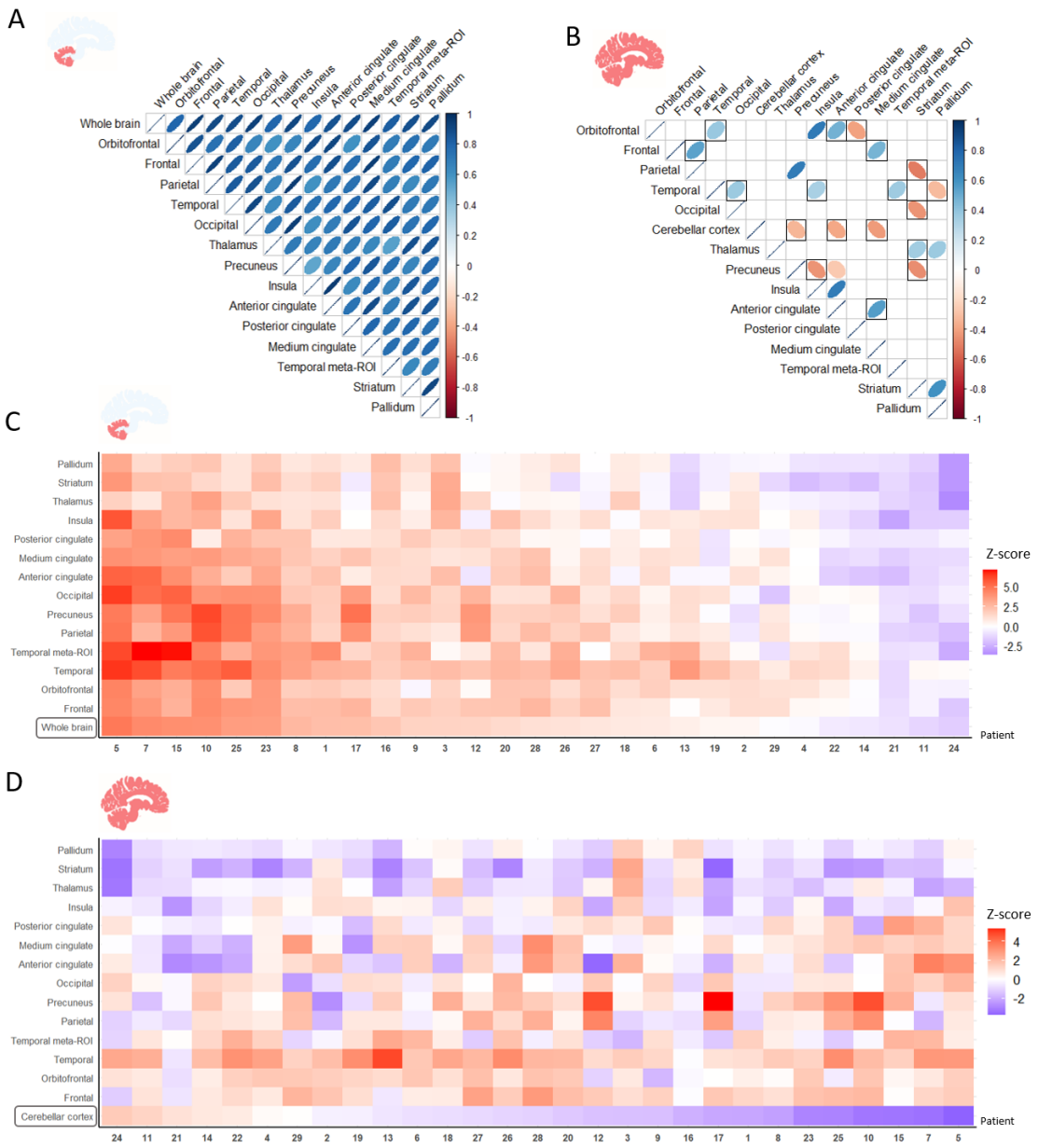
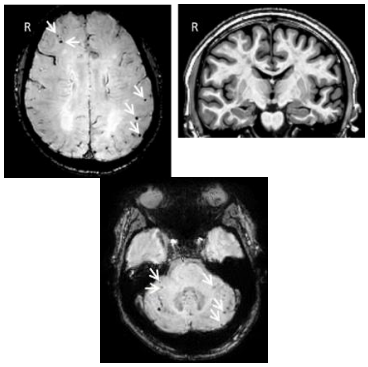
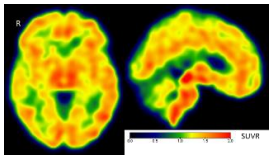
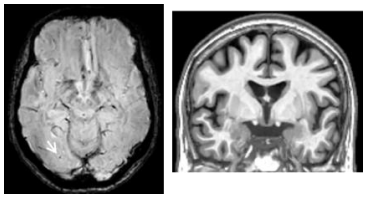
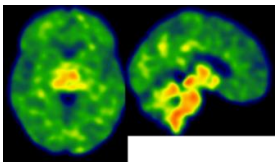
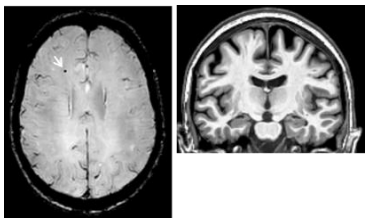
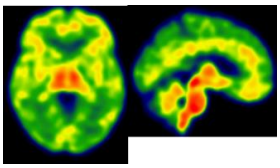
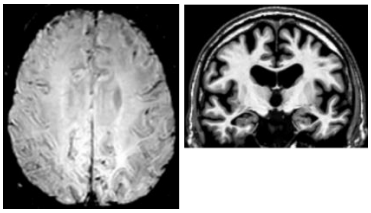
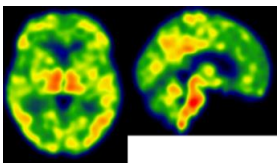


Figure 3: Topographical analysis of TSPO PET of neuroinflammation in early AD.

Figures 3A and 3B plot the correlation between regionally different SUVR using the cerebellar cortex or the whole brain as a reference, respectively. The Spearman's coefficient value is indicated in the legend and is represented by the width and orientation of the ellipse. The correlations that were not significant after applying Holm's correction for multiple correlation are encircled and non-significant correlations ($p>0.05$) are not presented. Figures 4C and 4D show the z-value matrix of regional SUVR of AD patients compared to HIs using the cerebellar cortex or the whole brain as a reference, respectively. Patients are classified according to the z-values in the reference region.

Table 3: Inter-individual variability of clinical and neuroinflammatory profiles in early AD.

Clinical findings	CSF & APOE	SWI & T1-weighted MRI scans	TSPO PET imaging (SUVR relative to the cerebellar cortex)	Proposition of ongoing neuroinflammatory processes
Case 5: a 64 y.o. man who was referred for a memory complaint. His medical history included traumatic brain injury, and headache. At screening, he had 24/30 MMSE, and impairment on episodic memory, denomination and categorical verbal fluency tests. On MRI, multiple lobar microbleeds without hemisiderosis were observed, as well as WMH (Fazekas's score of 8/9), and moderate cortical atrophy. In particular, multiple microbleeds were observed in the cerebellar cortex although this patient exhibited the lowest uptake in this region when the WB was used as a reference.	$A\beta_{42}$: 208 P-tau: 184 T-tau: 1449 APOE E3/E3			Toxic neuroinflammation associated with mixed angiopathy and AD pathological progression.
Case 21: a 59 y.o. woman with early onset symptoms and familial history of AD. Her medical history included psoriasis. At screening, she had 23/30 MMSE, and impairment on episodic memory, executive functions, processing speed, and categorical verbal fluency tests. Three lobar microbleeds, WMH (Fazekas's score of 3/9), and moderate cortical atrophy were observed on MRI. This patient exhibited the highest uptake in the cerebellar cortex when the WB was used as a reference.	$A\beta_{42}$: 462 P-tau: 140 T-tau: 768 APOE E3/E4			Low neuroinflammation associated with failure of CAA and AD pathological lesion clearance.
Case 2: a 66 y.o. woman with familial history of AD who was referred for a memory complaint. Her medical history included psoriasis. At screening, she reported an improvement in her memory abilities. She had 30/30 MMSE, preserved memory, executive functions, and processing speed but encoding impairment in visual recognition memory, and decreased scores on long-term forgetting tests. Two lobar and one deep microbleeds without hemosiderosis, WMH (Fazekas's score of 5/9), and moderate cortical atrophy were observed on MRI. A three-year follow-up failed to show a significant decline in cognition.	$A\beta_{42}$: 327 P-tau: 79 T-tau: 479 APOE E2/E4			Protective neuroinflammation that might be compensatory to the amyloid load in the frontal and cingulate regions in the absence of spread tau pathology and neurodegeneration.
Case 12: a 64 y.o. man with early onset atypical AD in a posterior cortical atrophy variant. He presented a familial history of AD but no significant personal medical history. At screening, he had 21/30 MMS, multi-domain cognitive impairment, and in particular constructive apraxia, visual apperceptive agnosia. WMH (Fazekas's score of 5/9) and cortical atrophy were observed on MRI.	$A\beta_{42}$: 481 P-tau: 103 T-tau: 669 APOE E3/E3			Toxic neuroinflammation associated with AD pathological progression, especially in posterior cortical regions.

All fourth patients are right-handed. TSPO PET imaging are represented in standard space in the same slice, whereas MRI scans are shown in native space.

4. Discussion

To summarize the findings of this study in early AD, we observed that: (1) patients exhibited higher uptake compared to age-unmatched HIs, (2) SUVR values were not correlated to neuropsychological measurements, and (3) there is a complex variability of the PET neuroinflammatory profiles among AD patients.

A substantial inter-individual heterogeneity in the intensity of neuroinflammation has already been observed at the early stage of AD[3,8]. Hamelin and colleagues observed that distinct inflammatory profiles of AD patients were associated with fast or slow cognitive decline, whether or not the patients had prodromal AD or dementia[8]. In that study, the patients whose neuroinflammation was high at baseline and stable during follow-up had a better cognitive prognosis compared to the patients with low inflammation at baseline that increased during follow-up. However, the results of our cross-sectional study suggest a more complex relationship between neuroinflammation and cognition. The patients in this study were selected based on the absence of interfering ongoing inflammatory disease and treatment. This means that the heterogeneity observed on PET results from the combined influence of common AD-related pathological changes and individual patients' vulnerability to neuroinflammation.

In our study, we observed that some patients have similar inflammatory PET but opposite neuropsychological profile, while other patients with the same neuropsychological profiles could have an opposite intensity of neuroinflammation on PET (table 3). The reason for this double dissociation remains uncertain.

One possibility could be that a similar intensity of neuroinflammation advances the pathological burden and cognitive deficits for some patients while being compensatory and protective against cognitive impairment for others. This might preclude observing a linear relationship between neuroinflammation and cognitive performances. In the first stages of AD, TSPO PET imaging studies showed that a protective neuroinflammation on PET is associated with better cognitive abilities and increased amyloid burden in the absence of a spread of tau pathology[3,4,24,25]. The acceleration of cognitive decline and the propagation of the tauopathy are associated with an increase in neuroinflammation on PET in AD patients with MCI and dementia[8,24]. This means that there is a transitional phase in AD continuum where neuroinflammation could have opposite relationships with cognitive functioning without being discernable on TSPO PET. This might be an explanation to the absence of correlation with cognition in our study.

Another explanation for such lack of association might be the influence of various pathological mechanisms unaligned with cognitive functioning. Neuroinflammation is susceptible to all brain pathological changes. Our results, however, showed that the SUVR was not correlated to APOE phenotype and to the presence and type of cerebrovascular co-pathology (figure 2). Although these observations should be interpreted with caution, they probably indicate that to some extent, neuroinflammation heterogeneity might rely on other pathological mechanisms in our results. Furthermore, the regional intensity of neuroinflammation was variable at both inter-individual inter-regional levels. The correlations were performed at the voxel, regional and global scale, and using two reference regions. Therefore, it seems unlikely that the absence of correlation resulted from this spatial heterogeneity of neuroinflammation.

Furthermore, it should be noted that recent neuropathological studies showed no correlation of TSPO expression with neuroinflammation and AD pathological changes[26–28]. The fact that TSPO level on PET might not be directly related to brain changes could explain the lack of association observed between PET and neuropsychological measurements in our study, and the spatial variability of neuroinflammation.

Despite of these considerations, most previously published cross-sectional studies on AD have described negative relationships between TSPO level and the MMS score[5]. In our study, we found no correlation with the MMS score. We explored the correlation with several neuropsychological tests. Therefore, this observation cannot be due to the mono-dimensionality of the assessment but rather the inter-individual variability of cognitive abilities in our population. A closer inspection of our data showed that the neuropsychological abilities of our patients were variable in terms of severity and typicality. For example, some amnestic patients had agnosia, which may have interfered with the memory assessment of visual material. For these patients, low memory performances might not be correlated to neuroinflammation in the temporal region. Besides, we included 15 patients with symptoms onset before 65 years. AD pathophysiological mechanisms are known to differ between early and late-onset AD[29]. This probably indicates different pathophysiological dynamics among the patients of our study. Therefore, the absence of correlation in our study might be due in part to the clinical heterogeneity.

We observed a tendency towards negative correlations, especially of the temporal meta-ROI SUVR and long-term memory scores when the correction for multiple-correlation was not applied. It was shown that accelerated long-term forgetting seems to be more sensitive to the objective memory impairment in patients with temporal lobe epilepsy and subjective memory complaint[12], and in presymptomatic autosomal dominant AD[13]. The generalization of these findings to sporadic AD remains uncertain and the absence validated norms at Mareal and the 7-day FCSRT limits the interpretation of our results. However, we observed that all patients had low scores in these tests, including those with MMS >27/30. Therefore, when tests with low sensitivity were used, the variability in the cognitive abilities of our population might have had a higher influence than when standard tests were used.

The cerebellar cortex was broadly used as a reference region in AD as this region is devoid of mature AD neuropathological changes in the early stages[30,31]. Previous PET studies showed an unchanged uptake in the cerebellar cortex of AD patients with MCI and dementia[3,8], and even a trend to increase when using the whole cerebellum[5]. In our study, we found a tendency towards a lower uptake in the cerebellar cortex of AD patients compared to HIs when the WB was used as a reference, with significance reached for MAB AD patients. This pattern probably results from the use of the WB as reference region. The diffuse neuroinflammation in AD brain may have resulted in an underestimation of the SUVR values when the WB was used as a reference. Although the use of two different reference region improve confidence in our analyses, supervised clustering approaches might remain the best alternative in AD[32,33].

One significant limitation of this study was the age of the HIs. One TSPO PET study showed that [^{11}C]-DPA-713 uptake was higher in elderly HIs compared to young HIs in a voxel-wise analysis, but not in a regional analysis[34]. In our study, it cannot be excluded that the uptake in AD patients was not higher than in elderly HIs in some regions. However, in our study, 6/16 HIs were >50 years old, which could attenuate age-related confounding variables. Furthermore, we observed strong differences in regional uptake even after correction for multiple comparisons. Closer inspection revealed that temporal cortex uptake was homogenously higher in AD patients compared to HIs. In addition, the presence of neuroinflammation in AD is a widely replicated results in TSPO PET studies, especially in the temporal region[5]. We also adjusted all the correlation analyses for age. Therefore, it seems unlikely that a low neuroinflammation intensity biased the results of our study.

In conclusion, we found that an unexpected heterogeneity of the PET inflammatory profiles in early AD and a considerable dissociation of these profiles with the neuropsychological characteristics. Further studies are warranted to assess the impact of the variability of neuroinflammation in early AD on disease progression.

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Glossary

Aβ; amyloid-β; AD; Alzheimer’s disease; DMS-48, delayed-to-matching 48; FAB, frontal assessment battery; FCSRT, free and cued selective reminding test; FLAIR, fluid-attenuated-inversion recovery; FWE, family-wise error; HAB, high affinity binder; HIs, healthy individuals; LAB, low affinity binder; MAB, mixed affinity binder; MCI, mild cognitive impairment; MMS, mini-mental state examination; ROI, region of interest; ROCF, Rey-Osterrieth complex figure; STAI-Y, State-Trait Anxiety Inventory; SUVR standard uptake value ratio; SWI, susceptibility weighted imaging; TMT, trail making test; TSPO, translocator protein; WB, whole brain; WAIS IV, Wechsler Adult Intelligence Scale fourth edition.

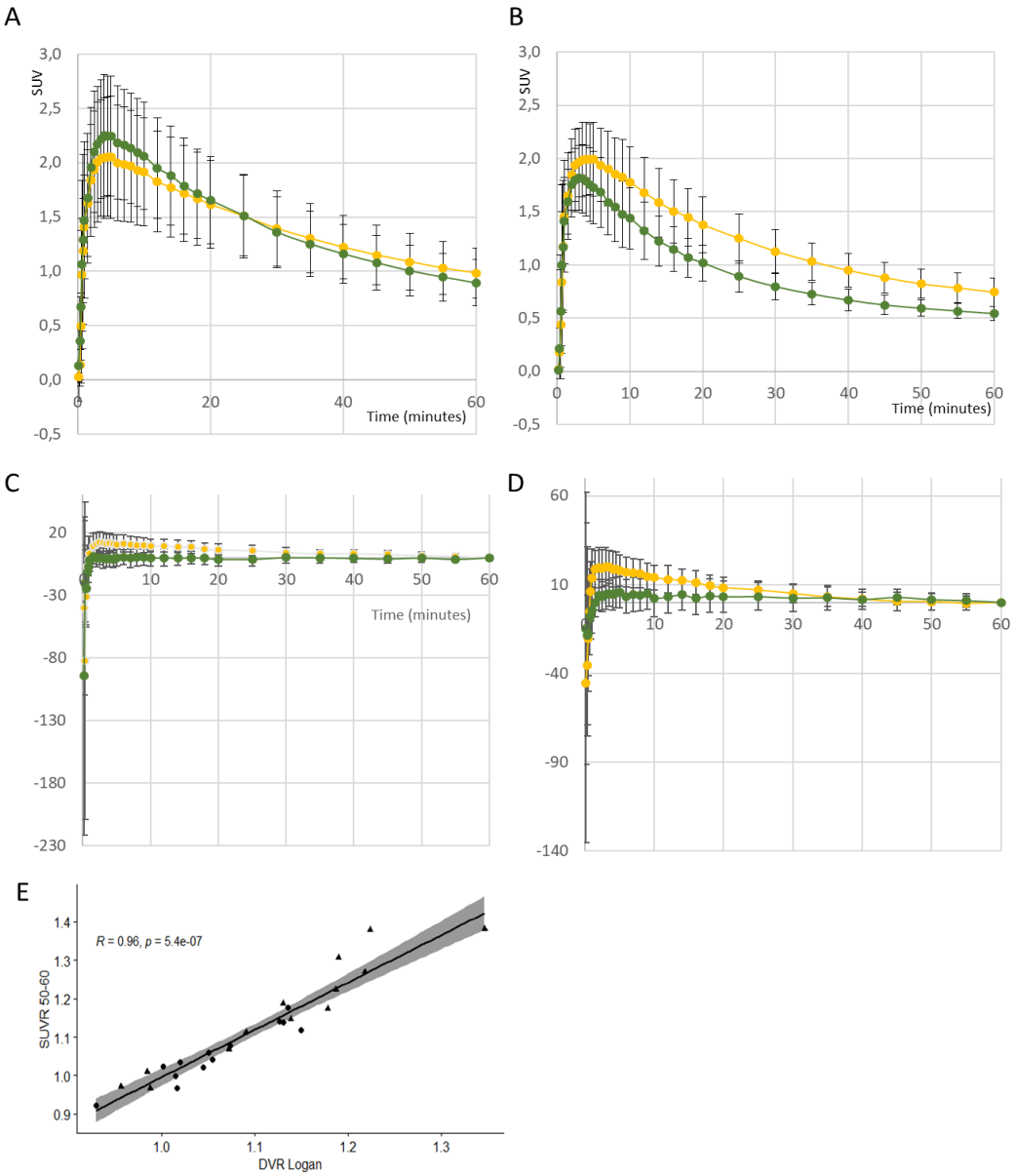
References

Note : *L’ensemble des références de cet article de revue a été placé en annexe 4.*

Paradigm of Mareal assessment		
First session		Second session
Mini-event 1		Questioning: What were the conditions of the previous meeting? Expected response: Date, hour, transportation, place, duration.
Mini-event 2		Questioning: Do you remember me asking you to give me any particular object during the meeting? Expected response: The examiner asked the participant to give him/her a green binder lying on a chair behind him/her.
Mini-event 3		Questioning: Was I absent for a few minutes? Expected response: The examinator was absent for 5 minutes to give a report to another patient.
Mini-event 4		Questioning: Could you describe the test you performed during my absence? Expected response: Puzzle from the WAIS IV.
Mini-event 5		Questioning: Did the telephone ring during my absence? Expected response: The telephone rang two times (4 rings each time, at one-minute intervals).
Mini-event 6		Questioning: Was there something different about me when I returned to the meeting room? Expected response: The gown was changed during the absence.
Mini-event 7		Questioning: Did I offer you something to drink during the meeting? Expected response: A glass of water or orange juice was offered.
Mini-event 8		Questioning: Could you describe the test you performed during the entire meeting? Expected response: MMS, FCSRT, DMS48, ROCF, digit span, verbal fluency, praxis and gnosis.

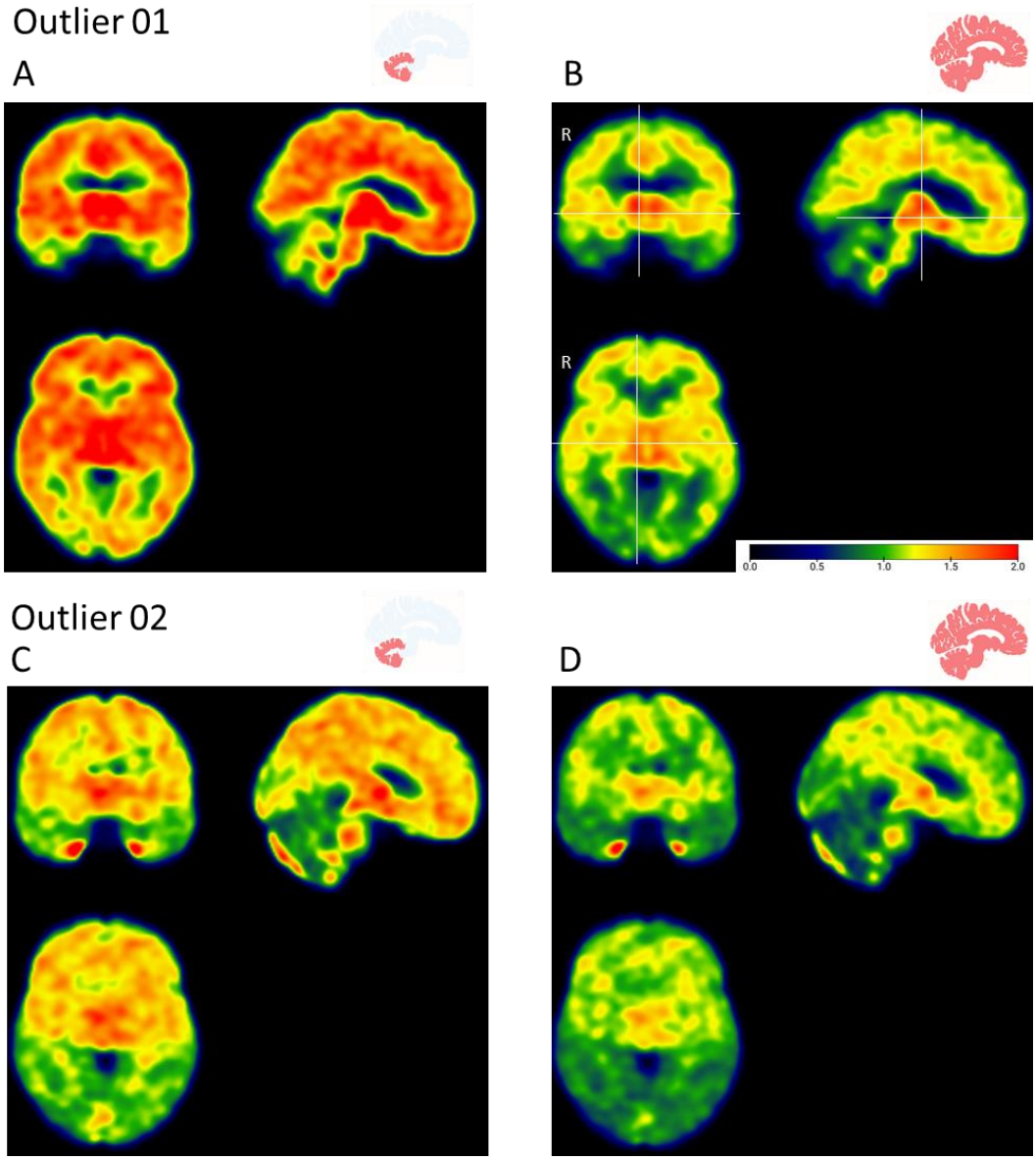
Supplementary Figure 1: Paradigm of the Mareal test.

Mareal is a new test designed to assess the 7-day retention of mini-events adapted from an assessment of accelerated long-term forgetting in temporal lobe epilepsy[12]. The height mini-events shown in this figure are interleaved with standard tests during the first session of neuropsychological assessment. The second session was performed after one week. The participant waits in the same waiting room as before the first session. No spatial or temporal clue is given, and none of the objects used during the first session remain, in order to avoid influencing recall. The examiner asks the participant to recall every detail that he/she can during the first session. This free recall phase is subsequently completed by cued recall, and subsequently by recognition phase if the participant failed to retrieve part or all of an event. The total recall score was calculated by summing up the free and cued scores. Please note that only the free recall and total recall of Mareal were used in this study.



Supplementary Figure 2: Kinetic study of [^{18}F]-DPA714 uptake.

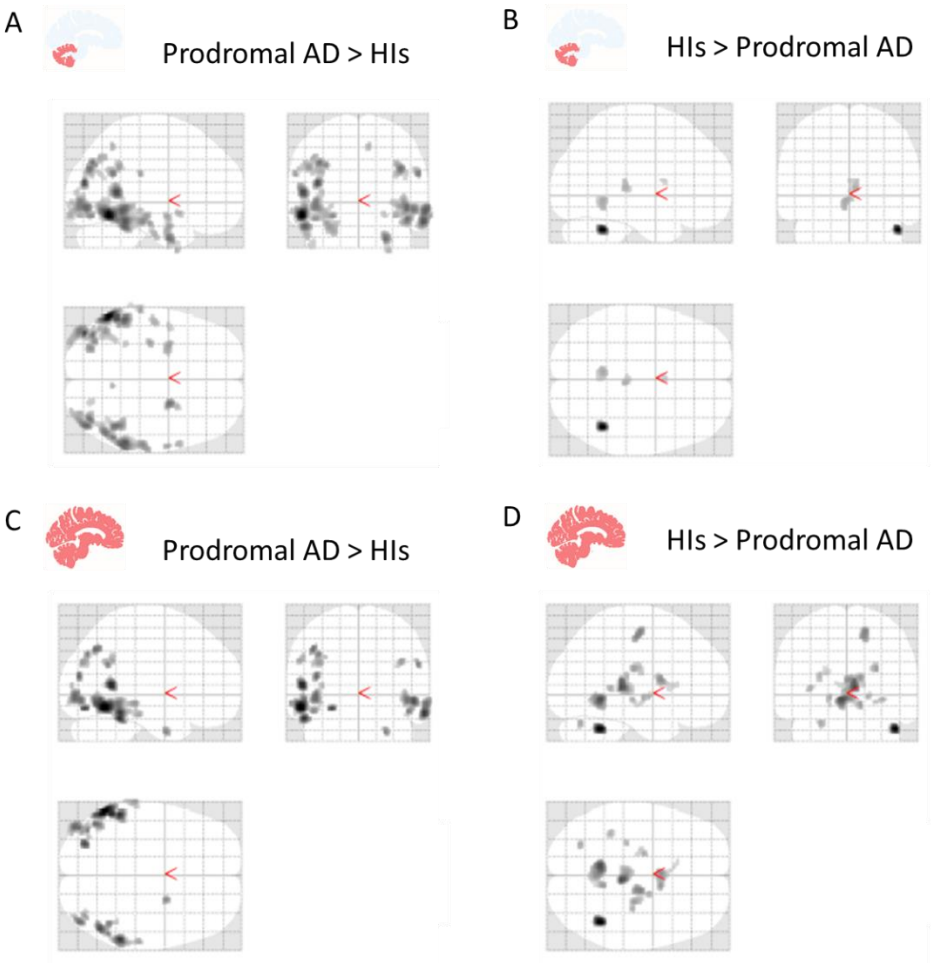
Panels A and B show the time-activity curves in the precuneus of HAB and MAB individuals, respectively. Values are mean ± standard deviation of SUV (g/mL) for AD patients in yellow (n=33), HIs in green (n=16). Panels C and D show the variations in SUVR in the precuneus of HAB and MAB individuals, respectively. Values are expressed as the mean ± standard deviation percentage of variation in the SUVR at 60 minutes for AD patients in yellow, and HIs in green. The variability between 50 and 60 minutes is inferior to 2.0 ± 5 %. Panel D shows the Spearman's correlation between the SUVR and the distribution volume ratio calculated using the Logan graphical model (HAB in circles, MAB in triangles). As input parameters for the Logan model, we used the k2' estimate from the simple reference tissue model and time t* based on a maximum error of 10%. In this analysis, we only used the AD patients and HIs for which the standard error of the distribution volume ratio was inferior to 5. These analyses were performed on PMOD software (v3.9.) using the PNEURO and PKIN tool, and R (v1.4.).



Supplementary Figure 3: Topography of [^{18}F]-DPA-714 SUVR in two outlier healthy individuals.

The cerebellar cortex (panel A and C) or whole brain (panel B and D) was used as a reference. The first case (panels A and B) is a 55-year-old HAB man. The second case (panels C and D) is a 34-year-old MAB man.

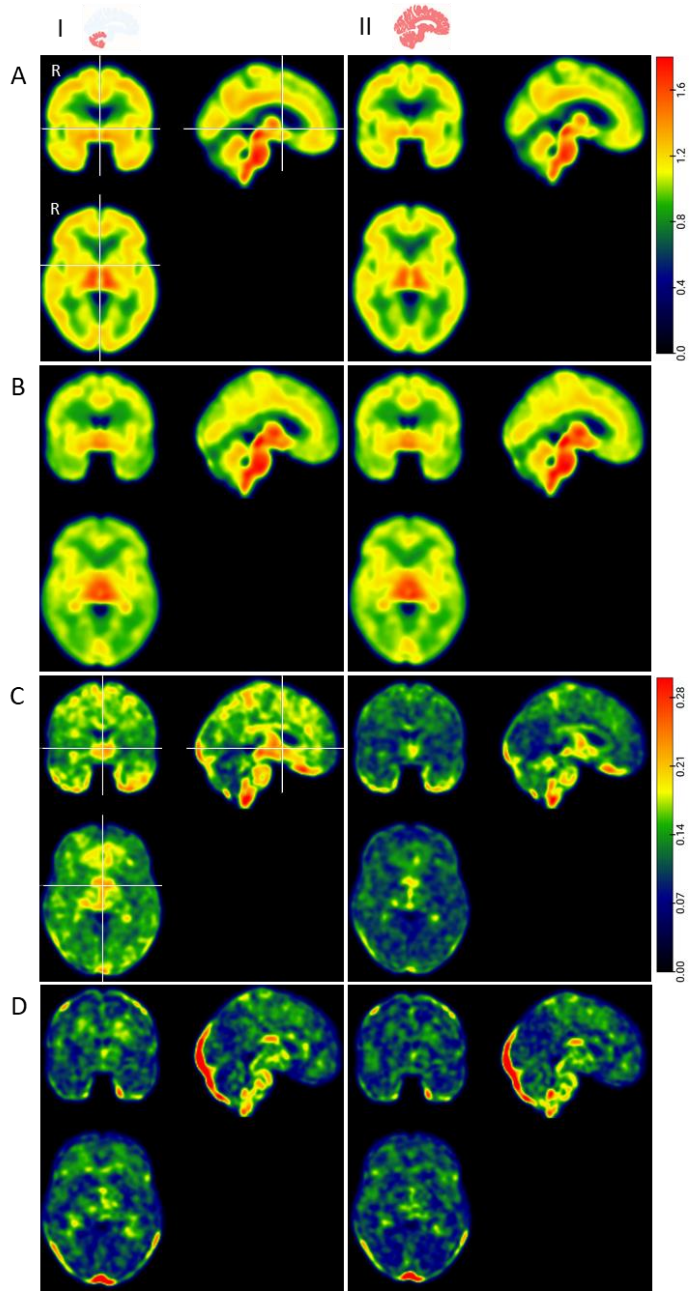
HAB, high affinity binder; MAB, mixed affinity binder, SUVR, standard uptake value ratio.



Supplementary Figure 4: Statistical parametric mapping of [^{18}F]-DPA-714 uptake between prodromal AD patients and HIs, FWE uncorrected for multiple comparisons.

Panels A and C show the glass brain representation of clusters with a significantly increased SUVR in AD patients, with the cerebellar cortex or the whole brain as a reference, respectively. Panels B and D show the glass brain representation of clusters with a significantly increased SUVR in HIs, with the cerebellar cortex or whole brain as a reference, respectively. Significance was set at 0.001, FWE uncorrected, adjusted for TSPO genotype and age, and k=20.

AD, Alzheimer's disease; FWE, family-wise error; HIs, healthy individuals; SUVR, standard uptake value; TSPO, translocator protein.



Supplementary Figure 5: Distribution of [^{18}F]-DPA-714 uptake.

Panels A and C show the mean parametric images for AD patients and HIs, respectively. Panels B and D show the standard deviation parametric images for AD patients and HIs, respectively. The SUVR images using the cerebellar cortex (I) and the whole brain (II) as a reference are represented, respectively.

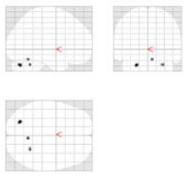
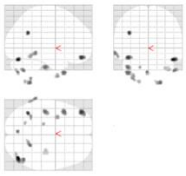
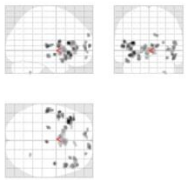
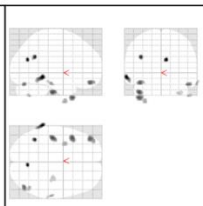
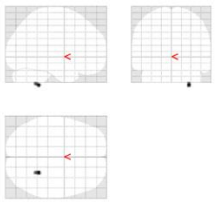
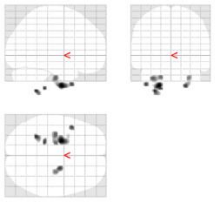
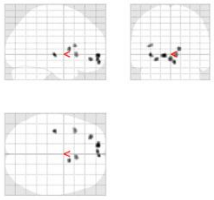
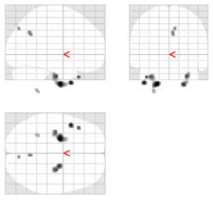
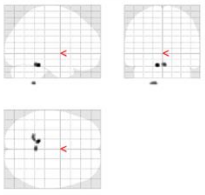
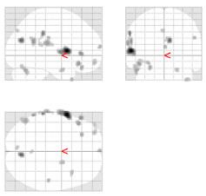
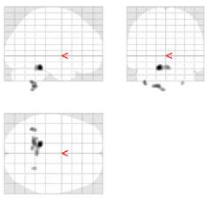
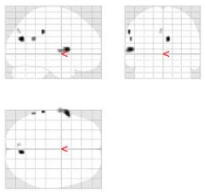
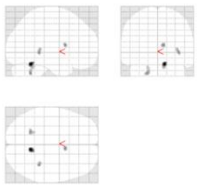
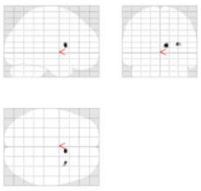
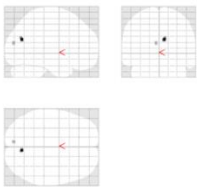
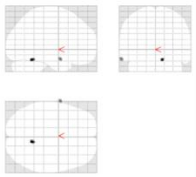
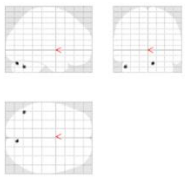
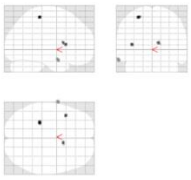
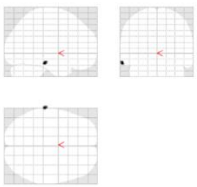
AD, Alzheimer's disease; HIs, healthy individuals; SUVR, standard uptake value.

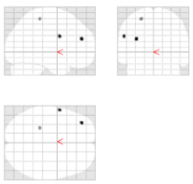
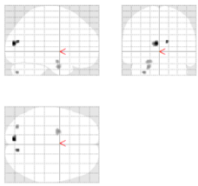
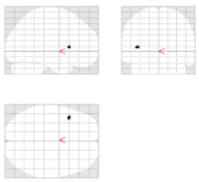
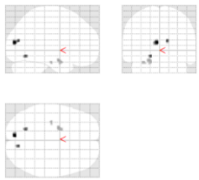
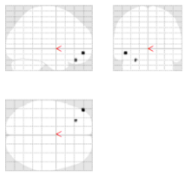
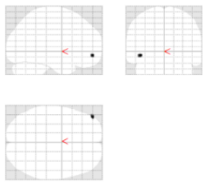
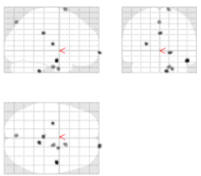
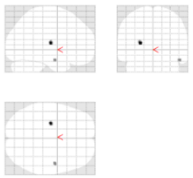
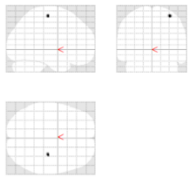
Supplementary Table 1: Example of scoring for a mini-event in the Mareal test.

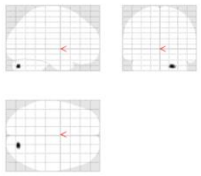
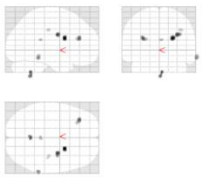
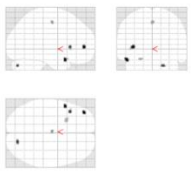
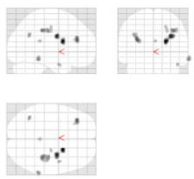
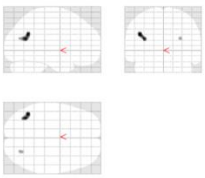
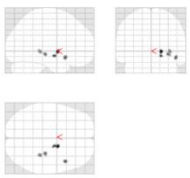
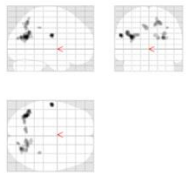
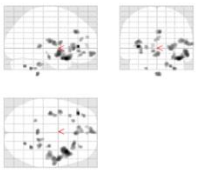
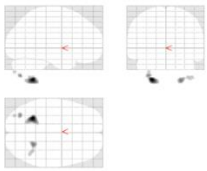
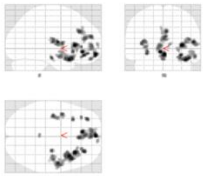
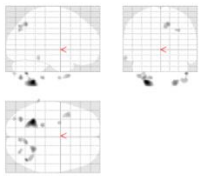
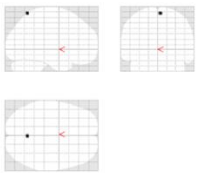
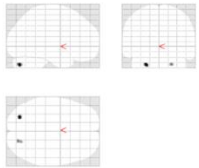
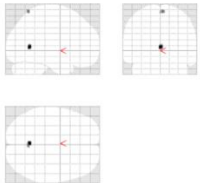
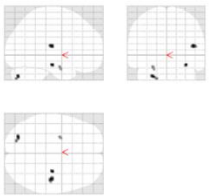
	Scoring event 5: Telephone						
	Free recall		Score	Cued recall: *Something special happened while I was away.*	Score	Recognition	Score
 E5	*What?*	The phone rang		What happened while I was away?		Did the janitor come into the office? Or did the phone ring?	
		Twice		How many times did the phone ring?		Did the phone ring once or twice?	
	Where?	Location of the phone		Where was the phone located?		Was the phone on the desk or on the shelf?	
	Free recall score: … /3			Free & cued recall score: …/3		Free & cued recall & recognition score: …/3	

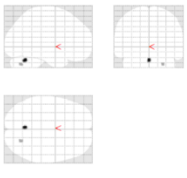
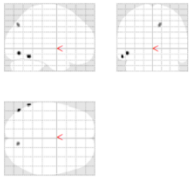
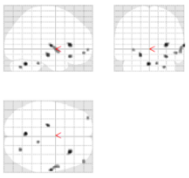
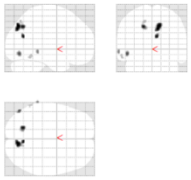
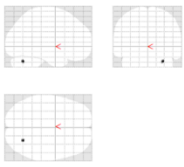
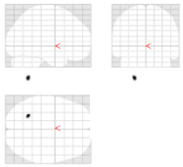
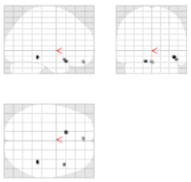
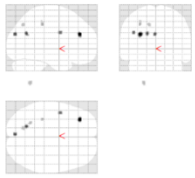
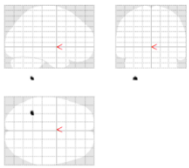
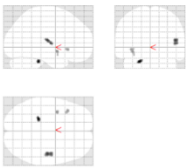
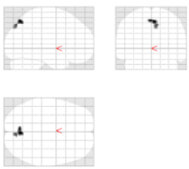
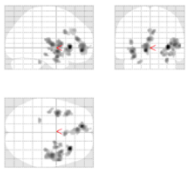
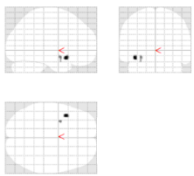
Example of event 5: During his/her absence, the neuropsychologist makes two phone calls in the examination room (4 rings each time, at 1-minute intervals). The neuropsychologist should count 1 point for each right answer. Please note that the “Recognition score” was not considered in the results presented in this study.

Supplementary Table 2: Statistical parametric mapping of [^{18}F]-DPA-714 SUVR correlation with neuropsychological measurements, FWE uncorrected.

Neuropsychology	SUVR with the cerebellar cortex as a reference		SUVR with the whole brain as a reference	
	Positive correlation	Negative correlation	Positive correlation	Negative correlation
Global cognitive efficiency				
MMS, (/30)				
Long-term forgetting				
Mareal, 7-day free recall, (/39)				
Mareal, 7-day total recall, (/39)				
FCSRT, 7-day free recall, (/16)				
FCSRT, 7-day total recall, (/16)				

Neuropsychology	SUVR with the cerebellar cortex as a reference		SUVR with the whole brain as a reference	
	Positive correlation	Negative correlation	Positive correlation	Negative correlation
Anterograde episodic memory				
FCSRT, 20-minutes total recall, (/16)	/	/		
FCSRT, total recall, (/48)	/	/		
DMS48, delayed recall, (/48)	/		/	
ROCF, delayed recall, (/36)		/		

Neuropsychology	SUVR with the cerebellar cortex as a reference		SUVR with the whole brain as a reference	
	Positive correlation	Negative correlation	Positive correlation	Negative correlation
Working memory				
Forward digit span				
Backward digit span	/			
Executive functions				
FAB (/18)				
Go/No Go, reaction time (ms)				

Neuropsychology	SUVR with the cerebellar cortex as a reference		SUVR with the whole brain as a reference	
	Positive correlation	Negative correlation	Positive correlation	Negative correlation
Executive functions				
Categorical (animal) verbal fluency				
Phonemic (p) verbal fluency				
Attention and processing speed				
Processing speed, reaction time (ms)				
Phasic alterness index	/	/	/	

Multiple linear regressions were performed between voxel-wise SUVR and neuropsychological results, FWE uncorrected, adjusted for TSPO genotype and age. For the Go/No Go, processing speed and phasic alertness tests, the number of false responses was used as an additional covariate. The table shows the glass brain of the correlation results with significance set at $p<0.001$, FWE uncorrected, and $k=20$. The non-significant results are not shown.

Abreviations: FAB, frontal assessment battery; FWE, family-wise error; DMS48, delayed matching-to-sample 48; FCSRT, free and cued selective reminding test; MMS, Mini-mental state examination; ROCF, Rey-Osterrieth Complex figure.

2.2.5. **La variabilité des profils de neurodégénérescence et de neuroinflammation**

2.2.5.1. **Faits introductifs**

Une réflexion a été menée pour trouver des explications possibles à la variabilité des profils de neuroinflammation en TEP des patients VIP. Cette réflexion a été menée à un niveau strictement physiopathologique. Il y a plusieurs explications d'ordre tout autre comme le choix de la méthode de quantification, le choix de la région de référence, l'influence de l'âge des sujets sains, pour en citer quelques-uns. Ces aspects n'ont pas été écartés de notre réflexion mais n'en sont pas l'objet principal.

Les patients de VIP ont été recrutés selon l'absence de co-pathologies pouvant avoir un impact sur la cognition, l'absence de maladies inflammatoires, actuelle ou récente, ou de l'absence de traitements inflammatoires. C'est pourquoi la variabilité des profils inflammatoires que l'on observe parmi ces patients provient vraisemblablement de la variabilité des changements pathologiques de la MA, et de l'influence de la vulnérabilité individuelle des patients à développer la neuroinflammation (Leng and Edison, 2021). Dans VIP, il est difficile d'étudier l'influence de la susceptibilité des patients à développer la neuroinflammation (cette possibilité sera discutée dans la section suivante). Une autre explication serait que différents changements pathologiques affectent les patients de VIP. L'hypothèse serait qu'il y aurait des dynamiques physiopathologiques cérébrales différentes dans la cohorte de patients que nous avons étudiée dans VIP indépendamment du stade de la MA (Hamelin et al., 2018).

L'hétérogénéité biologique de la MA a été étudiée à travers les disparités qu'on observe des changements pathologiques de la population amyloïde-positive. Cela a été fait dans une première étude rétrospective clinico-pathologique (Murray et al., 2011). Cette étude vérifie l'hypothèse que différentes distributions spatiales de la pathologie tau sont associées à des profils cliniques distincts. Ces distributions se situe dans les régions corticales en épargnant l'hippocampe pour un premier sous-type ('hippocampal-sparing' en anglais), dans les régions temporales internes ('limbic-predominant' en anglais), ou dans ces deux régions concomitantes pour un sous-type typique de MA ('typical' en anglais).

Depuis cette découverte, les explorations de ces sous-types se sont multipliées, en particulier dans des études utilisant des biomarqueurs (Ferreira et al., 2020). Les nouvelles connaissances à ce propos ont été recensées dans un article de revue récent (Ferreira et al., 2020). J'ai pu en mentionner une partie dans la section introductive dédiée aux avancés sur la physiopathologie.

Pour en revenir à VIP, la plus intéressante de ces avancés est sans-doute qu'il est possible de prédire la classification en sous-types de MA en utilisant l'IRM structurale. Il a été montré que le pattern d'atrophie régional à l'IRM permettait de prédire la distribution de la pathologie tau à l'autopsie (Whitwell et al., 2012). Plusieurs études ont montré par la suite que cette méthode permettait d'identifier des caractéristiques distinctes parmi les patients ayant une MA (Byun et al., 2015; Duara et al., 2013; Planche et al., 2021). Cependant l'atrophie est un biomarqueur de la neurodégénérescence non spécifique du type de changement qui la produit. On parlera dans ce cas de variations de sévérité plutôt que de typicalité (Ferreira et al., 2020), qui concerne un pattern spécifique d'une pathologie c'est-à-dire, par exemple comme la pathologie tau.

2.2.5.2. **Analyses exploratoires**

Nous avons réalisé une analyse exploratoire de classifications des données de SUVR en imagerie de TSPO. Cela permettait de vérifier la présence de sous-groupes de patients ayant un pattern régional différent.

Cette analyse a été faite avec le cortex du cervelet en région de référence. Nous avons testé la méthode des k-means et une méthode de classification hiérarchique visualisée sous la forme de dendrogramme. Ces deux méthodes sont basées sur la distance entre les données des patients entre eux. Les résultats donnent des sous-groupes rassemblant les patients dont les résultats sont les plus similaires. Cette analyse permettait de vérifier la présence de sous-groupe pouvant expliquer l'hétérogénéité des profils de neuroinflammation présentée dans la section précédente. L'hypothèse était qu'il serait possible de catégoriser la variabilité régionale des SUVR.

Par exemple il aurait été intéressant de mettre en évidence des sous-groupes de patients ayant une SUVR frontale et pariétale homogène et plus importante que d'autres patients. Nous aurions pu ensuite voir quels liens existent avec les caractéristiques cliniques et neuropsychologiques de ces sous-groupes.

Nous avons obtenu aucun résultat informatif dans les deux cas. Un résultat est toujours obtenu à l'issu d'une analyse des k-means, ou en faisant un dendrogramme. Ce qui était peu informatif était l'interprétation de la répartition obtenue. Dans le cas de la méthode des k-means, le choix du nombre de cluster était déterminé au préalable de la classification. Ce choix se base sur plusieurs indicateurs statistiques qui évaluent toutes les répartitions possibles en fonction de différents nombres de cluster, et leur associe un niveau de significativité. Ces indicateurs montraient que le nombre de cluster était identique à celui provenant d'un jeu de données dont la distribution serait uniforme (figure 7).

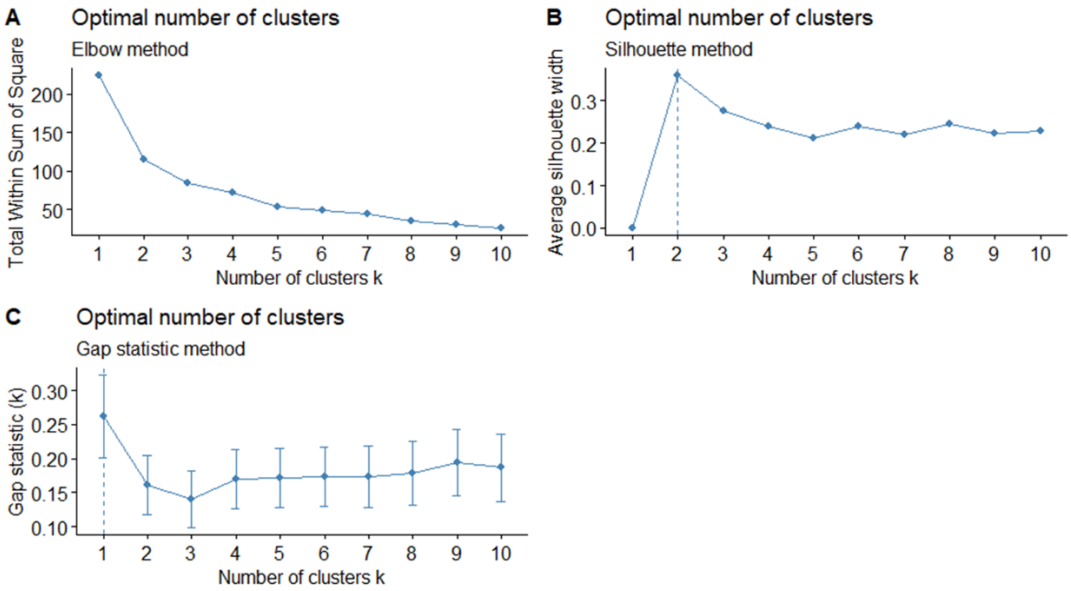


Figure 7 : Choix du nombre de clusters approprié pour une analyse en k-means. Ces résultats sont basés sur les SUVR avec le cortex cérébelleux en région de référence dans les régions frontales, temporales, occipitales, pariétales, précunéus, cingulaire antérieur et postérieur, et temporal meta-roi décrites dans l'étude 1 de VIP. La méthode de Elbow mesure la somme des distances au carré entre les points de chaque cluster. La méthode Silhouette indique la qualité de la répartition des points dans chaque cluster en fonction du nombre de cluster (plus le coefficient moyen est élevé, plus la qualité de répartition est bonne). La mesure de la statistique GAP indique la comparaison de la variation intra-cluster du jeu de données, à un celle d'un jeu de données dont la distribution serait uniforme (plus le coefficient est élevé, plus le nombre de cluster est approprié). Dans l'ensemble ces figures montrent que le choix du nombre de cluster se fait au hasard. Ces résultats ont été répliqués avec un choix différent de régions.

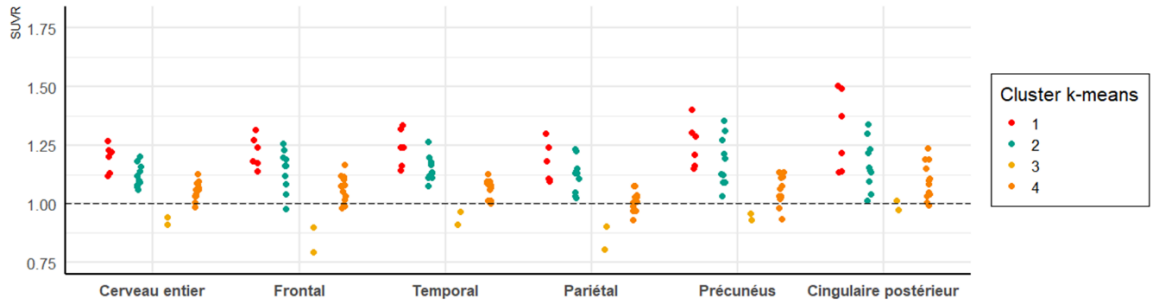


Figure 8 : Intensités des SUVR après une classification par méthode des k-means avec quatre clusters. Ces résultats sont basés sur les SUVR avec le cortex cérébelleux en région de référence dans les régions frontale, temporale, occipitale, pariétale, précunéus, cingulaire antérieur et postérieur, et temporal meta-roi décrites dans l'étude 1 de VIP. Ces résultats ont été répliqués avec un choix différent de nombre de cluster.

En effet, bien que l'intensité des SUVR était variable, la co-variance inter-régionale des SUVR était uniforme pour chaque patient, quel qu'en soit le choix du nombre de cluster, et le choix du nombre de régions (figure 8). Appliquer un k-means revenait à stratifier notre groupe de patients en sous-groupes d'intensité de SUVR de niveau similaire sans qu'un pattern régional soit spécifique à l'un de ces sous-groupes.

Nous avons aussi exploré une méthode de classification descendante hiérarchique. Cette méthode procède par l'identification et le test d'une classification visualisée sous la forme d'un dendrogramme. Dans ce cas, nous ne pouvions choisir que le nombre de région. Pour différents choix de ce nombre, la répartition obtenue était caractérisée à nouveau par une valeur de P indiquant la solidité d'un groupe à chaque branche du dendrogramme. Il s'avère que la solidité des stratifications observée sur le dendrogramme étaient faible pour la plupart, c'est-à-dire au niveau de la chance (figure 9).

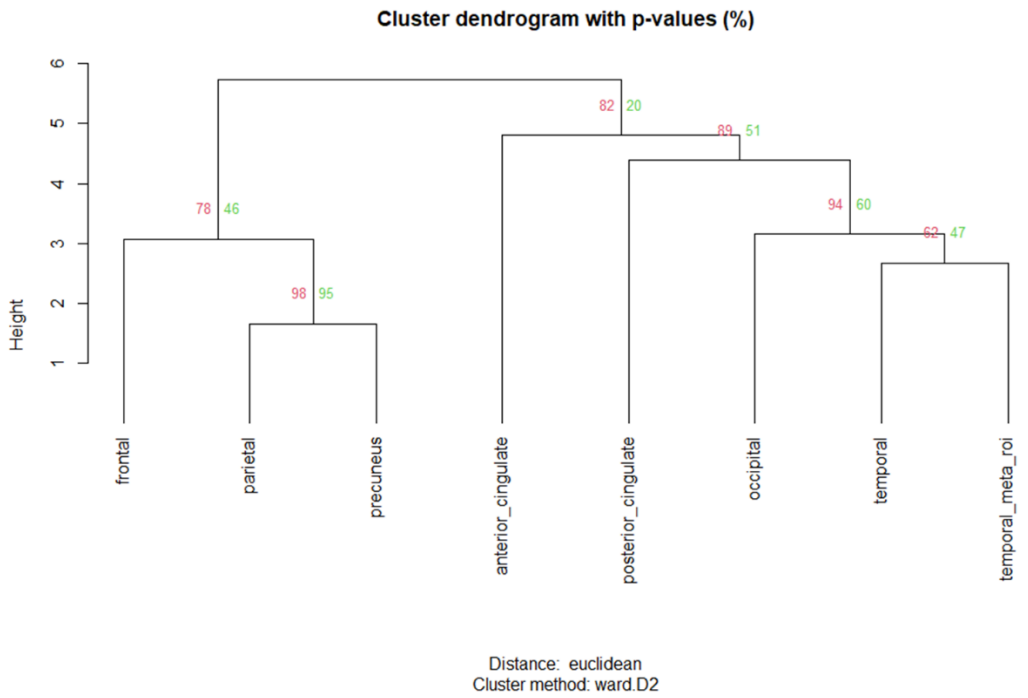


Figure 9 : Dendrogramme de classification des SUVR régionales. Ce résultat est basé sur les SUVR avec le cortex cérébelleux en région de référence dans les régions frontale, temporale, occipitale, pariétale, précunéus, cingulaire antérieur et postérieur, et temporal meta-roi décrites dans l'étude 1 de VIP. Les valeurs de P sont indiquées en rouge pour celles provenant de notre jeu de données, et en vert pour celles provenant d'une estimation par la méthode du bootstrap. Chaque valeur de P peut être compris entre 0 et 100. Une valeur de P >95 indique un groupe solide. Quel qu'en soit la méthode d'estimation, ces résultats montrent que la solidité de la stratification est faible.

Dans l'ensemble, ces analyses exploratoires montrent que la co-variance régionale intra-sujet des SUVR était uniforme, quel qu'en soit le choix du nombre de cluster, le choix du nombre de régions, et cela pour deux méthodes de classification. Il serait donc improbable d'obtenir des sous-groupes de patients de VIP associés à des profils régionaux distincts de neuroinflammation. Une limite de cette exploration est qu'elle n'ait pas été répliquée aux SUVR avec le cerveau entier en région de référence. Nous avons observé que la co-variance régionale intra-sujet des SUVR n'était pas uniforme avec le cerveau entier en région de référence. Il serait donc envisageable, non excluable du moins, de pouvoir catégoriser les SUVR régionales en changeant de référentiel.

2.2.5.3. **Méthode de classification des données volumétriques**

Nous souhaitions initialement tester l'hypothèse de l'influence de différents changements pathologiques de la MA sur la variabilité des profils de neuroinflammation en TEP. Pour cela, nous avons utilisé l'atrophie mesurée en IRM comme proxy des sous-types biologique de la MA (Whitwell et al., 2012).

Nous avions deux possibilités comme choix de la méthode de classification des données volumétriques. Nous pouvions procéder en ayant une hypothèse sur les régions qui serait affectées différemment par des sous-types de MA. Nous pouvions aussi procéder à une classification des données volumétriques sans faire ce choix au préalable. Cela consisterait à rassembler en sous-groupe les patients dont les résultats seraient les plus similaires, sans faire un choix de régions au préalable. Cette méthode aurait l'avantage d'apporter un résultat qui soit moins déterminé par notre réflexion.

Néanmoins, nous avons opté pour une méthode de classification des données volumétriques guidée par un choix de régions d'intérêt plutôt que par les données elles-mêmes. Ce choix a été fait d'abord pour des raisons d'ordre statistique. L'utilisation de méthodes statistiques multivariées de classifications, qu'elles soient supervisées ou non, sont pertinentes quand elles se basent sur un nombre de sujet plus important que celui dont nous disposons (une trentaine environ). Je fais référence à l'analyse en composante principale ou à la méthode des k-means. De plus, la structure du jeu de données de l'imagerie TEP de TSPO est influencée par le choix de la région de référence. L'utilisation de deux méthodes de classification (k-means et classification hiérarchique par dendrogramme) sur les données de l'imagerie TEP de TSPO n'a pas apporté de résultats significatifs. Il serait donc peu probable d'obtenir un résultat après avoir appliqué ces mêmes méthodes aux données volumétriques. Nous avons donc opté pour une méthode de classification permettant de tester directement l'hypothèse d'une corrélation régionale prédéfinie. Une telle méthode nous permettrait de discuter la présence de la neuroinflammation dans ces régions.

Après avoir établi une méthode classification, il fallait trouver le moyen de mettre en évidence une baisse de volume suffisamment proéminente pour être interpréter comme de l'atrophie. Cela est problématique car il n'y a pas de sujets contrôles sains âgés dans VIP. Nous avons donc utilisé ceux de l'étude TELLMA. Le projet TELLMA avait été mené au CHU de Toulouse et à Tonic quelques années avant VIP. Il s'agissait d'une étude du langage dans le vieillissement sain et la MA, sous la direction de Jérémie Pariente. TELLMA a fait l'objet de plusieurs articles auxquels le lecteur peut se référer pour plus de détails (A. Pistono et al., 2019; Aurélie Pistono et al., 2019; Pistono et al., 2021). Je me suis en contact avec deux des auteures de ces articles : Marie Rafiq, neurologue au CHU de Toulouse Purpan, et Aurélie Pistono, docteure en neuropsychologie et neurosciences clinique, actuellement à l'université de Gent (Belgique). Nous avons pu ainsi travailler sur VIP avec une nouvelle cohorte de sujets sains âgés. Cette cohorte ne montrait pas de différence significative en âge, genre, et niveau d'éducation, qui sont tous les trois des facteurs influant le niveaux d'atrophie (Bakkour et al., 2013; Taki et al., 2013).

Note : *Cet article a fait l'objet d'une soumission à une revue internationale. Il a été choisi de l'insérer dans le texte dans son format de soumission.*

2.2.5.4. **Etude 2 de VIP**

Neuroinflammation in atrophy-defined subtypes of Alzheimer's disease: an open-ended study

Dominique Gouilly[1], Anne-Sophie Salabert[1, 2], Hélène Catala[3], Elsa Bertrand[3], Marie Goubeaud[3], Johanne Germain[3], Marie Rafiq[1, 4], Aurélie Pistono[5], Marie Benaiteau[4], Jasmine Carlier[4], Leonor Nogueira[6], Mélanie Planton[4], Anne Hitzel[2], Déborah Méligne[1], Benjamine Sarton[1, 7], Stein Silva[1, 7], Pierre Payoux[1, 2, 3], Claire Thalamas[3], Béatrice Lemesle[4], Patrice Péran*[1] and Jérémie Pariente*[1, 3, 4].

1. Toulouse Neuroimaging Center, UMR 1214, Inserm/UPS, Toulouse, France.

2. Department of Nuclear Medicine, CHU Toulouse Purpan, Toulouse, France.

3. Center of Clinical Investigation, CHU Toulouse Purpan (CIC 1436), Toulouse, France.

4. Department of Cognitive Neurology, Epilepsy and Movement Disorders, CHU Toulouse Purpan, Toulouse, France.

5. Ghent University, Department of Experimental Psychology, Ghent, Belgium.

6. Laboratory of Cell Biology and Cytology, CHU Toulouse Purpan, Toulouse, France.

7. Critical Care Unit, CHU Toulouse Purpan, Toulouse, France.

Note : *Les figures et tableaux supplémentaires de cet article ainsi que le glossaire ont été placés à la suite du texte.*

Abstract

Background: Neuroinflammation is a pathological change in Alzheimer's disease (AD). However, how neuroinflammation is associated to biological subtypes of AD remains undescribed.

Methods: We performed a cross-sectional study using PET imaging of the translocator protein as a proxy for neuroinflammation in the atrophy-defined subtypes of AD. Thirty-three patients with early AD were classified using the MRI regional pattern of atrophy compared to 24 elderly healthy individuals (HI) matched for age, gender, and educational level. We used 16 HI with unmatched age as TSPO PET imaging control in a standard uptake value ratio analysis using the cerebellar cortex and the whole brain as a reference region.

Results: 16 AD patients (48%) presented a limbic-predominant atrophy, 11 (33%) had a typical atrophy, 5 (15%) had hippocampal-sparing atrophy, and 1 (3%) patient had minimal atrophy. In limbic-predominant and typical subtypes, we found that neuroinflammation was higher in the corresponding temporal regions used for atrophy measurement compared to the HI. However, no difference in neuroinflammation was observed between these subtypes. The clinical and neuropsychological features of these groups were comparable. In addition, no correlation was noted between neuroinflammation and the corresponding regional volume among all AD patients. Neuroinflammation was uniform in the temporal regions, but a high inter-individual variability was observed in the fronto-parietal regions.

Conclusion: Neuroinflammation appears to be neither related to the typicality nor to the severity of AD. The presence of distinct pathophysiological dynamics might explain the considerable variability in the neuroinflammatory PET profiles among atrophy-defined subtypes of AD.

1. Introduction

Alzheimer's disease (AD) is biologically defined by the amyloid and tau brain lesions[1]. The pathological heterogeneity of AD was initially classified in three subtypes according to the spatial distribution of tau pathology: limbic-predominant, hippocampal-sparing, and typical (cortical and limbic)[2]. It was further shown that the pattern of regional atrophy on magnetic resonance imaging (MRI) predicts classification into these subtypes at autopsy[3]. This also allowed the identification of a fourth subtype with minimal atrophy[4]. Furthermore, the use of positron emission tomography (PET) imaging of the translocator protein (TSPO) showed that neuroinflammation on PET mediates amyloid and tau synergy in AD[5]. However, the presence of neuroinflammation in subtypes of AD remains undescribed. We conducted a preliminary study of the relationship between neuroinflammation on PET and the patho-biological heterogeneity of AD using MRI as a proxy for classification in atrophy-defined subtypes.

2. Method

2.1. Participants

We recruited 33 patients with amnestic mild cognitive impairment (MCI), mini-mental state examination (MMS) >20/30, age ranging from 50 to 90 years (mean= 68±7.5; min=53; max=82), and cerebrospinal fluid biomarker evidence of AD[6] at the Neurology Department Memory Clinic of Toulouse University Hospital (France). The exclusion criteria were: (1) evidence of significant co-pathology including another neurodegenerative disease, a psychiatric disorder or an inflammatory condition, (2) ongoing anti-inflammatory treatment or recent (<30 days) medication changes with a potential to impact cognition, (3) a recent (<6 months) history of alcohol or illicit drug abuse, (4) the inability (for any reason) to undergo MRI, PET scan, or lumbar puncture.

In addition, we recruited healthy individuals (HI) with no evidence of any neurological or psychiatric disease. This included 24 elderly HI (eHI) (70±4 years; min=65; max=81) and cognitively normal (mean MMS=29±1.1) who were matched for age, gender, and educational level with AD patients ($p>0.05$). We also recruited 17 age-unmatched healthy individuals (uHI) (mean=40±19.2; min=20; max=75; $p<0.01$).

All the participants of this study gave their informed consent and have already been enrolled in ethically approved studies[7,8] (AD patients: French Ethics Comity "Comité de Protection des Personnes Sud-Est 1", reference number: 2017-78, and the French Drug Safety and Health Products Agency, reference number: MEDAECNAT-2018-01-0034; uHI: French Ethics Comity "Comité de Protection des Personnes Sud Méditerranée 5", reference number: 17-032, and the French Drug Safety and Health Products Agency, reference number: MEDSANAT-2018-07-00110; eHI: ethics committee; IDRCB: 2015-A01416-43).

2.2. Clinical and neuropsychological examination

AD patients underwent a neurological examination and a comprehensive battery of neuropsychological tests on two days within a week of each other. Cognitive functions were assessed using the MMS; the free and cued selective reminding test (FCSRT); the delayed-to-matching sample 48 (DMS48) test; the Rey-Osterrieth Complex figure (ROCF) test; forward and backward digit span from the Wechsler Adult Intelligence Scale fourth edition (WAIS IV); the frontal assessment battery (FAB); the trail making test A and B (TMT); the Go/No Go test; the phasic alertness test from the Test of Attentional Performance battery; a measurement of reaction time in neutral condition from the phasic alertness test used as an assessment of processing speed; the codes from the WAIS IV; two minutes phonemic (p) and categorical (animal) verbal fluency test; a test of denomination from the French GREMOTS battery; a test of identical figure identification for gnosis from the French PEGV battery; and Mahieux's battery for gestural praxis.

In addition, behavioral assessment included the State-Trait Anxiety Inventory scale (Stai-y) and the Beck's depression inventory. All these tests and the assessment techniques we used are detailed elsewhere[9].

Furthermore, AD patients underwent an assessment of accelerated long-term forgetting. We performed a 7-day delayed recall of the FCSRT. In addition, we used Mareal which is a new test of autobiographic memory developed by our team[8]. Mareal is composed of eight mini-events that are incidentally interleaved during the first session of the neuropsychological assessment. Each participant was asked to recall the memory of these mini-events one week later during the second session. The Mareal assessment is similar to the FCSRT, and includes a free and a cued recall, and a recognition phase.

2.3. Blood sample

For AD patients and uHI, blood samples were drawn to characterize TSPO genotypes and binding affinity phenotype. We obtained 16 AD patients and 8 uHI with high affinity binding (HAB) phenotype, 13 AD patients and 8 uHI with mixed affinity binding (MAB) phenotype, and 4 AD patients and 1 uHI with low affinity binding (LAB) phenotype. The LAB subjects were included in all statistical analyses except those for which the PET data were included.

2.4. MRI

2.4.1. Acquisition

For all the subjects, a T1-weighted MRI sequence was obtained on a 3T MRI scanner (Philips Achieva dStream, 32-channel head coil) at the INSERM/UPS Tonic technical platform. For all AD patients, a susceptibility-weighted imaging (SWI) was also acquired and reviewed by a trained rater (MP) to assess the presence of strictly lobar or deep cerebral microbleeds and the presence of focal or disseminated cortical superficial siderosis. AD patients were then classified as having possible or probable cerebral amyloid angiopathy (CAA) according to the modified Boston criteria[10]. Patients with both lobar and deep microbleeds were classified as having mixed angiopathy. However, one patient had one infra-tentorial microbleed and was classified as having 'absent' cerebrovascular co-pathology for compliancy. Another patient had severe artefacts on the SWI image and could not be classified.

2.4.2. Processing

For all participants, denoised and inhomogeneity bias-corrected T1-weighted MRI scans were segmented and spatially normalized on the standard Montreal Neurological Institute space using the CAT12 toolbox[11] on SPM12 implemented on MATLAB (v2019b.; Mathworks.inc). Smoothing was applied using a Gaussian filter with 8mm full-width at half-maximum. A voxel-based morphometry analysis was performed to compare eHI to AD patients using a t-test, adjusted for total intracranial volume and age. Significance was set at $p<0.05$ family-wise error corrected and a minimum-activated threshold of 20 voxels.

2.4.3. Classification into AD subtypes

For AD patients and eHI, the automated anatomical labelling 3 (AAL3)[12] atlas was deformed to each subject's T1-weighted MRI native space using the inverse deformation field used for spatial normalization on CAT12. The volume of the following bilateral regions of interest (ROI) was extracted from gray matter segment at p>0.5: frontal, parietal, temporal, hippocampal, and whole cortex. All volumes were normalized by total intra-cranial volume derived from CAT12 to correct for head sizes. The region-to-cortex ratio was then calculated for each normalized regional volume. Z-values were calculated for AD patients compared to eHI. AD patients were then classified into atrophy subtypes using the classification algorithm shown in figure 1. The cutoff of <25th percentile was used to defined the presence of atrophy as previously described[3,13]. AD patients without atrophy in any region were classified as having 'minimal atrophy'. AD patients were classified as 'hippocampal sparing' when they exhibited atrophy in at least one cortical region but no hippocampal atrophy. AD patients were classified as 'limbic-predominant' when they exhibited only hippocampal atrophy. AD patients were classified as 'typical' when they exhibited hippocampal atrophy and atrophy in at least one cortical region. Finally, when atrophy was observed only in the hippocampal and temporal region, AD patients were classified as 'limbic-predominant' but not as 'typical'.

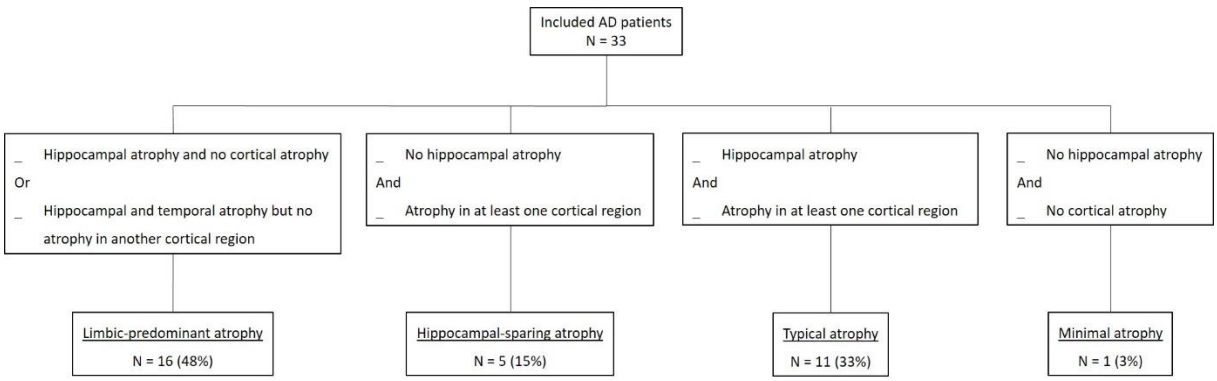


Figure 1: Flow-chart of patients' classification in atrophy-defined subtypes of AD.

2.5. TSPO PET imaging

2.5.1. Acquisition

For AD patients and uHI, an encephalic PET scan was performed on a hybrid PET/CT tomograph (Siemens Biograph TruePoint 6.0) within a week of the MRI scan. The CT scan was performed to correct for tissue attenuation before intravenous injection of [^{18}F]-DPA-714. The PET examination was acquired in list mode over 60 minutes following intravenous injection (3.5MBq/kg; AD patients: mean= 241MBq ±46; HIs: 233 ±57). All corrections (attenuation, radioactive decay, random and scatter coincidences) were incorporated in an iterative OSEM reconstruction using 3 iterations and 21 subsets. The dynamic data were reconstructed into 32 timeframes (6x10s; 8x30s; 5x1min; 5x2min; 8x5min).

2.5.2. Regional quantification

For quantification of TSPO PET imaging, we performed a 50–60-minute standard uptake value (SUV) analysis[8]. Reconstructed PET images were realigned and corrected for subject motion. Mean SUV parametric images were calculated on 50–60-minute interval. CT scans were co-registered on the T1-weighted MRI images. The transformation thereby derived was applied to the SUV PET images to co-register them on the corresponding T1-weighted images. A binary inclusive mask of pooled gray and white matter segment at $p>0.5$ was applied as an atrophy correction. The AAL3 atlas[12] was deformed to each subject's MRI native space with the inverse deformation field used for spatial normalization on CAT12. Mean SUV values were then extracted on bilateral regions corresponding to matching frontal, parietal, and temporal regions of the atrophy measurement using the PETPVE12 toolbox on SPM12[14]. In our previous report, the orbitofrontal and the precuneus were considered apart from the frontal and parietal regions[8]. In this study, the orbitofrontal and precuneus were comprised in the frontal and parietal ROI, respectively. In addition, we defined a temporal meta-ROI including the bilateral hippocampal, parahippocampal cortex, amygdala, and fusiform gyrus. Finally, we calculated the SUV ratio (SUVR) in all regions using the mean SUV of the cerebellar cortex or the whole brain (WB) as a reference.

2.6. Statistical analysis

The LAB subjects were included in all statistical analyses except those for which the PET data were included. Univariate non-parametric tests were performed for comparisons only when the number of patients was superior to five per subgroup. The Mann-Whitney, Kruskal-Wallis, Chi2, and Fisher's tests were used when appropriate. Dunn's test was used as post-hoc analysis of the Kruskal-Wallis test. We performed linear regressions of the regional volume for the corresponding SUVR measurement, adjusted for TSPO genotype and age. All analyses were performed on R software (v1.4.), with significance set at $p<0.05$, two-tailed, and Holm's correction was used for multiple testing when needed.

3. Results

3.1. Classification in atrophy subtypes

Voxel-based morphometry analysis of AD patients and eHI revealed subcortical limbic atrophy, especially in the hippocampal region ($p<0.05$; corrected; figure 2). The regional-based volume classification resulted in 16 patients (48%) with limbic-predominant atrophy, 11 (33%) with typical atrophy, five (15%) with hippocampal-sparing, and one (3%) patient with minimal atrophy (figure 1). When a more conservative threshold of -1 standard-deviation was used, the regional-based volume classification resulted in 16 patients (48%) with limbic-predominant atrophy, 8 (24%) with typical atrophy, four (12%) with hippocampal-sparing, and five (15%) patient with minimal atrophy. Only the results from the classification with the 25^{th} percentile as atrophy cutoff were used for further statistical analysis.

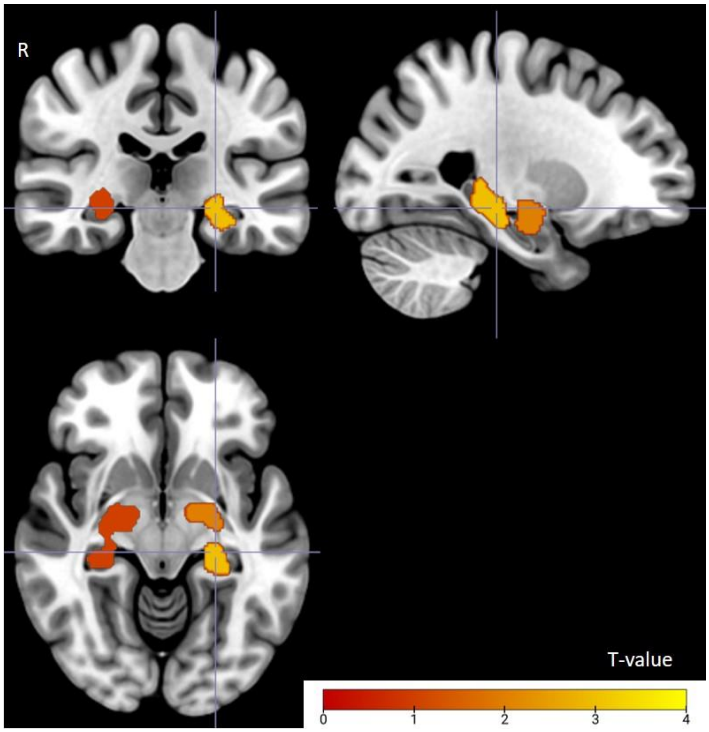


Figure 2: Voxel-based morphometry analysis reveals atrophy in limbic regions in patients with early AD (n=33) compared to eHI (n=24).

Gray matter density was compared using t-test adjusted for age and total intra-cranial volume. Significance was set at $p<0.05$ family-wise error corrected, and a minimum-activated threshold of 20 voxels.

AD, Alzheimer's disease; eHI, elderly healthy individual.

Table 1: Clinical and neuropsychological features of atrophy-defined subtypes of AD

Clinical and neuropsychological assessments	Limbic-predominant n = 16	Typical n = 11	Hippocampal-sparing n = 5	Minimal-atrophy n = 1
Demographics				
Gender, n (%)	8 (50%)	4 (36%)	3 (60%)	0
Age, mean (SD)	67.7 (6.9)	69.1 (9.1)	67.2 (7.4)	64
Educational level, years, mean (SD)	13.9 (3.6)	13.5 (2.7)	12.2 (1.1)	12
Time to diagnosis, months, mean (SD)	11.2 (12.6)	11.4 (16.6)	17.8 (8.8)	38
Familial history of AD, n (%)	11 (69%)	4 (36%)	2 (40%)	0
APOE4 carriage, n (%)	11 (69%)	7 (64%)	3 (60%)	1
Neuropsychological testing, median [IQR]				
MMS score (/30)	23.5 [21.8 – 25.3]	23 [21 – 26.5]	27 [22 – 30]	24
Long-term forgetting				
Mareal, 7-day free recall (/39)	3 [1.8 – 5.3]	3 [1.5 – 6]	5 [3 – 8]	2
Mareal, 7-day total recall (/39)	14.5 [11 – 16.6]	17 [11.5 – 20.5]	18.5 [18 – 21]	12
FCSRT, 7-day free recall (/16)	0 [0 - 1]	0 [0 - 2]	6 [5 – 7]	0
FCSRT, 7-day total recall (/16)	4.5 [1 – 9.5]	4 [2.5 – 8.5]	12 [8 – 12]	2
Anterograde episodic memory				
FCSRT, 20-minute delayed recall (/16)	9.5 [6.5 – 14.3]	10.5 [6.3 – 14.3]	16 [15 – 16]	5
FCSRT, immediate total recall (/48)	32.5 [26.5 – 38.3]	35 [15.5 – 44.3]	45 [44 – 47]	15
DMS48, one-hour delayed recall (/48)	44.5 [42 – 46.3]	44 [39.5 – 46.5]	45 [44 – 47]	39
ROCF, 5-minute delayed recall (/36)	5 [2 – 8]	7.5 [6 – 12.6]	10.8 [7.8 – 14.4]	2
Working memory				
Forward digit span	6 [4.8 – 7]	5 [4 - 6]	5 [4 – 5]	6
Backward digit span	4 [3 – 4.3]	3 [3 - 4]	5 [4 – 5]	4
Executive functioning				
FAB (/18)	14.5 [12.8 – 16]	14 [12.5 – 14.5]	15 [13 – 18]	16
Categorical (animal) verbal fluency, initiation	18 [13 – 24.8]	12 [8.5 – 15.5]	19 [16 – 24]	28
Phonemic (p) verbal fluency, initiation	21 [16.8 – 27]	17 [12.5 – 22.5]	26 [19 – 26]	31
Go/No Go, median reaction time in ms (mean number of false responses), inhibition	402 [390 – 509.5] (3.5)	492 [444.5 - 531] (2.8)	506.5 [485 – 528.3] (2.8)	330 (1)
Attention and processing speed				
TMT A, time (s)	59.5 [39.8 – 74]	67 [55.5 - 84]	36 [26 – 47.5]	70
The codes, WAIS IV (/53)	37 [23 – 48]	30.5 [27 – 34.5]	37.5 [30.5 – 43.5]	52
Processing speed, reaction time (ms) (mean number of false responses)	309.5 [274.5 – 518.3] (2.7)	368 [277.5 - 399] (1.7)	345 [317 – 349] (1.2)	326 (1)
Phasic alertness, reaction time index (mean number of false responses)	-0.03 [-0.11 – 0.001] (10.5)	-0.01 [-0.1 – 0.08] (7.2)	0.06 [-0.01 – 0.07] (6.6)	-0.06 (1)
Instrumental				
Language - Denomination (/36)	34 [32 – 34]	32 [31 – 33.5]	33.5 [30.8 - 35]	34
Gnosis – Test of identical figures (/10)	10 [8.8 – 10]	9 [9 – 9]	10 [10 – 10]	7
Praxis - Gestural praxis (/23)	22 [21 – 22]	21 [20 – 21]	22 [20 – 22]	21
Behavioral assessment, median [IQR]				
Stai-Y anxiety scale (/80)	46 [36 – 51.3]	44 [36 – 48.5]	43 [41 – 47]	34
Beck' depression inventory (/39)	4 [3 – 4.3]	4 [2.5 – 5.5]	4 [2 – 4]	1

We compared the clinical and neuropsychological features of AD patients with typical and limbic-predominant atrophy. No difference was observed in terms of age, gender, time from diagnosis, familial history of AD, educational level, APOE4 carriage, or neuropsychological performances ($p>0.05$; corrected; table 1).

3.2. [^{18}F]-DPA-714 uptake in atrophy-defined subtypes

The four excluded LAB patients were one patient with limbic-predominant and three patients with typical atrophy. We compared uHI (n=16) to both AD subtypes irrespective of the TSPO genotype. When the cerebellar cortex was used as a reference, we observed a higher temporal uptake in limbic-predominant (n=15) or typical (n=8) AD patients compared to uHI ($p<0.01$; corrected; figure 3A). We also observed a higher temporal meta-ROI uptake in typical AD patients compared to uHI ($p<0.05$; corrected; figure 3A). When the WB was used as a reference, we observed a higher temporal uptake in limbic-predominant and typical AD patients compared to uHI ($p<0.01$; corrected; figure 3B). No difference was observed between limbic-predominant and typical AD patients ($p>0.05$; corrected).

When a more conservative threshold of -1 standard-deviation was used for classification, the distribution of the SUVR values was similar between atrophy-defined subtypes (supplementary figure 1).

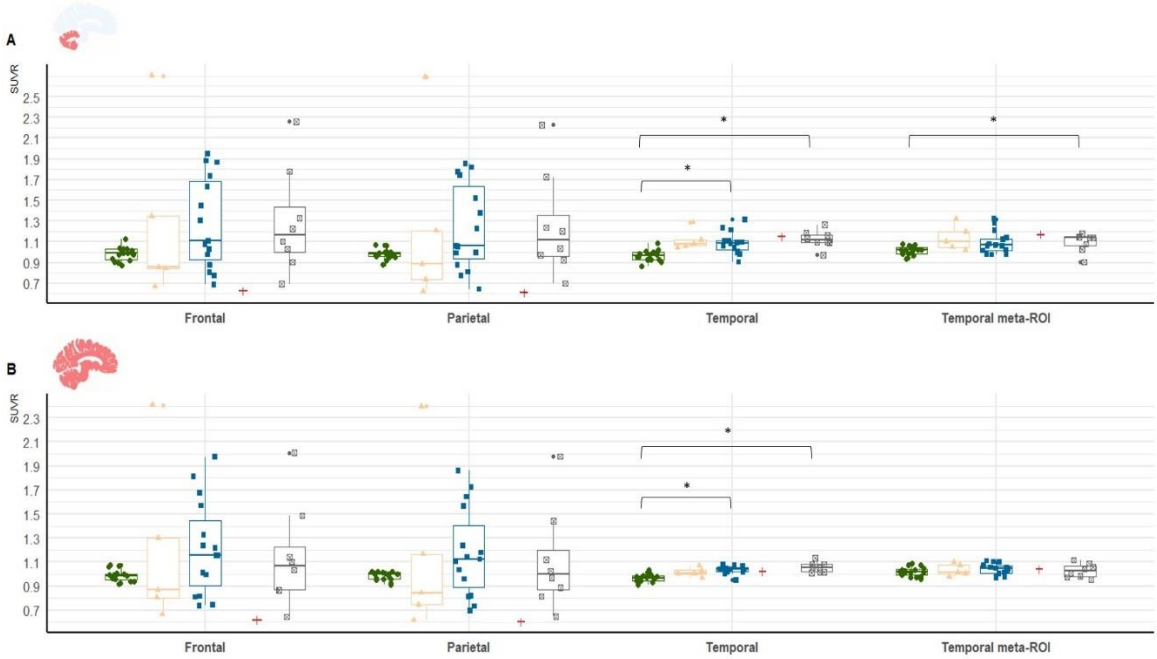


Figure 3: Neuroinflammation is uniform in the temporal regions but not in the fronto-parietal regions in atrophy-defined subtypes of AD.

Figures 2A and 2B represent SUVR values of uHI (in green circles; n=16) and AD patients with hippocampal-sparing atrophy (in beige triangles; n=5), limbic-predominant atrophy (in blue squares; n=15), minimal atrophy (in red cross; n = 1), and typical atrophy (in gray squares; n = 8) using the cerebellar cortex or the whole brain as a reference, respectively. Classification in these subtypes was obtained using the 25th percentile as atrophy cutoff. Regional SUVR were compared using the Kruskall-Wallis test, with significance set at 0.05, two-tailed. The results of post-hoc comparisons using Dunn's test are shown, with significance set at 0.05 and Holm's correction for multiple comparisons.

AD, Alzheimer's disease; uHI, age-unmatched healthy individuals; ROI, region of interest; SUVR, standard uptake value ratio.

*: $p<0.05$

3.3. Correlation analysis

Furthermore, we performed a correlation analysis of the regional SUVR with the corresponding atrophy measurement. No significant results were noted with adjustment for TSPO genotype and age ($p>0.05$; corrected; figure 4). With a more permissive threshold, we observed three significant correlations. When the cerebellar cortex was used as a reference, we observed a negative correlation of the temporal SUVR with the temporal volume ($p=0.04$; uncorrected; T value= -2.2; β= -0.03; 95%-CI= [-0.06 - -0.001]; adjusted R^2=11%). When the WB was used as a reference, we observed a positive correlation of the parietal SUVR with the parietal volume ($p=0.03$; uncorrected; T value= 2.3; β= 0.008; 95%-CI= [0.001 - -0.015]; adjusted R^2=13%), as well as a negative correlation of the temporal SUVR with the temporal volume ($p=0.02$; uncorrected; T value= -2.4; β= -0.09; 95%-CI= [-0.17 - -0.014]; adjusted R^2=15%). Finally, it would appear that the relationships between neuroinflammation and cognitive measurements, APOE4 carriage and cerebrovascular co-pathologies were not related to the atrophy-defined classification (supplementary figure 2).

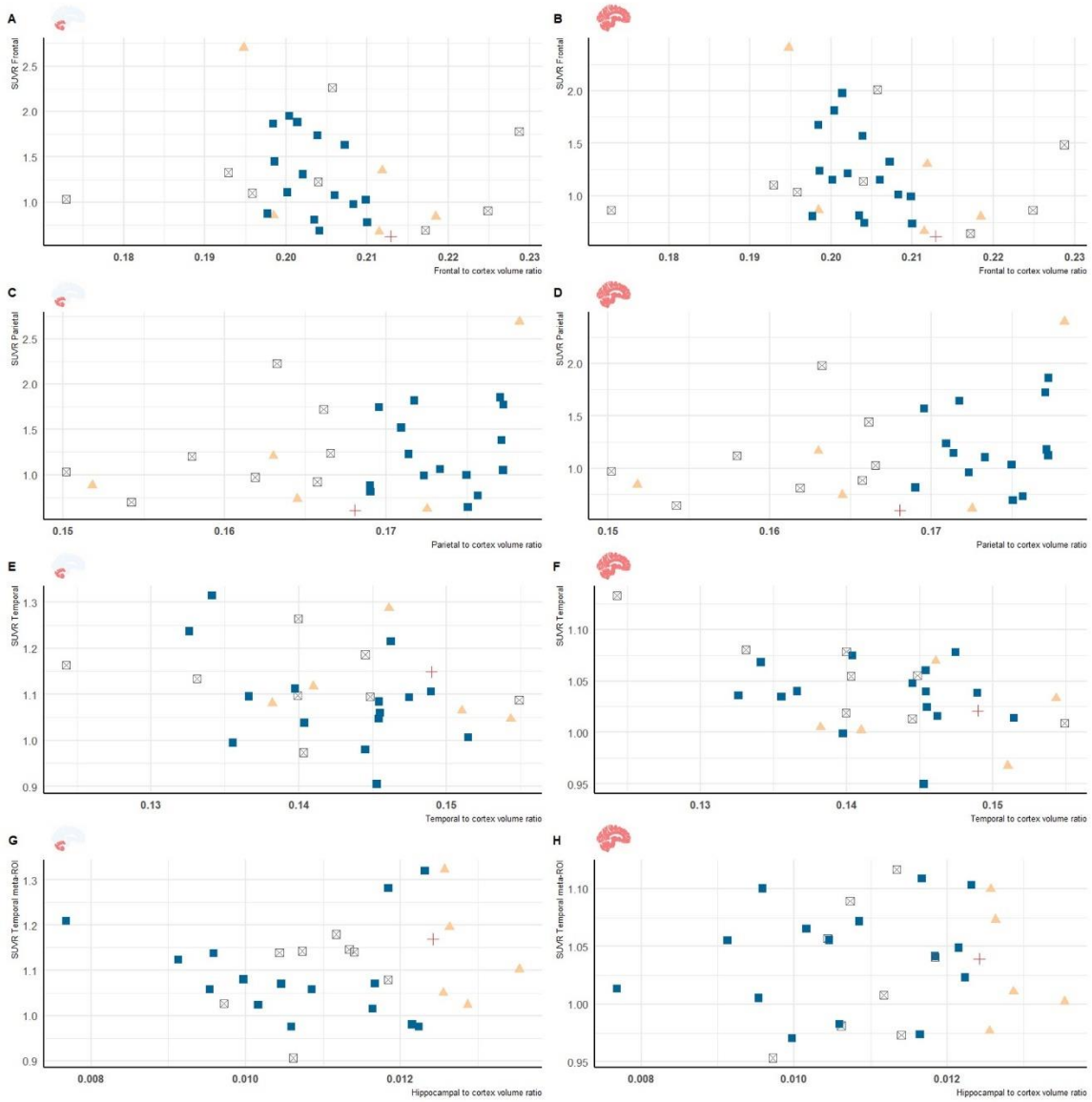


Figure 4: Neuroinflammation is not correlated the regional volume among atrophy-defined subtypes of AD.

The figure shows AD patients with hippocampal-sparing atrophy (in beige triangles; n=5), limbic-predominant atrophy (in blue squares; n=15), minimal atrophy (in red cross; n = 1), and typical atrophy (in gray squares; n = 8). Panels show the results for the frontal (A and B), parietal (C and D), temporal (E and F), and hippocampal/temporal meta-ROI (G and H) using the cerebellar cortex or the WB as a reference, respectively.

4. Discussion

In this study, we found that (1) half of the patients with early AD had limbic-predominant atrophy, (2) neuroinflammation was higher in the temporal regions of AD patients but did not differ between the typical and limbic-predominant atrophy subtype, and (3) neuroinflammation was not correlated with the corresponding regional volume.

Until now, biological subtypes of AD have been distinguished according to the level of typicality based on a specific pathological pattern (i.e. tau pathology), and the severity level based on the degree of neurodegeneration[4]. Previous studies have found that neuroinflammation on PET is more related to tau and neurodegeneration than to the amyloid pathology[15,16]. However, our results suggested that neuroinflammation is neither related to the typicality nor to the severity level of AD. Our study highlighted a considerable variability of neuroinflammation across AD atrophy-defined subtypes.

From a pathophysiological standpoint, one possibility is that patients with a typical atrophy pattern are pathologically more advanced than patients with limbic-predominant atrophy, with a higher susceptibility of future increase in neuroinflammation. This notion is supported by studies showing that patients with typical AD are susceptible to a worse cognitive decline than limbic-predominant patients[13,17,18], and that a longitudinal increase in neuroinflammation on PET is associated with an accelerated cognitive decline in AD patients[19,20]. Therefore, in our study, it is plausible that AD patients with typical atrophy would have a higher longitudinal increase in neuroinflammation and a worse prognosis than patients with limbic-predominant atrophy.

It was shown that the role of neuroinflammation varies according to disease stage, and that microglial activation on TSPO PET predicts the pattern of tau deposition across Braak stages[5,20]. In our study, we observed striking variability in the intensity of neuroinflammation in the frontal and parietal cortex but not in the temporal regions of AD patients with different atrophy subtypes.

One possibility is that such variability stems from regionally different pathophysiological dynamic, even for patients at the same clinical stage. In our results, this idea is probably supported by a tendency towards a negative correlation between the SUVR values and the corresponding temporal volume, and a tendency towards a positive correlation between the SUVR values and the corresponding parietal volume. These results might indicate a protective neuroinflammation in the frontal and parietal regions for some patients while a disease-associated neuroinflammation in the temporal regions. This idea suggests that different regions might be associated with distinct pathophysiological dynamic of neuroinflammation, even at the same disease stage.

Furthermore, the protective/toxic function of neuroinflammation cannot be identified on TSPO PET[21], and this precludes ascertaining these hypotheses. Both brain volume and neuroinflammation on TSPO PET could be interpreted as a reflection of disease progression or brain reserve, that is the ability to maintain cognitive functioning despite an increasing pathology. Therefore, further studies are warranted to elucidate the relationship between neuroinflammation and different subtypes of AD.

It should be noted that recent neuropathological studies have shown that TSPO expression in the brain is not correlated to the magnitude of neuroinflammation and AD pathological changes[22–24]. Therefore, another explanation of our results could be that the pattern observed on TSPO PET is simply dissociated from brain pathological changes.

Several methodological aspects should be considered. We used MRI regional atrophy as a proxy for classification[3]. However, neurodegeneration is unspecific to AD, and this precludes ascertaining the results of the classification. In our study, we observed different prevalence of AD subtypes than previously published studies[4], especially a higher prevalence of patients with limbic-predominant atrophy. However, in our study, this observation is consistent with the fact that most patients had early AD (MMS >20/30) with an amnestic presentation of the hippocampal type. This is also consistent with the distribution of atrophy revealed by the voxel-based morphometry analysis (figure 2).

Besides, we used a hypothesis-driven approach for classification instead of a data-driven analysis. Hypothesis-driven analysis is also histologically validated[2,3] and proved to be effective in identifying several clinico-biological differences between subtypes of AD[4]. In addition, (un)supervised data-driven classification methods gave cohort-dependent results, which may limit a broader exploration of our results. Regarding the classification method, we used two cutoffs for atrophy, and a cohort of eHI matched for age, gender, and educational level as controls. In addition, simple classification method using a single cutoff for atrophy previously enabled a distinction of AD subtypes in terms of cerebrospinal fluid amyloid biomarker values, gray matter atrophy, and clinical progression rates[17]. Therefore, it seems unlikely that our classification method would have significantly biased our analyses.

Some other methodological limitations of this study are specific to TSPO PET imaging. No ideal reference region exists for TSPO imaging, especially because of the brain-wide expression of TSPO. In our study, we replicated all the analyses with the WB as a reference in addition to the use of the cerebellar cortex. This improved the confidence in our results, although the use of supervised clustering reference might remain more appropriate in AD[25]. Another concern regards the age of uHI. It is known that lower neuroinflammation is observed on TSPO PET in young HI compared to eHI[26]. In our study, the use of uHI might have resulted in an overestimation of the SUVR values. However, 6/16 uHI were age >50 years old, which might have attenuated age-related confounding variables. In addition, the presence of neuroinflammation in AD is a widely replicated result in TSPO PET studies, especially in the temporal region[27]. Therefore, it seems unlikely that neuroinflammation was entirely absent from the brain of our patients.

In conclusion, we showed preliminary evidence of neuroinflammation in atrophy-defined subtypes of AD. Further studies are warranted to elucidate the presence of neuroinflammation in a larger population, and how neuroinflammation can be differentially related to disease progression in these subtypes.

Acknowledgment

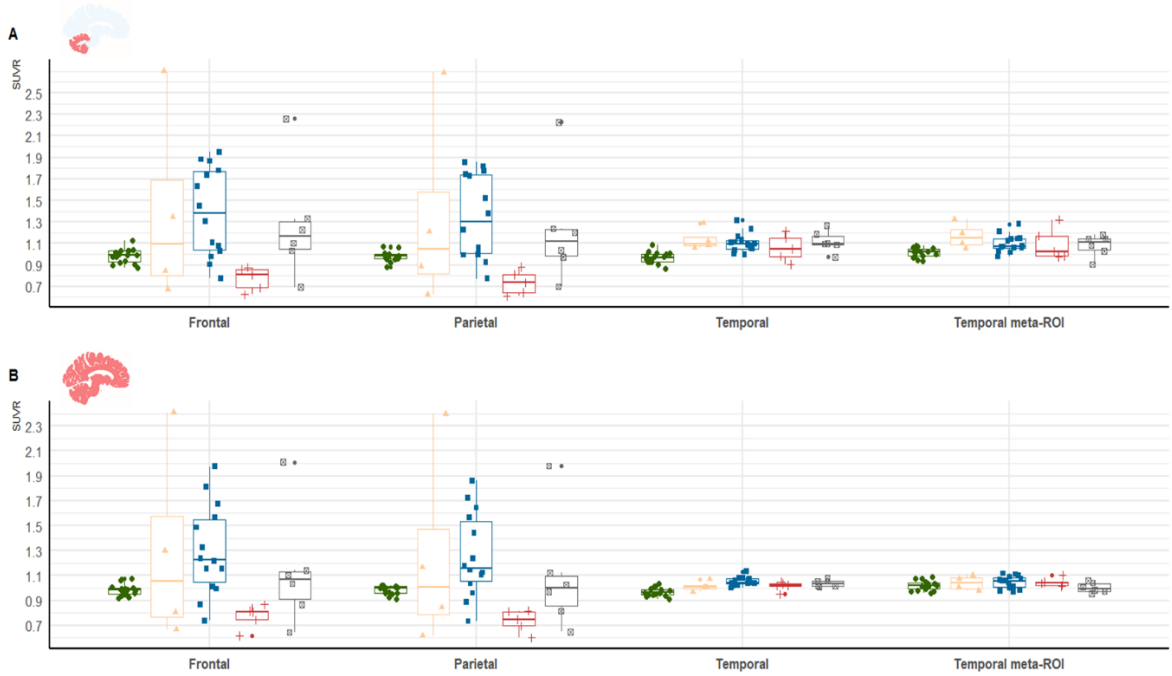
We would like to thank the Fondation Alzheimer for the support of this study, and the French National Agency for Research called “Investissements d’Avenir” IRON Labex. We also would like to thank the INSERM/UPS Tonic technical platforms and the Center of Clinical Investigation of the CHU of Toulouse.

Glossary

AD; Alzheimer’s disease; DMS-48, delayed-to-matching 48; FAB, frontal assessment battery; FCSRT, free and cued selective reminding test; HAB, high affinity binder; eHI, elderly healthy individuals; uHI, age unmatched healthy individuals; LAB, low affinity binder; MAB, mixed affinity binder; MCI, mild cognitive impairment; MMS, mini-mental state examination; MRI, magnetic resonance imaging; PET, positron emission tomography; ROCF, Rey-Osterrieth complex figure; ROI, region of interest; STAI-Y, State-Trait Anxiety Inventory; SUVR standard uptake value ratio; SWI, susceptibility weighted imaging; TMT, trail making test; TSPO, translocator protein; WB, whole brain WAIS IV, Wechsler Adult Intelligence Scale fourth edition.

References

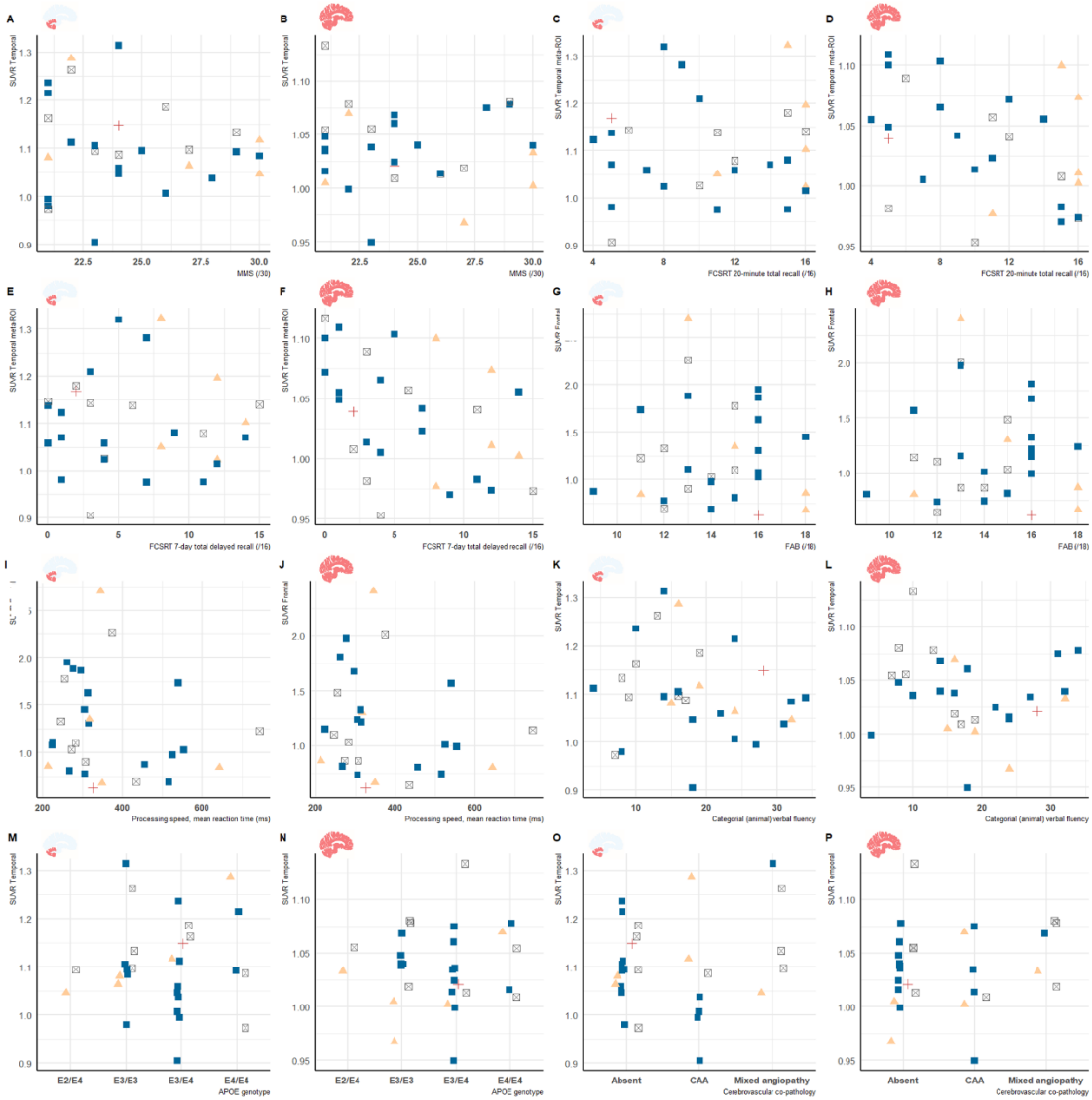
Note : *L’ensemble des références de cet article de revue a été placé en annexe 5.*



Supplementary figure 1: SUVR values in atrophy-defined subtypes of AD using -1 standard-deviation as atrophy cutoff for classification.

Panel A and B represent SUVR values of uHI (in green circles; n=16) and AD patients with hippocampal-sparing atrophy (in beige triangles; n=4), limbic-predominant atrophy (in blue squares; n=14), minimal atrophy (in red cross; n = 4), and typical atrophy (in gray squares; n = 6) using the cerebellar cortex or the whole brain as a reference, respectively.

AD, Alzheimer's disease; uHI, age-unmatched healthy individuals; ROI, region of interest; SUVR, standard uptake value ratio.



Supplementary figure 2: The relationships between neuroinflammation and cognitive measurements, APOE4 carriage, and cerebrovascular co-pathologies are not related to atrophy-defined subtypes of AD.

The figure shows AD patients with hippocampal-sparing atrophy (in beige triangles; n=5), limbic-predominant atrophy (in blue squares; n=15), minimal atrophy (in red cross; n = 1), and typical atrophy (in gray squares; n = 8). Panels show the results for the MMS (A and B), FCSRT 20-minutes total recall (C and D), FCSRT 7-day total recall (E and F), the FAB (G and H); processing speed (I and J); categorical (animal) verbal fluency (K and L); APOE genotype (M and N), and the presence and type of cerebrovascular co-pathology (O and P) using the cerebellar cortex or the WB as a reference, respectively.

Discussion et perspectives

3. Discussion

3.1. Généralités

Les études réalisées au cours de cette thèse se portent sur le développement des biomarqueurs de la MA. J'ai pu étudier différents types de biomarqueurs. L'étude sur l'$A\beta_{42}$ et du ratio $A\beta_{42/40}$ du LCS portent sur des biomarqueurs diagnostics. L'étude VIP porte sur l'imagerie TEP de TSPO, c'est-à-dire un biomarqueur de progression de la MA.

Les études réalisées au cours de cette thèse se situent à différents niveaux du développement de ces biomarqueurs. Les sections suivantes présentent les perspectives d'extension des projets de cette thèse. Le lecteur pourra se référer aux sections correspondantes à ces études pour trouver une discussion détaillée de leurs résultats.

3.2. Taking the A train? Limited consistency of $A\beta_{42}$ and the $A\beta_{42/40}$ ratio in the AT(N) classification

Cette première étude portait sur l'interprétation des taux d'$A\beta_{42}$ ou du ratio $A\beta_{42/40}$ dans le LCS dans le cas d'un diagnostic purement biologique de MA. Les limites de ce travail ont été décrites dans la section dédiée à cette étude. Deux limites peuvent néanmoins être mentionnées car elles sont l'objet de perspectives d'études futures.

La première concerne la méthode de quantification des biomarqueurs du LCS. Dans notre étude, il s'agissait de la méthode ELISA. Cette méthode a largement été employée dans le monde. Elle nécessite la manipulation manuelle des échantillons par un technicien expérimenté. Elle est maintenant progressivement remplacée par des méthodes de quantification automatique, notamment pour limiter la variabilité induite par la manipulation manuelle des échantillons. C'est le cas du CHU de Toulouse où la méthode de quantification par électroluminescence Lumipulse a été installée depuis septembre 2019 (Bayart et al., 2019).

Notre analyse pourrait donc être reproduite avec cette nouvelle méthode de quantification. Cela permettrait d'actualiser nos résultats en vérifiant l'influence potentielle de la méthode de quantification sur les taux des biomarqueurs mesurés.

Une autre limite concerne le nombre de sujets A+T+ ou A-T- pour lesquels le calcul du ratio $A\beta_{42/40}$ (c'est-à-dire le dosage de l'$A\beta_{40}$) a été fait de façon systématique. Ce nombre était peu élevé dans notre étude. Les patients que nous avons inclus réalisait une PL pour la première exploration de difficultés cognitives pour une suspicion de maladie neurodégénérative. Il s'agit donc de patients aux premiers stades symptomatiques de leur maladie. Ce recrutement a donc induit un biais de sélection naturellement. Ce choix provient de raisons d'ordre pratique et statistique. Nous avions accès à une base de données du Centre Mémoire et de la clinique de neurologie de Toulouse. Recruter les patients concernés par la première exploration de difficultés cognitives permettait de mieux comprendre l'utilisation de l'$A\beta_{42}$ et du ratio $A\beta_{42/40}$ dans ce cas. Cela permettait aussi de maximiser le nombre de patient inclus car il s'agit du cas le plus fréquent nécessitant une PL en clinique de neurologie. Une analyse sur des patients d'âge plus avancé pourrait permettre d'éviter ce biais. Cela permettrait d'étudier la question de la cohérence de l'$A\beta_{42}$ et du ratio $A\beta_{42/40}$ chez des patients où la symptomatologie et/ou la pathologie est plus avancée.

3.3. **Le projet VIP**

3.3.1. **Conclusion des études 1 et 2 sur VIP**

Le projet VIP étudie l'effet du neflamapimod (AINS, inhibiteur de la MAPK p38α) aux premiers stades de la MA. J'ai pu réaliser deux études ancillaires transversales à VIP sur les résultats d'inclusion des patients. La première étude permit de montrer l'absence de corrélation entre la neuroinflammation en imagerie TEP de TSPO et les performances neuropsychologiques. La deuxième permit de montrer l'absence de corrélation entre le niveau de TSPO en TEP et les profils d'atrophie en IRM structurale. Cette absence de corrélations révèle une variabilité des profils d'imagerie TEP de TSPO dans les patients de VIP.

Cette variabilité traduit peut-être la présence de changements physiopathologiques différents dans le continuum de la maladie, et l'existence d'une vulnérabilité individuelle pour développer la neuroinflammation. Cette variailité est peut-être associée à différents types d'activité immunitaire, neuroprotecteur ou toxique. Néanmoins, le fait que ces différents endophénotypes neuroinflammatoire soient indissociables en imagerie TEP de TSPO rend cette idée incertaine.

Des études supplémentaires sont nécessaires pour comprendre les déterminants et l'impact de l'hétérogénéité des profils de neuroinflammation sur la progression de la MA. Les perspectives d'extensions du projet VIP sur ces questions sont l'objets des sections suivantes.

3.3.2. **Extension 1 : le vieillissement et les patients de VIP**

Une limite substantielle des études 1 et 2 de VIP si situe dans l'absence de sujets contrôles sains âgés. Cela ne nous permit pas de comparer l'intensité de la neuroinflammation des patients de VIP à des individus du même âge, ou du moins d'un âge quasiment équivalent.

Le vieillissement sain est associé à une augmentation de la neuroinflammation. Cette augmentation provient des différents changements physiopathologiques liés à l'âge. Ces changements ont fait l'objet d'un article de revue récent auquel le lecteur peut se référer pour des détails supplémentaires (Hou et al., 2019). En particulier, la senescence cellulaire serait une base mécanistique déterminante l'apparition de la neuroinflammation et des changements pathologiques de la MA, d'une manière synergique (Saez-Atienzar and Masliah, 2020). En imagerie TEP de TSPO, une étude a montré une augmentation de la neuroinflammation entre une cohorte de sujet jeune et âgé (Yokokura et al., 2011).

Les résultats d'individus sains âgés seraient utiles non seulement de confirmer la présence de la neuroinflammation. Cela permettrait d'identifier la part pathologique du pattern spatial observé en retirant l'influence de l'âge. Il n'est pas excluable que les corrélations que nous avons testées dans ces études n'aient pas été significatives car elles se basaient sur des régions où la neuroinflammation n'était pas pathologique.

Au cours du projet VIP, une collaboration a pu être mis en place avec la professeure Marie Sarazin (hôpital Saint-Anne, Paris). Marie Sarazin est investigatrice principale du projet IMABio 3 sur l'imagerie TEP de TSPO dans la MA. Cette collaboration permettrait à l'équipe de Marie Sarazin de nous aider dans la compréhension des résultats de VIP. Elle permettrait le partage gracieux de données des sujets contrôles sains âgés du projet IMABio 3.

Cette collaboration m'a permis de réfléchir à une extension possible des analyses de VIP.

Dans le projet IMABio 3, la quantification de la fixation DPA avait été réalisée en SUVR après un prétraitement quasiment similaire au notre (Hamelin et al., 2018, 2016). Une différence importante réside dans l'intervalle post injection où la SUVR a été calculée qui était de 60ème à 90ème minute. Il avait été montré que la fixation du DPA était à l'équilibre sur cet intervalle chez le sujet sain. Cette méthode ne sera pas possible dans l'étude VIP car les acquisitions des images TEP étaient arrêtées à la 60ème minute post injection. Néanmoins, il est possible d'envisager une quantification de la SUVR de 50 à 60 minutes des données de l'étude IMABio 3 tout comme cela a été effectuée dans les études 1 et 2 de VIP.

La comparaison de la SUVR des sujets sains âgés de IMABio 3 et des patients de VIP révèlera le pattern pathologique de la neuroinflammation de ces patients. Il est probable que ce pattern recouvre les régions temporales. La plupart des études en imagerie TEP de TSPO dans la MA ont montré une augmentation du niveau de TSPO dans ces régions (Bradburn et al., 2019). De plus, l'étude 2 des profils d'atrophie des patients de VIP en IRM structurale révéla que les changements pathologiques semblent être situés principalement dans les régions temporales. Il est donc probable d'observer une augmentation de la neuroinflammation dans ces régions en comparant les patients de VIP à des sujets sains âgés. Cependant, la proportion de cette augmentation est moins prévisible. On pourrait par exemple observer la présence d'une augmentation dans des clusters éparses au niveau temporal en absence d'augmentation au niveau régional moyen.

L'augmentation de la neuroinflammation dans d'autres régions que les aires temporales est aussi incertaine. La littérature montre des résultats variables à ce sujets, et une forte hétérogénéité des résultats entre les patients aux premiers stades de la MA (Bradburn et al., 2019; Hamelin et al., 2016). Nous avons observé cette variabilité dans les études 1 et 2 de VIP. Il est donc possible qu'aucune différence ne soit significative.

3.3.3. **Extension 2 : les marqueurs inflammatoires du liquide cérébro-spinal**

La variabilité clinique des profils de neuroinflammation en TEP des patients de VIP procède probablement de l'influence combinée du stade de la maladie et de la vulnérabilité individuelle de ces patients à développer la neuroinflammation.

L'influence du stade de la maladie a été étudiée dans l'étude 1 et 2 de VIP à travers la relation de la neuroinflammation en TEP et des indicateurs de progression de la MA. Ces études sont limitées en particulier par la compréhension du processus de la neuroinflammation qui ne peut pas être révélé en imagerie TEP de TSPO en termes de neuroprotection ou toxicité. Par ailleurs, l'influence de la vulnérabilité individuelle des patients à développer la neuroinflammation n'a pas été étudiée dans les études 1 et 2 de VIP.

Une possibilité pour explorer ces aspects plus en profondeur serait l'utilisation de marqueurs inflammatoires du LCS. Ces marqueurs reflètent des processus moléculaires distincts reliée de près ou de loin à la neuroinflammation. Les biomarqueurs de la neuroinflammation du LCS sont de plus en plus employés. Certains ont été récemment ajoutés à la classification AT(N) (Hampel et al., 2021). Par exemple, des biomarqueurs d'une activité neuro-immunitaire pro-inflammatoire sont l'IL-1β, l'IL-6, YKL-40, et le TNFα (tumor necrosis factor alpha en anglais) (Morgan and Mielke, 2021). Des exemples de biomarqueurs d'une activité neuro-immunitaire anti-inflammatoire sont l'IL-4, l'IL-12, INFγ (interféron gamma), et le variant soluble de TREM2.

Au cours du projet VIP, une collaboration avec la professeure Claire Paquet (hôpital Lariboisière, Paris) a été mise en place. Cette collaboration permettrait le dosage de ces biomarqueurs inflammatoire du LCS.

Cette collaboration me permet de réfléchir à une deuxième possibilité d'extension des analyses de VIP.

Il serait possible de corréler les valeurs de SUVR à des biomarqueurs inflammatoires du LCS de manière transversale. Cela permettrait peut-être de comprendre le type de processus inflammatoire visualisé en TEP, neuroprotecteur ou toxique. Mais il reste improbable d'observer une relation linéaire avec l'un de ces marqueurs si différents profils de neuroinflammation sont reflétés par l'imagerie TEP de TSPO. Cela est d'autant plus improbable s'il peut exister différents profils de neuroinflammation entre différentes régions. Une possibilité serait de faire une analyse discriminante pour classer les patients en sous-groupes. Le principe de ce type d'analyse statistique a été présenté dans la section dédiée à l'étude 2 de VIP. De telle analyses permettrait d'observer l'association des valeurs de biomarqueurs de processus inflammatoires distincts avec la SUVR de différentes régions. Cela permettrait de décrire différents profils de neuroinflammation chez nos patients et de décrire la relation avec leurs performances neuropsychologiques.

Une autre partie de cette étude pourrait être consacrée à l'étude des relations entre les biomarqueurs du LCS et les performances neuropsychologiques des patients de VIP. L'interprétation d'une corrélation significative serait difficile. En effet, aucune corrélation n'a été observée entre la SUVR en imagerie TEP de TSPO et les performances neuropsychologiques des patients de VIP. La présence d'une corrélation significative avec les biomarqueurs inflammatoires du LCS pourrait suggérer une dissociation entre la neuroinflammation et la mesure de la SUVR en imagerie TEP de TSPO. Une telle dissociation expliquerait l'absence de corrélation dans l'étude 1 et 2 de VIP. Elle serait en accord avec les résultats des études montrant que la base biologique de l'imagerie TEP de TSPO n'est pas directement liée à la neuroinflammation, en particulier ceux d'études de neuropathologie récentes (Gui et al., 2020; Xu et al., 2019).

Une telle étude serait donc aussi inscrite dans le développement de l'imagerie TEP de TSPO. Elle permettrait d'élucider la relation entre sa mesure et celles d'autres biomarqueurs de la neuroinflammation.

3.3.4. **Extension 3 : imagerie transcriptomique de la neuroinflammation**

La susceptibilité d'un patient à développer la neuroinflammation a différentes lignes d'expression. L'influence du mode de vie et de l'environnement peut être étudiée par l'utilisation de marqueurs plasmatiques de l'inflammation. L'influence des déterminants génétiques sur la vulnérabilité à développer la neuroinflammation est une autre possibilité.

Le protocole de VIP prévoyait qu'une part des prélèvements sanguins soit exploitée pour une analyse transcriptomique. Cette perspective n'a pas été envisagée en pratique dans le temps de cette thèse. Néanmoins, on me permettra une petite disgression compte tenu de l'actualité de cette perspective. L'influence des changements régionaux d'expression génétique sur la vulnérabilité de la microglie et de l'astroglie a fait l'objet d'études récentes. Dans le vieillissement sain, la diversité régionale des profils transcriptomiques de la microglie a été associée à des régions où elle opère des fonctions homéostasiques mais aussi à des régions sensibles à ses dysrégulations et à la neurodégénérescence liées à l'âge (Grabert et al., 2016). Des premières explorations dans la MA révèlent la diversité des profils transcriptomiques (Boche and Gordon, 2022; Young et al., 2021). Certaines études ont pu relier des patterns régionaux d'expression génétique différentiels à des changements de connectivité fonctionnels (Yu et al., 2021).

Dans VIP, une analyse transcriptomique permettrait d'étudier la variabilité des profils d'expression des gènes de la neuroinflammation, pro ou anti-inflammatoire, entre les patients. Ces profils pourraient aussi être mis en relation avec les valeurs d'atrophie en IRM structurale et de SUVR en imagerie TEP de TSPO à différentes échelles spatiales. Un intérêt particulier pourrait être porté sur la voie de signalisation de TSPO (Batarseh et al., 2010, 2008). Il serait intéressant d'étudier l'association entre les variations régionales de l'expression des gènes de cette voie et les valeurs de SUVR reflétant le niveau de la protéine exprimée. Cela pourrait permettre l'étude des relations entre le processus cellulaire d'expression de TSPO au niveau transcriptomique et protéique et le pattern spatial neurodégénératif de la MA.

3.3.5. **Extension 4 : IRM multimodale et neuroinflammation en TEP**

Le protocole de VIP prévoyait l'acquisition d'autres séquences IRM en plus de la séquence pondérée en T1, et des séquences FLAIR et SWI. Il y avait l'acquisition d'une séquence de connectivité fonctionnelle au repos ('resting state' en anglais) et de perfusion cérébrale par marquage des spins artériels ('arterial spin labelling', ASL, en anglais). Je peux mentionner brièvement la possibilité d'extension des analyses de VIP par l'exploitation de ces séquences.

A ma connaissance, il n'y a aucun article publié dans la MA pour étudier la relation entre la neuroinflammation en imagerie TEP et la connectivité de réseau au repos, ou le débit sanguin cérébral en IRM. Une part des connaissances à ce propos a été décrit en introduction, et est disponible dans plusieurs articles de revue spécialisés.

Dans VIP, il pourrait être intéressant de mesurer les corrélations entre la déconnexion de régions au repos, les dysfonctions du débit sanguin cérébral et la neuroinflammation. Cela permettrait de mieux comprendre les interactions entre des changements pathologiques associées à la MA aux échelles moléculaire (la neuroinflammation), cellulaire (la connectivité de réseau au repos), métabolique (la perfusion cérébrale), et cognitive. Par exemple, il a été montré que la pathologie tau se propage des régions temporales internes aux régions associatives via les faisceaux de substance blanche en synergie avec la présence de la pathologie amyloïde dans ces régions (Jacobs et al., 2018). La propagation de la tauopathie via ces faisceaux est associée à des anomalies spécifiques de connectivité, et précède le déclin cognitif chez des patients aux premiers stades de la MA. Dans l'étude 2 de VIP, l'atrophie des régions frontale et pariétale n'était significative que pour 11 patients (33%) qui étaient ensuite classés en sous-type typique de MA. La neuroinflammation était hétérogène dans ces régions et n'était pas augmentée de façon significative. Il pourrait être intéressant de tester la présence d'une corrélation entre la neuroinflammation et la connectivité des régions temporales internes, des régions cingulaires, pariétale et frontale. Cela permettrait peut-être d'expliquer l'hétérogénéité de l'intensité de la neuroinflammation dans ces régions.

3.3.6. **Extension 5 : effet du neflamapimod sur les patients de VIP**

Le projet VIP est l'étude de l'effet du neflamapimod aux premiers stades de la MA. Il s'agit d'un essai de phase II, monocentrique, randomisé contre placébo, et dont le suivi des patients a une durée de trois mois. Le critère de jugement principal est mesuré en imagerie TEP de TSPO, tandis que les critères secondaires sont des mesures de la progression de la MA au niveau cognitif et en IRM structurale. Le rationnel scientifique de VIP, la conception de l'étude, et son protocole sont détaillés dans des sections dédiées auxquels le lecteur pourra se référer.

Il n'a pas été possible pour moi d'analyser les résultats de l'effet du traitement dans le temps de ma thèse. En effet, il était important de mettre au point la méthode de quantification pour l'imagerie TEP de TSPO, le critère de jugement principal de VIP. Un autre intérêt était d'améliorer notre compréhension des relations entre ce biomarqueur et les autres indicateurs de la progression de la MA chez les patients de VIP : les performances cognitives et l'atrophie en IRM structurale.

J'ai pu réfléchir à l'interprétation des résultats de cette étude.

Les études 1 et 2 de VIP sur les données précédant la prise du traitement ont montré une variabilité importante des profils de neuroinflammation en TEP. On pourrait penser que la présence de cette variabilité limite les chances d'observer un effet du traitement. Par exemple, il est possible que cette variabilité reflète la présence d'une neuroinflammation dont le phénotype prédominant a un impact neuroprotecteur pour certains patients, et neurotoxique pour d'autres. On peut donc envisager que le traitement soit inefficace à l'échelle du groupe, même s'il a un effet bénéfique pour les patients dont l'inflammation est neuro-toxique. Le pattern spatial de ce changement aura également un intérêt majeur. Par exemple, si une diminution est observée dans les régions temporales, son interprétation sera vraisemblablement bénéfique pour les patients. L'impact de la variabilité des profils TEP sera aussi influencé au hasard par la randomisation des patients.

Le neflamapimod inhibe la voix de signalisation pro-inflammatoire et neurotoxique de la MAPK p38α. L'engagement thérapeutique espéré est donc une diminution de la neuroinflammation en TEP. La possibilité d'observer un tel effet dépend de la présence d'une activation de la voix de la MAPK p38α, et de l'interaction entre cette voix d'activation et la voix d'expression de TSPO.

L'activation de la voix de la MAPK p38α est probable dès les premiers stades de la MA. Les résultats des premiers essais de phase I et II suggère la possibilité d'un engagement thérapeutique (Alam et al., 2017; Scheltens et al., 2018). Ces essais montrent aussi un effet modéré et bénéfique du traitement, en particulier sur les marqueurs des dommages synaptiques. Cependant, la présence d'une neuroinflammation neuroprotectrice chez certains patients suggère qu'une intervention avec le neflamapimod ne serait pas adaptée. Le rôle de la neuroinflammation en TEP est de nature associative. Il n'est donc pas excluable qu'un patient dont le pattern de neuroinflammation en TEP soit interprété comme étant neuroprotecteur puisse bénéficier du traitement. La neuroinflammation en TEP pourrait refléter un impact cellulaire global de la neuroinflammation, qui ne soit pas incompatible avec un effet du traitement bénéfique.

Une autre possibilité est que l'inhibition de la MAPK p38α interagisse avec la voix d'expression de TSPO indépendemment de l'effet du traitement sur la neuro-inflammation. La fonction de TSPO et sa régulation cellulaire chez l'homme dans la MA sont encore mal comprises. Peu d'études robustes confirment la corrélation entre le niveau d'expression de TSPO et l'activation microgliale. De plus, des études expérimentales sur des tissus humains, notamment des études de neuropathologie, ont suggéré que l'expression cérébrale de TSPO pourrait refléter le nombre de cellule plutôt qu'être corrélée à une activation immunitaire dont l'effet est pro-inflammatoire et neurotoxique (Gui et al., 2020; Owen et al., 2017). Il s'agit d'un débat en cours qui a été développé dans une des sections introductives de cette thèse.

Dans VIP, il est donc possible que l'intervention par le neflamapimod ait un effet sur la voix d'expression de TSPO et sur la neuroinflammation. Il est aussi possible que l'effet du traitement soit dissocié. Par exemple, si TSPO est reflète la densité cellulaire plutôt que l'intensité de la neuroinflammation toxique, il est possible que l'effet du traitement ne soit pas visible en TEP bien que l'engagement thérapeutique soit efficient. En effet, les voix de signalisation de la MAPK p38α et de TSPO sont étroitement liées (Batarseh et al., 2010, 2008). Comme la régulation cellulaire de TSPO est encore incertaine, l'effet d'une intervention par neflamapimod sur cette régulation l'est également.

L'interprétation de l'effet du neflamapimod sur en imagerie TEP de TSPO est donc difficile en raison de l'incertitude de la relation entre la mesure du niveau de TSPO et le changement tissulaire produit par l'intervention. Ces difficultés procèdent de la localisation de l'effet observé, de la variabilité des profils de neuroinflammation avant le début du traitement, et de l'incertitude de l'impact de l'intervention sur l'expression de TSPO. En apportant des résultats sur ces questions, la réalisation de l'étude VIP est inscrite dans le développement de l'imagerie TEP de TSPO dans la MA.

L'effet du traitement sur les critères secondaires peut donc jouer un rôle essentiel dans la discussion des résultats de VIP. La durée de l'intervention était de trois mois. Il est improbable d'observer un bénéfice clinique ou l'amélioration de scores neuropsychologiques sur une durée d'évolution aussi courte. La présence d'une amélioration significative serait donc une preuve claire du bénéfice du traitement.

En revanche, il est envisageable d'observer un effet sur d'autres biomarqueurs de la neuroinflammation ou du processus neurodégénératif si ces processus sont modifiés. L'étude de l'effet du traitement sur des biomarqueurs de la neuroinflammation du LCS serait intéressant en particulier. Leur utilisation permettrait d'étudier l'effet du traitement à travers des processus moléculaires multiples.

Par exemple, des études expérimentales ont montré que l'IL-1β est sécrété par l'activation de la MAPK p38α, et que sa présence a le potentiel de déclencher la tauopathie et la neurodégénérescence (Munoz and Ammit, 2010). On pourra donc interpréter une diminution de son taux dans le LCS comme une preuve d'engagement thérapeutique bénéfique.

Enfin, un autre facteur d'importance concerne l'exposition du traitement. Cette exposition dépend de la durée d'exposition, et de la dose reçue. Tous les patients ont reçu la même dose de traitement à la même posologie. Néanmoins, la durée d'exposition est légèrement variable en fonction des contraintes rencontrées pour faire les passations de l'étude VIP. Par exemple, l'examen TEP de la première patiente incluse dans l'étude fut reporté de 15 jours en raison d'une panne du cyclotron du CHU de Toulouse Purpan. Cela résulta à une prolongation du traitement, contrairement au quinzième patient qui dû interrompre la prise du traitement pendant 15 jours au milieu de la période de suivi, en raison d'une infection au COVID-19. L'influence de ces variabilités dans la durée d'exposition thérapeutique est donc possible.

Les essais de phase II du neflamapimod ont montré un effet dose-dépendant sur la cognition, et les taux de biomarqueurs de neurodégénérescence. L'étude VIP avait été élaborée avant la publication de ces données. Il n'a donc pas été prévu de faire l'étude de plusieurs doses. Ainsi il est possible que l'intervention ne soit effective que pour les patients dont le poids était suffisamment bas pour maximiser la pénétrance cérébrale du neflamapimod. Une telle contrainte serait difficile à contourner en raison de l'effectif des patients.

3.4. **La neuroinflammation dans la maladie d'Alzheimer**

Les études 1 et 2 de VIP ont montré une forte hétérogénéité des profils de la neuroinflammation dans la MA. Des études sont nécessaires pour confirmer nos résultats et comprendre les déterminants de ces profils.

La neuroinflammation dans la MA peut être influencée par des facteurs multiples. Pour en citer quelques-uns, il y a l'influence de la charge microbienne et infectieuse, de patterns génétiques complexes, l'intégrité du microbiote intestinal, le vieillissement, des antécédents de conditions de neuroinflammation aigue ou chronique (lésions vasculaires, troubles psychiatriques), ou des antécédents de maladies associées à une inflammation de système (obésité, diabète). Comment les différentes combinaisons de ces facteurs pourraient être permissif ou bien conduire le développement de la MA reste à élucider.

Par ailleurs, le potentiel thérapeutique d'intervenir sur différents profils de neuroinflammation est en cours d'étude (Hampel et al., 2020). Des thérapies immunologiques individualisées pourraient être paramétrées selon le stade des patients dans la MA, et la présence de facteurs de vulnérabilité génétique et du mode de vie. Néanmoins, ces thérapies ne sont pas encore à l'essai. Une autre possibilité serait l'établissement d'interventions multi-domaines sur le mode de vie et l'environnement qui soient personnalisées sur le profil de neuroinflammation. Ce type d'approche n'a pas été investiguée. Néanmoins, on peut citer l'approche proposée par l'équipe du docteur Dale Bredesen qui semble s'inscrire dans ce cadre (Bredesen, 2015, 2014; Bredesen et al., 2016; Rao et al., 2021), bien que plusieurs critiques à cette approche aient été rapportées (Hellmuth, 2020).

Plusieurs experts ont proposé que la neuroinflammation pourrait être l'étiologie de la MA. L'une de ces hypothèses a retenu mon attention. Il s'agit de l'hypothèse anti-microbienne développée par Rudolf E. Tanzi et ses collègues (Moir et al., 2018). Le groupe de Rudolf E. Tanzi travailla sur la cascade amyloïde, en particulier sur des aspects génétiques et moléculaires (Bertram and Tanzi, 2012; Tanzi, 2005). Plusieurs de leurs études ont montré que la déposition de peptides amyloïdes pourrait être une réponse anti-microbienne. Dans cette hypothèse, la cascade amyloïde n'est pas réfutée, mais plutôt intégrée dans un modèle où la déposition de peptides amyloïdes fait partie d'une réponse neuroinflammatoire protectrice (Moir et al., 2018). Cette idée modifie la conception de la MA. Comme l'ont suggéré Rudolf E. Tanzi et ses collègues, éradiquer la charge amyloïde cérébrale sera peut-être moins efficace que la diminuer. Peut-être aussi qu'il serait efficace de focaliser l'intervention sur les peptides amyloïdes ayant le plus de toxicité. Cela était mentionné comme une raison possible de l'efficacité du donanemab dans un essai de phase II, car cet anticorps monoclonal est spécifique des formes pathologiques les plus solubles des dépôts amyloïdes (Bouter et al., 2022).

L'hypothèse anti-microbienne suggère aussi que la MA pourrait avoir des déterminants différents que l'amyloïde. La déposition de peptides amyloïdes serait la part d'une réponse à une maladie, plutôt que la maladie elle-même. L'hypothèse anti-microbienne pourrait donc non seulement expliquer l'inefficacité des essais anti-amyloïdes. Elle pourrait changer la compréhension physiopathologique des troubles cognitifs associés à l'amyloïdopathie.

4. **Conclusion**

Cette thèse s'inscrit dans le développement des biomarqueurs de la MA. Trois études ont pu être réalisées sur des biomarqueurs de diagnostic et de progression.

La première étude montra des différences d'interprétation de l'$A\beta_{42}$ et du ratio $A\beta_{42/40}$ dans le cadre d'une définition purement biologique de la MA.

Les deux autres études ont porté sur l'imagerie de TSPO en TEP de la neuroinflammation. Elles permirent l'élaboration d'une méthode de quantification, et l'étude des relations de ce biomarqueur avec les performances neuropsychologiques, et les profils d'atrophie en IRM structural, de patients aux premiers stades de la MA. Ces trois études ouvrent de nouvelles perspectives d'amélioration de l'emploi de ces biomarqueurs en pratique de recherche.

Cette thèse s'inscrit également dans l'étude de la neuroinflammation dans la MA au niveau physiopathologique et thérapeutique. Les deux études portant sur ce sujet révélèrent une forte variabilité des profils de neuroinflammation en TEP. Les patients inclus dans ces études ont été suivi dans le cadre d'un essai de phase II d'un médicament anti-inflammatoire. L'analyse des résultats de ce suivi permettra de comprendre l'impact de la variabilité observée des profils de neuroinflammation sur la progression de la MA. Des études supplémentaires pourront être intéressantes pour comprendre les déterminants de différents profils de neuroinflammation dans la MA.

5. **Références du manuscrit**

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Annexe 1

Références de l'article de revue intitulé :

« Beyond the amyloid cascade: an update of Alzheimer's disease pathophysiology. »

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Annexe 2

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Annexe 3

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« Taking the A train? Limited consistency of Aβ42 and the Aβ42/40 ratio in the AT(N) classification »

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Annexe 4

Références de l'article intitulé :

« Clinical and neuropsychological variability of neuro-inflammatory PET profiles in early Alzheimer's disease »

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Annexe 5

Références de l'article intitulé :

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Résumé des productions associées à cette thèse

Articles publiés

Gouilly D, Tisserand C, Nogueira L, Saint-Lary L, Rousseau V, Benaiteau M, et al. Taking the A Train? Limited Consistency of Aβ42 and the Aβ42/40 Ratio in the AT(N) Classification. J Alzheimers Dis. 2021;83(3):1033-8.

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Articles soumis

Gouilly D, et al., Clinical and neuropsychological variability of neuro-inflammatory PET profiles in early Alzheimer's disease.

Gouilly D, et al., Neuroinflammation in limbic-predominant and typical atrophy-defined subtypes of Alzheimer's disease: an open-ended study.

Gouilly D, et al., Beyond the amyloid cascade: an update of Alzheimer's disease pathophysiology.

Présentations orales

Gouilly D, et al., ; Nouvelle évaluation écologique de la mémoire épisodique antérograde dans la maladie d'Alzheimer : le test Mareal ; Qui-Quoi-Où de la recherche sur les apprentissages et la mémoire à Toulouse – 2ème édition ; 06 décembre 2019 ; Toulouse ; France.

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Gouilly D, et al., Neuroinflammation in prodromal Alzheimer's disease, A trans-sectional TSPO PET imaging study, Preliminary results ; Groupe de travail international en imagerie TEP de TSPO dans les maladies neurologiques et psychiatriques ; visioconférence ; 18 janvier 2022.

Présentations affichées

Gouilly D, et al., Preliminary results: effect of p38α MAPK inhibitor on neuroinflammation assessed by DPA-714 in early Alzheimer disease ; 8èmes rencontres de la Fondation Plan Alzheimer ; 19 et 20 novembre 2019 ; Paris ; France.

Gouilly D, et al.; Taking the "A" train? Limited consistency of Ab42 and the Ab42/40 ratio in the AT(N); Réunions Francophones sur la maladie d'Alzheimer et syndromes apparentés ; 22-24 septembre 2021 ; Marseille ; France.

Résumé

Le système physiopathologique de la maladie d'Alzheimer (MA) s'organise à différentes échelles spatio-temporelles (moléculaire, cellulaire, cognitive...). L'organisation de ces sous-systèmes et de leurs perturbations dans la MA est à la base des stratégies diagnostiques et thérapeutiques.

Une première étude a été effectuée sur la valeur diagnostique des biomarqueurs amyloïdes du liquide cérébrospinal. Cette étude a permis de révéler de fortes incohérences dans le cas d'un diagnostic purement biologique de MA et de la classification ATN. Elle permit de discuter brièvement l'emploi et l'interprétation de ces biomarqueurs dans ce contexte.

La neuroinflammation prend une importance croissante dans la physiopathologie de la MA. Dans cette thèse, l'ensemble des travaux se sont basés sur le projet V.I.P. qui étudie le rôle de la neuroinflammation en imagerie tomographie par émission de positons (TEP) aux premiers stades de la MA. Ce projet est un essai clinique de phase 2 d'un composé anti-inflammatoire innovant dont l'effet est évalué en TEP scan ainsi qu'une évaluation neuropsychologique exhaustive. Une première étude a été effectuée sur les examens de la visite d'inclusion du projet V.I.P. et révéla l'hétérogénéité des profils neuroinflammatoires parmi les patients inclus, tant en termes de topographie que d'association avec leurs profils cliniques. Une deuxième étude montra que la variabilité des profils de neuroinflammation en TEP était également dissociée des profils de neurodégénérescence. Bien qu'introductifs à l'analyse longitudinale de l'effet du traitement, ces résultats montrèrent la difficulté de l'étude de la neuroinflammation aux premiers stades de la MA sur des aspects méthodologique et physiopathologique. La suite du projet V.I.P. permettra ainsi de discuter l'intérêt d'interventions immunologiques aux premiers stades de la MA.

Abstract

The pathophysiological system of Alzheimer's disease (AD) is organised at different spatio-temporal scales (genetic, molecular, cellular network, cognitive functioning…). The organisation of these subsystems and their dysfunctions in AD is the basis of diagnostic and early therapeutic strategies.

A first study was performed on the diagnostic value of amyloid biomarkers in the cerebrospinal fluid. This study revealed a low consistency of these biomarkers using a purely biological diagnosis of AD and the ATN classification scheme. The implications of this result on the use and interpretation of these biomarkers in routine clinical practice was briefly discussed in this study.

Neuroinflammation is gaining importance in AD pathophysiology and therapeutic research. In this thesis, a set of analyses was based on the V.I.P. project which is a phase two trial of a non-steroidal anti-inflammatory compound in early AD. Longitudinal difference on positron emission tomography (PET) imaging of the translocator protein is the primary end point of this project. A first trans-sectional study was performed using the baseline results of the V.I.P. project to elucidate the relationship of the inflammatory PET results with the neuropsychological measurements. This study revealed a strong heterogeneity of the inflammatory PET profiles in terms of intensity and highly variable relationships with the neuropsychological profiles. A second study showed that the variability of neuroinflammatory PET profiles was also unrelated to the regional atrophy profiles. These preliminary analyses highlight the need to study the impact of the heterogeneity of neuroinflammation in early AD on disease progression. The interest to implement immunological intervention in this context will be the subject of the V.I.P. trial.