Alzheimer's disease : epistemology, ethics, innovation

Timothy Daly

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Timothy DALY

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Alzheimer's disease: epistemology, ethics, innovation

Maladie d'Alzheimer : épistémologie, éthique, innovation

Sous la direction de :

Mme Anouk BARBEROUSSE – Sorbonne Université

M .Yves AGID – Sorbonne Université

M. Stéphane EPELBAUM – Sorbonne Université

Membres du jury :

Mme Lara KEUCK – Directrice de recherche, Institut Max Planck

Mme Wiesje VAN DER FLIER – Professeur des universités, Amsterdam UMC

M. Marc DHENAIN – Directeur de recherche, Institut de biologie François Jacob

M. Fabrice GZIL – Directeur adjoint, Espace Ethique Île-de-France

Declaration

I certify that the thesis I have presented for examination for the PhD degree of the Sorbonne University is solely my own work other than where I have clearly indicated that it is the work of others.

The copyright of this thesis rests with the author. Quotation from it is permitted, provided that full acknowledgement is made. I warrant that this authorisation does not, to the best of my belief, infringe the rights of any third party.

I declare that my thesis consists of approximately 60 000 words excluding references.

Déclaration

Je certifie que la thèse que j'ai présentée à l'examen du doctorat à l'Université Sorbonne est mon propre travail, à l'exception de celui pour lequel j'ai clairement indiqué qu'il s'agit d'un travail d'autrui.

Le droit d'auteur de cette thèse incombe à l'auteur. Citation du texte est autorisée, à condition qu'il soit pleinement reconnu. Je garantis que cette autorisation n'enfreint pas, à ma connaissance, les droits d'une tierce partie.

Je déclare que ma thèse consiste en approximativement 60 000 mots à l'exclusion des références.

Abstract

Alzheimer's disease (AD) is a major source of fear and misunderstanding and has become a public health priority. But biomedical research on AD has been marked by disappointment and fierce debate in recent decades. This three-part thesis mobilises different methods to study the controversies, explore their consequences, and propose solutions.

The first part is an empirical study that questions the dominance of the amyloid hypothesis through a bibliometric analysis of citation practices and an international survey of researchers promoted by the Alzheimer's Association. The second part uses a conceptual approach to consider research beyond the amyloid hypothesis and we propose a holistic model to maximise the quality and quantity of information useful to research and patients. The third part explores the ethics of the non-existence of validated treatments and the existence of non-validated treatments with the aim of protecting people's autonomy from non-validated treatments, moralistic attitudes towards prevention, and a fragile economic model underpinning drug development.

I argue that the biological and societal complexity of this disease defies reductionism and monopoly, and that the population as a whole, all of whom are potentially affected by the many problems AD poses for welfare and justice, should become agents of change to influence the direction of future research and policy.

Acknowledgements

"ton projet n'est pas inintéressant…"

("your [PhD] project is not uninteresting…")

– Dr. Stéphane Epelbaum, July 2017, after our first half-hour phone call in which I tried to convince him to be my co-supervisor just days before the deadline for PhD contract applications.

In 1624, my compatriot John Donne wrote that "No man is an island." Though this thesis bears my name, it would not have been written without the enormous influence of so many people in my life.

Firstly, this thesis would have been materially impossible without the financial support of an interdisciplinary Sorbonne Universités doctoral contract from 2017–2020 and the Fondation Médéric Alzheimer's generous doctoral bursary for the years 2019–2021. Secondly, if my thesis has any intellectual merit, it is because of my supervisors, Anouk Barberousse for her technical feedback on what can only be described as my pitiful attempts at writing, and Yves Agid for sharing his wide-reaching vision of neuroscience with me. *Merci*.

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I was also lucky to interact with fascinating researchers working on Alzheimer's disease during this PhD. In 2019, I spent an hour talking to John Hardy in London at UCL (incidentally, the day before Biogen announced the signal from aducanumab in one of their trials). I was absolutely struck by the intellectual honesty and humility of a man partly responsible for an explosion of necessary research into this disease. When I found out he knew where Bridgnorth was (my hometown), which he so matter-of-factly drives past on his way up north to Newcastle from London, well… my admiration only grew. When he found out I had an Irish passport and called me a "****ing b**tard" for not having to worry about visa issues on the continent, between Northeners (I suppose I'm a fake Northener, since we left Yorkshire just before my 6th birthday), I knew that was his way of saying, *you're alright, Tim*. Though others worked on formulating the amyloid hypothesis, he is the researcher who for me incarnates the heuristics of the amyloid research agenda (as described in the Introduction) so fully. Thanks also to Karl Herrup with whom I chatted briefly at the Alzheimer's Association International Congress in LA in 2019, whose 2015 "case for rejecting the amyloid hypothesis" proved fundamental in the writing of this thesis. A final thanks to Jason Karlawish for being kind about my work in our brief internet correspondance.

As for my personal life, my parents, Drs. Mike and Jan Daly, were my first source of inspiration. Their scientific outlook on the world has influenced them, and thereby me, at every level: education, health, politics. I would not have thought it interesting to become "Dr. Daly" if I had not had two stellar examples of Dr. Dalys in my life. Thanks to both of them for their comments on different aspects of my articles and manuscript, including help on Figure 1! Moreover, their influence on me is a testament to the influence of their parents' on them, so I must mention the late Nicolas & Mavis Daly, and Patrick & Gwen Nolan, all of whom I was lucky enough to meet,

and what I did not have the chance to learn through them directly, I learnt through the people they made and raised. Thanks also to my uncle Prof. Mike Nolan for his input and perspective on dementia research.

My brothers, Christopher and Alexander, have provided me with constant sources of inspiration at different periods of my life. Chris, first and foremost, for his academic brilliance: I dug deep to get "straight A*s" in my A-levels (the British equivalent of the "bac") because of his fine example. Alex, because of the moral man he strives to be on a daily basis, is a constant reminder that family should come first, something I too easily forget. Thanks too to their wonderful wives: to Dr. Heather Currin/Daly for sharing her perspective of a PhD in Alzheimer's disease research, and Marta Daly for showing me the wonderful country Poland in which she is taking care of my younger brother.

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And finally, to the *raison d'être* of this thesis: my "unofficial" co-supervisor, Stéphane Epelbaum. Looking at the front cover, "Thesis to obtain the grade of doctor from Sorbonne Université", forgive me for being a little moved and thinking of Albert Camus's letter to his teacher when he received the Nobel Prize for Literature: "*Sans vous, sans cette main affectueuse que vous avez tendue ... rien de tout cela ne serait arrivé.*" It is therefore to you, Stéphane, that I

dedicate this thesis, for without your faith in me, your intellectual and human example, your constant guidance, none of this would have happened. Thank you from the bottom of my heart!

Table of Contents

Position de thèse

Les travaux entrepris dans le cadre de cette thèse doctorale ont consisté à aborder les recherches biomédicales menées sur la maladie d'Alzheimer dans une perspective philosophique pluridisciplinaire. Pour ce faire, trois perspectives ont été privilégiées—empirique, conceptuelle, éthique. La philosophie empirique des sciences telle qu'elle est comprise ci-dedans, se situe au niveau des chercheurs et leurs opinions sur la maladie. La philosophie conceptuelle se situe au niveau de leurs concepts au niveau théorique pour comprendre ses bases physiopathologiques. L'éthique se situe au niveau des patients et l'impact que les recherches biomédicales sont susceptibles d'avoir sur eux, tant sur le plan individuel que sociétal.

Trois constats ont fait naître ce projet : d'abord, l'absence de traitement susceptible de modifier l'évolution de la maladie. Ensuite, un paysage théorique très riche dans lequel un poids très inégal est accordé aux hypothèses sur la physiopathologie de la maladie et sur les stratégies thérapeutiques qui s'ensuivent. En effet, l'approche dominante de ces 30 dernières années s'est fondée sur le ciblage pharmacologique des lésions de la maladie décrites soigneusement par le docteur Alzheimer. Mais cette stratégie thérapeutique est passée de déboire en déboire depuis les années 2000, malgré des lueurs d'espoir controversées de ces deux dernières années. Enfin, l'émergence de nouvelles pistes thérapeutiques, voire traitements « alternatifs », suggérant un éloignement de l'étude des causes cérébrales de la *dementia* au profit de l'étude des facteurs de risque au cours du vieillissement.

En creusant ces constats, mon travail s'est situé entre la description et l'évaluation de l'activité scientifique. Les questions que je me suis posées — sous la co-direction de la philosophe Anouk Barberousse (Sorbonne Université) et les neurologues Yves Agid et Stéphane Epelbaum (Hôpital Pitié-Salpêtrière) — étaient comme suivent : comment le savoir théorique s'est-il construit au

cours des 30 dernières années ? Est-il bien fondé aux yeux des scientifiques ? Peut-on poser d'autres modèles ? Quelles sont ces nouvelles tendances, quels peuvent être leur apport à l'amélioration du bien-être des actuels et futurs patients, mais aussi les éventuelles dérives ? Pour aborder ces questions, il a été nécessairement non seulement d'étudier notre époque contemporaine, mais aussi l'évolution de l'étude et la conceptualisation de la maladie depuis le début du 20ème siècle.

L'introduction de la thèse consiste en une présentation historique de cette maladie, des outils philosophiques utilisés pour la comprendre, et une présentation de la recherche contemporaine basée sur cette compréhension historique et philosophique de la recherche contemporaine.

En bref, la maladie d'Alzheimer a commencé comme un concept explicatif d'un cas rare de troubles cognitifs amnésiques chez une femme d'âge moyen et de cas similaires en Allemagne pour devenir, dans les années 1970, la cause majeure de millions de cas de *dementia* et donc une menace pour la santé publique à l'échelle mondiale. Pour que cela se produise, le syndrome clinique de *dementia* et les lésions pathologiques trouvées dans le cerveau de *persons with dementia* (*PWD*) ont dû subir une « médicalisation », c'est-à-dire qu'ils ont dû être interprétés comme des objets d'étude légitimes de différentes branches de la médecine. Notre ère biomédicale contemporaine est née de la convergence de la medicalization de la dementia et des lésions de la maladie d'Alzheimer.

Pour aborder cette période, des outils analytiques issus de la philosophie des sciences ont été nécessaires. Il est soutenu que la rigueur déductive stricte de Karl Popper, est moins applicable au cas de la recherche biomédicale que ce que l'un de ses disciples, Imre Lakatos, appelle la méthodologie des programmes de recherche scientifique. La logique de Popper dépeint chaque test des prédictions faites par une théorie comme étant définitif. En revanche, selon Lakatos,

l'unité avec laquelle les scientifiques travaillent est une séquence hiérarchique basée sur un noyau théorique et des hypothèses auxiliaires. La théorie fait des prédictions (ainsi guidées par ce qu'il appelle une « heuristique positive ») et lorsque ces prédictions ne sont pas corroborées par l'observation expérimentale, les hypothèses auxiliaires peuvent être modifiées pour protéger le noyau théorique (« heuristique négative »). Ainsi, les scientifiques peuvent travailler avec des théories imparfaites même si toutes leurs prédictions ne sont pas corroborées par les observations. En fonction du rapport entre les prédictions faite par une théorie et les résultats de l'observation, la théorie peut donc devenir plus ou moins « dégénérée » au fil du temps.

Il est soutenu que les stratégies anti-amyloïdes peuvent être comprises comme faisant partie de ce que le chercheur éminent John Hardy appelle en 2006 le *research agenda (*« programme de recherche ») étudiant l'implication de la bêta-amyloïde dans la maladie d'Alzheimer. Cet agenda est interprété à la Lakatos : il consiste d'abord en un noyau dur basé sur l'étude de différentes maladies selon lesquelles le mauvais repliement et l'accumulation pathologiques des protéines cérébrales (protéinopathie) jouent un rôle pathogène dans la neurodégénérescence. Ensuite, il y a une série d'hypothèses auxiliaires qui mettent le noyau en contact avec les données expérimentales (« heuristique positive »), et qui peuvent aussi protéger le noyau de la réfutation (« heuristique négative »). Ces hypothèses sont comprises comme des mécanismes proposés par les scientifiques pour expliquer comment la bêta-amyloïde s'accumule et comment son accumulation provoque la neurodégénérescence en aval. Enfin, étant donné le manque de succès des stratégies pharmacologiques ciblant la bêta-amyloïde chez les *PWD*, la couche externe du programme est constituée de ce qu'Eric Karran et collaguès appellent en 2011 des scénarios de maladie qui pourraient expliquer pourquoi certains essais cliniques avec des stratégies anti-amyloïdes n'ont pas fonctionné.

Cette compréhension historique et philosophique de la recherche contemporaine nous permet de comprendre les tendances actuelles de la recherche. Deux groupes de travail internationaux soutiennent que le ciblage précoce de la pathologie caractéristique de la maladie - les protéines bêta-amyloïde (Aβ) et tau - avant l'arrivée des symptômes de la *dementia* peut représenter la meilleure option de traitement modificateur de la maladie disponible. Cett approache se fonde sur une definition de plus en plus biologique de la maladie. À l'inverse, les membres de deux commissions de la revue médicale *The Lancet* mettent l'accent sur le décalage entre l'accumulation de la pathologie de la MA et la *dementia* et affirment que 40 % des cas de *dementia* pourraient être évités si la société pouvait agir tout au long de la vie contre 12 facteurs de risque touchant à la santé physique, mentale et sociale. L'idée est de favoriser la résilience des personnes face aux marqueurs neuropathologiques associés à la *dementia*.

Les données, les concepts et les stratégies thérapeutiques de ces deux grandes approches sont presque entièrement opposés. Mais elles sont unies dans ce qu'elles révèlent sur la structure hiérarchique de la recherche contemporaine : ces articles sont co-rédigés par de grandes équipes internationales et publiés dans des revues de premier plan et sont très cités. D'autres approches, au-delà du ciblage de l'Aβ et de la promotion de la résilience, existent également dans le cadre de la biologie fondamentale, mais il n'y a pas encore eu de consensus d'experts commes les deux approaches soulignées, sur la façon de choisir entre ce que Herrup appelle en 2015 la « longue liste de possibles causes de la maladie d'Alzheimer ».

Reconnaissant que les débats entre les différentes approches n'ont pas encore de réponses définitives, le but de cette thèse de doctorat est d'étudier la MA d'un point de vue épistémologique avec une variété de méthodes empiriques et conceptuelles, afin de mieux appréhender cet exemple de la façon dont la recherche médicale aborde une maladie complexe et

chronique dans notre ère moderne riche en avancées technologiques et scientifiques. Les objectifs de cette thèse sont principalement de représenter les désaccords, d'explorer leurs conséquences pour les patients et pour la recherche, et de proposer des solutions.

La thèse se divise en trois parties—empirique, conceptuelle, éthique. Mon approche méthodologique peut être située dans ce que Thomas Pradeu a appelé la philosophie *in* science, la philosophie *dans* la science plutôt que *sur* la science. Une préoccupation centrale a été d'essayer de rendre mes recherches aussi pertinentes que possible pour les chercheurs. Pour ce faire, j'ai essayé de me concentrer sur des questions que les chercheurs se posent réellement, j'ai cherché à publier dans des revues savantes qu'ils sont susceptibles de lire. De manière générale, j'ai essayé de me positionner aux côtés des chercheurs, armé d'outils philosophiques pour offrir des perspectives uniques sur cette maladie complexe.

La première partie est une étude empirique de pour interroger le bien-fondé de la dominance de l'hypothèse amyloïde par le biais d'une analyse bibliométrique des pratiques de citation et un sondage international auprès des chercheurs promue par l'Alzheimer's Association.

Premièrement, nous avons essayé de voir si les citations révélaient une attitude « moutonnière » envers l'hypothèse amyloïde au niveau de la communauté des chercheurs travaillant sur cette maladie. Dans cette période d'incertitude concernant la centralité de l'amyloïde-β (Aβ) dans la physiopathologie de la maladie d'Alzheimer, et avec la communauté apparemment divisée sur la validité de l'hypothèse amyloïde, nous avons utilisé les pratiques de citation comme mesurer comment les chercheurs ont investi leur croyance dans l'hypothèse entre 1992 et 2019. Nous avons échantillonné 445 articles citant la formulation originale de l'hypothèse par John Hardy & Gerald Higgins en 1992. Nous avons classé la polarité de leur citation selon une taxinomie de citations positives, neutres et négatives selon la méthodologie de Greenberg élaborée en 2009.

Puis nous avons testé quatre hypothèses sur les pratiques de citations. Nous avons identifié deux attitudes majeures à l'égard : une majorité (62%) d'attitudes neutres avec des propriétés cohérentes sur toute la période, et une attitude positive (35%), tendant à citer l'hypothèse plus tôt dans la bibliographie au fil du temps, tendant à prendre cet article comme une autorité établie. Malgré la majorité de citations neutres de cet article, il y avait une majorité positive d'attitudes à l'égard des différentes versions de l'hypothèse amyloïde et des stratégies thérapeutiques anti-amyloïdes (65%), ce qui soutient l'existence d'un programme de recherche évolutif sur l'amyloïde et la maladie d'Alzheimer, avec des hypothèses auxiliaires actualisées. Enfin, sur les 110 articles originaux de l'échantillon testant également l'hypothèse de manière empirique, une majorité écrasante (89%) a retourné un résultat positive, suggérant que l'affirmation centrale de l'hypothèse est reproductible.

Ensuite, par le biais d'un sondage, nous avons cherché à déterminer directement si l'hypothèse amyloïde domine toujours les opinions des chercheurs travaillant sur la maladie d'Alzheimer et à explorer les implications de cette question pour les orientations futures de la recherche. Au cours de 2019, nous avons entrepris une enquête internationale promue avec l'aide de l'Association Alzheimer avec des questions sur les théories et les traitements de la maladie. D'autres efforts pour promouvoir une étude similaire en 2021 n'ont pas permis de recruter un nombre significatif de participants. 173 chercheurs ont participé à l'enquête de 2019, dont 22% avaient des opinions « pro-hypothèse amyloïde ». Ces chercheurs avaient tendance à avoir plus de publications, étaient plus susceptibles d'être des hommes et d'avoir plus de 60 ans. Ainsi, l'opinion pro-hypothèse-amyloïde pourrait désormais être minoritaire dans le domaine mais constitue néanmoins l'hypothèse sur laquelle se fondent la plus grosse part des essais cliniques, ce qui suggère un biais de représentation. Le vote populaire des 173 participants suggère que les

traitements liés au mode de vie et les médicaments anti-tau sont source de plus d'optimisme thérapeutique que les traitements anti-amyloïdes. Nous proposons une structure de recherche plus démocratique qui augmente la probabilité que des théories prometteuses soient publiées et financées équitablement, favorise une vision scientifique plus large de la maladie d'Alzheimer et réduit la dépendance de la communauté au sens large à l'égard d'un modèle économique fragile.

La deuxième partie emploie une approche conceptuelle pour envisager les recherches au-delà de l'hypothèse amyloïde, dans laquelle nous proposons un modèle holistique visant à maximiser la qualité et la quantité d'informations utiles à la recherche et aux patients. Nous soutenons que si la communauté décide d'aller sensiblement au-delà de l'étude de l'amyloïde, qui a été étudiée à notre époque contemporaine dans le cadre d'un programme de recherche hiérarchisé, il faut qu'il y ait une certaine forme de hiérarchie sur la façon de décider entre les autres processus physiologiques impliqués dans la maladie. Nous réfléchissons donc à une manière d'avancer vers un modèle plus holistique de théories et de thérapies pour la maladie en procédant à une analyse conceptuelle de « l'association », un terme très utilisé dans la littérature sur la maladie d'Alzheimer pour impliquer certains processus physiologiques dans la maladie. Cette analyse nous amène à proposer un modèle ontologique qui nous permettrait de hiérarchiser la recherche sur la base de trois critères spécifiques : la spécificité de certains processus associés à la maladie (*disease-associated processes, DAPs*) pour la maladie d'Alzheimer, comme l'amyloïde, la fréquence à laquelle le DAP apparaît chez les PWD, et l'intensité pathogène du DAP pour la *dementia*. Nous soutenons que de nombreux processus associés à la maladie d'Alzheimer ont leur place dans notre ontologie ADAPT (*Alzheimer's Disease-Associated Processes and Targets*), mais pour des raisons différentes. Nous discutons également de la manière dont le rôle des DAPs dans la maladie est mis à l'épreuve. Nous soutenons que les contraintes d'interprétation sont

telles que les mises à l'épreuve doivent être aussi simples que possible afin que des informations significatives puissent en être extraites.

La troisième partie explore l'éthique de l'inexistence de traitements validés et l'existence de traitements non validés avec l'objectif de protéger l'autonomie des personnes contre les traitements non-validés, les attitudes moralisatrices à l'égard de la prévention, et un modèle économique fragile qui sous-tend le développement des médicaments. Nous soutenons qu'il existe une grande incertitude quant au type d'approche thérapeutique qui sera utile aux patients et que, par conséquent, il convient de faire preuve d'une réelle retenue dans la communication sur les affirmations qui sont faites dans la presse scientifique et profane, ainsi que dans les campagnes de santé publique visant à encourager les actions en faveur d'un mode de vie sain. Nous étudions la promotion d'un cas particulièrement problématique de promotion d'un traitement non validé de la maladie d'Alzheimer : les « protocoles d'amélioration du métabolisme ». Nous utilisons des outils issus de l'éthique de la recherche médicale, de la pratique médicale, de la communication scientifique et de la politique de santé publique. Notre conclusion est que les recommandations thérapeutiques sont donc infondées et inapplicables et risquent de faire du mal aux patients et leurs familles.

Ensuite, nous identifions la négligence des inégalités de santé comme un écueil possible des campagnes de santé publique axées sur le « mode de vie ». Car des données émergentes indiquent que les inégalités socio-économiques qui caractérisent de plus en plus nos sociétés ont un impact sanitaire majeur, et il n'est pas surprenant que les personnes ayant moins accès à des environnements enrichis au cours de leur vie aient un risque accru de déclin cognitif plus tard dans la vie. nous nous opposons à la moralisation du risque, et soutenons que nous devons

imaginer une société plus juste qui maximise la santé physique, mentale et sociale de ses membres afin d'anticiper le problème croissant de la *dementia*.

Enfin, nous essayons d'envisager comment le modèle économique du développement des médicaments peut être modifié afin que les essais cliniques des traitements puissent être une source d'information utile pour la communauté au sens large, et ainsi accélérer le développement des médicaments.

Le travail m'a poussé à trois conclusions. Premièrement, que dans notre époque contemporaine, la publication scientifique et les problèmes associés aux normes de publication exercent une influence majeure sur la production et l'interprétation des informations sur la maladie d'Alzheimer. Une étude plus approfondie de l'influence d'autres articles, des avis d'experts au-delà de la littérature publiée, des problèmes de normes de publication dans un domaine international qui attribue plus de crédibilité à certains chercheurs et hypothèses, mais aussi de ce qui se passe lorsqu'elles ne sont pas respectées et de la manière dont elles pourraient être améliorées, pourrait fournir des pistes fructueuses de recherches philosophiques ultérieures sur cette maladie et d'autres.

Deuxièmement, qu'il existe une véritable crise informationnelle dans l'obtention d'informations cliniquement significatives pour les patients qui devrait inciter à repenser la manière dont les chercheurs visent à traduire des connaissances théoriques en piste thérapeutique. Il est donc nécessaire d'améliorer la communication entre les différentes approches concernant la fixation des priorités, le type de résultats qui sont significatifs pour les patients et les méthodes pour les obtenir, et d'élaborer des modèles théoriques plus inclusifs.

Troisièmement, et enfin, que l'absence d'informations utiles aux patients a fragilisé l'image de la maladie d'Alzheimer dans la science et la société en général. La légitimité contestable de la

définition biologique de la maladie qui contraste fortement avec la compréhension populaire, l'absence de traitement, l'existence d'alternatives non validées et la désinformation font que la recherche biomédicale risque de ne pas être en mesure de répondre aux besoins de cette énorme source de peur pour le public. Mais cette fragilité est aussi l'occasion de conduire à une reconstruction plus démocratique du sens de la maladie d'Alzheimer pour le présent et l'avenir.

Je soutiens donc que la complexité tant biologique que sociétale de cette maladie échappe à tout réductionnisme et monopole, et que la population dans son ensemble, toutes potentiellement affectées par les nombreux problèmes posés par la maladie d'Alzheimer pour le bien-être et la justice, devrait devenir des agents du changement afin d'influencer la direction des recherches et politiques futures. Le caractère inscrutable de cette maladie qui nous touche tous directement ou indirectement est l'occasion pour la recherche et la société dont elle fait part d'être le reflet d'une pensée et de valeurs diverses et démocratiques.

Thesis statement

The work undertaken in this doctoral thesis consisted in approaching biomedical research on Alzheimer's disease from a multidisciplinary philosophical perspective. To this end, three perspectives were privileged—empirical, conceptual, ethical. The empirical philosophy of science, as understood here, is situated at the level of researchers and their opinions on the disease. Conceptual philosophy is at the level of their concepts at the theoretical level to understand its pathophysiological basis. Ethics is at the level of patients and the impact that biomedical research is likely to have on them, both individually and socially.

Three observations gave rise to this project: first, the absence of a treatment capable of modifying the evolution of the disease. Secondly, a rich theoretical landscape in which very unequal weight is given to hypotheses on the pathophysiology of the disease and their ensuing therapeutic strategies. Indeed, the dominant approach over the last 30 years has been based on pharmacological targeting of the disease lesions carefully described by Dr Alzheimer. But this therapeutic strategy has struggled to show a positive impact since the 2000s, despite controversial glimmers of hope in the last two years. Finally, the emergence of new therapeutic avenues, even 'alternative' treatments, suggesting a shift away from the study of the cerebral causes of dementia towards the study of risk factors during aging.

By digging into these observations, my work has been situated between the tasks of describing and assessing scientific activity. The questions I asked myself—under the co-direction of the philosopher Anouk Barberousse (Sorbonne University) and the neurologists Yves Agid and Stéphane Epelbaum (Hôpital Pitié-Salpêtrière)—were as follows: how has theoretical knowledge been built up over the last 30 years? Is it well founded in the eyes of scientists? Can other models be posited? What are these new trends, what can they contribute to the improvement of the well-being of current and future patients, but what might be their possible downsides? To address

these questions, it was necessary to study not only our contemporary era, but also the evolution of the study and conceptualisation of disease since the beginning of the 20th century.

The introduction to the thesis consists of a historical presentation of the disease, the philosophical tools used to understand it, and a presentation of contemporary research based on this historical and philosophical understanding.

In short, Alzheimer's disease began as an explanatory concept for a rare case of amnesic cognitive impairment in a middle-aged woman and similar cases in Germany, and by the 1970s had become the major cause of millions of cases of dementia and thus a threat to public health worldwide. For this to happen, the clinical syndrome of dementia and the pathological lesions found in the brains of persons with dementia (PWD) had to undergo 'medicalisation', i.e. they had to be interpreted as legitimate objects of study by different branches of medicine. Our contemporary biomedical era has arisen from the convergence of the medicalization of dementia and the lesions of Alzheimer's disease.

To address this period, analytical tools from the philosophy of science have been necessary. It is argued that Karl Popper's strict deductive rigour is less applicable to the case of biomedical research than what one of his disciples, Imre Lakatos, calls the methodology of scientific research programmes. Popper's logic portrays every test of the predictions made by a theory as definitive. In contrast, according to Lakatos, the unit with which scientists work is a hierarchical sequence based on a theoretical core and auxiliary hypotheses. The theory makes predictions (thus guided by what he calls a 'positive heuristic') and when these predictions are not corroborated by experimental observation, the auxiliary hypotheses can be modified to protect the theoretical core ('negative heuristic'). Thus, scientists can work with imperfect theories even if all their predictions are not corroborated by observations. Depending on the relationship

between the predictions made by a theory and the results of observation, the theory can thus become more or less 'degenerate' over time.

It is argued that anti-amyloid strategies can be understood as part of what the eminent researcher John Hardy called in 2006 the “research agenda” studying the involvement of beta-amyloid in Alzheimer's disease. This agenda is interpreted in the Lakatos way: it consists first of all of a core group based on the study of various diseases in which the pathological misfolding and accumulation of brain proteins (proteinopathy) plays a pathogenic role in neurodegeneration. Second, there is a series of auxiliary hypotheses that bring the core into contact with the experimental data ("positive heuristics"), and that can also protect the core from refutation ("negative heuristics"). These hypotheses are understood as mechanisms proposed by scientists to explain how beta-amyloid accumulates and how its accumulation causes downstream neurodegeneration. Finally, given the lack of success of pharmacological strategies targeting beta-amyloid in PWD, the outer layer of the programme consists of what have been called “disease scenarios” that could explain why some clinical trials with anti-amyloid strategies have not worked.

This historical and philosophical understanding of contemporary research helps us to understand current research trends. Two international working groups argue that early targeting of the characteristic disease pathology - the beta-amyloid (Aβ) and tau proteins - before the onset of dementia symptoms may represent the best disease-modifying treatment option available. This approach is based on an increasingly biological definition of the disease, separate from the clinical syndrome it is thought to cause. In contrast, members of two panels in the medical journal The Lancet focus on the discrepancy between the accumulation of AD pathology and dementia and argue that 40% of dementia cases could be prevented if society could take lifelong

action against 12 risk factors affecting physical, mental and social health. The idea is to foster people's resilience to the neuropathological markers associated with dementia.

The data, concepts and treatment strategies of these two major approaches are almost entirely opposite. But they are united in what they reveal about the hierarchical structure of contemporary research: these papers are co-authored by large international teams and published in leading journals and are highly cited. Other approaches, beyond targeting Aβ and promoting resilience, also exist within basic biology, but there has yet to be an expert consensus, like the two approaches highlighted, on how to choose between what Karl Herrup called in 2015 the 'long list of possible causes of Alzheimer's disease'.

Recognising that the debates between the different approaches do not yet have definitive answers, the aim of this PhD thesis is to study Alzheimer's disease research from an epistemological perspective with a variety of empirical and conceptual methods, in order to better understand this example of how medical research addresses a complex and chronic disease in our modern era of technological and scientific advances. The objectives of this thesis are primarily to represent the disagreements, to explore their consequences for patients and for research, and to propose solutions.

The thesis is divided into three parts—empirical, conceptual, ethical. My methodological approach can be situated in what Thomas Pradeu and colleagues have called philosophy in science rather than philosophy *on* science. A central concern has been to try to make my research as relevant as possible to scientific researchers. To do this, I have tried to focus on questions that researchers actually ask; I have sought to publish in scholarly journals that they are likely to read. Overall, I have tried to position myself alongside researchers, armed with philosophical tools to offer unique perspectives on this complex disease.

The first part is an empirical study to interrogate the validity of the dominance of the amyloid hypothesis through a bibliometric analysis of citation practices and an international survey of researchers promoted by the Alzheimer's Association.

First, we tried to see whether the citations revealed a "herd-like" attitude towards the amyloid hypothesis in the Alzheimer's research community. In this period of uncertainty about the centrality of amyloid-β (Aβ) to the pathophysiology of Alzheimer's disease, and with the community apparently divided over the validity of the amyloid hypothesis, we used citation practices as a measure of how researchers invested their belief in the hypothesis between 1992 and 2019. We sampled 445 papers citing the original formulation of the hypothesis by John Hardy & Gerald Higgins in 1992. We classified the polarity of their citation according to a taxonomy of positive, neutral and negative citations following Greenberg's methodology developed in 2009. We then tested four hypotheses about citation practices. We identified two major attitudes to the hypothesis: a majority (62%) of neutral attitudes with consistent properties over the whole period, and a positive attitude (35%), tending to cite the hypothesis earlier in the bibliography over time, tending to take this article as an established authority. Despite the majority of neutral citations of this article, there was a positive majority of attitudes towards different versions of the amyloid hypothesis and anti-amyloid therapeutic strategies (65%), supporting the existence of an evolving research agenda on amyloid and Alzheimer's disease, with updated auxiliary hypotheses. Finally, of the 110 original papers in the sample that also tested the hypothesis empirically, an overwhelming majority (89%) returned a positive result, suggesting that the central claim of the hypothesis is reproducible.

Second, through a survey, we sought to determine directly whether the amyloid hypothesis still dominates the views of researchers working on Alzheimer's disease and to explore the

implications of this question for future research directions. During 2019, we undertook an international survey promoted with the help of the Alzheimer's Association with questions on theories and treatments of the disease. Other efforts to promote a similar survey in 2021 failed to recruit a significant number of participants. 173 researchers participated in the 2019 survey, of whom 22% held "pro-amyloid hypothesis" views. These researchers tended to have more publications, were more likely to be male and to be over 60 years old. Thus, the pro-amyloid hypothesis view may now be in the minority in the field but is nevertheless the hypothesis on which the largest proportion of clinical trials are based, suggesting a representation bias. The popular vote of the 173 participants suggests that lifestyle treatments and anti-tau drugs were the source of more therapeutic optimism than anti-amyloid treatments. We propose a more democratic research structure that increases the likelihood that promising theories will be published and funded equitably, promotes a broader scientific view of Alzheimer's disease, and reduces the dependence of the wider community on a fragile economic model.

The second part employs a conceptual approach to looking beyond the amyloid hypothesis, in which we propose a holistic model to maximise the quality and quantity of information useful to research and patients. We argue that if the community decides to go significantly beyond the study of amyloid, which has been studied in our contemporary era as part of a hierarchical research agenda, there needs to be some form of hierarchy on how to decide between the other physiological processes involved in the disease. We therefore consider how to move towards a more holistic model of theories and therapies for the disease by undertaking a conceptual analysis of 'association', a term much used in the Alzheimer's literature to implicate certain physiological processes in the disease. This analysis leads us to propose an ontological model that would allow us to prioritise research on the basis of three specific criteria: the specificity of

certain disease-associated processes (DAPs) for Alzheimer's disease, such as amyloid, the frequency with which DAPs occur in PWD, and the pathogenic intensity of DAPs for dementia. We argue that many processes associated with Alzheimer's disease belong in our ADAPT (Alzheimer's Disease-Associated Processes and Targets) ontology, but for different reasons. We also discuss how the role of DAPs in the disease is tested. We argue that the constraints on interpretation are such that testing must be as simple as possible so that meaningful information can be extracted.

The third part explores the ethics of the non-existence of validated treatments and the existence of non-validated treatments with the aim of protecting people's autonomy from non-validated treatments, moralistic attitudes towards prevention, and a fragile economic model that underpins drug development and leads to inadequate clinical trials. We argue that there is great uncertainty about what kind of therapeutic approach will be useful to patients and that, therefore, real restraint is needed in communicating claims in the scientific and lay press, and in public health campaigns to encourage healthy lifestyle actions. We study the promotion of a particularly problematic case of promotion of an unvalidated treatment for Alzheimer's disease: 'metabolic enhancement protocols'. We use tools from medical research ethics, medical practice, science communication and public health policy. Our conclusion is that the treatment recommendations based on these protocols are unfounded and unworkable and risk harming patients and their families.

Secondly, we identify the neglect of health inequalities as a potential pitfall of 'lifestyle' public health campaigns. We argue against the moralisation of risk, and argue that we need to imagine a fairer society that maximises the physical, mental and social health of its members in order to anticipate the growing problem of dementia.

Finally, we consider how the economic model of drug development can be changed so that clinical trials of treatments can be a useful source of information for the wider community, and thus accelerate drug development.

The work has led me to three conclusions. Firstly, that in contemporary times, scientific publication and the problems associated with publication standards have a major influence on the production and interpretation of information on Alzheimer's disease. Further study of the influence of other articles, of expert opinion beyond the published literature, of the problems of publication standards in an international field that gives more credibility to certain researchers and hypotheses, but also of what happens when they are not met and how they could be improved, could provide fruitful avenues for further philosophical research on this and other diseases.

Secondly, that there is a real informational crisis in obtaining clinically meaningful information for patients that should prompt a rethink of how researchers aim to translate theoretical knowledge into a therapeutic lead. There is therefore a need to improve communication between different approaches about priority setting, the type of outcomes that are meaningful to patients and the methods for obtaining them, and to develop more inclusive theoretical models.

Third, and finally, that the lack of useful information for patients has made for a very fragile image of Alzheimer's disease in science and society at large. The disputed legitimacy of the biological definition of the disease, which contrasts sharply with popular understanding, the lack of a treatment, the existence of unvalidated alternatives and misinformation, mean that biomedical research is in danger of failing to meet the needs of this huge source of public fear. But this fragility is also an opportunity to lead to a more democratic reconstruction of the meaning of Alzheimer's disease for the present and the future.

I argue, therefore, that the biological and societal complexity of this disease defies reductionism and monopoly, and that the population at large, all potentially affected by the many problems posed by Alzheimer's disease for well-being and justice, should become agents of change to influence the direction of future research and policy. The complexity of this disease that affects us all directly or indirectly is an opportunity for research and the society of which it is a part to reflect diverse and democratic thinking and values.

Résumé en français

1. Présentation d'ensemble

De nos jours, la maladie d'Alzheimer (MA) suscite autant d'incompréhension que d'inquiétude. Incompréhension car le sens accordé à ces mots a connu des bouleversements depuis sa naissance au début du vingtième siècle. Inquiétude car elle est considérée comme la cause principale des 55 millions de cas de *dementia* (le terme latin est préféré au français en raison de sa neutralité) dans le monde, selon l'Organisation Mondiale de la Santé (OMS 2021). Son pronostic, 115 ans après la découverte des premiers cas de cette maladie chez des personnes d'âge moyen, reste plus ou moins inchangé, faute de thérapie capable de modifier son évolution.

Face à la complexité de cette maladie à différents niveaux, plusieurs objectifs de recherche ont été définis. Il y a la recherche de meilleures façons d'accompagner les personnes atteintes de *dementia* : quels types de traitements et stratégies peuvent être utilisés, pharmacologiques et non pharmacologiques, pour améliorer la qualité de vie des individus et de leurs aidants ? Il y a la recherche d'un traitement curatif : comment identifier et cibler les processus responsables de l'évolution de la maladie ? Et de plus en plus, la recherche se développe sur la manière de prévenir la *dementia* au niveau de la santé publique et sur la meilleure façon d'anticiper les changements dans une société vieillissante pour la rendre plus accueillante et bienveillante envers les personnes atteintes de *dementia*.

Notre thèse se concentre sur les tentatives de trouver un remède curatif dans le cadre de la science biomédicale qui mobilise des hypothèses biologiques pour guider la quête d'un traitement de la maladie. Mais malgré des douzaines de tentatives pendant 20 ans, le ciblage de la neuropathologie dans les cerveaux des patients n'a pas toujours pas fait ses preuves, malgré

des lueurs d'espoir controversées de ces deux dernières années. De nouvelles approches se sont développées récemment, et la recherche biomédicale connaît donc une époque de déceptions et de débats acharnés.

2. Méthodes et objectifs principaux

Cette thèse en trois parties mobilise différentes méthodes pour étudier les controverses, explorer leurs conséquences et proposer des solutions. L'approche méthodologique peut être située dans ce que Thomas Pradeu et ses collègues (Pradeu et al. 2021) ont appelé la philosophie *in* science, la philosophie *dans* la science plutôt que *sur* la science. Car une préoccupation centrale a été d'essayer de rendre nos recherches aussi pertinentes que possible pour les chercheurs dans la communauté biomédicale afin d'entamer ce qui nous semble être des débats de fond très importants pour le bien-être des recherches et de la société. Pour ce faire, nous avons essayé de nous concentrer sur des questions que les chercheurs se posent réellement, nous avons cherché à publier dans des revues savantes qu'ils sont susceptibles de lire. De manière générale, nous avons essayé de nous positionner aux côtés des chercheurs, armé d'outils philosophiques pour offrir des perspectives uniques sur cette maladie complexe.

A la suite d'une introduction historique et conceptuelle, cette thèse se divise en trois parties, intitulées de la façon suivante. La première partie s'appelle « Philosophie empirique des sciences : la prédominance du programme de recherche sur la bêta-amyloïde dans la recherche biomédicale sur la maladie d'Alzheimer ». Elle se résume en une étude empirique qui questionne le bien-fondé de la dominance de l'hypothèse amyloïde par le biais d'une analyse bibliométrique des pratiques de citation et un sondage international auprès des chercheurs promue par

l'*Alzheimer's Association* états-unienne. La deuxième partie s'intitule « Philosophie conceptuelle des sciences : La recherche biomédicale sur la maladie d'Alzheimer au-delà du programme de recherche sur l'amyloïde ». Nous y employons une approche conceptuelle pour envisager les recherches au-delà de l'hypothèse amyloïde et y proposons un modèle holistique visant à maximiser la qualité et la quantité d'informations utiles à en tirer pour la recherche et les patients. La troisième et dernière partie, « Neuroéthique et innovation : les enjeux éthiques d'un besoin majeur non comblé en santé publique », explore l'éthique de l'inexistence de traitements validés et l'existence de traitements non validés avec l'objectif de protéger l'autonomie des personnes contre les traitements non-validés, les attitudes moralisatrices à l'égard de la prévention, et un modèle économique fragile qui sous-tend (et ralentit) le développement des médicaments.

2. L'introduction de la thèse

Nous retraçons d'abord l'histoire de la maladie jusqu'à l'époque contemporaine, qui est l'objet d'étude de cette thèse. Pour que cette maladie acquiert son statut actuel d'être associé, de manière répandue, à la perte de soi (Ballenger 2006), elle a dû attendre : d'abord, que le problème de la *dementia* chez les personnes âgées obtienne une légitimité médicale dans un siècle marqué, comme tant d'autres, de préjugés contre les personnes du grand âge. Ensuite, que les lésions décrites par le Dr. Alzheimer (1864–1915) soient considérées comme étant la cause principale de la *dementia* chez ces personnes. Ces lésions sont les plaques séniles extracellulaires et dégénérescences neurofibrillaires intracellulaires qui s'accumulent dans les cerveaux des patients (l'histoire de la description de ces lésions est soigneusement décrite dans la thèse de Fabrice Gzil (Gzil 2008)). La converge de cette médicalisation a eu lieu pendant les années 1970

pour faire naître notre époque contemporaine marquée par une approche biomédicale de la MA (Ballenger 2006).

Ensuite, pour aborder cette période de recherche, des outils analytiques issus de la philosophie des sciences ont été nécessaires en raison de la complexité de l'appareillage théorique pour comprendre la physiopathologie de la maladie. Car depuis la médicalisation de ces deux aspects de la MA – *dementia* et lésions – l'approche dominante de ces 30 dernières années s'est fondée sur le ciblage des composantes protéiques de ces lésions – l'amyloïde-bêta (Aβ) des plaques, la protéine tau de la neurodégénérescence neurofibrillaire. Ces stratégies sont soutenues par un travail théorique très élaboré, et l'hypothèse physiopathologique dominante de la MA est l'hypothèse de la cascade amyloïde (HCA, (J.A. Hardy and Higgins 1992)).

Nous avançons que la rigueur déductive stricte de Karl Popper, est moins applicable au cas de la recherche biomédicale que ce que l'un de ses disciples, Imre Lakatos, appelle la méthodologie des programmes de recherche scientifique. La logique de Popper dépeint chaque test des prédictions faites par une théorie comme étant définitif (Popper 2006). En revanche, selon Lakatos, l'unité avec laquelle les scientifiques travaillent est une séquence hiérarchique basée sur un noyau théorique et des hypothèses auxiliaires (Lakatos 1976). La théorie fait des prédictions (ainsi guidées par ce qu'il appelle une « heuristique positive ») et lorsque ces prédictions ne sont pas corroborées par l'observation expérimentale, les hypothèses auxiliaires peuvent être modifiées pour protéger le noyau théorique (« heuristique négative »). Ainsi, les scientifiques peuvent travailler avec des théories imparfaites même si toutes leurs prédictions ne sont pas corroborées par les observations. En fonction du rapport entre les prédictions faite par une théorie et les résultats de l'observation, la théorie peut donc devenir plus ou moins « dégénérée » au fil du temps.

Dans cette thèse, les stratégies anti-amyloïdes sont comprises comme faisant partie de ce que le chercheur éminent John Hardy appelle (J. Hardy 2006) le *research agenda (*« programme de recherche ») étudiant l'implication de l'Aβ dans la MA. Ce programme est interprété à la Lakatos : il consiste d'abord en un noyau dur basé sur l'étude de différentes maladies neurodégénératies (comme les maladies de Huntington et Parkinson) qui partagent une approche semblable. Selon cette approche, le mauvais repliement et l'accumulation pathologiques des protéines cérébrales (protéinopathie) jouent un rôle pathogène dans la neurodégénérescence (Golde et al. 2013). Pour chaque maladie, c'est une protéine différente qui l'entraîne — dans le cas de la MA, c'est la logique de « si Aβ, alors MA ».

Ensuite, il y a une série d'hypothèses auxiliaires qui mettent le noyau en contact avec les données expérimentales (c'est l' « heuristique positive » du programme), et qui peuvent aussi être reformulées afin de protéger le noyau de la réfutation (c'est l'« heuristique négative » du programme). Ces hypothèses auxiliaires sont comprises comme des mécanismes proposés par les scientifiques pour expliquer comment l'Aβ s'accumule et comment son accumulation provoque la neurodégénérescence en aval (Hardy & Higgins, 1992). Enfin, étant donné le manque de succès des stratégies pharmacologiques ciblant l' Aβ chez les personnes atteinte de *dementia*, l'heuristique négative est constituée de ce qu'Eric Karran et collègues appellent (Karran, Mercken, and De Strooper 2011) des « *disease scenarios* » (scénarios de maladie) qui pourraient expliquer pourquoi certains essais cliniques avec des stratégies anti-amyloïdes n'ont pas fonctionné. L'hypothèse est mise à jour en fonction des avancées de la recherche, selon les heuristiques positive et négatives (Selkoe & Hardy 2016).

Cette compréhension historique et philosophique de la recherche contemporaine nous permet de comprendre les tendances actuelles de la recherche. Deux groupes de travail internationaux

soutiennent que le ciblage précoce de la pathologie caractéristique de la MA - les protéines Aβ et tau - avant l'arrivée des symptômes de la *dementia* peut représenter la meilleure option de traitement modificateur de la maladie disponible (Dubois et al. 2014; Jack et al. 2018). Cette approche se fonde sur une définition de plus en plus biologique de la maladie, au dépens du syndrôme clinique. À l'inverse, les membres de deux commissions de la revue médicale *The Lancet* mettent l'accent sur le décalage entre l'accumulation de la pathologie de la MA et la *dementia* et affirment que 40 % des cas de *dementia* pourraient être évités si la société pouvait agir tout au long de la vie contre 12 facteurs de risque touchant à la santé physique, mentale et sociale (Livingston et al. 2017; Livingston et al. 2020). L'idée est de favoriser la résilience des personnes face aux marqueurs neuropathologiques associés à la *dementia* en promouvant la santé pour faire croître le décalage entre la neuropathologie et la *dementia*.

Les données, les concepts et les stratégies thérapeutiques de ces deux grandes approches sont presque entièrement opposés. Mais elles sont unies dans ce qu'elles révèlent sur la structure hiérarchique de la recherche contemporaine : ces articles sont co-rédigés par de grandes équipes internationales et publiés dans des revues de premier plan et sont très cités. D'autres approches, au-delà du ciblage de l'Aβ et de la promotion de la résilience, existent également dans le cadre de la biologie fondamentale, mais il n'y a pas encore eu de consensus d'experts commes les deux approches soulignées, sur la façon de choisir entre ce que Herrup (Herrup 2015) appelle la « longue liste de possibles causes de la maladie d'Alzheimer » découverte par les biologistes.

3. Première Partie

La première partie de ce travail explore les attitudes des chercheurs à l'égard de l'hypothèse physiopathologique dominante - la fameuse hypothèse "amyloïde" - qui a animé le domaine au cours des 30 dernières années. Cette hypothèse a été étudiée à la fois par une analyse bibliométrique des pratiques de citation, et par une enquête internationale auprès des chercheurs promue par l'Alzheimer's Association.

Car si l'HCA de la maladie d'Alzheimer a bénéficié du statut qu'elle a eu, c'est parce que la communauté au sens large a joué un rôle actif pour laisser son statut se développer. L'avenir des traitements anti-amyloïdes déterminera si l'influence de l'HCA est finalement une bonne chose pour les patients qui ont besoin d'un traitement. Pourtant, avant même que ce jugement ultime ne soit prononcé, il existe des outils permettant d'entreprendre une étude empirique qui fournirait une mesure quantitative de la mesure dans laquelle la communauté de recherche sur la MA a accepté l'HCA et le programme de recherche qui en découle.

Le premier chapitre utilise une approche appelée bibliométrique (littéralement, la mesure de la littérature). La littérature scientifique publiée a été choisie comme source car elle constitue, de loin, le plus grand stock d'informations scientifiques que l'on puisse trouver sur la MA. L'étude des citations, qui consiste à étudier la façon dont les scientifiques citent une idée, a été choisie comme mesure d'impact d'un article. Elles ont été étudiées en utilisant une méthode inspirée d'une étude empirique menée par Greenberg (Greenberg 2009). Ce dernier a étudié comment les gens citaient l'idée que « l'Aβ, une protéine accumulée dans le cerveau dans la maladie d'Alzheimer (MA), est produite par, et blesse le muscle squelettique, chez les patients atteints de myosite à corps d'inclusion ». Il a constaté non seulement un biais important en faveur de la citation positive de cette idée (ce qu'il a appelé un « biais de positivité »), mais aussi des cas où «

les distorsions de citation créent une autorité non fondée », où la citation a été utilisée pour aller au-delà des revendications de l'auteur original.

Compte tenu de la controverse autour du rôle de l'Aβ dans la MA, nous avons entrepris d'utiliser cette méthode comme un outil unique pour mesurer un aspect de l'éthique scientifique au sein de la recherche biomédicale autour de la MA, étant donné la dominance de l'HCA (Liu et al. 2019). Cependant, si les citations suggèrent la pertinence de la recherche citée pour le domaine, elles ne sont pas une mesure parfaite de la qualité scientifique. Yves Gingras a critiqué des dérives de l'évaluation de la recherche (Gingras 2014). Il n'existe pas de mesure unique pour juger de la qualité scientifique d'un article, d'un chercheur ou d'une institution de recherche. Les taux de citations varient considérablement d'un domaine à l'autre, certaines revues ont une plus grande visibilité que d'autres dans le même domaine en raison de « facteurs d'impact » différents (taux de citation annuel moyen des revues), et il existe même des exemples de "cartels" de citation dont les membres font des efforts concertés pour citer en priorité les chercheurs qui en font partie, dans la même institution de recherche ou dans des institutions différentes.

Ainsi, la quantité de citations d'un article donné ne garantit pas sa qualité scientifique, car des facteurs extérieurs à l'article jouent un rôle dans sa citation. L'étude des citations de Greenberg (2009) soulève la question de savoir si les scientifiques qui citent un article l'ont même lu. Au-delà de ces facteurs externes, il peut également y avoir des facteurs internes à un article qui augmentent sa citabilité. Par exemple, Hardy (J. Hardy 2006) reconnaît que Hardy & Higgins (1992) « est simple, clair et court : trop d'articles sont compliqués, confus et longs : même un investisseur ou un PDG d'entreprise peut le lire jusqu'à la fin » (p. 152, *ibid*). Mais un article peut être bien écrit, concis et convaincant, et pourtant l'hypothèse qu'il défend peut être fausse.

Néanmoins, même si le profil des citations n'est pas un garant parfait de la qualité scientifique, il est intuitif d'affirmer que les scientifiques éthiques ne devraient pas citer des idées de manière problématique afin d'éviter qu'elles ne développent une « autorité infondée » (Greenberg, 2009). Mais étant donné la complexité de ce qui pousse les scientifiques à avoir certaines opinions sur une théorie (dont l'existence de cette thèse témoigne), nous considérons que l'étude des citations ne devrait pas être utilisée pour évaluer les comportements des individus et leur responsabilité personnelle. C'est pourquoi une étude à l'échelle de la communauté d'un grand échantillon de citations et une analyse statistique associée ont été menées.

L'hypothèse nulle utilisée consistait à vérifier si la formulation originale de l'HCA, (J.A. Hardy and Higgins 1992) « HH92 », avait été citée de manière à suggérer une acceptation de type grégaire. Si tel était le cas, cela pourrait suggérer qu'il existe une adhésion problématique au programme de recherche sur l'amyloïde parmi les scientifiques. En revanche, si ce n'est pas le cas, cela pourrait contribuer à dissiper le scepticisme concernant la prédominance de l'HCA dans la recherche sur la MA.

Reconnaissant la nature imparfaite de la citation en tant que mesure, la deuxième partie de l'étude bibliométrique s'est penchée sur le soutien empirique de l'HCA pour tenter de répondre aux questions concernant son bien-fondé scientifique. Pour ce faire, nous avons divisé les articles citant le HH92 en articles de *Review* (synthèse) et en études empiriques. Les articles de synthèse font généralement le point sur l'état de l'art d'un sujet, par opposition aux études empiriques qui testent des hypothèses. Cela a permis de comparer s'il y avait des différences entre les auteurs qui commentent l'HCA et ceux qui testent réellement ses prédictions. Pour ce faire, nous avons étudié les conclusions de ces articles empiriques afin de nous faire une idée du soutien empirique que l'on peut trouver en faveur de l'HCA.

Prises ensemble, ces deux méthodes de l'article sur la bibliométrie peuvent être comprises comme une tentative de déterminer si l'HCA jouit de ce que Greenberg appelle (2009) « une autorité infondée ».

Le deuxième article est une discussion sur l'amyloïde et la démocratie dans la recherche sur la MA, à la suite d'un sondage anonyme en ligne auprès des chercheurs sur la MA. Une enquête a été entreprise auprès des chercheurs afin d'avoir un accès direct à leurs opinions sur les théories et les traitements de la MA. Plusieurs raisons ont motivé l'adoption de cette approche.

Tout d'abord, la structure de la science est hiérarchique, ce qui signifie que tous les chercheurs ne voient pas leurs travaux financés et publiés dans la même mesure. Il est également vrai que certains chercheurs de la MA sont cités beaucoup plus fréquemment que d'autres dans la littérature (Sorensen 2009). En outre, il existe des normes en matière de publication scientifique qui laissent peu de place aux opinions personnelles dans les articles publiés. Cela signifie que pour avoir accès à une idée précise de ce que les chercheurs pensent réellement des hypothèses et des thérapies de la MA, il faudrait peut-être consulter autre chose que la littérature scientifique publiée.

Afin de préparer les questions de l'enquête, plusieurs entretiens formels et informels ont été menés avec des chercheurs biomédicaux travaillant sur la MA. Une hypothèse de travail a été adoptée, selon laquelle les chercheurs sont répartis en fonction des questions sur le rôle de l'amyloïde dans la MA. En utilisant cette méthode, il serait possible de savoir qui pense quoi sur la MA et, en particulier, si les « pro-HCA » représentent une opinion dominante. De même, quels chercheurs considèrent que les autres thérapies sont une source d'optimisme, et qui défend ces approches ? Les prédicteurs de succès — tels que le nombre de publications et le fait de recevoir

des fonds de recherche de l'industrie pharmaceutique — permettent-ils d'expliquer pourquoi les chercheurs adhèrent à l'HCA ?

L'un des objectifs de cette recherche est de déterminer s'il y a des avantages potentiels à rendre la recherche biomédicale sur la MA plus démocratique, dans la mesure où la communauté pourrait bénéficier de l'écoute des opinions collectives des chercheurs lors des choix de financement des théories alternatives. En adoptant une vision plus pluraliste de la recherche sur la MA, on réduit la possibilité de deux injustices, d'une part pour les patients, si les traitements anti-amyloïdes ne répondent jamais à l'espoir qu'ils offrent, et d'autre part pour les chercheurs qui travaillent sur différentes hypothèses de la MA et qui pourraient autrement avoir du mal à gagner en crédibilité au sein de la communauté et ainsi contribuer à améliorer la vie des personnes atteintes de *dementia*.

Les résultats empiriques de la première partie suggèrent que les débats en cours autour de l'HCA et de sa prédominance ne concernent pas seulement son adéquation empirique, mais plutôt le potentiel de dépendance et d'adhésion excessives à son égard. Une réévaluation de la place de l'HCA dans la recherche sur la MA pourrait avoir des conséquences majeures pour cette dernière, étant donné que les théories peuvent influencer le développement de traitements modificateurs de la maladie pour les patients atteints de cette maladie chronique complexe. C'est à cette réévaluation que nous nous consacrons dans la deuxième partie.

4. Deuxième Partie

Après la première partie, consacrée à l'étude du programme de recherche sur l'amyloïde, cette partie de la thèse pose la question suivante : à quoi ressemblerait la recherche sur la MA sans le programme de recherche sur l'Aβ comme guide dominant pour trouver un traitement ? Pour répondre à cette question, une brève discussion des controverses autour de l'HCA est présentée, ainsi qu'un résumé de la recherche de ces 10 dernières années qui suggère un changement dans la réflexion sur les causes de la maladie.

Plusieurs critiques ont été écrites sur la place de l'amyloïde dans la recherche sur la MA. Le problème le plus évident pour l'idée de la centralité de l'amyloïde dans la MA a été l'existence de dizaines d'essais infructueux avec des médicaments ciblant l'Aβ dans le cerveau des patients atteints de MA. Mais d'autres données ont remis en cause sa validité, notamment la valeur prédictive imparfaite de l'accumulation de la neuropathologie de la MA vis-à-vis du fait que les individus développeront ou non une *dementia*.

Ainsi, la question de l'adéquation empirique de l'HCA est à la fois vitale pour l'établissement des priorités de la recherche sur la MA, mais aussi exceptionnellement difficile à résoudre. Il a été dit dans l'introduction que l'HCA fait partie d'un programme de recherche plus vaste sur l'amyloïde et qui est constamment mis à jour. Il existe néanmoins un consensus croissant – mais sans le type d'unité que l'on peut trouver dans les approches de ciblage neuropathologique et de promotion de la résilience décrites dans l'introduction – selon lequel « une cascade linéaire ... est incompatible avec les observations » (p. 794, Herrup, 2015). Selkoe & Hardy (2016) « ...s'accordent à dire qu'après le déclenchement de la maladie, la complexité des processus pathogènes en aval augmente » (p. 604, (Selkoe and Hardy 2016).

En effet, les données les plus convaincantes suggérant que l'amyloïde est au cœur de la MA proviennent de la génétique des mutations. Toutefois, ces données ne s'appliquent peut-être

qu'aux formes héréditaires rares, très agressives et familiales. Les patients atteints de cette forme de la maladie peuvent presenter des troubles amnésiques dès la trentaine. Or, la grande majorité (>99% des cas) de la MA est « sporadique » et ces cas surviennent après l'âge de 65 ans. Des études sur des jumeaux suggèrent néanmoins que jusqu'à 80% du risque de MA est génétique (Gatz et al. 2006). Cela signifie qu'il existe ce que l'on appelle une *missing heritability* « héritabilité manquante » (Bertram, Lill, and Tanzi 2010) : car d'où vient ce risque, si ce n'est de mutations pathogènes très graves ? On ne le sait pas encore tout à fait, mais l'étude des associations génétiques de ces 15 dernières années semble pointer vers le système immunitaire du cerveau (Bellenguez et al. 2020).

Parallèlement à cette étude du risque génétique, l'intérêt pour le mode de vie s'est fortement accru. On sait aujourd'hui qu'il existe 12 facteurs de risque modifiables (Livingston et al., 2020). Ces facteurs agissent tout au long de la vie. Ils comprennent : le début de la vie (moins d'éducation), le milieu de la vie (perte d'audition, traumatismes crâniens, hypertension, consommation élevée d'alcool, obésité) et la fin de la vie (tabagisme, dépression, isolement social, inactivité physique, diabète et pollution atmosphérique). Enfin, en biologie fondamentale, différents chercheurs ont proposé d'examiner les conséquences de la complexité de la MA sur différents types de cellules et processus biochimiques (Herrup, 2015).

Dans son plaidoyer pour le rejet de l'HCA, Herrup (2015) offre une vision différente de la recherche sur la MA, avec des conséquences majeures pour la quête d'un traitement de la MA par rapport au programme de recherche sur l'amyloïde. Le " programme de recherche " sur l'amyloïde a pour centre les mutations productrices d'amyloïde et est donc hiérarchisé dans la manière dont certaines données sont interprétées en son sein : l'heuristique positive du programme de recherche sur l'amyloïde tente d'intégrer les nouvelles connaissances à travers le

prisme de l'amyloïde (Hardy, 2006). À l'inverse, selon Herrup, il n'existe pas de centre ou de hiérarchie significative.

Nous employons un outil conceptuel appelé l' « association » qui est suffisamment large pour permettre d'établir des comparaisons entre les facteurs de risque génétiques et non génétiques. Mais pour être utile, il doit être analysé dans ses composantes. C'est ce que notre analyse au chapitre trois vise à fournir afin de combler le fossé entre les défenseurs de l'hypothèse amyloïde et ses détracteurs.

Cette analyse nous amène à proposer un modèle ontologique de la MA qui nous permettrait de hiérarchiser la recherche sur la base de trois critères spécifiques : la spécificité de certains processus associés à la maladie (*disease-associated processes, DAPs*) pour la MA, la fréquence à laquelle le DAP apparaît chez les patients atteints de *dementia*, et l'intensité pathogène du DAP pour la *dementia*. Nous soutenons que de nombreux processus associés à la maladie d'Alzheimer ont leur place dans notre ontologie *ADAPT (Alzheimer's Disease-Associated Processes and Targets)*, mais pour des raisons différentes.

Le Chapitre Quatre aborde la meilleure façon de tester la valeur thérapeutique des traitements possibles. Le fait de retirer l'amyloïde du centre d'une vision de la causalité de la MA conduit à une vision thérapeutique très différente de la MA, que nous appelons un schéma thérapeutique « additif ». Nous insistons sur la nécessité de ce que Herrup appelle des « victoires progressives ». En effet, pour créer un traitement efficace, il ne suffit pas d'avoir une simple chose (par exemple, un médicament) — les médicaments ont des notices qui doivent être respectées afin de maximiser la sécurité et l'efficacité en vue d'atteindre un certain objectif, et ils sont approuvés en tant que tels (Kimmelman and London 2015). Si un essai avec un seul composant ne fonctionne pas, il peut au moins être une source d'information - peut-être qu'un médicament autrement utile

a été administré trop tard, ou avec une dose trop faible, etc. Mais nous soutenons que le fait de combiner des traitements dans une thérapie combinée avant que chaque traitement ne soit validé individuellement signifie qu'un essai ne peut même pas être une source d'information utile. Et il y a un grand besoin de solutions généralisables pour un problème de santé publique aussi massif.

5. Troisième Partie

La deuxième partie a souligné le besoin de clarté conceptuelle dans la compréhension de la contribution des différents processus à l'aggravation du pronostic de la maladie, ainsi que la nécessité que les tests de traitements fonctionnent comme des sources d'informations utiles pour les chercheurs et les patients. Cette troisième partie de la thèse explore les conséquences de ce que l'absence de traitements capables de ralentir la *dementia* a signifié pour les patients au niveau individuel et sociétal. Nous critiquons un exemple de promotion problématique d'un traitement innovant de la *dementia* auprès de patients individuels, et nous explorons également les limites éthiques et thérapeutiques de ce qui peut être fait au niveau de la santé publique pour prévenir la *dementia* par des campagnes d'action sur le mode de vie.

Racine (Racine 2010) définit la neuroéthique comme "une réponse interdisciplinaire et collective aux défis éthiques des neurosciences et des soins cliniques" (ix, ibid). La dernière partie de cette thèse de doctorat a été motivée par la nécessité de protéger les patients à un moment où aucune des approches dominantes de la prévention de la *dementia* - cibler la neuropathologie de la MA ou promouvoir la résilience à la *dementia* en agissant sur les facteurs de risque - n'offre une voie de traitement entièrement approuvée pour eux. La peur que représente la MA et l'absence de traitements approuvés peuvent créer un contexte dans lequel beaucoup de mal peut être fait.

Tant qu'un traitement ralentisseur de la maladie n'est pas disponible, les traitements non validés constituent une source évidente de mal potentiel. Hellmuth et ses collègues mettent en garde contre « la montée de la pseudomédecine pour la *dementia* et la santé cérébrale » (Hellmuth, Rabinovici, and Miller 2019). La promotion de traitement non-validés se caractérise par un appel à l'absence de traitements disponibles, un recours aux témoignages individuels au lieu d'une science rigoureuse, et l'obtention de gains financiers.

Le chapitre cinq, qui se place résolument dans la perspective de la neuroéthique axée sur les soins de santé, est une tentative de combattre la promotion d'un traitement actuellement non validé de la MA, que nous appelons des « protocoles d'amélioration métabolique », promus par le Dr. Dale Bredesen. En utilisant des outils issus de l'éthique de la recherche médicale, de la pratique médicale, de la communication scientifique et de la politique de santé publique, notre conclusion est que les recommandations de traitement basées sur ces protocoles sont infondées et inapplicables et risquent de nuire aux patients et à leurs familles.

À l'inverse, les deuxième et troisième chapitres traitent chacun de la neuroéthique au sens « socio-politique » en ce qui concerne les différentes approches de la prévention identifiée dans l’introduction.

Dans le chapitre six, des efforts ont été faits pour protéger les personnes actuelles et futures d'une interprétation moralisatrice de la possibilité de prévenir la *dementia* en agissant sur les facteurs de risque, étant donné l'inexistence de preuves solides que les individus peuvent agir pour réduire définitivement leur risque individuel de développer une *dementia* par des interventions sur le mode de vie. Si les programmes de prévention de *dementia* doivent être ambitieux, se concentrer uniquement sur le mode de vie de la population d'âge moyen ne va pas assez loin : il faudra étudier le risque tout au long de la vie en tenant compte des déterminants sociaux de la santé tels

que les inégalités socio-économiques pour rendre la société aussi saine et donc aussi résiliente que possible à la *dementia*.

Le chapitre sept étudie l'exemple controversé de l'approbation accélérée de l'aducanumab par l'agence américaine de médicamenta, la *FDA*. Il est d'abord décrit comme une décision compliquée prise en période de crise - désaccords sur l'avenir de la recherche (comme on l'a vu dans cette thèse), absence de traitement entièrement approuvé et promotion de traitements non validés (chapitre cinq). Un modèle alternatif de financement du développement des médicaments est proposé, qui implique la coopération du gouvernement avec l'industrie pharmacologique afin que des essais plus longs et plus satisfaisants de traitements anti-amyloïdes et d'autres traitements prometteurs puissent être maintenus à flot au lieu d'être interrompus pour des raisons financières avant que les effets possibles du traitement ne soient observés. Des essais plus longs fourniraient également un retour d'information plus approfondi sur la validité des cibles thérapeutiques et sont doc plus utiles aux patients et à la recherche.

6. Conclusions principales

L'introduction a d'abord cherché à établir que cette entité autrefois rare est désormais considérée comme une menace majeure pour la santé publique. Ensuite, que le programme de recherche sur l'amyloïde est l'approche dominante pour expliquer la maladie et trouver un traitement ralentisseur de la maladie. Enfin, que les problèmes découlant des récentes définitions de la maladie et de l'échec des stratégies anti-amyloïdes ont conduit à ce que les approches de modification de la maladie soient principalement divisées entre le ciblage de la neuropathologie

de la MA et la promotion de la résilience à la dementia en agissant contre les facteurs de risque dits « modifiables ».

La première partie présente deux perspectives empiriques différentes sur la prédominance de l'hypothèse de la cascade amyloïde (HCA) dans la recherche biomédicale sur la maladie d'Alzheimer (MA). Leurs différences sont révélatrices de la complexité du paysage plus large de la recherche sur la MA, qui va bien au-delà de la littérature scientifique publiée.

L'étude bibliométrique suggère que les pratiques de citation de l'HCA sont nuancées, sans positivité problématique dans les citations de la formulation originale de l'HCA à trouver dans Hardy & Higgins (1992, HH92). Les scientifiques ont eu tendance à citer cette version de manière neutre, car ils ont reconnu la nature évolutive du « programme de recherche » basé sur l'HCA, qui postule un rôle central pour l'Aβ dans la pathogenèse de la MA. Ces nouvelles versions du programme ont en effet été citées plus favorablement que la formulation originale trouvée dans HH92. La relation « si Aβ, alors MA » est donc toujours considérée comme un guide pour la recherche, bien que les spécificités de cette relation soient susceptibles d'être mises à jour à la lumière de la recherche empirique. En outre, le fait que 89 % de notre échantillon d'articles empiriques (N=110) soient parvenus à une conclusion favorable à l'HCA en se fondant sur la vérification des prédictions de l'HCA ou des observations connexes suggère que les citations favorables à l'HCA dans ces articles sont justifiées. Une affirmation selon laquelle il existerait un comportement moutonnier au sein de la communauté des chercheurs n'est pas corroborée par notre (petite) enquête empirique sur les pratiques de citation.

Ces résultats indiquent que l'éthique communautaire des scientifiques travaillant sur la MA semble être intacte selon cette étude bibliométrique. Toutefois, cela ne signifie pas qu'il n'y a pas de comportement problématique ailleurs dans la communauté de la MA, ni de cas d'individus

violant les codes d'éthique professionnelle (voir l'exemple de Higgins dans la discussion du chapitre 1, et voir la troisième partie de la thèse). Cette communauté est en effet vaste - plus de 33 000 personnes de plus de 160 pays ont participé au congrès international de l'Association Alzheimer (AAIC) en 2020, et il semble raisonnable de postuler qu'il existe des complexités au sein d'une telle communauté qui vont bien au-delà de la littérature scientifique publiée et des pratiques de citation en son sein.

Dans notre sondage, lorsque 173 chercheurs ont répondu en 2019 à des questions sur les théories et les thérapies de la MA, seuls 22 % semblaient être « pro-HCA ». Il y a plusieurs façons d'interpréter ce résultat, mais il n'est pas surprenant au vu de la proportion d'essais cliniques testant des agents anti-amyloïdes par rapport aux essais testant des agents basés sur d'autres hypothèses. La figure 1 de Liu et al. (2019) sur l'histoire récentes des hypothèses de la MA montre que 22,3 % des essais menés jusqu'en 2019 étaient fondés sur l'HCA, l'hypothèse qui attire le plus de fonds. Il est intéressant de noter que l'enquête a indiqué que certains chercheurs étaient plus optimistes quant aux thérapies anti-tau et aux interventions sur le mode de vie qu'aux traitements anti-amyloïdes. La majorité des participants à l'étude - même la majorité des répondants favorables à l'HCA - ont affirmé que l'adhésion à l'HCA était problématique dans certaines parties de la communauté des chercheurs sur la MA. Cela a des implications sur le niveau des politiques de publication et de financement qui pourraient influencer indûment l'établissement des priorités dans la communauté de la recherche biomédicale sur la MA. Cette enquête ne reflète toutefois que les opinions des chercheurs en 2019. Ceux qui ont répondu à l'enquête l'ont fait avant l'approbation de l'Aducanumab par la FDA et avant que les résultats originaux avec les anticorps tels que le Lecanemab et le Donanemab ne soient disponibles. Dans ce domaine de la recherche biomédicale en constante évolution, il est quelque peu difficile de

suivre l'attitude de la communauté des chercheurs sur la pathophysiologie et les meilleurs moyens thérapeutiques pour lutter contre la maladie d'Alzheimer.

L'utilisation de ces deux outils empiriques pour étudier la place de l'HCA a été limitée à la fois par le petit échantillon d'articles dans l'étude bibliométrique, ainsi que par le nombre de chercheurs approchés dans l'enquête. Néanmoins, l'étude montre à quel point la question du recours à l'HCA est complexe, tout en offrant des pistes pour des recherches plus approfondies sur cette théorie et d'autres. En effet, cette étude a montré le potentiel de l'utilisation d'outils empiriques, tels que la bibliométrie et les enquêtes, pour recueillir des informations auprès des chercheurs et analyser leur comportement. Il est intéressant de noter que des chercheurs de l'University College London (UCL) se sont associés à *l'Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment* (ISTAART) pour promouvoir une enquête auprès des chercheurs en début de carrière actuels et anciens dans le domaine de la recherche sur la dementia afin d'identifier les obstacles auxquels ils sont confrontés.

L'approche de la deuxième partie, comme nous l'avons dit, a été directement inspirée par ce que Pradeu et al. (2021) appellent la « philosophie dans la science » dans laquelle les chercheurs « utilisent des outils philosophiques pour aborder des problèmes scientifiques et fournir des propositions scientifiquement utiles ». Le problème scientifique est le suivant : Étant donné que le ciblage du dépôt amyloïde chez les patients atteints de la maladie d'Alzheimer - le *DAP* le plus prometteur - ne s'est pas encore avéré entièrement fructueux (malgré la récente approbation accélérée de l'aducanumab par la FDA) et qu'il n'existe aucun autre traitement susceptible de ralentir la maladie qui soit entièrement validé pour la maladie d'Alzheimer, comment prendre des décisions concernant l'établissement de priorités en tenant compte de la "longue liste d'options

causant la maladie" ? L'analyse conceptuelle de l'association proposée ici est l'outil que nous proposons pour apporter une réponse.

Les arguments de Herrup (2015) pour rejeter l'HCA peuvent être résumés comme suit : il y a de bonnes raisons de croire que le modèle linéaire reliant l'amyloïde et la MA a été réfuté. Par conséquent, nous devrions rejeter l'HCA. En ce qui concerne l'heuristique positive du programme de recherche que nous avons décrit, la pensée centrée sur l'amyloïde ne devrait plus être utilisée comme un prisme à travers lequel comprendre d'autres associations : peut-être que d'autres DAP fonctionnent via des mécanismes indépendants de l'amyloïde pour contribuer à une aggravation du pronostic de la maladie. Quant à l'heuristique négative, selon l'argument, toutes les hypothèses auxiliaires à l'ordre du jour ont été réfutées, et le problème auquel la communauté est confrontée est qu'il n'y a plus d'événement central à la MA, et certainement pas de "dépôt amyloïde" (Hardy & Allsop, 1991).

Le passage, au cours des 15 dernières années, de la recherche sur la MA de la valeur heuristique de la découverte de mutations à l'étude plus large de l'association peut être compris à la lumière du programme de recherche Lakatos et des conclusions de la première partie de cette thèse. Selon nous, l'avenir de la recherche est moins une question de bifurcation (rejeter ou ne pas rejeter telle ou telle approche) qu'une question de pertinence des formulations simples à la lumière de l’évidente complexité de cette maladie.

Compte tenu de cette complexité, un schéma thérapeutique plus « additif » devient de plus en plus probable. Lorsque l'on fonde les traitements sur la longue liste de causles possibles de la MA - tels qu'ils ont été identifiés par Herrup (2015), les études d'association pangénomique et les facteurs de risque liés au mode de vie (Livingston et al. 2020) - il peut en effet être nécessaire de choisir toutes les options possibles, comme l’affirme Herrup. Mais nous soutenons que si nous «

les choisissons toutes » il conviendrait de le faire « une par une ». Des tests simples signifient minimiser le nombre d'hypothèses auxiliaires sur la raison pour laquelle un traitement fonctionne ou non. En minimisant le nombre d'hypothèses auxiliaires, on peut ainsi obtenir plus d'informations sur les effets du traitement.

En résumé, si l'on se concentre trop sur le "matériel" (c'est-à-dire l'objet du traitement plutôt que tout l'ensemble informationnel d'un traitement), on risque de ne pas explorer certaines pistes de traitement autrement prometteuses. Il convient de souligner les approches anti-amyloïdes pourraient bien porter des fruits thérapeutiques. Il serait préférable, d'après nous, d'être plus agnostique à l'égard de la source de l'effet du traitement (qu'elle soit pharmacologique ou non pharmacologique, amyloïde ou autre) et plus rigoureux dans l'obtention d'informations utiles pour comprendre les effets du traitement et leur absence.

Un thème clé de la troisième partie de la thèse est la protection de l'autonomie des personnes — à risque ou déjà atteintes de dementia — contre la désinformation, la moralisation et les essais cliniques moins utiles sous-tendus par un modèle économique fragile à haut risque.

Un enjeu majeur pour une maladie complexe sans traitement est la représentation qu'on en a auprès de la population des patients. Il existe différentes sources d'information sur la dementia : le médecin généraliste, les neurologues et gériatres spécialisés, les médias et Internet sont les principales sources. L'existence du protocole « Bredesen » a certainement changé la représentation de la MA, puisqu'il y a au moins un neurologue de renommée mondiale qui affirme que la MA est réversible, que les « premiers survivants de la maladie d'Alzheimer » (2021) existent déjà, et que le succès commercial de ses livres et de ses protocoles en constante évolution contraste fortement avec les "échecs" des médicaments dans la recherche biomédicale plus conventionnelle. Mais malheureusement, ces affirmations sont fondées sur des témoignages

plutôt que sur la science, et sont des exemples d'exagération avec des coûts potentiels importants pour la communauté des patients. La promotion de ces protocoles pour la MA suggère la « nécessité de réviser la déclaration d'Helsinki » (Asplund and Hermerén 2017). Notre proposition de mise à jour de cette déclaration est basée sur la nécessité d'un examen externe avant de proposer un traitement expérimental, en particulier si un clinicien risque d'en tirer un bénéfice financier. Dans tous les cas, une participation accrue à des recherches rigoureuses via des essais contrôlés randomisés est préférable à une utilisation généralisée de traitements non validés, étant donné la nécessité de trouver des solutions généralisables pour des millions de patients.

L'arrivée de la pandémie de Covid-19 a offert de nombreuses leçons pour l'étude d'autres maladies (Fernandez Lynch et al. 2021). Pour ce qui concerne nos travaux, d'abord, la pandémie a vu l'arrivée d'une « infodémie » avec diverses sources de désinformation sur la gravité de la maladie, sa transmission et ses traitements, causant des dommages possibles et réels aux individus et aux groupes. L'exemple du succès du Dr Bredesen montre que la désinformation est un problème actuel et futur auquel est confrontée la recherche sur la dementia. La pandémie de Covid-19 a également fait remonter à la surface les préjugés que l'on peut trouver dans les attitudes envers les malades et les personnes âgées. Le chapitre six était une tentative de montrer qu'il n'y a pas de bonnes raisons pour mettre une pression morale sur les personnes d'entreprendre un « mode de vie sain » afin qu'elles cherchent à réduire leur risque de la dementia. La stigmatisation, qui sévit déjà à l'égard des maladies de l'esprit et du cerveau, est un obstacle majeur à une meilleure santé publique (OMS, 2021). Nous soutenons qu'une autre leçon possible pour le développement de médicaments contre la MA pourrait être l'utilisation de partenariats entre le gouvernement et l'industrie pour créer un modèle économique plus stable dans lequel des essais de médicaments plus longs peuvent avoir lieu. Cela pourrait encourager

les investissements nécessaires, alléger la pression sur le mécanisme « d'approbation accélérée » de la FDA, et fournir des informations plus importantes à la communauté.

Il est indéniable qu'une approche de la médecine centrée sur la pathologie locale a permis à l'humanité de faire d'énormes progrès en matière de santé publique, comme les antibiotiques, les interventions chirurgicales et les traitements anticancéreux. Pourtant, une telle approche ciblant les lésions de la MA n'a pas encore fait ses preuves. L'anthropologue Margaret Lock soutient que la complexité de la MA est telle que celle-ci ne peut pas être « éradiquée » à l'instar d'une maladie infectieuse et que nous devrions privilégier un changement politique global pour nous engager dans la réalité du vieillissement (Lock 2013). En d'autres termes, pour résoudre le problème de santé publique que constitue la dementia, il faudrait s'éloigner des approches thérapeutiques de type "remède miracle" (Caspi 2019). Cela peut s'appliquer aussi bien au ciblage de la neuropathologie qu'à la promotion de la résilience. Par exemple, malgré la promesse des données et des arguments des commissions du Lancet, les facteurs de risque liés au mode de vie ne devraient pas être considérés comme la prochaine "solution miracle" pour la dementia, car une telle façon de pensée pourrait détourner l'attention de l'étude des disparités en matière de santé contribuant au risque de développer la *dementia*. En effet, il nous semble important de mettre en garde contre les interprétations étroites des « facteurs de risque modifiables de la *dementia* ». Qu'est-ce qui est considéré comme modifiable ? Seulement le comportement d'un individu ? Qu'en est-il de la structure d'une société qui conspire à rendre certains individus plus susceptibles de souffrir de fragilité et de déclin cognitif à un âge avancé, en raison de la pauvreté, de la pollution ? Quelle est la politique appropriée en matière d'éducation et de retraite ? Ce sont des questions ouvertes qui ne peuvent être laissées aux

experts et aux politiciens, car les choix politiques qui seront faits sur cette base nous affecteront tous.

Dans l'ensemble, après avoir tenté de clarifier les points de désaccord dans ce domaine biomédical emblématique, nous proposons des solutions possibles telles que l'augmentation de la participation démocratique dans la prise de décision à l'échelle de la communauté, l'amélioration de la définition des priorités dans la recherche de cibles thérapeutiques grâce à l'ontologie ADAPT, et la révision de la déclaration d'Helsinki pour protéger les patients des innovations non éthiques. Notre enquête nous pousse à trois conclusions. Premièrement, que dans notre époque contemporaine, la publication scientifique et les problèmes associés aux normes de publication exercent une influence majeure sur la production et l'interprétation des informations sur la maladie d'Alzheimer. Une étude plus approfondie de l'influence d'autres articles, des avis d'experts au-delà de la littérature publiée, des problèmes de normes de publication dans un domaine international qui attribue plus de crédibilité à certains chercheurs et hypothèses, mais aussi de ce qui se passe lorsqu'elles ne sont pas respectées et de la manière dont elles pourraient être améliorées, pourrait fournir des pistes fructueuses de recherches philosophiques ultérieures sur cette maladie et d'autres. Il est également nécessaire d'éduquer le grand public et la presse non spécialisée sur ce qui constitue une véritable recherche rigoureuse et sur le problème des pratiques de publication prédatrices. L'éducation doit également s'étendre aux décideurs politiques, qui ne sont pas des spécialistes de la recherche sur la maladie d'Alzheimer. Par exemple, depuis 2018 en France, les inhibiteurs d'anticholinestérase ne sont plus remboursés par les soins de santé publics, mais la plupart des spécialistes français de la maladie avec lesquels nous avons parlé ont critiqué cette décision.

Deuxièmement, qu'il existe une véritable crise informationnelle dans l'obtention d'informations cliniquement significatives pour les patients qui devrait inciter à repenser la manière dont les chercheurs visent à traduire des connaissances théoriques en piste thérapeutique. Il est donc nécessaire d'améliorer la communication entre les différentes approches concernant la fixation des priorités, le type de résultats qui sont significatifs pour les patients et les méthodes pour les obtenir, et d'élaborer des modèles théoriques plus inclusifs.

Troisièmement, et enfin, que l'absence d'informations utiles aux patients a fragilisé l'image de la maladie d'Alzheimer dans la science et la société en général. La légitimité contestable de la définition biologique de la maladie qui contraste fortement avec la compréhension populaire, l'absence de traitement, l'existence d'alternatives non validées et la désinformation font que la recherche biomédicale risque de ne pas être en mesure de répondre aux besoins de cette énorme source de peur pour le public.

Au sein de la recherche, les essais cliniques sont une source majeure de controverse, et bien qu'il y ait désaccord sur la mesure dans laquelle on peut dire qu'ils réfutent les affirmations du programme de recherche sur l'Aβ, la récente approbation accélérée de l'aducanumab est perçue comme un affront aux normes scientifiques par certains chercheurs (Karlawish and Grill 2021) et comme une impulsion nécessaire à la recherche par d'autres (Selkoe 2021).

S'il est essentiel de protéger l'autonomie des patients face aux traitements non validés et aux interprétations moralisatrices des preuves actuelles concernant les interventions basées sur les facteurs de risque liés au mode de vie, une vision démocratique plus ambitieuse de la dementia est nécessaire, tant au sein de la recherche que dans la société au sens large. En effet, cette fragilité est aussi l'occasion de conduire à une reconstruction plus démocratique du sens de la maladie d'Alzheimer pour le présent et l'avenir.

La recherche devrait être structurée de manière à éviter les injustices à l'encontre des chercheurs qui s'efforcent de trouver des remèdes alternatifs à cette maladie sur la base d'approches différentes, en respectant les valeurs de rigueur et de pluralisme. En outre, le rôle de la *dementia* dans la société au sens large doit également changer, et les recherches récentes sur les facteurs de risque liés au mode de vie et les disparités en matière de santé devraient être considérées comme des preuves suffisantes pour montrer que la société ne doit pas être considérée comme un agent passif attendant un changement de la part de la communauté de la recherche biomédicale. Les débats sur l'établissement des priorités avec les membres de la communauté des patients et les représentants de la société dans son ensemble sont absolument nécessaires pour déterminer comment utiliser l'argent public pour financer des actions contre les disparités en matière de santé et les facteurs de risque reconnus, et pour financer davantage d'essais alternatifs d'éventuels traitements modificateurs de la maladie. Les essais devraient être conçus de manière à refléter la réalité des personnes atteintes de *dementia*, représentatives de personnes du monde entier et de sociétés différentes (Manly & Glymour, 2021).

Nous soutenons donc que la complexité tant biologique que sociétale de cette maladie échappe à tout réductionnisme et monopole, et que la population dans son ensemble, toutes potentiellement affectées par les nombreux problèmes posés par la maladie d'Alzheimer pour le bien-être et la justice, devrait devenir des agents du changement afin d'influencer la direction des recherches et politiques futures. Le caractère inscrutable de cette maladie qui nous touche tous directement ou indirectement est l'occasion pour la recherche et la société dont elle fait part d'être le reflet d'une pensée et de valeurs diverses et démocratiques.

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Introduction

Biomedical research on Alzheimer's disease is currently a source of much debate around how this disease is defined, caused, and ultimately treated. Since the turn of the 20th century, when the German clinician–scientist Alois Alzheimer (1864–1915) made his first observations about the disease that would later bear his name, there have been constant debates worldwide about the concepts of this complex condition.

Alzheimer described a case of dementia in a woman in her 50s, Madam Auguste Deter (1850–1906), at a time when the more common elderly "senile" dementia was not fully understood as a legitimate object of medical study and attention. He completed his clinical description of this patient with a post-mortem examination of her brain tissue and was able to describe a peculiar pattern of cellular pathology whose significance is still debated to this day—senile plaques outside neurons and neurofibrillary tangles inside them. He first described this "clinico-pathological" entity in 1906 which would become known as Alzheimer's Disease (AD) in 1910 when his mentor, the psychiatrist Emil Kraepelin (1856–1926), included the disease as a distinct entity in the 8th edition of his influential textbook 'Ein Lehrbuch der Psychiatrie' (A Textbook: Foundations of Psychiatry) (Kraepelin 1910). Kraepelin devoted much of his career to the classification of specific psychiatric diseases, each with its own biological signature thought to play a causal role, and Dr Alzheimer's work can be placed squarely in this project. He himself argued that "we must not be satisfied to force [this entity] into the existing group of well known disease patterns" (quoted in (J. Hardy 2006a)).

Since then, both AD and dementia have undergone major conceptual transformations, and AD today is recognised as a major, growing threat to public health in an ageing society. But the fact that there are no fully-approved disease-modifying treatments for AD despite more than a

hundred years having passed since the description of the first cases has led to unsettled debates about the best approach to conceptualising and treating the disease.

This thesis has focused primarily on contemporary debates and disagreement within AD research. However, a historical introduction will be necessary so as to introduce the reader to the concepts still debated today. This introduction will focus on three aspects of this complex history. Firstly, how the clinico-pathological entity "Alzheimer's Disease" became recognised as a major threat to public health. Secondly, how research into the neuropathology of AD became the dominant approach to finding a disease-modifying treatment. Thirdly, the recent bifurcation of research into two major approaches towards the prevention of dementia following the reconceptualization of AD using a partly or wholly biological definition of the disease.

The first section is based on articles from the history of medicine and science written by historians (Fox 1989; J. J.F. Ballenger 2006a, 2017; Gzil 2008; Wilson 2014; Keuck 2018; J.F. Ballenger 2006b) and practicing clinicians and scientists (Maurer, Volk, and Gerbaldo 1997; J. Hardy 2006b, 2006c; Liu et al. 2019).

The second section is based on the original scientific literature as well as literature from philosophy of science to describe the different aspects of what Hardy (2006b) terms the "[amyloid] research agenda." The last section draws most heavily on *Position* or *Perspective* papers where expert groups make policy recommendations within biomedical research and at the level of public health. To end this introduction, there will be a brief description of the contemporary debates to which it is hoped this thesis will offer some solutions, along with a description of the approaches used to do so.

A) Alzheimer's Disease as a major threat to public health

The conceptual changes that have taken place in the history of AD research are understood here according to the concept of medicalisation, which describes how a phenomenon within society gets treated as a medical problem and studied with medical methods (Conrad 2007). Dr. Alzheimer himself described AD as composed of two aspects: brain lesions and clinical dementia. (J.F. Ballenger 2006a) describes the respective medicalisation of lesions and dementia in different stages.

The neuropathological lesions that Dr. Alzheimer described—senile plaques and neurofibrillary tangles—had been previously reported in post-mortem brain tissue. Yet as Gzil argues:

Alzheimer considerably improved their description and understanding: he developed new histological methods to reveal them, he proposed original hypotheses concerning their nature and genesis, and he completely renewed their diagnostic interpretation. ... Alzheimer may not have "discovered" the characteristic lesions of the disease that bears his name, but he "invented" them, because he showed the meaning and value of these phenomena (p. 184, (Gzil 2008)).

These descriptions were then used by Emil Kraepelin to establish AD as a 'pre-senile dementia' despite "the fact that the pathological hallmarks, clinical symptoms, and natural history of both pre-senile and senile dementia were virtually identical" (J.F. Ballenger 2006a). Thus, somewhat paradoxically from the point of view of today where AD is considered a major threat to public health, Kraepelin appeared to emphasise the rareness of the "AD" entity in order to legitimise its place in his classification of mental disorder. But AD appears not to have been offered as a rigid diagnostic category at the time. Keuck argues that the "peculiar cases" of AD in Kraepelin's clinic functioned as "material to think about the limits of the category of senile dementia," and

the corresponding label "AD" was treated as "an exploratory category for the clinical and histopathological investigation of varieties of organic brain diseases" (Keuck 2018).

The problem of dementia as a clinical syndrome had been described as early as ancient Greece. But there remained less than two dozen published studies on senile dementia or AD in leading psychiatry or neurology journals up until the 1930s (J.F. Ballenger 2006a). However, in the United States, the aging population offered more and more cases of what the psychiatrist David Rothschild termed *Senile Psychoses* in 1937. This clinico-pathological research of the elderly population found no clear relationship between age and aforementioned senile plaques. The German pathologist N. Gellerstedt (Gellerstedt 1933) reported cases of elderly people who had died with their cognitive function intact despite having multiple senile plaques in their brains. While Rothschild concluded that 'psychoses of the aged now appear as the leading problems of psychiatry' (p. 324, (Rothschild 1941)), the increased medicalisation of the syndrome of dementia was not accompanied by a simultaneous medicalisation of the lesions of AD.

At the time, the importance of neuropathological changes in explaining mental dysfunction was hotly debated. Not only was the tradition of psychiatry slower at describing and defining mental disorders compared to other branches of medicine, the ability to pathologically define disorders affecting the brain without having a therapeutic grasp on the diseases drew into question its value to the medical community (J.F. Ballenger 2017). At the Meeting of the Psychiatrists of South West Germany, November 3, 1906, where Alois Alzheimer gave his lecture based on Auguste Deter, it appears there were at least as many talks on psychoanalysis as on neurology (J.F. Ballenger 2006a).

The story of Austrian physician Sigmund Freud (1856-1939) can provide insights into the conflict between classificatory neuropsychiatry and psychoanalysis at the turn of the 20th

century in Central Europe. Freud undertook extensive research in neuropathology and electrophysiology (Galbis-Reig, 2004) before studying electrophysiology in the laboratory of Ernst Brücke (1819–1892). Freud applied Brücke's dynamic physiology—according to which organisms are energy-systems bound by the principle of the conservation of energy—to the human mind. According to psychodynamics, the contextual and dynamic interaction between the psyche and its environment results in a mind overtaken by the challenges and traumas of life, and is functionally responsible for patients' disorders. The therapeutic strategy derived from psychodynamic theory is psychoanalysis, a term coined by Freud in 1896 before the publication of his On the Analysis of Dreams (Freud 1900) which emphasised the role of unconscious mental processes in psychic dysfunction.

Rothschild applied the psychodynamic way of thinking to *Senile Psychoses*. Finding no clear organic origin of cognitive decline, Rothschild argued that the elderly developed this condition because society had no further function for them, and this indicated that the elderly required better integration into society as a preventive measure (J.F. Ballenger 2006a). Ballenger (J.F. Ballenger 2006b) offers the following quote from Sir William Osler (1849–1919), Canadian physician and reformer of medical education, as an example of ageist attitudes in medicine and larger society which may have led Rothschild to his conclusion:

"…all the great advances have come from men under 40 … a very large proportion of the evils may be traced to the sexagenarians—nearly all the great mistakes politically and socially…" (William Osler, quoted on p. 11 (J.F. Ballenger 2006b).

The fact that psychodynamic explanations took into account the entirety of the psyche's lifelong interaction with its environment made for a 'mixed picture' view of mental suffering which did not make major clinical distinctions between transient psychiatric symptoms and long-term neurodegenerative diseases (Wilson 2014) (Wilson, 2014). This idea of a functional explanation of a mixed picture view of mental suffering was thus the philosophical competitor to Kraepelin's project of classifying specific disorders with an organic explanation.

Thus, for the dominant view of AD as a specific entity to prevail as it arguably does now, this mixed picture view had to be challenged. In Kraepelinian fashion, Martin Roth in England undertook a classificatory scheme of mental illness as distinct entities. The 'Newcastle Study' he was involved in consisted of a detailed and painstaking study to separate dementia from other psychiatric ailments. Having done so, in conclusion, the authors claimed to find a 'highly significant correlation between mean plaque counts and scores for dementia' (p. 804, (Blessed, Tomlinson, and Roth 1968)). This dealt a major blow to functional psychodynamic explanation of dementia as well as the mixed picture view of mental suffering. In that same year, the philosopher of science Sir Karl Popper (about which more will be said in section B) argued that psychoanalytic theory was pseudoscientific, leading to untestable hypotheses (Popper 1968). There has been a general loss of favour of psychoanalysis amongst psychiatrists and physicians since this period. (Though see for example (Grant and Harari 2005)'s critique of Popper's "misunderstanding and misrepresentation of psychoanalysis").

Thus, in the 1970s AD neuropathology was also increasingly medicalised for its possible contribution to studying the course of dementia (prognosis) and finding a treatment (therapeutics).

The public health profile of AD has increased markedly since this research. By the 1970s, both specialist and lay media started to refer to dementia as a silent epidemic in need of further study (Wilson 2014). In the United States, the neurologist Robert Katzman (Katzman 1976) went as far as proposing that the diagnostic label "senile dementia" be replaced with "AD" and he recommended that the latter be recognised as a "major killer." Katzman's proposal was broadly accepted, and the label "Alzheimer's Disease" was recognised as a major threat to public health and included in the landmark 1984 diagnostic criteria for AD (G. McKhann et al. 1984). Patient associations were born during this period to raise awareness and funds for research (Fox 1989). This was also a period of an unprecedented increase in fear around cognitive decline, as AD was seen to represent the loss of self, a dearly-held concept to Western society (J.F. Ballenger 2006b). There have been several criticisms of the "Alzheimerisation of dementia" (Adelman 1995; Royall 2003).

The World Health Organisation (WHO) now offers the following definition of the public health problem posed by AD: "Currently more than 55 million people live with dementia worldwide, and there are nearly 10 million new cases every year … Alzheimer's disease is the most common form of dementia and may contribute to 60-70% of cases" (WHO 2021).

In summary, for AD to acquire this status, it first had to be legitimised as a specific entity and separated from senile dementia. Once senile dementia was more heavily medicalised, and the pathological similarity of AD and senile dementia confirmed, so then could Katzman's proposal of "AD = senile dementia" be accepted. The biomedical period of AD research—in which both the AD neuropathological lesions and the clinical syndrome of dementia were seen as legitimate objects of medicine, and thus medicalised—then came to be (J.F. Ballenger 2006a).

B) Targeting the neuropathology of Alzheimer's Disease: the amyloid research agenda

The philosophy of science informing this section of the introduction as well as the thesis at large is understood as an attempt to describe the activity of scientists and to offer different norms with which to assess science. And in the case of the biomedical period of research into a cure for AD, *biological* knowledge has been applied to the *medical* problem of Alzheimer's disease to "guide[] the efforts to find treatments" (p. 296 (J. Hardy et al. 2014)). Such *biomedical* science requires the philosopher to describe and offer norms for assessing not just knowledge from biology but also its application to medical ends.

Hardy (J. Hardy 2006a) describes "three basic science research tracks" used to understand AD's pathophysiology in the contemporary biomedical period:

The first … to develop an understanding of … selective neurotransmitter loss in Alzheimer's … The second … its pathognomic lesions, the neuritic plaque and the neurofibrillary tangle, and the third … a positional cloning strategy in Mendelian forms of Alzheimer's to find the causative variants behind the disease etiology … (pp. 3-4, ibid).

The first, the "neurochemical pathology work," found that AD patients had a serious "loss of neurons in the basal forebrain" which produces the neurotransmitter acetylcholine (Whitehouse et al. 1982) as well as "region specific loss of glutamate innervation" in cortical pyramidal neurons (J. Hardy et al. 1987). These two neurotransmitters are involved in cognition and memory. The only available drugs for the management of AD are based on a "transmitter replacement approach" for acetylcholine and glutamate (Povysheva and Johnson 2016). However, while they can improve symptoms for patients, they do not slow down the disease

process and have undesirable side effects associated with their use. Hardy (p.4, ibid) argues that "the transmitter replacement approach to Alzheimer's therapy has likely reached the limit of its potential." The possible contribution of the neurochemical approach to the future of AD research is nevertheless still debated today as new approaches to the treatment of neuropsychiatric symptoms acting on other neurotransmitters are explored (Cummings 2021).

Concerning the pathology approach, in 1984, the starch-like amyloid-beta protein, made up of peptides of 36–43 amino acids, was found to be the major protein component of senile plaques (Glenner and Wong 1984). The year after, tau protein was identified as the component of the neurofibrillary tangles (Brion et al. 1985). Hardy describes that "*the positional cloning strategy and the pathology approach led to a convergent outcome, which has led to an integrated approach to trying to develop an understanding of the disease pathogenesis*" (pp. 3-4, Hardy, ibid).

Hardy (2006b) offers the following quote from his former mentor, Bob Williamson, when describing the positional cloning approach:

"*all you needed to know about a disease was its mode of inheritance. Positional cloning would lead you to the mutant gene which, unambiguously, caused disease. And after that, there would be no argument: pathogenesis would start from there*" (p. 151, (J. Hardy 2006b)).

In the 1980s and 1990s there came a wave of genetic evidence from different diseases suggesting that the processing of the amyloid precursor protein (APP) that produces amyloid-beta, the gene of which was eventually found on chromosome 21, had some central role to play in neurodegeneration. The strongest data arguing for the role of amyloid-beta in AD came from

families with a mutation in the APP-amyloid-beta pathway who invariably developed an early-onset, aggressive dominantly inherited AD (DIAD). All these data converged on the idea that the accumulation of amyloid-beta triggered a pathogenic "cascade" leading to dementia. This led to the formulation of the "amyloid cascade hypothesis" (ACH) of Alzheimer's disease (J.A. Hardy and Higgins 1992). AD neuropathology was thus medicalised to the point that ridding the brain of amyloid has been the dominant approach to finding a disease-modifying treatment (DMT) for AD since the 1990s (Liu et al. 2019).

The idea that amyloid-beta triggers a neurodegenerative cascade is at the core of what Hardy (2006b) terms a "research agenda:"

"[Hardy & Higgins, 1992] … was intended to generate ideas and act as a framework for a *research agenda*, not to be a definitive statement" (italics mine, p. 153, Hardy, 2006b).

The amyloid research agenda will be described using ideas from the tradition of philosophical work starting with the aforementioned philosopher of science Sir Karl Popper (1902–1994), whose ideas on science and pseudoscience played a major role in post-War thought in the twentieth century. A brief summary of the work of Popper, Thomas Kuhn, and Imre Lakatos on scientific rationality will now be offered. It will then be argued that the amyloid research agenda can be usefully understood as a biomedical research programme, based on an adaptation of the work of Imre Lakatos.

Popper argued that science was essentially the activity of proposing and attempting to falsify hypothetical conjectures containing predictions about the world (Popper 1968). According to the philosophy of falsificationism, science gives not truth but falsehood. If your theory makes

incorrect predictions even once then you should reject it (assessment of science). Theories without testable hypotheses were not considered by Popper to be scientific theories.

Falsificationism had a major impact on scientists and philosophers which continues to this day. It is therefore tempting to offer a Popperian analysis of AD research. If it is true that theories in biomedical science are indeed judged on their ability to produce useful treatments, then the ultimate test for a treatment—and the theory it is based on—is the clinical trial. It seems intuitive that we should have a low tolerance for error, *à la Popper*. Does a treatment improve desired outcomes in a clinical trial, yes or no? There are those researchers who offer a Popperian view of the "dead" amyloid hypothesis (Abbott and Dolgin 2016). Hardy (J. Hardy 2006c) himself argues that:

"the amyloid hypothesis cannot be proved, only disproved: and it will only have been truly useful if it leads to the development of a treatment based on its therapeutic implementation" (p. 72, ibid).

This idea that a theory can never be proved but only disproved is a testament to the influence of Popper on scientists. But the generation of philosophers that Popper inspired post-World War Two saw his description and assessment of science as giving too much importance to deductive inference. They offered examples where scientists didn't just reject an entire theory because of one failed test or prediction. So this left an option. Perhaps most scientists were just irrational. Or the falsification criterion was too strict.

Thomas Kuhn (1922–1996) argued in his famous work *The Structure of Scientific Revolution* (Kuhn 1962) that scientific change is not incremental and logical *à la Popper*. Instead changes

happen in paradigm shifts when a critical mass of anomalies "subvert[s] the existing tradition of scientific practice … lead[ing] the profession at last to a new set of commitments, a new basis for the practice of science… [which we find] associated with the names of Copernicus, Newton, Lavoisier, and Einstein" (p. 6, ibid). Instead of logical Popperian *rules* dictating how theories should be accepted, Kuhn in *Structure* used the idea of paradigmatic epistemic *values* (i.e. concerned with attitudes towards knowledge) which serve to influence the beliefs held by defenders of a theory. For Kuhn, other values than deductive rigour were at play in science and choosing between rival theories. He offered empirical accuracy, simplicity, consistency, explanatory scope, and experimental fertility as possible values which are freely chosen by scientists.

In short, scientists continue to work on a theory despite some known empirical anomalies. This possibility is denied by Popper's strict adherence to empirical adequacy. Yet it fits better with a description of how scientists defending the ACH have worked since the early 2000s, updating the ACH in the light of emerging data, as will be described in this section.

However, the applicability of Kuhn's idea of a paradigm to the amyloid research agenda is limited by what he terms the "incommensurability thesis". According to this thesis, there is no common measure between paradigms "because they use different concepts and methods to address different problems" (see Section 1 of (Oberheim and Hoyningen-Huene 2018)'s entry on the Incommensurability thesis in the *Stanford Encyclopedia of Philosophy [SEP]*). And yet because of the very nature of contemporary biomedical science—using biological knowledge to guide treatment efforts against a particular disease—there is a common measure for different hypotheses: have they offered treatments, and if not, what is the probability that they will lead to successful treatments?

Further clarification is provided here by another of Popper's disciples, the Hungarian Imre Lakatos (1922–1974). In "Falsification and the Methodology of Scientific Research Programmes," Lakatos (Lakatos 1976) was clearly inspired by the idea of falsification but he argued that it did not lead to instant rejection of a theory. He defended the idea that scientists work with a sequence of conjectures at any one time and that this sequence is hierarchical. He proposed the concept of a "research programme" made up of a theoretical hard core and a set of outer auxiliary hypotheses. The theoretical core is made up of a number of assumptions which give the programme its impetus and *raison d'être*. This core is not falsifiable in the Popperian sense because it is a general statement which does not directly come into contact with particular instances of empirical observation. The outer auxiliary hypotheses are what bring the programme into contact with empirical data.

It is well-known that hypotheses make predictions that are not always borne out in reality. Yet they continue to guide problem-solving, thus they have "heuristic value." Lakatos argues that there is a negative and positive heuristic associated with research programmes:

The negative heuristic of the programme forbids us to … [refute] … this "hard core". Instead, we must use our ingenuity to articulate or even invent "auxiliary hypotheses", which form a protective belt around this core … which has to bear the brunt of tests and gets adjusted and re-adjusted, or even completely replaced, to defend the thus-hardened core … The positive heuristic consists of a partially articulated set of suggestions or hints on how to change, develop the "refutable variants" of the research programme, how to modify, sophisticate, the "refutable" protective belt. (Lakatos quoted in 2.2, (Musgrave and Pigden 2021)).

Lakatos thus outlines the research programme as containing two entities—a stable theoretical core, and malleable auxiliary hypotheses—guided by a positive and negative heuristic. In this introduction (and by extension, the thesis of which it is an integral part), these three aspects (core, hypotheses, heuristics) will be used to understand the amyloid research agenda.

The first layer is a theoretical core that puts amyloid at the centre of the pathogenicity of AD. Moving outwards, the particularity of this research agenda is that the auxiliary hypotheses are split into two kinds. The first is based on the positive heuristic, "that part of the program which direct[s] scientists toward fruitful avenues of enquiry"[1]—i.e., the way that the amyloid hypothesis has guided research down certain avenues. This medial layer of the agenda is based on mechanisms proposed by researchers by which amyloid accumulates and causes neurodegeneration. The outer layer is the negative heuristic: how anti-amyloid therapeutic strategies have led to explanatory strategies to save the research agenda. These outer auxiliary hypotheses have taken the form of "disease scenarios." Each component will now be explained.

[1] Quoted from Dr. Paul Knox https://www.liverpool.ac.uk/~pcknox/teaching/phil/lakatos.htm

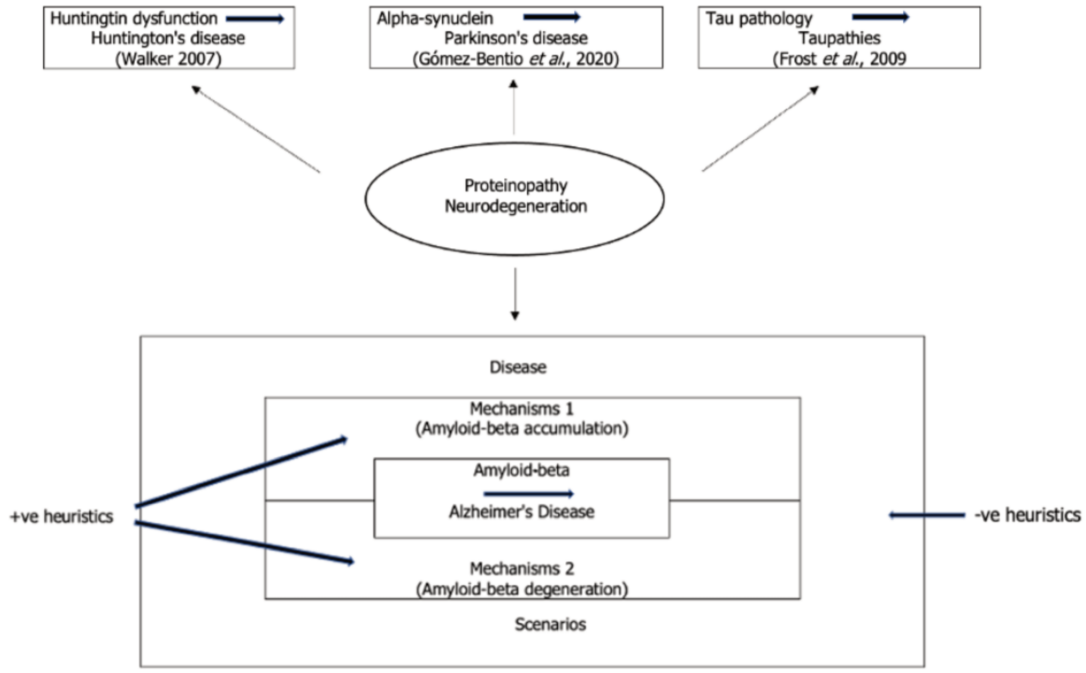

Figure 1 – The amyloid research agenda as part of a broader research programme into different neurodegenerative disorders understood as proteinopathies (Alzheimer's (AD), Huntington's (HD) and Parkinson's disease (PD), and Tauopathies). Each disease research agenda has its own core. In the case of AD research, that core is: "Amyloid deposition as the central event in the aetiology of Alzheimer's disease" (J. Hardy and Allsop 1991). There are then auxiliary hypotheses derived from and protecting the core: mechanisms1 (of amyloid deposition) and mechanisms2 (degeneration) (J.A. Hardy and Higgins 1992) according to the agenda's positive heuristic, and disease scenarios (Karran, Mercken, and De Strooper 2011) as per the negative heuristic.

B1. The theoretical core of the amyloid research agenda

It must not be forgotten that the agenda's orientation is therapeutic: the agenda "*will only have been truly useful if it leads to the development of a treatment based on it[]*" (J. Hardy 2006c).

This orientation can also be found in another defender of the agenda, Dennis Selkoe, writing in 2007:

The discovery of the genes involved in the mechanisms of amyloid beta-protein build-up in AD, coupled with cell culture and animal models of their involved pathways, has led to the development of specific pharmacological strategies to lower amyloid beta-protein levels as a way of treating or preventing all forms of the disease (p. S239, (Selkoe 2007)).

The theoretical core of this programme therefore "parallel[s] work on other neurologic and psychiatric diseases … for developing mechanism-based therapies" (J. Hardy 2006a). Alzheimer's disease and other neurodegenerative diseases such as Parkinson's (PD) and Huntington's Disease (HD) have been described as proteinopathies (Golde et al. 2013). At the core of this larger research programme linking the study of these different diseases is the theoretical conjecture that the accumulation of misfolded proteins ("proteinopathy") is pathogenic and results in brain lesions that induce neurodegeneration. Each disease within this broader programme is defined by the protein that causes a different type of neurodegeneration and therefore a different clinical syndrome. In the case of AD, amyloid-beta accumulation is thought to reliably produce the pathology of AD and not another kind of pathology. (The question of mixed pathologies will be studied in Part 2 of this thesis). Many AD researchers also work on these diseases in which protein misfolding, aggregation, and accumulation are involved with disease onset and outcome.

The centrality of proteinopathy draws heavily on the study of inheritance of genetic diseases. Entirely hereditary diseases lend themselves particularly well to this kind of causal explanation.

For example, in HD patients, the length of the repeats of a trinucleotide (CAG) in the huntingtin (HTT) gene coding the huntingtin protein, has been robustly shown to predict age of onset and age of death of such patients (Langbehn et al. 2010). This means that the idea that "HD = hereditary HTT dysfunction" has a very high explanatory weight for HD. However, in the case of AD and PD, as well as "familial" (hereditary) forms of disease that make up a minority of cases, there is also an overwhelming majority of "sporadic" cases, where family history itself is not sufficient to explain why a patient develops the disease. It is perhaps not surprising that several processes have been identified and the resulting explanations of sporadic AD and PD are more complex (Herrup 2015; Johnson et al. 2019). This programme nevertheless groups different forms of AD and PD together based on the fact that "the overall similarities in pathology and clinical presentations between sporadic and familial forms indicate that the pathological cascades are likely to be more conserved than disparate" (p. 1847, (Golde et al. 2013)).

It is the conjecture of the conserved cascade between DIAD and sporadic AD that allowed Hardy & Allsop in 1991 (J. Hardy and Allsop 1991) to formulate their paper titled: "Amyloid deposition as the central event in the aetiology of Alzheimer's disease." This is the theoretical core of the amyloid research agenda. Similar formulations can be found in the theoretical core of the other specific diseases in this proteinopathy research programme (Figure 1). There may also be crossover between different diseases when "looking laterally across a spectrum of diseases to understand common pathological mechanisms downstream of the triggering proteinopathy" (p. 1849, Golde et al., 2013).

B2. The positive heuristic: mechanisms of amyloid build-up and neurodegeneration

The first layer of auxiliary hypotheses of the amyloid agenda, between the theoretical core and disease scenarios, is based on the study of those "pathological mechanisms" (Golde et al., 2013)

involved in AD. Several mechanisms have been proposed linking amyloid-β to AD. They can be divided into two types based on Hardy & Higgins (1992)'s two-step mechanistic description of the ACH:

"two successive events are needed to produce Alzheimer's pathology. First, [amyloid-beta protein] (ABP) must be generated as an intact entity ... Second, this molecule must facilitate or cause neuronal death and neurofibrillary tangle formation" (p. 184, Hardy & Higgins, 1992).

Selkoe (2007) refers to this first "event" as part of "the *mechanisms* of amyloid beta-protein build-up in AD". Indeed, this description of "events" and entities" offered by Hardy & Higgins (1992) will be interpreted as *mechanisms*. The study of mechanisms, particularly as they are used in biology, is a rich topic of research in contemporary philosophy of science (see (Craver and Tabery 2015)). But what is a mechanism? Craver & Tabery (2015) argue that:

"*Mechanists have generally eschewed the effort to spell out necessary and sufficient conditions for something to be a mechanism. Instead, they offer qualitative descriptions designed to capture the way scientists use the term and deploy the concept in their experimental and inferential practices*" (Section 2, Craver & Tabery, 2015).

Nevertheless, there has been enough consensus in the philosophical literature for Illari & Williamson (2012) to offer a "consensus concept" that will be retained for the purposes of this introduction:

A mechanism for a phenomenon consists of entities and activities organized in such a way that they are responsible for the phenomenon (Illari and Williamson 2012).

Thus, Hardy & Higgins's description of events and entities can be understood as a two-part mechanism:

Mechanism1: Some entities (A,B,C…) with activities responsible for the accumulation of amyloid-beta protein (ABP).
Mechanism2: An entity (ABP) with activities responsible for neuronal death & NFT formation.

Taken together, mechanisms1+2 "produce Alzheimer's pathology" (Hardy & Higgins, 1992). Thus, this layer of the amyloid research agenda is constituted of mechanisms 1+2, i.e. of amyloid accumulation(1) and ensuing neurodegeneration(2).
These mechanisms have been updated since Hardy & Higgin's 1992 formulation of the ACH. Hardy & Selkoe have co-written extremely influential articles in which they have provided updates on the research agenda—(J. Hardy and Selkoe 2002; Selkoe and Hardy 2016). For an indication of their impact, and thus of the impact of the positive heuristic of the amyloid research agenda, these articles have been cited approximately 14,500 times and 3,200 times respectively as of October 1st, 2021.
In Hardy & Selkoe (2002), ten years after the first formulation of the ACH, the theoretical core of the agenda can be seen to remain intact:

“According to the amyloid hypothesis, accumulation of A-Beta in the brain is the primary influence driving AD pathogenesis” (p. 353, Hardy & Selkoe, 2002).

The article then offers a scheme of mechanisms1 and mechanisms2 in its Figure 1:

“Mutations in APP, PSEN1, PSEN2 [mechanism1] … increased A-Beta42 production and accumulation … A-Beta42 oligomerization and deposition as diffuse plaques [mechanism2] … Subtle effects of A-Beta oligomers on synapses [mechanism2] … Microglial and astrocytic activation [mechanism2] … progressive synaptic and neuritic injury [mechanism2] … Altered neuronal ionic homeostasis; oxidative injury [mechanism2] … Altered kinase/phosphatase activities → tangles [mechanism2] … dysfunction and cell death with transmitter deficits … dementia” (p. 354, Hardy & Selkoe, 2002).

The mechanisms1 (leading to amyloid production and accumulation) remain entirely genetic in this Figure from 2002. It is only amyloid-beta with length 42 that is identified as a neurotoxic molecule, which can either oligomerise or form plaques. Both forms are implicated in different mechanisms2 (i.e. of neurodegeneration), with direct effects of amyloid-beta oligomers on synapses and activation of the brain’s immune response (microglia and astrocytes), leading to neurofibrillary tangle formation and cell death.

However, this concerns only genetic cases, recognised by Hardy & Higgins (1992):

“most cases of Alzheimer's seem to occur in a sporadic fashion, suggesting that there must be other causes of the disease. The cascade hypothesis suggests that other causes of Alzheimer's act by initially triggering ABP deposition” (p. 185, Hardy & Higgins, 1992).

By 2016, there are certain changes offered in this update to the agenda. Looking at the theoretical core, it is argued that:

“an *imbalance* between production *and clearance* of Aβ42 and related Aβ peptides is *a* very early, *often* initiating factor in Alzheimer's disease (AD)” (p. 595, Selkoe & Hardy, 2016, my italics).

The idea of an *imbalance* between production and clearance of “Aβ42 and related Aβ peptides” marks a shift away from the sufficiency of Aβ deposition to cause AD as suggested by the focus on DIAD. So as to incorporate sporadic AD into the causal schema, Selkoe & Hardy (Figure 1, 2016) build upon Figure 1 from 2002 by offering "failure of Abeta clearance mechanisms" as a substitute for the mutations found in DIAD. “Related Aβ peptides” include “Aβ42, Aβ43, and longer Aβ peptides [which] are highly self-aggregating, whereas Aβ40 may actually be anti-amyloidogenic” (Selkoe & Hardy, 2016). In the abstract, they summarise their position:

all dominant mutations causing early-onset AD occur either in the substrate (amyloid precursor protein, APP) or the protease (presenilin) of the reaction that generates Aβ [mechanism1]. Duplication of the wild-type APP gene in Down's syndrome leads to Aβ deposits in the teens [mechanism1], followed by microgliosis, astrocytosis, and neurofibrillary tangles typical of AD

[mechanism2]. Apolipoprotein E4, which predisposes to AD in > 40% of cases, has been found to impair Aβ clearance from the brain [mechanism1]. Soluble oligomers of Aβ42 isolated from AD patients' brains can decrease synapse number, inhibit long-term potentiation, and enhance long-term synaptic depression in rodent hippocampus [mechansim2], and injecting them into healthy rats impairs memory [mechanism2]. The human oligomers also induce hyperphosphorylation of tau ... and cause neuritic dystrophy in cultured neurons [mechanism2]. Crossing human APP with human tau transgenic mice enhances tau-positive neurotoxicity [mechanism2]. In humans, new studies show that low cerebrospinal fluid (CSF) Aβ42 and amyloid-PET positivity precede other AD manifestations by many years.

Referring to amyloid as "a … factor in AD" instead of "*the* central event" reflects the fact that it is increasingly well-recognised that "after disease initiation, the complexity of the downstream pathogenic processes increases" (p. 604, Selkoe & Hardy, 2016). Proposed downstream processes include activation of the brain's immune response (Hardy & Selkoe, 2002; Selkoe & Hardy, 2016) and damage to cell membranes (J. Hardy 2017) which can be understood as part of what De Strooper & Karran (2016) (De Strooper and Karran 2016) term the "cellular phase" of AD, which will be discussed in Part 2 of this thesis. Nevertheless, despite this downstream complexity, the authors argue for "a key role for Aβ dyshomeostasis in initiating AD" (Box 1, Selkoe & Hardy, 2016). Thus, the core of "triggering proteinopathy" (Golde et al., 2013) from the proteinopathy research programme can still be found here in AD research in 2016. The finding that an Icelandic mutation in APP reduced amyloid accumulation, and protected against AD, also bolstered the programme (Jonsson et al. 2012).

To close this section on the positive heuristic of the research agenda, a brief description of the models used to study the "involved pathways" of the disease is given. As Selkoe (2007) alluded to, "cell culture and animal models" have been used extensively to study the "involved pathways" of the disease. As concerns cell culture, in vitro cell culture was long considered an inferior model as compared to animal models until the recent arrival of "induced pluripotent stem cells" technology using three-dimensional neural models derived from patients' stem cells (Penney, Ralvenius, and Tsai 2020).

As concerns animal models, mouse models have been the most frequently used in AD research (LaFerla and Green 2012). Within these mouse models, Gzil (2008) distinguishes between

"two types of modelling ... transgenic mice, ... a mimetic ... attempt to reproduce the physiopathological cascade observed in the familial forms of the disease ... to transpose a therapeutic strategy to humans) ... [the other model] ... mice placed in water mazes ... [to understand the neural basis of cognitive aging] ... to extrapolate the experimental results .... to humans" (p. 187, ibid).

The interested reader can find a video description of the water maze protocol and its application in (Bromley-Brits, Deng, and Song 2011). As concerns the transgenic models, (Games et al. 1995) developed the first successful transgenic mouse model of AD. (Schenk et al. 1999) showed that "Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology" in this "PD-APP" (with a mutation in the APP gene termed "V717F") transgenic mouse model and provided the basis for this therapeutic strategy in humans. The immunisation molecule, AN1792 (Elan Pharmaceuticals), was first tested in humans in September, 2000. Holmes et al. (Holmes et al.

2008) showed in long-term follow-up that "Although immunisation with Aβ42 resulted in clearance of amyloid plaques in patients with Alzheimer's disease, this clearance did not prevent progressive neurodegeneration" (p. 216, ibid). There are many other different *in vivo* models based on the genetics of DIAD, and others based more heavily on the sporadic forms of disease (LaFerla and Green 2012). But it remains the case that no model captures the entirety of the complexity of human disease—both of the pathological lesions as well as major loss of brain volume and cognitive abilities (King 2018). Mouse models in particular have been criticised for their lack of ability to predict therapeutic outcomes in human trials (Franco and Cedazo-Minguez 2014).

B3. The negative heuristic: disease scenarios

So far, the interpretation of "auxiliary hypotheses" as defended by Lakatos has led to the distinction between two types of mechanisms as described by Hardy & Higgins (1992): those leading to amyloid deposition or lack of clearance (mechanism1), and those leading to ensuing neurodegeneration following that deposition or lack of clearance (mechanism2). But those mechanisms have not taken into account the therapeutic attempts at targeting amyloid, the major goal of the programme. In 2011, following the failure of three anti-amyloid strategies to improve cognitive outcomes in patients with AD, Karran et al. (2011) proposed four "disease scenarios" when interpreting the role of amyloid-beta in the neurodegeneration of AD: as a driver, threshold, trigger, and bystander. These scenarios can be understood in light of the negative heuristic of the Lakatosian research programme: when the hopeful clinical trial fails, instead of blaming the core claim of proteinopathy triggering neurodegeneration, auxiliary hypotheses are offered. These scenarios are tabulated in Table 1, except for the "bystander" scenario, according to which "amyloid-β is an entirely innocent bystander of the disease process … [which is]

“unlikely as it is not reconcilable with genetic evidence that mutations in APP are sufficient to cause Alzheimer’s disease” (p. 853, (J. Hardy and De Strooper 2017) and is not compatible with the amyloid research agenda as described here. Here, these scenarios are not termed mechanisms. Even though there is an entity (“amyloid-β”) proposed to be responsible for a phenomenon (“the disease process”), the activities by which this occurs are omitted.

Feature	Driver	Threshold	Trigger
Description	"amyloid-β was proposed as a driver of the disease process"	“amyloid-β has to reach a certain threshold to cause harm”	“amyloid-β is proposed to be only a trigger of the disease process”
Therapeutic consequence	“any lowering of amyloid-β would slow disease progression”	“If amyloid-β therapy is not able to lower the amyloid-β level in the brain below that threshold, then no beneficial effects ... would be expected.”	“amyloid-β directed drugs would have no effect at all after the disease process has been initiated”

Intact despite failures of anti-amyloid treatments?	"This possibility is ruled out by the failed clinical trials."	"failed trials are consistent with both the threshold and the trigger scenarios"

Table 1 – Three possible disease scenarios for neurodegeneration in Alzheimer's disease mediated by amyloid-beta. Based on Karran et al. (2011) and Hardy & De Strooper (2017). These serve as auxiliary hypotheses protecting the amyloid research agenda of Alzheimer's Disease from failed anti-amyloid trials. Interestingly, the "driver" scenario was proposed in Hardy & Selkoe's 2002 formulation of "accumulation of A-Beta in the brain is the primary influence *driving* AD pathogenesis" (Hardy & Selkoe, 2002). All quotes come from p. 853, Hardy & De Strooper (2017).

As of 2021, there have been dozens of attempts with antibodies targeting amyloid-beta and the inhibition of enzymes involved in producing it. None of these strategies has shown a major disease-modifying impact (Cummings et al. 2021). There has been a general shift to less optimistic clinical endpoints in trials. Instead of trying to reverse the disease, researchers attempt to slow it down. And there is a glimmer of hope that anti-amyloid strategies may slow down the cognitive decline associated with AD. Biogen/Eisai's Aduhelm (aducanumab) is a monoclonal antibody derived from healthy human brain which targets amyloid-beta. Two phase III trials, "ENGAGE" and "EMERGE" were halted in March 2019 because of the apparently futile results they provided. While aducanumab significantly reduced levels of beta-amyloid, it did not appear to slow down the loss of cognitive abilities. Yet later that year Biogen researchers undertook another analysis in which they excluded certain participants with a very aggressive disease

progression from the ENGAGE trial data. Results of this sub-analysis suggest that high-dose aducanumab could slow down mild AD. They made a case for FDA approval and got accelerated approval for use in mild AD on June 7, 2021. The drug may be of use to some patients with mild cognitive impairment. But its accelerated approval poses a plethora of ethical problems, particularly if Biogen/Eisai make profits before the drug's therapeutic value is determined (Fleck 2021). Other antibodies are also being tested, including donanemab (Mintun et al. 2021), lecanemab (NCT04468659 for the clinical trial reference) and gantenerumab (NCT01224106). As of now, no anti-amyloid drug has received full approval for use in AD.

B4. The neuropathology of Alzheimer's disease beyond amyloid: tau protein

To finish this section on the study of AD neuropathology, though the amyloid hypothesis has dominated research, there has also been considerable interest in tau protein that is responsible for the neurofibrillary degeneration inside neurons associated with "tangles". For comparison, as of writing (September, 2021) "amyloid" "Alzheimer's disease" returns cc. 48 000 articles in PubMed, whereas "tau" "Alzheimer's disease" returns cc. 17 000. Liu et al. (2019) found that 22.3% of clinical trials up to 2019 had been testing the "Amyloid Hypothesis" whereas 12.2% had tested the "Tau propagation Hypothesis" (Liu et al., 2019).

Tau protein is known for its involvement in "tauopathies" such as some fronto-temporal dementias, progressive supranuclear palsy, cortico-basal degeneration and lastly Primary age-related tauopathy (PART) with neurofibrillary tangles similar to AD, but without abnormal amounts of amyloid plaques. Tau protein has long been used to define the neuropathological stages of AD (Braak and Braak 1991). The causal role of tau in AD has long been disputed, with a major question being: "(so) what if tangles precede plaques?" (Price and Morris 2004). In 2009, the tau propagation hypothesis was proposed as a mechanism for causing

neurodegeneration in various neurodegenerative disorders, according to which "Tau aggregates can propagate a fibrillar, misfolded state from the outside to the inside of a cell … [and] spreads through the brains of tauopathy patients" (Frost, Jacks, and Diamond 2009). There are researchers who defend it as an "initiating factor" of AD (Arnsten et al. 2021). A 2021 Phase II trial with the monoclonal anti-Tau antibody semorinemab appears to have shown an impact on cognition in patients with AD (NCT03828747). There are also calls for tau protein to be used as a less expensive and invasive blood biomarker of AD than amyloid and tau imaging biomarkers (Brickman et al. 2021) (Brickman et al., 2021). These biomarkers will now be described in the following section.

To conclude this section on AD neuropathology, writing in 2006, Hardy (2006a) recognised that "it has to be acknowledged that no therapies for any neurologic or psychiatric disease have, as yet, been developed by this approach" (p. 8, Hardy, 2006a) in the proteinopathy research programme. This changed, however, in 2017, with the discovery of "successful gene-based therapies for spinal muscular atrophy ... caused by mutations in the SMN1 gene":

"This development is clearly important for patients with spinal muscular atrophy … However, the wider importance of this breakthrough is that it is the first mechanistic therapy for a neurodegenerative disease … it bodes well for oligonucleotide strategies for other genetic diseases: APP for Alzheimer's disease, tau for frontotemporal dementia and progressive supranuclear palsy, α-synuclein for Parkinson's disease, huntingtin for Huntington's disease, and so on. Let us hope that this breakthrough is the first of many to come for all these devastating diseases" (p. 3, (J. Hardy 2018)).

C. Contemporary approaches to prevention

C1. The reconceptualization of Alzheimer's Disease

It was seen in the first section of this introduction that the major re-definition that the AD entity underwent following Kraepelin (Kraepelin 1910) was between 1976 (Katzman 1976) and 1984 (G. McKhann et al. 1984). The 1984 diagnostic criteria were elaborated as a collaborative effort between the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer Disease and Related Disorders Association (ADRDA), the forerunner to the Alzheimer's Association (AA), now the biggest AD patient association in the world. They endorsed Katzman's (1976) re-labelling of AD as the major cause of senile dementia. These criteria outlined typical clinical presentation of AD dementia along eight cognitive domains, offered criteria for excluding other causes of dementia, and diagnosed individuals with possible (for more atypical presentations) or probable (more typical) AD pending post-mortem neuropathological examination for a definitive AD diagnosis (McKhann et al., 1984).

This definition has played a vital role in the contemporary biomedical period of AD research. And yet it had deficiencies. For example, it required the presence of symptoms known not to be specific for AD-type dementia (Knopman et al. 2001). The resulting entity was therefore probabilistic rather than a definitive diagnosis. Specificity became a major issue when it was found that a significant number of patients that had undergone anti-amyloid trials were actually negative for amyloid (Landau et al. 2016).

But studying the living brain has long posed methodological and ethical problems which have extended into our contemporary period, meaning that researchers have depended on the imperfect aforementioned animal models of disease and post-mortem tissue examination in humans. The arrival of advances in brain imagery has meant that positron emission tomography

(PET) as well as magnetic resonance imaging (MRI) can be used to study the structure and function (functional MRI) of the living human brain. The first markers available for use in the study of AD were MRI measures of brain atrophy and PET markers of glucose metabolism, before amyloid and tau measured in cerebrospinal fluid (CSF) and via PET meant that the biology of AD could be studied before the symptoms of dementia arrive. In 2007, Dubois et al. proposed using imaging markers of amyloid and tau proteins and offered:

"research criteria ... revising the NINCDS-ADRDA criteria ... centred on a clinical core of early and significant episodic memory impairment. ... there must also be at least one or more abnormal biomarkers" (p. 734, (Dubois et al. 2007)).

According to the "new lexicon" of the International Working Group (IWG) for New Research Criteria for the Diagnosis of Alzheimer's Disease for the redefinition of AD (Dubois et al. 2010), "in-vivo markers of Alzheimer's pathology … can include: CSF amyloid β, total tau, and phospho-tau; retention of specific PET amyloid tracers; medial temporal lobe atrophy on MRI; and/or temporal/ parietal hypometabolism on fluorodeoxyglucose PET" (p. 4, ibid). The diagnosis of AD "is now restricted to the clinical disorder … two different stages might still be meaningful: a prodromal and a dementia phase." (p. 4, ibid). Prodromal or "predementia" AD is also a clinico-biological entity with AD biomarkers and cognitive decline which is "not sufficiently severe to affect instrumental activities of daily living" (p. 4, ibid). Conversely, according to the IWG, people given the label "mild cognitive impairment (MCI) … do not meet the proposed new research criteria for AD, in that they deviate from the clinico-biological phenotype of prodromal AD because they have memory symptoms that are not characteristic of

AD or because they are biomarker negative" (p. 5, ibid). They propose the term "asymptomatic at risk for AD (AR-AD) "for individuals with biomarker evidence of Alzheimer's pathology " (p. 4, ibid). In 2014, the IWG-2 expands and refines the biomarker evidence: they proposed the inclusion of "downstream topographical biomarkers of the disease, such as volumetric MRI and fluorodeoxyglucose PET, [which] might better serve in the measurement and monitoring of the course of disease" (p. 614, (Dubois et al. 2014).

In 2011, another expert group, "the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease" (NIA-AA, (G.M. McKhann et al. 2011), updated the 1984 criteria, and "bio-marker evidence was also integrated into the diagnostic formulations for probable and possible AD dementia for use in research settings" (p. 263, McKhann et al., 2011). In that same year, the NIA-AA group also proposed to "develop recommendations to determine the factors which best predict the risk of progression from "normal" cognition to mild cognitive impairment and AD dementia … [and] provide a common rubric to advance the study of preclinical AD" (p. 280, (Sperling et al. 2011)). The efforts of both groups converged in 2016 when they co-wrote a paper on the definition, natural history, and diagnostic criteria of preclinical AD (Dubois et al. 2016). This unified group proposed "to consider the terms of "preclinical AD" when the risk is particularly high (e.g., both Aβ and Tau markers beyond pathologic thresholds) and that of AR-AD when the evolution to a clinical AD is less likely or still needs to be determined (only one pathophysiological marker considered abnormal)" (p. 296, Dubois et al., 2016).

In summary, it can be seen that the conceptual changes made possible by technological advances have led to further medicalisation of AD neuropathology along diagnostic and prognostic lines,

with the aim of "ultimately, aid[ing] the field in moving toward earlier intervention at a stage of AD when some disease-modifying therapies may be most efficacious" (p. 280, Sperling et al., 2011).

In 2016, a new framework emerged to specifically consolidate this latter goal. Instead of using biomarkers to assist clinical diagnosis, the idea was to use biomarkers to find eligible patients for drug trials in order to try and arrest or prevent dementia in those at risk. The amyloid/tau/neurodegeneration (AT(N)) framework was thus established (Jack et al. 2016). The idea behind the ATN framework is that biomarker-positive people (A+/T+/N+) are eligible subjects for the testing of anti-amyloid, anti-tau, and other preventive therapies combating neurodegeneration.

In 2018, its defenders argued for an entirely biological definition of AD where "A+T+(N+) = AD" (Jack et al. 2018). AD is not pre-fixed (preclinical, prodromal), and no symptoms are required for this categorisation. AD is thus kept conceptually separate from the dementia it causes in its end stage.

This represents a significant transformation of the concept of AD from a clinico-pathological entity to an entirely biological one. It is what Schermer & Richard (Schermer and Richard 2019) term "the reconceptualization" of AD. These *in vivo* biomarkers are not pathognomonic (literally. "*fit to judge pathology*")—they are not entirely specifically characteristic of AD. Many A+/T+/N+ patients never go on to develop dementia. Thus, defining AD entirely biologically may rest on an exaggerated prognostic and therapeutic value of AD neuropathology which leads to ethical conflict between the interests of the individual and the interests of anti-amyloid research (Schermer & Richard 2019).

Recognising the "debate and challenges regarding [the] use in everyday clinical practice" of "preclinical AD," the IWG has reiterated its position:

"that Alzheimer's disease diagnosis be restricted to people who have positive biomarkers together with specific Alzheimer's disease phenotypes, whereas biomarker-positive cognitively unimpaired individuals should be considered only at-risk for progression to Alzheimer's disease" (p. 484, (Dubois et al. 2021).

The idea that there can be harmful medical knowledge opens a debate about the legitimacy of the medicalisation of a phenomenon. Kaczmarek (Kaczmarek 2019) offers an analysis of medicalisation in terms of "well-founded medicalisation and over-medicalisation" (p. 119, ibid). She identifies four levels at which (over)medicalisation can have an impact: health, economic, psychological, and social. While medicalisation can undoubtedly do a lot of good for individuals who benefit from it, it can also cause harm along those dimensions. For example, Largent et al. (Largent et al. 2020) undertook "The Study of Knowledge and Reactions to Amyloid Testing (SOKRATES)" and found that receiving knowledge of elevated amyloid on a PET scan had "implications for identity, self-determination, and stigma." Bunnik et al. (Bunnik et al. 2018) argue that AD biomarker information has low "personal utility" to individuals who receive it.

In summary, it can be seen that the "AD = senile dementia" concept inherited from Katzman (1976) and consolidated in McKhann et al. (1984) for the purpose of diagnosis has been gradually replaced by the research concept of AD for the inclusion of eligible people in preventive trials. The idea that "AD = senile dementia" nevertheless remains the lay conception and talk about cascades and cognitive continuums remains the language of specialists and not

larger society (Smedinga et al. 2020). Thus, communicating AD biomarker information and making clinical decisions based on it in a time of uncertainty as to its practical value is increasingly scrutinised. There is therefore an emerging literature on whether AD biomarkers are currently over-medicalised.

C2. The bifurcation of prevention of dementia: neuropathology targeting and resilience promotion

The nature of this literature on the definition of AD and the research priorities it seeks to inspire reveals the structure of contemporary research. These consensus definitions were based on *Perspectives* and *Position Papers* published in leading specialist journals (The Lancet, Alzheimer's & Dementia) by international expert groups. Together, they have been cited several thousands of times, and serve as a reference for defining priority setting within the community. While there are critiques of these papers written by individuals and small groups, they have had a major impact on the direction of research. However, the NIA-AA and IWG approach is not the only way of conceptualising and attempting to treat or prevent dementia.

What follows is an alternative expert consensus on the public health problem of dementia. The therapeutic approach *à la NIA-AA / IWG* described so far, to which aducanumab belongs, could be termed "neuropathology targeting." If the neuropathology of AD causes degeneration, it makes sense to rid the brain of it as early as possible. Yet there are a growing number of researchers emphasising the discrepancy between AD neuropathology and dementia as did Rothschild back in the 1930s. There are other causes leading to dementia including traumatic brain injury, age-related decay of brain blood vessels, and genetic mutations involving other proteinaceous brain lesions (WHO 2021). Now that dementia is recognised to be a major public health problem affecting over 50 million people worldwide, there have been major efforts within the field of population epidemiology to study factors leading to it. This represents a

methodological shift away from individual patients, their dementia and their neuropathology, to trends with much larger groups of patients.

The Lancet has commissioned two expert panels to argue for policy shifts in dementia (Livingston et al. 2017; Livingston et al. 2020). The main message from this epidemiology literature is the possibile avoidability of dementia as a public health problem. This has required studying non-specific risk factors for dementia rather than the specific lesions of AD. According to these expert panels, 40% of dementia cases might be prevented by taking action against 12 modifiable risk factors across the lifetime (Livingston et al. 2020): early life (less education), midlife (hearing loss, brain injury, hypertension, alcohol consumption, obesity), late life (smoking, depression, social isolation, physical inactivity, diabetes, air pollution).

These authors study "all the different types of dementia" because "some people with neuropathological changes of AD do not have dementia" (pp. 2675–2676, Livingston et al., 2017). Thus, what was referred to as the prognostic and therapeutic value of AD neuropathology is seriously questioned by these authors: "amyloid-β and tau biomarkers indicate risk of progression to Alzheimer's dementia but most people with normal cognition with only these biomarkers never develop the disease" (p. 413, Livingston et al., 2020). Instead of arguing in favour of targeting AD neuropathology, they defend a "broader approach to prevention of dementia, including promoting resilience [which] makes sense in our ageing societies" (p. 2677, Livingston et al., 2017).

Resilience to dementia is understood as the phenomenon that some individuals with significant brain pathology (particularly AD neuropathology) maintain cognitive function in spite of it. Promoting resilience means taking individual and society-wide action against risk factors which might be making individuals less resilient to the effects of brain pathology.

A shift away from AD neuropathology also means a shift away from its diagnosis as a specific entity. Here, there is a move towards a mixed picture view of dementia, limited to dementia and not other forms of mental dysfunction in older adults (cf. the mixed picture of psychodynamics in section A):

The complexity and mixed nature of dementia in older adults has been shown repeatedly, but these findings remain somehow inconvenient and are disconnected from the major investments in new interventions. Population studies show that relations between neuropathology and the expression of dementia symptoms are not so deterministic at older ages; β amyloid related neuropathology can be severe in older adults without dementia and virtually absent in those with dementia (p. 1, Le Couteur et al., 2016 (Le Couteur, Hunter, and Brayne 2016)*).*

Thus, while AD as an entity appears to be resistant to attempts to treat and prevent, broad action against mixed dementia may lead to up to 40% of cases being avoidable by action against risk factors. However, despite this ambitious claim, it is recognised that "little evidence exists for any single specific activity protecting against dementia" (p. 413, Livingston et al., 2020). Evidence in favour of specific activities comes from multi-domain lifestyle interventions. The Finnish Geriatric "FINGER" study was a 2-year multi-domain physical and cognitive interventional trial with people aged 60-77 (Ngandu et al. 2015). The intervention consisted of nutritional guidance; exercise; cognitive training and social activity; and management of metabolic and vascular risk factors versus regular health advice for controls. It led to "a small group reduction in cognitive decline" (p. 426, Livingston et al. 2020) in the approximately 600 cognitively at-risk people vs. controls. However, it has not been replicated by similar studies: the French Multi-domain

Alzheimer's Prevention Trial ("MAPT") with omega-3 supplementation and lifestyle intervention and the Dutch "Prevention of dementia by intensive vascular care" (PreDIVA) studies did not find significant beneficial effects on cognition of these interventions in people of similar ages. The worldwide FINGERS initiative is testing FINGER-style protocols in different countries with the following goals in mind:

to prevent cognitive impairment and dementia … generating high-quality scientific evidence to support public health and clinical decision-making … [and] support the implementation of preventive strategies and translation of research findings into practice (p. 29, (Rosenberg et al. 2020)).

In summary: the two major approaches towards dementia are neuropathology targeting and resilience promotion (summarised in Table 2). The term approach is used here because they are approaches to treatment based on different promising data, which have led to a theory about the relationship between AD neuropathology and dementia, and a therapeutic strategy based upon that theory. The approach of resilience promotion will not be analysed here according to a Lakatosian research programme primarily because it is still in its infancy. Though it has a positive heuristic (increased study of and action against risk factors), the heterogeneous nature of these interventions means that further philosophical work will require waiting for the results of the worldwide FINGERS initiative before studying the approach's negative heuristic.

The two approaches are not mutually exclusive. Frisoni et al. (Frisoni et al. 2020) argue that they can be understood as primary prevention ("target cognitively normal persons with modifiable

risk factors through lifestyle and multiple domain interventions (including general cardiovascular health))" and secondary prevention ("target cognitively normal persons at high risk of dementia due to Alzheimer's disease pathology with future anti-amyloid, anti-tau, or other drugs") (pp. 1457-1458, Frisoni et al., 2020). There have also been efforts to bridge the gap between them, for example, via the study of the biological mechanisms of resilience (Arenaza-Urquijo and Vemuri 2018) and the elaboration of concepts such as social health which take into account the interaction between, brain, body and a broadly-construed environment (Vernooij-Dassen et al. 2021).

Finally, it will become clear in Parts 1 and 2 of the thesis that there are many biological researchers working on the biology of AD whose approach does not fall under neuropathology targeting or resilience promotion. For example, Liu et al. (2019) found that 17% of clinical trials up to 2019 had tested the "mitochondrial cascade hypothesis and related hypotheses" (Liu et al. 2019). The mitochondrial cascade hypothesis places aging at the centre of sporadic AD and offers an increase of oxidative stress within mitochondria as a possible mechanism leading to amyloid deposition and later neurodegeneration (Swerdlow and Khan 2004). Other hypotheses exist and more will be said about them in Part Two of this thesis. What can be said now is that there is a lack of expert consensus amongst biologists on how to choose between the "long list of disease-causing options" (Herrup, 2015).

Having established these two major approaches to dementia prevention, the debates at the heart of this thesis can now be stated (Table 2). They are understood respectively as epistemological (concerned with knowledge) and ethical (concerned with how individuals and communities should behave).

Content of the debate	Position held by defenders of neuropathology targeting	Position held by defenders of resilience promotion
1) Are the lesions of Alzheimer's disease a major cause of dementia? (Epistemological debate.)	Yes, dementia and neuropathology are separated primarily by time (Jack et al., 2018).	No, dementia and neuropathology are separated primarily by resilience (Livingston et al., 2017, 2020).
2A) What is the appropriate behaviour of the scientific community with respect to choosing between theories that guide efforts to find treatments for dementia? (Scientific ethics debate).	Positive and negative heuristics of the amyloid research agenda and other hypotheses within the proteinopathy research programme (e.g. tau propagation hypothesis).	The need to "invest in a much broader research programme" (p.1, Le Couteur et al., 2016)

2B) What kind of decisions should be made regarding treatment in people at risk of developing, or with early signs, of dementia? (Medical ethics debate).	Early identification and targeting of amyloid/tau/neurodegeneration (Jack et al., 2018).	"Political drive to screen for pre-dementia: not evidence based and ignores the harms of diagnosis" (Le Couteur et al. 2013)

Table 2 – Three debates that divide defenders of the neuropathology of Alzheimer's disease and of promoting resilience to dementia: epistemology, scientific ethics, and medical ethics.

Motivation for & structure of this thesis

Just as there are several approaches studying the problem of AD, this is equally true of the philosophy of science, which was briefly defined before as an attempt to describe scientific activity and also offer norms to evaluate it. There are three major philosophical approaches defended within this thesis that have been used to frame and offer solutions to the epistemological and ethical debates summarised in Table 2. Though it must be stated that the debates concerning the validity of different approaches are long-standing, the existence of this thesis is a testament to the idea that it nevertheless seems important that there be a meaningful discussion about priority setting in such a diverse community even though those debates are unlikely to be resolved immediately.

The first approach, found in Part One, will be called "empirical philosophy of science". The second approach, found in Part Two, will be called "conceptual philosophy in science." The third approach, found in Part Three, will be called "neuroethics and innovation."

Part One uses empirical methods so as to frame the problem of the dominance of the amyloid research agenda in biomedical AD research. This is done firstly through a bibliometric study of scientific articles citing the original formulation of the ACH by Hardy & Higgins (1992). We were looking for possible "unfounded authority" (Greenberg 2009) of ACH made possible by "herd-like" citation behaviour of the article written by Hardy & Higgins (1992). The other method in this first part was an international survey promoted with the help of the Alzheimer's Association so that we could get direct access to what a diverse sample of researchers thought of the epistemological and ethical debates as well as their possible solutions.

The second part of the thesis uses conceptual analysis to examine the complexity of dementia beyond the specific lesions of AD. It was heavily inspired by Karl Herrup (2015)'s highly-cited "case for rejecting the amyloid cascade hypothesis." He argues there are lots of different physiological processes associated with AD ("disease-associated processes," DAPs) which might offer new therapeutic targets. Yet he offers little in the way of explicit criteria for choosing between DAPs. We argue that his reasoning is based on association, which is too vague to be a technical concept. We therefore try to offer criteria so as to sort DAPs into a holistic theoretical and therapeutic scheme, the *Alzheimer's Disease-Associated Processes and Targets* (ADAPT) Ontology. Nevertheless, despite the benefits of a more holistic vision of AD, constraints of clinical trials and statistical analysis lead us to defend simple tests of treatments being validated before more complex treatment ensembles get put together and promoted.

Thirdly and finally, we turn to the case of the ethics of treatment for this disease that represents an enormous personal, familial, and societal burden. We identify a particularly problematic case of what we call "innovative practice" in AD and offer more stringent guidelines than the declaration of Helsinki for using and promoting alternative treatments for AD. We also discuss the limits of resilience promotion in public health policy by arguing against a moralising view of action against risk factors, and also argue in favour of a reform of the economic model on which drug development for AD is based so that drug trials can go on longer and thereby be more useful to patients and research by offering better feedback on the validity of therapeutic targets.

It is hoped that the findings lead to improved communication around priority setting in the research community, that the methods are useful to other researchers, and the larger debate of use to patients and their families.

Part One — Empirical philosophy of science: the dominance of the amyloid research agenda in Alzheimer's Disease research

If the amyloid cascade hypothesis (ACH) of AD has enjoyed the status it has enjoyed, it is because the larger community has played an active role in letting its status grow. Whether or not the ACH's influence is ultimately a good thing for the patient community in need of treatment will depend on the future of anti-amyloid treatments. Yet even prior to that ultimate judgment being pronounced, there are tools available to undertake an empirical study that would provide a quantitative measure of the extent to which the AD research community has accepted the ACH and the research programme built on it. In 2011, there was a debate around whether the ACH had "misled the pharmaceutical industry" ("The amyloid cascade hypothesis has misled the pharmaceutical industry" 2011). It is important that this provocative and metaphorical title not be interpreted as though the research community and pharmaceutical industry were passive entities. Chapter One of this thesis contains a study of citation practices. This study employs an approach called bibliometrics (literally, measuring the literature). The published scientific literature was chosen as a source because it is, by far, the biggest stock of scientific information to be found on AD. A citation study, which meant studying how scientists quote an idea, was chosen because citations "represent long-run credit … the uptake the article receives in the scientific community" (p. 646 (Heesen and Bright 2021)). They were studied using a method inspired by an empirical study conducted by Greenberg (Greenberg 2009). He studied how people cited the idea that "β amyloid, a protein accumulated in the brain in Alzheimer's disease (AD), is produced by, and injures skeletal muscle, of patients with inclusion body myositis." He found not only a major bias towards citing this idea favourably (what he termed a 'positivity bias'), but also cases where "citation distortions create unfounded authority" where the citation was used to

go beyond the claims of the original author.

Given the controversy around the role of β amyloid in AD, we undertook to use this method as a unique tool to measure an aspect of scientific ethics within the biomedical research around AD, given the dominance of the ACH (Liu et al. 2019).

However, while citations suggest the relevance of the cited research for the field, they are not a perfect measure of scientific quality. Yves Gingras (Gingras 2014) has criticised the downward slide of the evaluation of research. There is no one-size-fits-all measure for judging the scientific quality of a paper, researcher, or researcher institution. Rates of citation vary greatly between fields, certain journals have greater visibility than others within the same field due to different "impact factors" (average annual citation rates of journals), and there are even examples of citation "cartels" whose members make concerted efforts to prioritise citing researchers within it, at the same or different research institutions.

Thus, the quantity of citations of any particular paper is no guarantee of its scientific quality, since factors beyond the paper play a role in its being cited. Greenberg (2009)'s study of citations raises the question of whether scientists citing a paper have even read it. Beyond these external factors, there may also be factors within a paper that increase its citability. For example, Hardy (J. Hardy 2006) recognises that the paper we study in Chapter One, the original formulation of the ACH "is simple, clear and short: too many articles are complicated, muddy and long: even a venture capitalist or a corporate CEO can read to the end of it" (p. 152, ibid). But a paper might be well-written, concise and convincing, and yet the hypothesis defended within it could nevertheless be false.

Nevertheless, even if citation behaviour is not a perfect guarantor of scientific quality, it is intuitive to argue that ethical scientists shouldn't cite ideas in problematic ways so as to avoid

them developing an "unfounded authority" (Greenberg, 2009). But given the complexity of what makes scientists hold certain opinions about a theory (see Introduction), studying citations should not be used to assess individuals' behaviours and their personal accountability. For this reason, a community-wide study of a large sample of citations and associated statistical analysis was conducted.

The null hypothesis used was to test whether or not the original formulation of the ACH ((J.A. Hardy and Higgins 1992)"HH92") had been cited in ways suggestive of a herd-like acceptance. If this was the case, that might suggest that there is a problematic adherence to the amyloid research agenda amongst scientists. If not, then it might help to dispel scepticism (and even cynicism) around the dominance enjoyed by the ACH theory in relation to research into AD.

Recognising the imperfect nature of the citation as a metric, the second part of the bibliometrics study looked at empirical support for the ACH to try and answer questions about its scientific well-foundedness. To do this, we divided articles citing HH92 into "Review" articles vs. empirical studies. Review articles generally review the state of the art of a subject as opposed to empirical studies that test hypotheses. This allowed a comparison to test whether there were differences amongst authors reviewing the ACH and those actually testing its claims. This was done by studying the conclusions of those articles testing its claims so as to get an idea of the empirical support to be found in favour of the ACH.

Taken together, these two methods in the bibliometrics article can be understood as an attempt to ascertain whether the ACH enjoys what Greenberg terms (2009) "*unfounded* authority."

The second article is a discussion on amyloid and democracy in AD research following an anonymous online survey of AD researchers. A survey was undertaken with researchers in order to get direct access to their opinions on theories and treatments for AD. There were several

reasons for adopting this approach.

Firstly, the structure of science is hierarchical, meaning that not all researchers have their work funded and published to the same extent. It is also the case that there are AD researchers who are cited much more frequently in the literature than others (Sorensen 2009). Furthermore, there are norms within scientific publication that leave little room for personal opinion in published articles.

And yet at certain scientific talks and conferences, the tension between different opinions is palpable and might be playing more of a role in the kind of decisions that get made in AD research than the published literature might suggest. Each year the US Alzheimer's Association organises an international scientific congress where researchers and clinicians meet, the Alzheimer's Association International Congress (AAIC). At the AAIC in Los Angeles in July 2019, in her keynote address to the 5,700 researchers and clinicians in attendance, Dr Maria Carrillo, Chief Scientific Officer of the Alzheimer's Association, called for unity in the fight against Alzheimer's, despite the lack of therapeutic fruits borne at the time by the dominant paradigm, although she acknowledged that "the clinical trial data presented at this year's AAIC reflect the diversity of approaches" being used to develop treatments for Alzheimer's disease. Questions asked at different sessions revealed the extent of disagreement between defenders of different approaches.

This means that getting access to an accurate idea of what researchers really think about theories and therapies for AD requires something other than the published literature.

In order to prepare the survey questions, several formal and informal interviews were conducted with biomedical researchers working on AD. A working hypothesis was adopted that placed researchers into "two broad groups; those that support the amyloid cascade hypothesis and those

that do not" (Hunter, Friedland, and Brayne 2010) based on questions about amyloid's role in AD. Using this method, it would be apparent who opined what about AD, and in particular, would "pro-ACH" represent a dominant opinion? Similarly, which researchers considered other therapies are a source of optimism, and who defends such approaches? Do predictors of success – such as publication count and receiving research funding from the pharmaceutical industry – offer an explanation as to why people adhere to the ACH?

An aim of this research is to determine if there are potential benefits to making biomedical research into AD more democratic, insofar as the community could benefit from listening to the collective opinions of researchers when making choices about funding alternative theories. By taking a more pluralistic view of AD research there is a reduced possibility of two injustices, firstly to patients, if anti-amyloid treatments never deliver on the hope they offer, and secondly, to researchers working on different theories of AD from different perspectives who might otherwise struggle to obtain funding and thereby make their contribution to improving patients' lives.

Chapter One: Beta-amyloid in Alzheimer's Disease: A study of citation practices of the amyloid cascade hypothesis between 1992 and 2019

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Timothy Daly[2], Marion Houot[3,4], Anouk Barberousse[1], Yves Agid[2], Stéphane Epelbaum[2,3]

ABSTRACT

The amyloid cascade hypothesis (ACH) has dominated contemporary biomedical research into Alzheimer's disease (AD) since the 1990s but lacks confirmation by successful clinical trials of anti-amyloid medicines in human AD. In this uncertain period regarding the centrality of beta-amyloid (Aβ) in the AD disease process, and with the community apparently divided about the ACH's validity, we used citation practices as a proxy for measuring how researchers have invested their belief in the hypothesis between 1992 and 2019. We sampled 445 articles citing Hardy & Higgins ("HH92") and classified the polarity of their HH92 citation according to Greenberg (2009)'s citation taxonomy of positive, neutral, and negative citations, and then tested four hypotheses. We identified two major attitudes towards HH92: a majority (62.7%) of neutral attitudes with consistent properties across the time period, and a positive attitude (35.0%), tending to cite HH92 earlier on within the bibliography as time went by, tending to take HH92 as

[2] Philosophy Department, Sorbonne Université, Paris, France.
Mail: Timothy Daly, timothy.daly@paris-sorbonne.fr

[3] Centre of excellence of neurodegenerative disease (CoEN), ICM, CIC Neurosciences, APHP Department of Neurology, Pitie-Salpêtriere Hospital, University Paris 6, Paris, France.

[4] Department of Neurology, Institute of Memory and Alzheimer's Disease (IM2A), Pitie-Salpêtriere Hospital, AP-HP, Boulevard de l'hôpital, Paris, France.

an established authority. Despite the majority of neutral HH92 citations, there was a positive majority of attitudes towards newer versions of the ACH and anti-amyloid therapeutic strategies (67.4%), suggesting that the ACH has been dominant and has undergone significant refinement since 1992. Finally, of those 110 original articles within the sample also testing the ACH empirically, an overwhelming majority (89%) returned a pro-ACH test result, suggesting that the ACH's claim is reproducible. Further studies will quantify the extent to which results from different methods within such original studies convergence to provide a robust conclusion vis-à-vis Aβ's pathogenicity in AD.

INTRODUCTION

There are and have been several aetiological hypotheses of Alzheimer's disease (AD), but the amyloid cascade hypothesis (ACH), which claims that cerebral beta-amyloid deposition is the driving pathogenic factor of AD, has been the most dominant over the last 25 years [1, 2]. Interestingly, despite the dominance of the ACH, there have been no successful clinical trials with anti-amyloid agents (though see promising results from [3]. The ACH's scientific merit has been drawn into question on multiple occasions [4], and many experts are skeptical, even cynical about the status it has enjoyed[5].

The ACH is a biomedical hypothesis in that its evaluation is both biological and medical. In biology, it must adequately explain the etiology of AD. In medicine, it will be evaluated by its ability to help the development of disease-modifying therapies based on its claims. It is because of the dual biomedical nature of the hypothesis that not only its confirmation, but also its refutation, is extremely difficult.

The philosopher Sir Karl Popper (1902-1994), famous amongst contemporary biomedical scientists, proposed that testing hypothetical conjectures was the essential activity of science. Furthermore, he proposed that negative results tell us more about the truth of a hypothesis than confirmatory ones: the accumulation of supposedly confirmatory data can continue *ad infinitum*, whereas the obtention of a false test result supposedly tells us that something is wrong with the theory now[6].

However, Popper's intuition about falsification can only take us so far, logically speaking. It is extraordinarily difficult with a clinical trial to test the theoretical core of the ACH (that beta-amyloid deposition is central to human AD) due to the number of "auxiliary hypotheses" or background assumptions involved in the test of any one anti-amyloid agent [7]. In short, the ACH predicts that an anti-amyloid agent, in patients correctly diagnosed, given at the appropriate stage of the disease, targeting the correct species of beta-amyloid, with the correct targeting mechanism (see debates around passive vs. active immunisation), at the right dose, will have some important disease-modifying effect. It is only when all of these obstacles have been overcome that we can say that the hypothesis is being truly tested by a clinical trial.

Given these difficulties, we reason that studying confirmation and refutation of the ACH cannot be soundly pursued at this stage by a bibliometric study, but have chosen instead to study the beliefs of scientists towards the ACH. In his famous 1877 article[8] "The Fixation of Belief," the scientist-philosopher Charles Sanders Peirce (1839-1914) suggested that there were 4 methods by which we arrive at our beliefs: individual tenacity, collective authority, a priori racionation, and science. The scientific method, he claims, is the only method "by which our beliefs may be determined by nothing human, but by some external permanency – by something upon which our thinking has no effect" (CP5.385).

As early as 2001 in AD research, certain researchers have felt that human factors have contributed to the dominance of the ACH: Joseph et al. [9] called this phenomenon "The Church of the Holy Amyloid"; Mudher and Lovestone [10] used religious language to refer to "TAUists" (defending the primacy of tau involvement) and "BAptists" (defenders of the ACH) defending the role of these proteins in AD aetiology.

In light of the difficulties testing the logical confirmation or refutation of the ACH, and the hypothesised existence of divided belief with the possibility of ideology within the AD community, we have chosen to study the acceptance of the ACH and test certain hypotheses about how it has been accepted, using citations as a proxy for acceptance or refusal of the idea by researchers within the field, as a way of measuring their belief in the ACH's validity. The main question we asked about such practices was, "When the authors of scientific papers cite this paper devoted to explicitly defending the ACH, do they tend to do so in a polarised (positive, neutral, or negative) way?" The methodology used in this study was inspired by Greenberg[11], who likewise used citation practices to measure the "belief in a specific scientific claim by studying the pattern of citations among papers stating it." He found that when the authors of a scientific paper encounter and cite the claim that β-amyloid is associated positively with inclusion body myositis, he could divide the citation into those receiving the idea positively, neutrally, and negatively. He also discovered that amongst citing articles there was an overwhelming preponderance to cite the idea positively.

We tested four hypotheses about citation practices of articles citing HH92. Firstly, we wished to test Hardy et al. [1]'s claim of the dominance of the ACH. Secondly, validation of the citation metric: whether HH92 citations could be used to predict how scientists positioned themselves towards the ACH. Thirdly, whether it pays to cite HH92 favourably, leading to higher citation

rates of positively-citing articles. Fourthly, whether HH92 was cited earlier within articles with time; for example, as a growing authority on AD.

Finally, recognising the importance of reproducibility of evidence in favour of a hypothesis, as a measure of its scientific support, we measured how many original articles in our sample tested the ACH and how many arrived at a favourable test result.

Thus, our study classifies citations according to Greenberg's taxonomy, as a measure of how researchers encounter the idea of "Amyloid deposition as the central event in the aetiology of Alzheimer's disease," and tests hypotheses about such practices and their consequences.

METHODS

HUB SELECTION AND SAMPLING

Four candidates for the ACH hub were identified [12–15]. "Alzheimer's Disease: The Amyloid Cascade Hypothesis" ("HH92") was chosen, since firstly, as its title suggests, the claims of the ACH are most explicitly laid out, and secondly, this article has the most citations within this wave of "pro-ACH" articles [Figure 1].

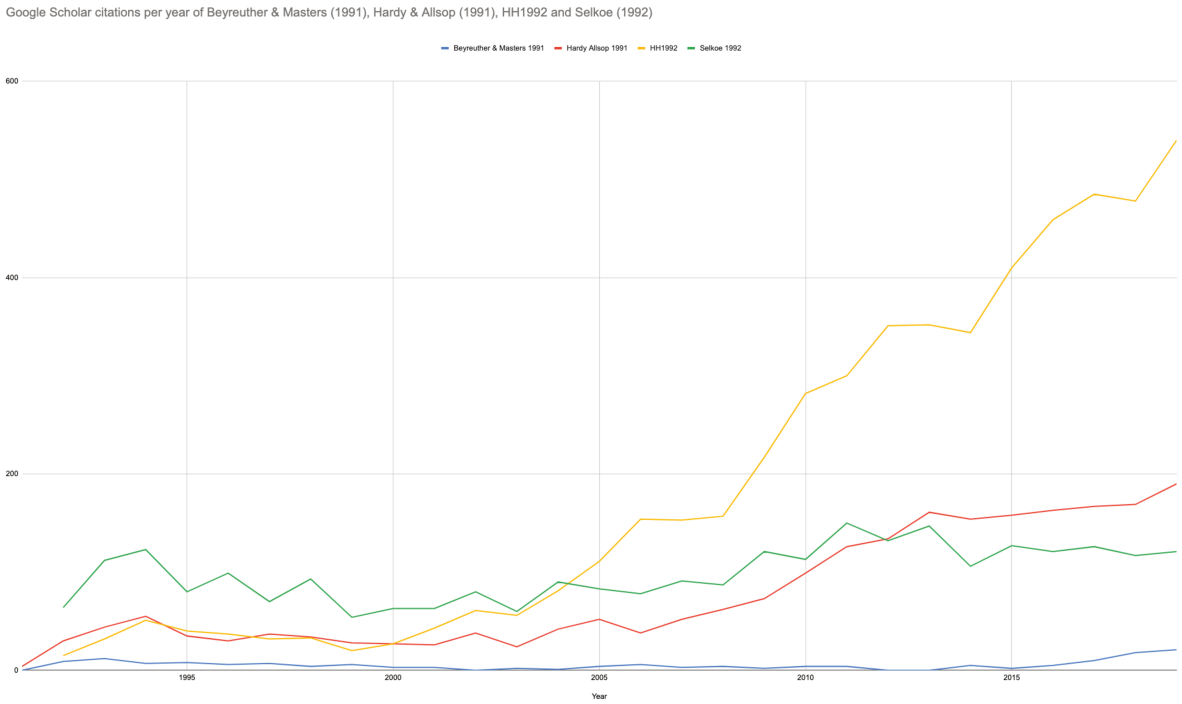

Figure 1 – HH92 is the ACH hub most likely to be influencing the beliefs of citing authors due to the explicit nature of its title as a defence of the ACH and its growing impact in the literature in terms of citations.

A sample of 1 in 10 random articles was chosen (540 / 5400 articles). 95 articles were excluded: those not written in English, not published in peer-reviewed scientific journals, or with 0 citations since their publication (since we wished to measure the transmission of the major idea of the ACH, and an article with 0 citations has no citation-related impact).

DETERMINING HH92 CITATION AND ACH VALENCE

Inspired by Greenberg's study[11], who "classified each citation as supportive, neutral, or critical according to how its underlying statement supported the belief" [p. 2], it was

hypothesised that articles cite HH92 in a potentially non-neutral way; that is, they may tend to position themselves vis-à-vis the theoretical statement being made explicit within HH92 (that beta-amyloid deposition is the central event in the aetiology of AD). Each citation was therefore classified as "negative" (unconvinced of HH92's ACH's validity) "neutral" (no definitive claim made about the ACH's veracity, or suggesting the need for further evidence before making claims about it) or "positive" (already convinced of the ACH's validity at the time of citing) by Timothy Daly.

Furthermore, since it was recognised that the ACH as defended within HH92 is but one version of the ACH, in light of the changes that the field has undergone since 1992 [16, 7], the overall conclusion of the article with respect to the suitably of beta-amyloid as a target as compared to other possible therapeutic strategies was also measured ("ACH conclusion"). This conclusion was typically suggested by the study's results, or found explicitly mentioned in the title, abstract, and/or discussion; it was also classified as negative, neutral, or positive in the same way as HH92 citations.

Thereafter, articles were divided into "Original" and "Review" articles, classified by date, citation rate in Google Scholar (measured as citations per year, to account for articles being published during different years). For each article, the place within the bibliography that HH92 occupied was noted (for articles using a quantified bibliography, 303 articles out of 445). The geography of first-author affiliation was also noted as a function of continent (North America: NA, Europe: EU, Asia: AS, Africa: AF, Australasia, AU).

IDENTIFYING SUPPORT FOR THE ACH FROM ORIGINAL STUDIES WITHIN THE SAMPLE

110 original articles within our sample tested the ACH's basic claim. For each article, we obtained the "post-test result" from a semantic analysis of the article's results and discussion section, divided post-test results into "positive," "inconclusive," or "negative." In "inconclusive" articles, we included those articles whose authors, following their test of the ACH, stressed the need for further testing and interpretation before making claims about the ACH's veracity. We then proceeded to test the reproducibility of pro-ACH test results within the sample.

HYPOTHESES

STATISTICAL ANALYSES

Data are presented as counts and percentages for categorical variables and as mean ± standard deviation for normal distribution numerical variables or as median [first quartile $Q_{0.25}$, third quartile $Q_{0.75}$] for non-normal distribution numerical variables.

Fisher's exact test were performed to compare category distribution of a categorical variable between several groups. Welch's t-test for normal distribution numerical variables or Wilcoxon rank-sum test were performed to compare distribution of a numerical variable between two groups. To compare more than two groups, ANOVA Fisher test or Kruskal-Wallis test were performed when appropriate followed by Tukey's HSD test or pairwise Wilcoxon rank-sum tests with Benjamini Hochberg correction for *post hoc* comparisons.

In order to test the hypothesis that as time passes, HH92 is mentioned earlier in the articles, a one-sided Spearman's rank test between the year of the publication of the articles and their citations per year was performed with rho < 0 as alternative hypothesis.

HYPOTHESES AND OBJECTIVES: ARTICLE VALENCES

By measuring citation practices, we hoped to gain information regarding the attitudes of practicing scientists within the AD field towards the ACH. In this way, positive citations were used as a proxy for acceptance of the authors' belief that beta-amyloid might indeed have some central role to play in AD; neutral citations were seen as a more reserved attitude in need of more compelling evidence; negative citations were seen to represent authors' mistrust of the ACH's basic claim given the available evidence. The various hypotheses we put forward tested the distribution of citation valences, as well as the consequences of citation valence.

INVESTIGATING HARDY ET AL. (2014)'S CLAIM OF ACH DOMINANCE

We hypothesised that within our sample of articles, given the central place of HH92 in the broader AD literature, there should be a positive majority of both HH92 citations and "pro-ACH" overall article conclusions.

Furthermore, given the 27-year period over which we measured citation practices, we also measured whether citation valence was associated with three other properties: the article's

overall conclusion with respect to the ACH; the Google Scholar citation rate of the citing article itself; and the position of the HH92 within the bibliography of the citing article.

HH92 CITATION AS A PREDICTOR OF ACH VALENCE

When HH92 is cited positively, we hypothesised that it would result in the author's belief "feeding in" to a pro-ACH overall conclusion, whereas neutral and negative citations would not allow for prediction of overall conclusion based on HH92 citation practice due to confounding factors. This allowed us to measure just how much the HH92 served as a positive influencer of the beliefs of citing authors.

THE IMPACT OF ARTICLE VALENCE ON CITATION RATE OF ARTICLES

We wanted to know if articles citing HH92 favourably, or with a favorable conclusion towards the ACH, were themselves cited more frequently than neutral or negative citers, thus contributing to more "pro-ACH" traffic in the literature, which might explain the success of the ACH compared to its competitors.

THE EFFECT OF TIME ON THE POSITION OF HH92 CITATION WITHIN THE BIBLIOGRAPHY

Finally, we wanted to test whether articles citing HH92 favourably cited it earlier on than articles in previous years, as a proxy for measuring how belief in the AD towards the role of β-amyloid

in AD has evolved since 1992, with the idea of its central role becoming more of a foregone conclusion in such positively-citing papers as a function of time.

SUPPORT FOR THE ACH FROM ORIGINAL ARTICLES

Given that the ACH has been dominant, as a necessary scientific condition to justify such dominance, the original articles should provide reproducible support for the ACH in their post-ACH test results. Within each testing article, we studied the nature of the inference made based on the results from the test (as evidence in favour of the ACH; as inconclusive vis-à-vis the ACH; as evidence against the ACH).

RESULTS

GENERAL CHARACTERISTICS AND FINDINGS

Of the 445 articles citing HH92 in the sample, 26 (5.8%) were written between 1992-1999; 97 (21.8%) between 2000 and 2009, and 322 (77.4%) between 2010 and 2019. 219 articles (49.2%) were original research articles and 226 (50.8%) were review articles. Within the 219 original research papers, 110 (50.7%) tested the claims of the ACH. 98 (89.1%) of 110 articles returned a positive test result, suggesting reproducible support for the ACH from original tests.

The majority (343, 77.1%) of papers were produced by European and North American research teams, with Asia being the third most productive continent (81, 18.2%).

	all N=445	original N=219 (49.21%)	review N=226 (50.79%)	p
Period of publication				0.471
[1992-2000[	26 (5.84%)	13 (5.94%)	13 (5.75%)	
[2000-2010[	97 (21.80%)	53 (24.20%)	44 (19.47%)	
[2010-2019[	322 (72.36%)	153 (69.86%)	169 (74.78%)	
ACH tested	110 (24.83%)	110 (50.69%)	0 (0.00%)	<0.001 *
Result of the ACH test (MD=285)				
ACH positive		98 (89.09%)		
ACH inconclusive		5 (4.55%)		
ACH negative		7 (6.36%)		
ACH valence				<0.001 *
positive	289 (64.94%)	169 (77.17%)	120 (53.10%)	
neutral	109 (24.49%)	37 (16.89%)	72 (31.86%)	
negative	47 (10.56%)	13 (5.94%)	34 (15.04%)	
HH92 valence				0.1294
positive	155 (34.83%)	84 (38.36%)	71 (31.42%)	
neutral	276 (62.02%)	131 (59.82%)	145 (64.16%)	
negative	14 (3.15%)	4 (1.83%)	10 (4.42%)	
Citation Rate	9.01 ± 13.07	7.75 ± 10.89	10.23 ± 14.81	0.045*
Geography of 1st author				<0.001 *

Asia	81 (18.20%)	58 (26.48%)	23 (10.18%)	
Australasia	10 (2.25%)	2 (0.91%)	8 (3.54%)	
Europe	175 (39.33%)	81 (36.99%)	94 (41.59%)	
North America	168 (37.75%)	76 (34.70%)	92 (40.71%)	
Central & South America	11 (2.47%)	2 (0.91%)	9 (3.98%)	
HH92's place in the bibliography (MD=142)	0.20 ± 0.23	0.17 ± 0.20	0.24 ± 0.26	0.011*

Notes. Data are given as mean ± standard deviation for continuous variables and as count (percentages) for categorical variables. Welch's t-test was used to compare groups for continuous variables and Fisher's exact test for qualitative variables.
Abbreviations: MD = missing data.

Table 1. Sample characteristics of the 445 articles within the sample citing Hardy & Higgins (1992).

POSITIVITY OF HH92 CITATIONS AND ACH CONCLUSIONS WITHIN THE SAMPLE

Within the entire sample, concerning HH92 citation, 155 (34.8%) cited HH92 favourably, 276 neutrally (62.0%), and 14 negatively (3.2%). Concerning overall ACH conclusion, 289 articles (64.9%) had a pro-ACH conclusion, 109 (24.5%) a neutral conclusion towards the ACH, 47 (10.6%) an anti-ACH conclusion. No differences were found between HH92 citation valence according to article types (original/review), geographical origin of first author's affiliation or citation rate, whereas statistical differences were found between ACH conclusion valence for all these characteristics.

In overall pro-ACH conclusion articles, there were significantly more original articles compared to negative or neutral ACH conclusion articles (58.5% original articles in pro-ACH, 33.9% in neutral and 27.7% in negative , Cramér's V=0.25, $p_{overall}<0.001$) ; they tended to test the ACH more than in neutral ACH conclusion articles (32.4% in pro-ACH, vs 8.3% ($p<0.001$) in neutral and vs 17.0% in negative ($p=0.039$), Cramér's V=0.24, $p_{overall}<0.001$); their first author affiliation was more significantly from Asia compared to negative-ACH (20.8% for pro-ACH vs 4.3% for negative-ACH, Cramer's V=0.19, $p=0.009$).

THE ASSOCIATION BETWEEN HH92 CITATION AND ACH VALENCE

The ACH conclusion of the articles tended to be different according to HH92 citation practice (Cramer's V=0.33, $p<0.001$). Indeed, the ACH conclusion was positive in 85.8% of articles citing HH92 positively, in 55.8% citing HH92 neutrally and only in 14.3% citing HH92 negatively.

HH92 CITATION POSITIVITY AND CITATION RATE OF ARTICLES

Positively-citing articles had a mean ± standard deviation citation rate (CR) of 7.8±10.1 citations per year; neutral articles had a CR of 9.6±14.3; negatively-citing articles had a CR of 12.0±16.4, although these differences were not statistically significant ($p=0.208$).

Concerning overall ACH conclusion, negative articles had a higher mean CR of 13.6±15.7, neutral 10.1±17.6, and positive 7.9±10.1. Negative articles had a significantly higher CR than positive-ACH articles (Cliff's delta=-0.25, p=0.007).

CHANGES IN HH92'S PLACE WITHIN THE BIBLIOGRAPHY WITHIN POSITIVELY-CITING ARTICLES

303 (68.1%) articles had a numerical bibliography, which we used to measure the place of the HH92 within the bibliography. These articles were not a perfect representation of the greater sample, principally since they tended to cite HH92 more positively than the articles with non-numerical bibliography (37.6% v 28.9%, p=0.040 and Cramer's V = 0.12).

We found no association between the year of publication and HH92's place in the bibliography for the entire sample (rho=-0.05, p=0.371), but when looking at articles citing HH92 positively, we found an association between place in the bibliography as a function of decade (rho=-0.19, p=0.020) whereas there was no association on articles citing HH92 neutrally (rho=0.03, p=0.670) [Figure 2]. Only 6 articles cited HH92 negatively so we did not calculate the Spearman correlation coefficient.

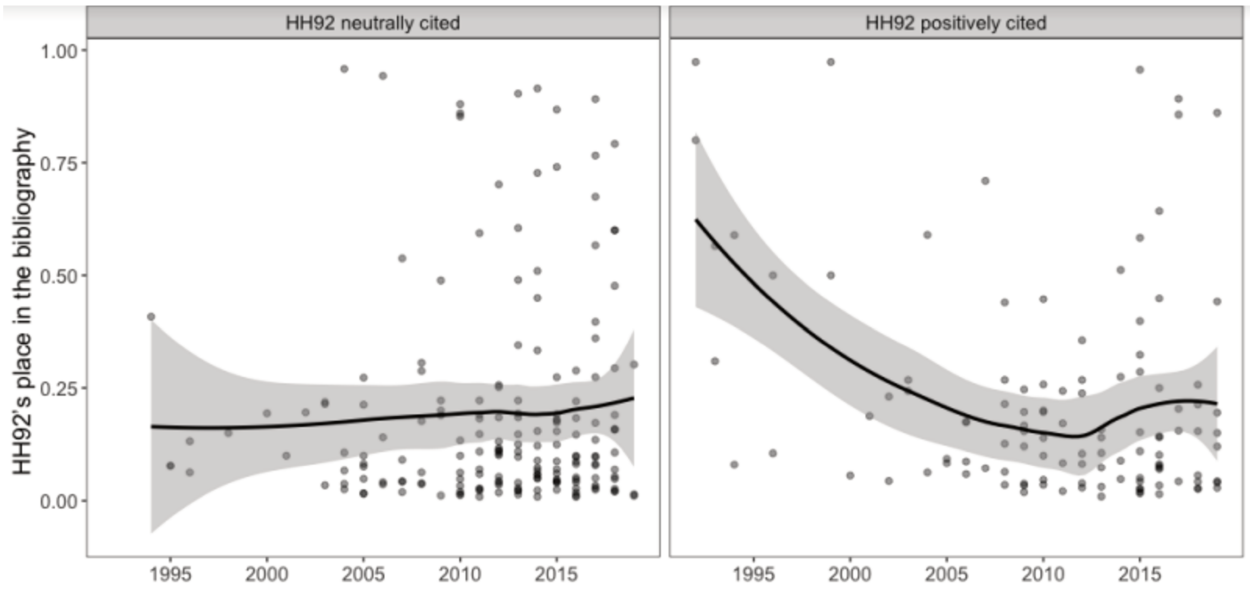

Figure 2: The identification of two major trends within citing articles: neutral attitudes were consistent between 1992 and 2019; the group of articles citing HH92 positively had a tendance to cite it earlier in the paper in latter years, taking it as an established authority.

DISCUSSION

The results of this bibliometric study support neither "herd-like behaviour" [17] nor Hunter et al.'s claim of the existence of "two broad groups"[18] for and against the ACH, for at least three reasons. Firstly, the majority of authors encountering the idea that beta-amyloid has some central role to play in AD do not cite HH92 positively. Secondly, the majority is actually made up of "neutral" citing authors. Thirdly, any negative citations or anti-ACH traffic were in a small minority, and thus such "anti-ACH" opinions are not in a "broad group." In summary, the large amount of "pro-ACH" conclusions and traffic in this network of articles cannot be explained by a bias towards the positivity of HH92 citation practices.

We identified two major trends within citing behaviour: a group of articles citing HH92 positively and tending towards taking it as an established authority with time, versus an unchanging majority of articles with a neutral attitude towards HH92. Negative HH92 citations were exceedingly rare, and anti-ACH traffic in the network represents a 10.6% minority. We did not encounter "herd-like" behaviour: those original articles testing the ACH found an overwhelming majority (89%) of pro-ACH test results (thus justifying their pro-ACH conclusion), and there was no majority of positive HH92 citations or pro-ACH conclusions in review articles. Further studies with actual citation networks, as opposed to individual articles, could shed greater light on the question of the potential "herd-like" behavior of the AD field.

Hardy et al. [1]'s claim that the ACH has dominated opinion appears true given the majority (67.4%) of pro-ACH conclusions. HH92 can only accurately predict ACH conclusion when HH92 citation is positive (in 86.8% of cases). However, positive HH92 citation did not have a favorable effect on CR, but rather a tendency towards the opposite effect. If anything, our results suggest that coming to an anti-ACH conclusion is a more favourable way of achieving a higher CR.

The results suggested here do not suggest that one scientific paper can fully "fix belief" in an authoritative manner in a community of researchers. It is clear that ideas around beta-amyloid's central role in AD have remained alive in the literature, but the theoretical changes the ACH has undergone have clearly been taken into account by the community.

Furthermore, the empirical support we identified for the ACH was overwhelmingly positive, in terms of the amount of empirical studies with a pro-ACH test result in our sample. In further

studies, we will discuss the limits of reproduction as a model of confirmation of a hypothesis, and discuss the idea of the "triangulation" of "different lines of evidence" from different methods [19].

This paper is not the first bibliometric study of the AD field [20, 21]. However, previously study have focused on trends, and ours is the first to test hypotheses about the reception of an idea as the central focus of the paper. Furthermore, placing this paper within the context of the intellectual space occupied by the ACH, it is the first time–to the best of our knowledge–that a hypothesis made outside the scientific AD literature (Lovestone's claim that "Our failing in the Alzheimer's field is to have acted like a herd" in a *Financial Times* article) has been tested by an article within it. Indeed, although the ACH is the object of intense debate within the scientific literature, outside the strict publishing norms of published science such as journalistic interviews, scientists have their say on efforts within the field. Recognising that the scientific literature does not give absolute transparency with regards to scientists' intuitions about research, our group will also publish results from an anonymous, international survey in collaboration with the Alzheimer's Association with scientists and clinicians to have direct access to their opinions on the ACH and other theories and treatments of AD without having to pass through the filter of the literature.

Concerning the limitations of the present study, we were well aware when we started this work that GA Higgins, co-author of HH92, is a discredited researcher. The retraction of Kawabata et al. [22] (*2*)(*1*)in which he appeared to have exaggerated the extent of neuronal degeneration in a transgenic mouse model of AD overexpressing APP was rightly seen as a scandal. However, we

consider the fact that pro-ACH ideas have survived until 2020 in spite of such unfavourable coverage as a testament to the wide evidence base in favour of them.

Furthermore, we recognise that the number of articles (445) in our sample represents a drop in the ocean of the 35,000 papers studying beta-amyloid in AD. However, defense of the ACH represents a broad church–there is no one amyloid hypothesis–and there are various ways in which authors might defend the ACH alone or integrate it into more complex aetiologies. There is no denying that comparative studies between the fates of the ideas in this hub and those in others would enrich the empirical study of the ACH's place within the literature. One can see our manuscript as a first attempt to grasp the epistemology of the ACH in the vast field of Alzheimer's disease research. Confirmatory studies, including natural language processing analyses of the literature would certainly be important before drawing definitive conclusions about citation practices within the ACH field, but we feel they are outside of the scope of this manuscript.

Finally, beyond the problem of sample size, the fact that the majority of citations were neutral suggests that nuances within this heterogenous community of researchers are real but not well-captured by Greenberg's (2009) methodology. For example, scholars in philosophy of science[23] have previously distinguished between a scientist accepting a theory as a basis for action (i.e. testing its claims and comparing it to other theories within the field in review articles) versus believing it to be factually true. It is not obvious that the citation polarity used herein allows us to distinguish between these subtleties and further studies could conduct further linguistic analyses to distinguish between such nuances. Furthermore, although the classic

distinction between “original” and “review” articles allows us to divide articles in a simple way, there are different kinds of reviews, such as classical “narrative” reviews, meta-analyses, etc., and the lack of distinction between these groups risks glossing over important nuances between article types.

In conclusion, we consider that this objective, empirical study of citation practices and support for the ACH suggests that the ACH has indeed been dominant in the field, has quantitatively good empirical suggest but that there are no problematic citation practices or herd-like behaviour identified. Further studies, using more nuanced measures of scientific belief, as well as more elaborate models of scientific confirmation, could provide further insight into the acceptance of the ACH by the scientific community as well as suggesting ideas on how to improve the ACH’s robustness.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Chapter Two: A proposal to make biomedical research into Alzheimer's disease more democratic following an international survey with researchers

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Timothy Daly[1], Marion Houot[2,3], Anouk Barberousse[1], Amélie Petit[4], Stéphane Epelbaum[2,3]

1 Sorbonne Université, Science Norms Democracy, UMR 8011, Paris, France.

2 Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, Inserm, CNRS, APHP, Hôpital de la Pitié Salpêtrière, Paris, France

3 AP-HP, Hôpital de la Pitié Salpêtrière, Institute of Memory and Alzheimer's Disease (IM2A), Centre of Excellence of Neurodegenerative Disease (CoEN), National Reference Centre for Rare and Early Dementias, Department of Neurology, Paris, France.

4 Université Paris Saclay, Inserm, CESP, U1018.

Corresponding author address: Timothy Daly, Science Norms Democracy UMR 8011, 1 Rue Victor Cousin, 75005 Paris, France. E-mail address: timothy.daly@paris-sorbonne.fr

Author Disclosures

Timothy Daly, Marion Houot, Anouk Barberousse, and Amélie Petit declare no conflicts of interest. Stéphane Epelbaum has received consulting fees from Biogen, Roche, Eisai and GE Healthcare.

Abstract

Background: Therapeutic research into Alzheimer's disease (AD) has been dominated by the amyloid cascade hypothesis (ACH) since the 1990s. However, targeting amyloid in AD patients has not yet resulted in highly significant disease-modifying effects. Furthermore, other promising theories of AD etiology exist.

Objectives: We sought to directly investigate whether the ACH still dominates the opinions of researchers working on AD and explore the implications of this question for future directions of research.

Methods: During 2019, we undertook an international survey promoted with the help of the Alzheimer's Association with questions on theories and treatments of AD. Further efforts to promote a similar study in 2021 did not recruit a significant number of participants.

Results: 173 researchers took part in the 2019 survey, 22% of which held "pro-ACH" opinions, tended to have more publications, were more likely to be male, and over 60. Thus, pro-ACH may now be a minority opinion in the field, but is nevertheless the hypothesis on which the most clinical trials are based, suggestive of a representation bias. Popular vote of all 173 participants suggested that lifestyle treatments and anti-tau drugs were a source of more therapeutic optimism than anti-amyloid treatments.

Conclusion: We propose a more democratic research structure which increases the likelihood that promising theories are published and funded fairly, promotes a broader scientific view of AD, and reduces the larger community's dependence on a fragile economic model.

Keywords

alzheimer's disease; amyloid beta; pharmaceutical industry; tau protein; lifestyle factors; dementia prevention; lifestyle interventions; diversity in science; women in science; gender

Introduction

Disagreement is an obvious fact of science and medicine, but how much is a good thing, and for how long, is worth asking. The community of clinicians and researchers working on Alzheimer's disease (AD) is an amalgam of distinct communities with different approaches to treating cognitive decline in the elderly. The dominant strategy for finding an AD cure since the 1990s has been targeting AD pathology (amyloid-β (Aβ) and tau proteins, with Aβ being the major therapeutic target in our contemporary period (Fig. 1, Liu et al., 2019: "up to 2019 … the amyloid hypothesis was the most tested (22.3% of [human clinical] trials)"(*3*)). Writing in 2014, Hardy et al. open their paper by claiming that "There is no doubt that for the last 20 years, the ACH has dominated opinion about the aetiology and pathogenesis of AD, as well as guided the efforts to find treatments" (*4*). Nevertheless, there has been a recent shift towards prevention and promotion of resilience to dementia through lifestyle interventions, as well as towards other drug targets, given the uncertainty around the clinical utility of anti-Aβ strategies(*3*). Indeed, this shift bears witness to the existence of a variety of promising theories for AD with compelling evidence in favour of them (two examples being microbes(*5*) and tau protein initiation(*6*)).

Scientists are guided in their decision-making by scientific data, but also by opinion. Zollman(*7*) studied how extreme beliefs and the unequal distribution of information within the research community can lead to "harmful homogeneity in science" (p. 19). The religious language used to describe debates around the suitability of therapeutic targets (defenders of Aβ and tau proteins as targets being termed BAptists and TAUists, for example[(*8*)), while perhaps used jokingly, is

nevertheless suggestive of the possibility of extreme opinions in the AD community. An empirical study of productivity in AD research suggests that "a small percentage of researchers"(*9*) has access to a large portion of the research apparatus, and while this does not entail that *information* is distributed unequally, it does suggest the strong influence of an unrepresentative minority holding a hierarchical sway over the broader direction of the field, at least at the level of publications.

Furthermore, scientific "gatekeeping" in the form of peer review and broader editorial policy offers the advantage of improving the mean quality of published science, yet also increases the risk that more unconventional work is rejected(*10*). Indeed, critiques of current funding and publishing models for biomedical research exist beyond the AD field, arguing that conformity to dominant models tends to lead to more funding(*11*).

These conditions suggest there might well be "harmful homogeneity" in AD research. However, the presence of an influential minority suggests that getting access to most researchers' opinions about AD should not be done via published literature, which cannot adequately represent most researchers working on this disease. We therefore decided to opt for direct access to researchers' opinions about theories and treatments of AD, creating the first anonymous survey into researcher opinions towards theories and treatments of AD. Firstly, we wanted to test Hunter et al.(*12*)'s hypothesis of "two broad groups; those that support the amyloid cascade hypothesis and those that do not" (p. 254). Secondly, we tested the constituent characteristics of the "pro-ACH" group, before thirdly, looking at possible gender differences in the popular vote towards treatments for AD at different disease stages.

Methods

Ethical approval

The project received ethical approval from the Research Ethics Community of *Université Paris Descartes* and the data analysis complied with the French *Commission nationale de l'informatique et des libertés* (CNIL) guidelines. All the data were anonymous and were analysed in aggregate form. All of the raw survey data are available as Supplementary Material.

Survey design and promotion

Questions and responses comprised two categories: research (on theories and treatments of AD) vs. personal (age, profession, country of primary affiliation, clinical vs. academic researcher). All questions were optional and multiple choice, based on extensive literature review and consultation with colleagues. The participant filled out the form by following the URL to the Google Forms sheet.

We used Twitter (the account of The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment "@ISTAART," and T.D.'s personal account, "@PhilAlz") and a poster at The Alzheimer's Association International Conference (AAIC) 2019 to promote the link to the Google Forms to recruit survey participants between January 1st 2019 - 31st December, 2019. A second wave of promotion was undertaken in January 2021, but with less than 20 responders, thus only data from 2019 are analysed herein.

Hypothesis testing and statistical analysis

Three hypotheses were tested concerning participant responses. Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.) Participant characteristics were compared between the pro-ACH and non-ACH groups using Wilcoxon-Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables. Discrepancies in participant response numbers were due to the optional nature of every question.

Hypothesis 1: Pro-ACH responders will account for the majority of the participants.

When participants were asked which categories of drugs gave them hope for a treatment of AD, if they answered "BACE inhibitors" and/or "Anti-Aβ antibodies" (which we combine in Results as "ACH drugs") and also considered "Aβ physiology (production, clearance, etc.)" to be the number 1 priority in pre-clinical, early, or late stage AD, then they were considered to be "pro-ACH."

Hypothesis 2: The ACH-group will have different constitutive characteristics as compared to the non-ACH group.

In order to describe the profiles of pro-ACH and non-ACH survey participants, we performed the Classification And Regression Tree (CART) algorithm. The CART algorithm, also known as a "decision tree", is a non-parametric supervised technique that combines variables in such a way as to best discriminate between two groups. We trained a decision tree of depth 5 through entropy minimization with characteristics such as age higher than 60 ; gender ; country : USA; number of publications ; clinical researcher (vs. academic) ; key opinion leader (KOL) ; has received money from the pharmaceutical industry ; whether or not the researcher thinks that "there is problematic adherence to the ACH from either industry, academia, associations or

funding bodies". We used the term adherence so as to insist upon the ACH's ability to guide research.

Hypothesis 3: There will be gender differences in the popular vote towards treatments of AD.

We investigated the top 3 therapeutic targets at pre-clinical, early-stage, and established AD according to popular vote of all the survey participants, pro-ACH and non-ACH taken together. Furthermore, if there are gender differences to be found in the pro-ACH/non-ACH groups, we might expect to find gender differences in the popular vote. Only participants identifying as M/F were included in the gender differences so as to use comparable group sizes for significance testing (n= 7 of "trans/prefer not to say/other").

Results

One hundred and seventy three participants from across the world filled out the questionnaire, with a median age of 35, 83 (49.7%) being women. We identified 38 (22.0%) "pro-ACH" participants, the majority (65.8%) of whom were men (Table 1). Pro-ACH participants were more likely to report writing more than 100 publications (27.0% vs 10.5% in the non-ACH group, p=0.016), to be a self reported key opinion leader (KOL) (26.3% vs 12.4%, p = 0.045), to be aged over 60 (21.1% vs 7.5%, p=0.031), and to have received money from the pharmaceutical industry (29.0% vs 13.5%, p=0.047), than non-ACH participants. However, median age group differences did not reach significance. In the non-ACH group, 80.2 % argued that there was problematic adherence to the ACH from within and outside the scientific community, versus 54.1% of pro-ACH (54.1% vs 80.2%, p=0.002). No difference was found for country or profession.

Concerning the lack of therapeutic progress made in AD research, 79.0% of pro-ACH (vs. 34.4% of non-pro, p<0.001) agreed with Tanzi(*13*) that "the clinical trials are failing the hypothesis, the hypothesis is not failing the trial." 84.2% (vs. 42.8%, p<0.001) agreed with Tanzi(*14*) in favour of earlier anti-amyloid strategies in humans, only 5.3% (vs. 39.7% of non-ACH) agreeing with Davies(*15*) that such strategies were akin to "flogging a dead horse" when referring to targeting amyloid-β. As regards the ACH's future, 18.4% of pro-ACH (vs. 57.7% of non-ACH, p<0.001) agreed with Herrup(*16*) that "clinging to an inaccurate disease model" was the worst option for the future facing the community. Finally, in order to better discern pro-ACH vs. non-ACH opinions, we used a decision tree (Figure 1).

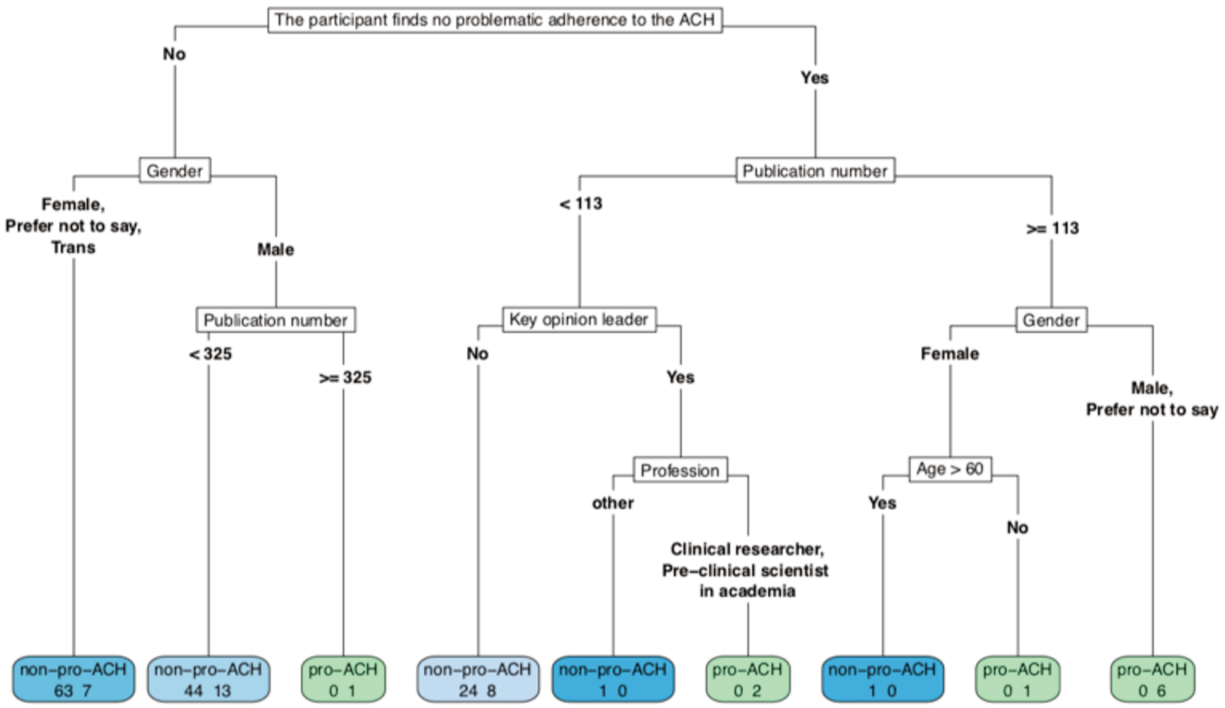

Figure 1 – A decision tree revealing pro-ACH/non-ACH differences according to the participant's view on whether or not there is problematic adherence to the ACH. We cut the

depth of the tree to 5. Leave nodes (i.e. the final node, coloured in the figure) present the number of pro-ACH participants on the right and the number of non-ACH participants on the left. They are light blue to dark blue as a function of the proportion of non-ACH in the leave node, or they are light green to dark green as a function of the proportion of pro-ACH in the leave node. In the non-ACH group, 63 participants (47.37%) not identifying as male argue that there is problematic adherence to the ACH, compared to only 7 (18.42%) of the pro-ACH group with these characteristics. Conversely, on the other end of the scale, 6 males (or preferred not to say) of the pro-ACH group (15.79%) argued that there was no problematic adherence to the ACH, and had more than 113 median publications. None of the non-ACH had this profile.

We also studied the popular vote of all participants towards treatments and possible gender differences to be found in it. Anti-tau treatments were the highest source of optimism (61.0% of participants), followed by anti-Aβ antibodies (39.0%) and BACE inhibitors (19.5%). No significant gender differences were found in responses concerning optimism about drug types.
Lifestyle factors were the top therapeutic priority in pre-clinical and prodromal AD (winning 43.5% and 31.0% of the popular vote respectively). In preclinical AD, Aβ (19.4%) and inflammation (12.9%) were the next most popular targets, and in prodromal AD, Tau & NFTs (25.0%), Aβ and inflammation (15.2% and 16.5% respectively) the next most popular. In established AD, Tau & NFTs were the highest therapeutic priority (28.2% of the popular vote), followed by lifestyle factors (24.4%) and inflammation (18.6%). Concerning gender differences, only at preclinical AD did gender differences reach significance ($p<0.02$), with men voting comparatively less for lifestyle factors (39.7% vs 47.0% for women), and more for Aβ (28.2% vs 12.1% for women), probably a reflection of the gender division between pro-ACH and non-ACH opinions.

	all N=173	Non-ACH N=133 (76.88%)	pro-ACH N=38 (21.97%)	p ‡
age > 60 yo	19 (11.05%)	10 (7.52%)	8 (21.05%)	0.031*
Gender				0.035*
Female	83 (49.70%)	71 (55.47%)	12 (31.58%)	
Male	80 (47.90%)	54 (42.19%)	25 (65.79%)	
Prefer not to say	3 (1.80%)	2 (1.56%)	1 (2.63%)	
Trans	1 (0.60%)	1 (0.78%)	0 (0.00%)	
Continent of Major Affiliation				0.243
North Africa	1 (0.60%)	0 (0.00%)	0 (0.00%)	
North America	101 (60.12%)	78 (60.47%)	23 (60.53%)	
South America	11 (6.55%)	10 (7.75%)	1 (2.63%)	
Asia	9 (5.36%)	9 (6.98%)	0 (0.00%)	
Europe	40 (23.81%)	28 (21.71%)	12 (31.58%)	
Oceania	6 (3.57%)	4 (3.10%)	2 (5.26%)	
publications number > 100	24 (14.04%)	14 (10.53%)	10 (27.03%)	0.016*
Profession				
Clinical researcher	67 (38.73%)	51 (38.35%)	15 (39.47%)	0.236
other	18 (10.40%)	16 (12.03%)	1 (2.63%)	
Pre-clinical scientist in academia	88 (50.87%)	66 (49.62%)	22 (57.89%)	
Key Opinion Leader (Yes)	26 (15.48%)	16 (12.40%)	10 (26.32%)	0.045*
Received money from pharma company (Yes)	29 (16.86%)	18 (13.53%)	11 (28.95%)	0.047*
Questions regarding the ACH's validity				
ACH drugs are NOT a source of optimism for treating human AD.	*86 (54.09%)*	*86 (71.67%)*	*0 (0.00%)*	*<0.001**
Beta-amyloid is NOT the #1 therapeutic priority either at preclinical, early, or	*119 (69.59%)*	*119 (90.15%)*	*0 (0.00%)*	*<0.001**

late-stage AD				
There is problematic adherence to the ACH from either industry, academia, associations or funding bodies	125 (73.96%)	105 (80.15%)	20 (54.05%)	0.002*
Moving forwards (2019–), the ACH is a useful tool to guide research.	60 (35.50%)	35 (26.92%)	24 (63.16%)	<0.001*
Agree with Tanzi (2015): "The clinical trials are failing the hypothesis, the hypothesis is not failing the trial."	76 (44.71%)	45 (34.35%)	30 (78.95%)	<0.001*
Agree with Tanzi (2017): "we need to find people with amyloid buildup on their brain early" and target it.	89 (52.35%)	56 (42.75%)	32 (84.21%)	<0.001*
Agree with Davies (2016): "we're flogging a dead horse" (A-beta)	54 (31.76%)	52 (39.69%)	2 (5.26%)	<0.001*
Agree with Herrup (2015): "clinging to an inaccurate disease model is the option we should fear most."	82 (48.52%)	75 (57.69%)	7 (18.42%)	<0.001*

Table 1 – Differences in the constitutive characteristics and opinions towards the ACH of pro-ACH and non-ACH groups identified in the 173 survey participants. Gender differences were significant between the pro-ACH and non-ACH groups, with significantly more men being pro-ACH. Taken together, these results suggest an association between having pro-ACH opinions and more publications, industry money, and self-identifying as a key opinion leader.

‡ Fisher's exact test was used to compare groups for categorical variables.

	all N=173	Female N=83 (49.70%)	Male N=80 (47.90%)	p ‡
Optimism towards the following drugs				
Anti-tau	97 (61.01%)	50 (66.67%)	40 (53.33%)	0.133
Anti-AB antibodies	62 (38.99%)	24 (32.00%)	33 (44.00%)	0.178

BACE inhibitors	31 (19.50%)	15 (20.00%)	12 (16.00%)	0.671
#1 Therapeutic Priority in preclinical AD				0.020*
Lifestyle factors (diet, smoking, etc.)	*74 (43.53%)*	39 (46.99%)	31 (39.74%)	
Aβ physiology (production, clearance, etc.)	33 (19.41%)	10 (12.05%)	22 (28.21%)	
Inflammation, Microglia, & Astrocytes	22 (12.94%)	10 (12.05%)	11 (14.10%)	
#1 Therapeutic Priority in prodromal AD				0.060
Lifestyle factors (diet, smoking, etc.)	*49 (31.01%)*	24 (32.00%)	22 (29.73%)	
Tau & NFTs	40 (25.32%)	22 (29.33%)	15 (20.27%)	
Inflammation	*26 (16.46%)*	13 (17.33%)	11 (14.86%)	
#1 Therapeutic Priority in established AD				0.928
Tau & NFTs	44 (28.21%)	19 (25.68%)	21 (28.38%)	
Lifestyle factors (diet, smoking, etc.)	38 (24.36%)	20 (27.03%)	17 (22.97%)	
Inflammation, Microglia, & Astrocytes	29 (18.59%)	14 (18.92%)	13 (17.57%)	

Table 2 – The popular vote of all researchers (pro-ACH and non-ACH taken together) towards therapeutic priorities in AD research, tabulated according to participants' gender. Concerning pharmacological treatments, anti-tau drugs offered more optimism than drug classes inspired by the ACH (anti-Aβ antibodies and/or BACE inhibitors). The top three therapeutic targets at preclinical, prodromal, and established AD were also investigated. Lifestyle interventions were a top-3 therapeutic priority at all stages of AD. Taken as a whole, the data suggest a favourable opinion regarding lifestyle factors and tau protein intervention. Gender differences in therapeutic priority were only significant for preclinical AD, with significantly more males arguing in favour of anti-Aβ strategies at this stage. ‡ Fisher's exact test was used to compare groups for categorical variables.

Discussion

According to our international survey with 173 participants, pro-ACH opinions did not represent the dominant opinion of researchers working on AD as of 2019; approximately 22% of researchers belonged to what we defined as the pro-ACH group. This group tended to argue that the ACH was a useful tool to guide research, and that there was therapeutic interest in the early targeting of beta-amyloid, as opposed to the other "broad group" of researchers(*12*). Furthermore, more publication and industrial money is to be found more in the pro-ACH group than in the non-ACH group.

Nevertheless, the fact that more than half of "pro-ACH" participants agree that there is problematic adherence to the ACH in the larger community (54% vs. 80% of non-ACH) is consistent with certain researchers that we have interviewed more extensively (TD, AP): they are not ready to let go of the ACH, continue to rely on certain heuristic aspects of it, and at the same time, they are slowly embarking on other paths. This suggests that community-wide movements away from the ACH are more incremental than revolutionary.

Finally, women were under-represented in the pro-ACH group, representing 32% of the pro-ACH and 55% of the non-ACH group respectively. Concerning gender and age differences, it must not be forgotten that the social structure of biomedical science is hierarchical, with research strategies being mostly directed by principal investigators, i.e. experienced medical doctors and scientists. Differences observed in gender and age may therefore not be related to these variables so much as to the social positions occupied by doctors in the research hierarchy, in which older

males are over-represented. Moreover, gender differences themselves may partly have been explained by age, since there were more over 60s to be found in the group of men (16.3% vs. 4.8%). Our anecdotal observations (TD, SE) from *AlzForum*, an influential online community for AD researchers, suggest that the majority of influential commentators on current affairs in AD research tend to be men in these dominant social positions.

When looking at the popular vote in this survey, anti-tau compounds were a source of greater therapeutic optimism than anti-amyloid strategies, and lifestyle factors were considered to be a top therapeutic priority at all stages of human AD. We will now discuss one way of making AD research more faithful to popular vote. Nevertheless, before we do so, it is worth noting that there are major limitations to this study.

Study limitations

Firstly, 173 Twitter-using researchers represent a small minority of AD researchers (for example, *AAIC* in Los Angeles in 2019 alone counted 5,700 researchers). And this small sample may have been biased: only those with a strong opinion responding and giving theirs. Thus, the generalizability of our findings may be low. Forcing the research community into polarised groups ("pro-ACH" vs. the rest) may not reflect the nuance in opinions that researchers have towards theories which can be studied thanks to other methods, such as bibliometrics(*17*). This polarisation is aggravated by the fact that quotes taken out of context from the scientific and lay literature (e.g. from Rudolph Tanzi) were used as sources of survey questions.

Concerning self-identification of individuals, our gender categories were highly limited, and our relatively small sample did not allow us to undertake statistical analysis on the contributions of non-traditional or non-conforming gender identities to the popular vote on treatments for AD. It is clear that there is need for greater work on "accountability, justice and representation" for

gender minorities in STEM(*18*). Furthermore, we did not ask questions on ethnicity, which other STEM researchers are indeed asking so as to "boost diversity in science" (*19*). Finally, we did not offer an explicit definition of a "key opinion leader," an ambiguous term whose value to these results is debatable because of the fact we let participants self-identify as KOL or not.

Moreover, as regards the ACH, just as our results suggest that there is some diversity of opinion within the pro-ACH group (e.g. their view of possible problematic adherence to the ACH), it is also clear that non-ACH opinions are not of one kind: some researchers are vocally in favour of "rejecting the amyloid cascade hypothesis"[14] and would be more aptly described as "anti-ACH."

Finally, these results are time-sensitive: as different results from clinical trials and other studies are published, so do opinions change towards theories and treatments. The fact that our final round of survey promotion was unsuccessful warrants further analysis into researchers' susceptibility to change their opinion on a scientific topic over a short period of time. The lower participation in 2021 could be due to current events in the field (see Conclusion), complications due to the Covid-19 pandemic, or simply the same participant population not wishing to undertake another similary survey. However, any such explanatory hypothesis would be highly speculative, and the issues being discussed in this paper (i.e. the possibility that there might be publishing and funding advantages of supporting the ACH) are worthy of further discussion and investigation. Limitations on the speed with which such research can be designed, ethically approved, undertaken, and published, should be taken into account in further studies with similar objectives.

A proposal to make biomedical research into AD more democratic

It is well-known that biomedical science, as a complex social activity, is guided by non-scientific factors, such as economic interests(*20*). Reiss and Kitcher(*21*) argue that well-ordered biomedical science should follow the "fair-share principle," where the amount of global funds spent on different diseases should be proportional to the suffering caused by them on a global scale. By analogy, we might ask: within the study of a single disease, how should resources best be dedicated to testing hypotheses and developing therapies based on them according to a "fair-share principle"? In other words, how can we make sure that promising theories of AD get their fair share of study and funding?

Solving this incredibly difficult problem is well beyond the scope of this article, but we will offer a sketch of a pro-democracy argument based on "crowd wisdom," the empirical finding that informed collectives outperform individuals in estimating true values of different variables[13], before underlining two tragedies if the AD community does not succeed in organising science better.

Kitcher(*22, 23*) argues in favour of a democratic deliberation process: taking the points of view of different segments of the community and attempting to guide research according to them. This does not *have* to mean a majority vote, but the phenomenon known as the wisdom of the crowd(*24*) suggests that the average value of multiple estimates tends to be more accurate than any one single estimate. Therefore, listening to the popular vote of researchers—at fora such as the yearly AAIC, and pooling a certain percentage of available funding towards the therapeutic leads suggested by popular vote—would mean drawing on many thousands of collective years of experience and perspective, which could lead to more accurate estimates of the causes of AD, and the best treatments to pursue. There is also increasing research being done with dementia patients in a co-research role in gerontology research (for example(*25*)); there is also much

unexplored scope for including the patient community in deliberation processes concerning curative and preventive research into AD, and popular vote could also be used here.

The major idea defended here is that projects should be funded in a way that better represents the plurality of therapeutic leads offered by the research community. A yearly popular vote could be one step in that direction. But this leaves many questions open which we cannot definitively answer in one article, including, but not limited to the following:

How could we improve representation on funding bodies and editorial boards, including a role for the patient community?

Upon what kinds of evidence should publication and funding decisions be based so that both scientific pluralism and plausibility are guaranteed in AD research according to a fair-share principle?

What kind of funding model would be most suited to a more democratic approach: private and/or public ventures?

Are there some domains and methods within biomedical science might be particularly under the influence of monopolised ways of thinking? (e.g. at the level of pre-clinical or clinical research?)

Could publication and funding quotas be used to make monopolised domains more inclusive?

How, and to what extent, could the themes of calls for contributions and projects by publishers and funders be broadened on a long-term, community-wide scale?

Furthermore, a more democratic model itself would not be perfect, particularly if it were taken to the extreme of eroding individual expertise, which is and should remain a cornerstone of rigorous science. Instead, the model we propose serves to reduce monopoly, and thereby take any possible institutionalised brakes off the contributions of individual scientists.

In any case, if research cannot become better organised, we anticipate two major tragedies. The first concerns the survival of the fragile economic model underlying therapeutic research into AD, without which patients will never receive disease-modifying treatment. The second concerns science itself.

Indeed, the current high-risk model encourages the opposition between patient need and return on investment for innovators. Bringing an AD drug to market is estimated to cost $5.6 billion(*26*). The developer of the first monopolised disease-modifying treatment of AD would stand to gain an astronomical return on their major investment. Conversely, when a clinical trial of a much-anticipated AD treatment fails, the market value of the pharmaceutical company that developed it loses as much as 40% overnight, as in the case of Eli Lilly and solanezumab(*15*). In January 2018, the pharmaceutical company Pfizer decided to stop its research on AD and Parkinson's disease by laying off 300 researchers due to numerous drug failures amid a dismal context for research on neurodegenerative diseases: pulling out was part of "an exercise to reallocate spend across our portfolio," according to the company(*27*). It is not clear what the future of AD research looks like, but it is fragile and, in its current state, mostly dependent on amyloid being a viable target, with millions of patients and families living in hope. By ensuring that other promising theories are funded, at a community-wide level, it would allow bets to be hedged against the possibility that the ACH does not deliver on its promises.

The second tragedy, done against science itself and those individuals who defend it, is “epistemic injustice,” a term coined by philosopher Miranda Fricker as “wrong done to someone specifically in their capacity as a knower”(*28*). Fricker draws on examples from literature and history where factors such as race and gender have led to points of view being ignored and condemned. Within AD research, there are surely examples of intellectually honest researchers defending controversial hypotheses of AD who have struggled to get data published, receive funding, and

retain their place within academia. In other words, certain hypotheses might be rejected not because of scientific argument but rather the social structure of the field of biomedical research. We finish by noting that the results from our small sample tentatively suggest that the majority of women do not support the ACH, and may therefore be particularly vulnerable to the negative consequences of a community gatekeeping bias. Taking the example of hypotheses concerning the role of microbes in AD(*5*), Fig. 1 from Liu et al. (2019) showed that "…up to 2019 … 0.5% of trials tested the virus hypothesis"(*3*). Concerning this "fringe theory … now, researchers are taking it seriously"(*29*), but the fact that up to 2019 only 1 in 200 clinical trials were dedicated to testing a direct viral contribution to AD, does beg the question: are theories of AD being funded according to fair-share principle? Ruth Itzhaki, first author on the previously cited(*5*) editorial on microbes in AD, has described "a series of battles … awful problems getting [research] published"(*30*). This example does point to the possibility of epistemic injustice in AD research, and suggests the existence of perspectives whose contribution to improving the lives of AD patients has not yet been fully taken into account. This seems like community-wide oversight, since the perspectives of marginalised individuals in institutionalised social structures may offer particularly insightful contributions to research, since they may recognise patterns in the world that those in more dominant groups may be blinded to(*31*).

Conclusion

The recent, controversial accelerated FDA approval of Biogen/Eisai's Aducanumab for use in mild AD is a testament to the influence of the ACH and its defenders on the scientific and wider community. The tentative results found in our survey suggest that there is a complex scientific landscape behind the scenes which risks becoming even more polarised following such divisive decision-making(*32*). Given the hardships of the research community in finding a disease-

modifying treatment for AD, we argue that further efforts should be made to explore democratic solutions to overcome research monopolies so that their potential consequences for patients and scientists can be reduced, and clinically useful treatments for AD be found as soon as possible. It appears that the optimism towards the ACH which has motivated industry and the recent FDA decision may well not be shared by the majority of researchers working on AD. This study offers one tool to study this otherwise silent majority, whose collective wisdom, we argue, could and should be taken into further consideration for the future of vital research into this devastating, complex disease.

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Part Two — Conceptual philosophy in science: Alzheimer's disease research beyond the amyloid research agenda

This second part of the thesis is composed of two chapters of unequal size whose approach to studying research is conceptual rather than empirical. Those empirical findings from Part One suggest that on-going debates around the ACH and its dominance are not concerned merely with its empirical adequacy, but rather on the potential for over-reliance on and adherence to it. A re-evaluation of the ACH's place in AD research could lead to major consequences for AD research, given the potential for theories to influence the development of disease-modifying treatments for patients with this complex, chronic disease. It is to this re-evaluation that we turn in Part Two.

Following the first part, which was devoted to the study of the amyloid research agenda, this part of the thesis asks: what would research into Alzheimer's disease (AD) look like without the amyloid research agenda as the dominant guide for finding a treatment? To answer this question, there is a brief discussion of the controversies around the amyloid cascade hypothesis (ACH) and a summary of research these last 10 years that suggests a shift in thinking about the causes of disease. This discussion leads us to propose what we call a disease ontology—a computer system for ordering and understanding the role of biological processes in AD. The second short chapter is a reminder that tests of treatments for AD should be kept simple to maximise the information that can be garnered from such tests.

There have been several critiques written about the place of amyloid in AD research (for some examples, see (Joseph et al. 2001; Bishop and Robinson 2002; Mudher and Lovestone 2002; Pimplikar 2009; Morris, Clark, and Vissel 2014; Herrup 2015; De Strooper and Karran 2016). The most obvious problem for the idea of the centrality of amyloid in AD has been the existence

of dozens of unsuccessful trials with drugs targeting beta-amyloid in the brains of AD patients. But there are other data that have drawn into question its validity, from the mismatch of the time course of neuropathology staging (Braak and Braak 1991) and the imperfect predictive value of the accumulation of AD neuropathology vis-à-vis whether individuals will develop dementia (Morris, Clark, and Vissel 2018).

Thus, the question of the ACH's empirical adequacy is both vital to priority setting within AD research but also exceptionally difficult to answer. It was argued in the Introduction that the ACH is part of a larger amyloid research agenda, which is constantly being updated. There is nevertheless a growing consensus—though without the kind of unity to be found in the neuropathology targeting and resilience promotion approaches described in the Introduction—that "a neuron-centric, linear cascade initiated by Aβ and leading to dementia … is incompatible with clinical observations" (p. 603, De Strooper & Karran, 2016). Or in the words of Herrup (2015), "with the passage of time, growing amounts of data have accumulated that are inconsistent with the basically linear structure of this hypothesis" (p. 794, Herrup, 2015). Selkoe & Hardy (2016) "...concur, after disease initiation, the complexity of the downstream pathogenic processes increases" (p. 604, (Selkoe and Hardy 2016)).

The most convincing data suggesting the centrality of amyloid to AD come from naturally-occurring mutations in dominant inherited Alzheimer's Disease (DIAD), a rare and particularly aggressive form of disease that runs in families. In their Table 2 (p. 598, Selkoe & Hardy, 2016), titled "Toward a more complete modeling of the pathogenesis of AD amyloid," it is noteworthy that in all the cited studies within the table, the data come from mutation genetics.

The hypothesis that the findings from mutations could be applied to the development of therapeutics for sporadic AD is controversial, as alluded to in De Strooper & Karran (2016) and

Herrup (2015). Nevertheless, this hypothesis could be tested in the "theoretically" perfect population of patients: patients with DIAD who invariably develop AD. However, it took until June 2021 for the first data published from studies targeting amyloid with the Dominantly Inherited Alzheimer Network (DIAN) to be published (Salloway et al. 2021). Though there are several explanations as to why trials might have taken relatively long and as to why they failed to slow down cognitive decline, it is nevertheless noteworthy that dozens of trials have been undertaken in sAD patients testing anti-amyloid agents since the early 2000s (Liu et al. 2019), despite the fact that the therapeutic logic linking the two forms has been hypothetical. The results published so far from DIAN are far from convincing as to whether reducing amyloid in this population improves cognitive outcomes in these patients.

However, over the last 15 years, there has been a shift away from the heuristics of the positional cloning strategy described by Hardy (2006b) in which "*Positional cloning … lead[s] you to the mutant gene which, unambiguously, caused disease" (p. 151, (Hardy 2006))*. The major risk variant for sporadic AD is a person's genotype of Apolipoprotein E (APOE), a plasma protein involved in cholesterol metabolism, which predisposes to AD in over 40% of cases and also predisposes to other diseases (Smith 2000). The role of APOE genotype was discovered using a candidate gene approach based on *a priori* knowledge of how the gene functions (Zhu and Zhao 2007).

In contrast, Genome Wide Association Studies (GWAS) scan the entire genome for associations between genetic variants (the most common is the single-nucleotide polymorphisms, SNPs, pronounced "snips") and human disease. These studies have shown that DIAD and sAD may reflect quite different biological realities. Instead of identifying genetic loci like the deterministic genes involved in DIAD, it represents a shift to the study of "susceptibility loci that are common

in the general population, but exert only very small risk effects" (Bertram, Lill, and Tanzi 2010). Studies from twins suggest that, together with APOE genotype, those "small risk effects" may count for up to 80% of risk—that is, up to 80% of risk for sporadic AD is genetic (Gatz et al. 2006). Bertram et al. (2010) term this the "missing heritability" of sporadic AD and argue that it is a kind of "dark matter … one is sure it exists, can detect its influence, but simply cannot see it (yet)" (Manolio et al. 2009).

Which genes might be responsible for that 80% of risk? It appears to come from other genes involved in cholesterol metabolism, as well as "amyloid/Tau pathways, … microglia and interaction with APP metabolism" (Bellenguez et al. 2020). Together with astrocytes, microglia are the cells responsible for the brain's innate immune response.

How much of that "genetic dark matter" has been discovered by known loci? There are now 75 of them (Bellenguez et al., 2021). Hardy (quoted (AlzForum 2021)), one of the co-authors on the Bellenguez et al. paper, argues the percentage of heritability is still unknown, since "estimates of heritability are extremely problematic in diseases with age-dependent penetrance."

Beyond genes, different researchers have proposed looking at the consequences of AD's complexity for different cell types (De Strooper & Karran, 2016) and biochemical processes (Herrup, 2015). The focus in this Part of the thesis has been on Herrup (2015), though De Strooper & Karran's (2016) work is mentioned in the first article of this Part Two.

In his *case for rejecting the amyloid cascade hypothesis*, Herrup (2015) offers a different vision of AD research with major consequences for the quest to find a treatment for AD compared to the amyloid research agenda:

AD can be viewed as a disease of amyloid. Yet AD can also be viewed as a tauopathy … a failure of autophagy and/or lysosomal function … a loss of Ca2+ homeostasis … a failure of neuronal cell cycle control … the central role of neuroinflammation … A genetic etiology is plausible as well … Progressive oxidative damage that accumulates with age or DNA damage … a loss of mitochondrial function … a complex senescence phenotype … glucose metabolism … or a general metabolic compromise … the length of this list … serves as the best explanation for our hesitancy to reject the amyloid cascade hypothesis—the heart of our fears. Were we to reject it, we would move from simplicity to complexity … be faced with a long list of disease-causing options … have no clear guidance as to how to focus our quest to understand and treat AD … the true risk lies precisely in not rejecting the hypothesis. The answer to the question of which option shall we choose is probably fairly simple: choose them all (p. 797, Herrup, 2015).

The amyloid "research agenda" has amyloid-producing mutations at its centre and is therefore hierarchical in how certain data are interpreted within it: the positive heuristic of the amyloid research agenda attempts to incorporate new knowledge through the lens of amyloid (Hardy 2006). Conversely, in Herrup's view there is no meaningful centre or hierarchy. Instead, he enunciates an ever-growing list of biological processes that show some loose "association" with AD outcome. (He does not use this term, nor make reference to GWAS in his article.) Furthermore, he does not discuss lifestyle DAPs, known to be of increasing importance in dementia research (Livingston et al. 2017; Livingston et al. 2020).

This non-technical concept of association offers the advantage of breadth spanning different biological levels, types of data, and approaches, but is also an imperfect tool to guide future research. It allows for an ever-growing list of processes known to be involved in AD without

offering clear guidance as to how to sort them, and therefore requires being analysed into several parts so as to make more sense of association. There is a "wide range of explanatory styles" for explanations in biology, from mechanisms, derivation from scientific laws, to evolutionary accounts of phenomena, and "the field of biology is a natural place to turn for support for the idea that causal information is explanatory" (Potochnik 2013). Medicine draws heavily on biological explanations when it comes to understanding the causes of disease (as evidenced by the Introduction of this thesis). However, when attempts are made to publish data on the relationship between biological and medical phenomena, a tension can appear between explanatory and publishing norms. Within the Journal of the American Medical Association (JAMA)'s "Instructions for Authors," the following advice is given:

"*Causal language (including use of terms such as effect and efficacy) should be used only for randomized clinical trials (RCTs). For all other study designs ...* ***results should be described in terms of association or correlation and should avoid cause-and-effect wording***" (emphasis and italics ours) (JAMA 2021).

Furthermore, there is a growing problem of "claim inflation" in a system that tells "basic scientists, especially trainees, that their work's value lies in its translatability" because of the "emphasis that funding agencies place on impact and translation" (Kaelin 2017). Thus, scientists working in "basic" biology are under pressure to show impact, whilst also being discouraged to use richer causal and explanatory language and to thus prefer "association."

This tension between explanation and publication makes for problems for AD research. First, there is the risk that a growing list of processes studied by biologists ends up being "associated"

with a disease's outcome because of a pressure on scientists to emphasise "translatability." Arguably, this is already the case with Herrup (2015)'s "long list of disease-causing options." The field of neuroscience is particularly rife with talk about association, which has been described by Carl Craver (Craver 2007) as a filler term and "which indicates the lack of an explicit conceptual framework" linking elements in a causal explanation (p. 485, (Krakauer et al. 2017). There is thus a major risk that a move away from amyloid as the centre of AD is accompanied by lack of clarity about the role of other biological processes in AD.

The "long list of disease-causing options" given by Herrup is understood here as a list of disease-associated processes (DAPs) for AD. Given that association is not a particularly useful technical concept, further efforts to tease out the nature of association could help reveal how different DAPs are associated with AD and what might be expected from targeting them. The use of the word "process" allows us to capture on-going events that produce some result over time. In this case, DAPs are associated with a change in disease prognosis. It also captures the use of language given by AD researchers, e.g. Herrup's "*Progressive oxidative damage that accumulates with age or DNA damage … a loss of mitochondrial function",* and Hardy & Allsop (Hardy and Allsop 1991)'s formulation that it is beta-amyloid *deposition*—a process—that leads to AD.

We offer three criteria for understanding the nature of association in AD: specificity of a DAP for AD, the frequency of its appearance in AD patients, and pathogenic intensity for dementia. The reason that specificity is mentioned first is because of how important specific DAPs are to the amyloid research agenda, i.e. mutations in DIAD. It is striking that what these mutations, collectively what Hardy & Allsop (1991) term "mismetabolism" of the amyloid precursor protein (APP) that produces amyloid-beta, invariably lead to AD-like changes and not to other

pathologies in patients with DIAD. This DAP—APP mismetabolism—is therefore highly specific and given its almost 100% penetrance, highly associated with pathogenic intensity for dementia. But it is also very rare, and therefore of low frequency. In the first article of this part of the thesis we explore other DAPs with different properties and offer some comparisons.

The idea is that all known DAPs can be combined together into a computer system, the Alzheimer's Disease-Associated Processes and Targets (ADAPT) Ontology which would use a standardised language for different DAPs. There are different uses for disease ontologies like ADAPT, but one of them could be to make for more coherent communication around priority setting in the diverse research community working on different DAPs. For example, each DAP could receive a "score" based on the values attributed to it from knowledge of the scientific literature.

The second article in this part of the thesis deals not with the theory of the "long-list of disease-causing options" but rather how best to test the therapeutic value of possible treatments. Taking beta-amyloid away from the centre of a vision of AD causality leads to a very different therapeutic vision of AD, as in Herrup (2015):

In truth it is likely that we will need to address all of the listed options if we are to cure AD or completely prevent it. This is a daunting task, but it is likely that each treatment will make a difference, so that our victories will be small and incremental but frequent—a hopeful concept (p. 797, Herrup, 2015).

We will call this a “piecemeal” therapeutic scheme proposed by Herrup. (“Piecemeal” is defined in the Oxford dictionary as “*done or happening gradually at different times and often in different ways, rather than carefully planned at the beginning*.”)

We emphasis the need for what Herrup terms “incremental victories”. There is a major problem with combining therapies for AD. As we will argue, they must first be validated individually before they get combined. This is because it is not just some thing (e.g. a drug) that is used to treat a condition—drugs have labels that must be respected so as to maximise safety and efficacy with respect to attaining some endpoint, and they receive approval as such (Kimmelman and London 2015). If a trial with a single agent doesn’t work, it can at least be a source of information—perhaps an otherwise useful drug was given too late, or with too weak a dose, etc. But we argue that combining treatments in a combination therapy before each treatment is validated individually means that a trial cannot even be a source of useful feedback. And there is great need for generalizable solutions for such a massive public health problem.

Chapter Three: Beyond association: the Alzheimer's Disease-Associated Processes and Targets (ADAPT) ontology

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Timothy Daly, MA[1], Mathieu Bourdenx, PhD[2,3], Vincent Henry, PhD [4,5], Fabrizio de Vico Fallani, PhD [4,5], Stéphane Epelbaum, MD PhD [4,5,6]

1 Science Norms Democracy, UMR 8011 Sorbonne University, Paris, France
2 Université de Bordeaux, Institute des Maladies Neurodégénératives, UMR 5293, Bordeaux, France
3 CNRS, Institute des Maladies Neurodégénératives, UMR 5293, Bordeaux, France
4 Inria Paris, Aramis Project Team, Paris, France
5 Sorbonne University, UPMC Univ Paris 06, Inserm U-1127, CNRS UMR-7225, Institut du Cerveau et de la Moelle Epinière, Hopital Pitié-Salpêtrière, Paris, France
6 AP-HP, Hôpital de la Pitié Salpêtrière, Institute of Memory and Alzheimer's Disease (IM2A), Centre of Excellence of Neurodegenerative Disease (CoEN), National Reference Centre for Rare and Early Dementias, Department of Neurology, Paris, France.

Corresponding author: Timothy Daly, Philosophy Department, Sorbonne University, 1 Rue Victor Cousin, 75005 Paris, France. E-mail: timothy.daly@paris-sorbonne.fr.

Author declarations

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Abstract

Since the 1990s, biomedical research into Alzheimer's Disease (AD) has been guided by the amyloid cascade hypothesis (ACH), which has not yet managed to deliver viable therapies. Herrup (2015) offers a radical post-ACH vision for research, suggesting that the community could benefit from studying other disease-associated processes (DAPs) for AD and should "choose them all." However, this strategy leaves all DAPs on the same footing. We sort DAPs using three properties: specificity for AD, frequency in patients, and pathogenic intensity for dementia. We describe these properties and exemplify qualitative specificity analysis with tau pathology and autophagy to reveal their differential implication in AD and show how DAPs fit into our disease ontology, the Alzheimer's Disease-Associated Processes and Targets (ADAPT) ontology. We define risk factors, causes, and markers of AD, and offer ADAPT to improve much-needed communication, priority setting, and guide future experiments in the diverse AD research community.

Introduction

Since the initial description of Alzheimer's Disease (AD)(*33*), the massive growth of the AD field has prompted us to apply an agnostic, transversal and analytical process to AD research to propose a broad hypothetical framework which might foster a coherent strategy between diverse research efforts.

Alois Alzheimer first described Alzheimer's Disease (AD) in 1906 as a dementing syndrome with hallmark neuropathological features(*33*). Since that time, there has been a long-standing historical debate about whether AD neuropathology (now known as "amyloid-β" and "tau") plays a significant causative role in age-related cognitive decline(*34*). Since the work of

Katzman and Karazu in the 1970s(*35*), it is thought that AD is responsible for up to 70% of dementia cases. Pathology-targeting drug strategies have since been the dominant therapeutic strategy against AD(*3*) without yet bearing therapeutic fruit. There is now a shift towards prevention, and the idea of promoting resilience to neuropathology through lifestyle intervention against modifiable risk factors is gaining traction(*36*).

The dominant pathology-targeting strategy since the 1990s is based on the amyloid cascade hypothesis(*37*). Herrup(*38*) underlines the limits of the anti-amyloid and reductionist approaches towards AD. Arguing that amyloid-β deposition is not the sole disease-associated process (DAP, our term which we define herein) for AD, Herrup proposes a multi-factorial approach which brings together all the known molecular DAPs. He uses preclinical and clinical data to attempt to demonstrate "that a simple linear pathway tracing disease progression from amyloid-β to AD is inadequate as a formal hypothesis" (Herrup, 2015, p. 3). However, he also refutes the conceptual "hierarchical scheme" (Herrup, 2015, p. 2) of the ACH, which "focuses our quest to understand and treat AD" (Herrup, 2015, p. 4). He offers "a number of alternative ways of viewing the disease" (Herrup, 2015, p. 4). His alternative to the ACH is to embrace "the list of disease-causing options ... [recognising no formal] guidance as to how to focus our quest to understand and treat AD" (Herrup, 2015, p. 4). For example, despite the ACH's shortcomings, Herrup recognises that "along with APP and the secretases, [amyloid-β] can and should remain a central part of our thinking on the pathophysiology of the disease" (Herrup, 2015, p. 3). His model results in piecemeal therapeutics, i.e. where "each treatment will make a difference" (Herrup, 2015, p. 4). He summarises: "AD can be viewed as a disease of amyloid … [can] also be viewed as a tauopathy … failure of autophagy and/or lysosomal function … loss of Ca2+ homeostasis … failure of neuronal cell cycle control … [the] central role of neuroinflammation … The answer to the question of which option shall we choose is ... choose them all" (Herrupm

2015, p. 4). Herrup's theoretical and therapeutic scheme lacks hierarchisation, and the "choose them all" strategy does not offer priority to any DAP and concerns only the molecular level (from genes to cellular pathways), thus overlooking a whole portion of the literature, such as population epidemiology, and is also challenging to apply to clinical research.

Nevertheless, before we continue Herrup's crucial initiative by attempting to order DAPs, it is worth noting that a criterion previously used to argue for the centrality of a particular DAP is chronology. A significant trend in the AD research field, across different camps, is towards earlier intervention to achieve disease-modifying therapy. De Strooper & Karran(*39*), for example, go as far as identifying the "real causes of sporadic disease … [as being] upstream of … proteopathies [amyloid & tau], and are likely manifold, with aging being the major driver" (De Strooper & Karran, 2016, p. 605). However, the validity of the assumption that "early causes are real causes" of AD is questioned by the examples of lifestyle or genetic risk factors that are present chronologically early in the patient's life without being sufficient to cause AD *per se*. Such DAPs lack the specificity for AD-related changes required to be classified as "real causes" of AD, but instead are usefully considered as non-specific DAPs contributing to the dementing process. While the literature is full of observational studies making claims about "which DAP comes first"(*6*), drawing conclusions about chronology is highly complex(*40*).

No single DAP fully explains the totality of AD-related dementia. In this article, in order to build on Herrup(*38*), we propose a systemic approach that offers a holistic theoretical framework of AD by adding new property-based dimensions to represent DAPs for AD according to different levels of specificity, while allowing for the existence of DAPs at biological levels other than the molecular level. We offer definitions of causes, risk factors, and markers for AD based on our DAP properties and suggest future directions for research. Our

framework is termed the Alzheimer's Disease-Associated Processes and Targets (ADAPT) Ontology.

1 - Defining DAP properties

A DAP is a process defined as being "associated with" onset and prognosis. This vague definition, which we shall improve upon, is precisely so because the biomedical literature is replete with an ever-growing number of review articles referring to various processes "associated with" AD. In behavioural neuroscience, Krakauer et al.(*41*) argue that the existence of "filler terms" such as *contributes to*, *is involved with*, *participates in*, *is associated with*, *mediates* suggests "the lack of an explicit conceptual framework for the mapping between circuit and behavior .... [which] just fills in for it". These verbs are often used instead of *correlates with* (for example when a biological process is modulated coordinately with disease stages), which bears the comparative advantage of having a formal statistical definition. Moreover, such terms often tacitly imply a form of causation and are used to justify the necessity to target the given DAP to therapeutic ends.

Therefore, to more accurately describe the relationship between a given DAP and disease according to explicit, quantifiable criteria, we identified three separate primary properties of DAPs by which they are defined as "associated." DAPs derive their association with AD because of their specificity for AD, and/or frequency of appearance in AD patients, and/or pathogenic intensity with respect to dementia. For reasons we will clarify in these definitions, these properties should be understood separately, since it is not because a DAP lacks association in one of the dimensions that it does not occupy a worthy place within a holistic scheme of AD theory and therapeutics.

1.1 Specificity

This scale sorts DAPs according to an inverse function of the probability of their association with other pathologies, reflecting the extent to which a change in the DAP leads to AD and not to other pathologies. Controversies around the definition of AD suggest the improbability of a broadly-defined DAP (such as "amyloid deposition") being exclusively involved in AD, versus healthy aging or other pathologies(*40*). Furthermore, comorbidities are the rule in the elderly brain, not the exception. Nevertheless, some DAPs are more specific to AD than to other diseases, even if this specificity is not absolute. We use the concept of 7 levels of specificity with some example DAPs to illustrate our hierarchy (**Table 1** and **Figure 1**). [Thesis note: for Figures & Table, see the end of the manuscript.]

[Table 1]

Specificity offers three advantages. Firstly, it establishes a first hierarchy of the DAPs, beyond the molecular level (**Figure 1**). Secondly, it is based on accessible biomedical knowledge. Finally, this scale is sufficiently detailed to be able to specify sub-processes of broad DAPs. With this in mind, we perform a qualitative analysis of tau-related pathology and autophagy dysfunction (Figure 2). Tau protein dysfunction has a relatively high level of specificity for AD without being entirely specific, as it is also found in tauopathies such as progressive supranuclear palsy (PSP) for example (**Figure 2A**). Autophagy is an evolutionary-conserved, ubiquitous, cellular pathway allowing for the degradation of cellular components in lysosomes, and is our second example of specificity analysis (**Figure 2B**). These examples show how DAPs at the same biological "level" can be more or less specific for AD, and how DAPs identified at different levels are interrelated within a single coherent framework (e.g. lifestyle "diet" affecting "autophagy" and its various sub-DAPs).

[Figure 1]

[Figure 2]

1.2 Frequency

What we define as frequency is the percentage of AD patients with the DAP vs. healthy controls or other conditions. Thus, by definition, the appearance of amyloid-β in senile plaques and tau in neurofibrillary tangles is observed in 100% of cases, given that these DAPs define the disease. However, *Apolipoprotein E (APOE)* haplotype demonstrates the separability of frequency and specificity. The presence of 1 or 2 copies of the epsilon 4 "ε4" (APOE4) allele is a risk factor for various neurodegenerative diseases and is observed in over >50% of AD patients(*42*), making it three folds more common among AD patients than it is among the non-AD population, but it is possible to have sporadic AD without it, i.e. its frequency is not at 100%.

This second dimension makes it possible to establish a hierarchy of DAPs independent of specificity. However, working out the details of the hierarchy of DAPs according to this scale is more difficult to apply than for specificity, since it is based on knowledge derived from technology-dependent large-scale cohort analysis which remains to be undertaken for the vast majority of DAPs (though see 1.3).

1.3 Pathogenic Intensity

Pathogenic intensity is a reflection of the extent to which a change in the DAP is associated with a worsening of AD prognosis, and how much therapeutic impact would be likely to be obtained from targeting the DAP. Figure 3 offers a visual representation of the 3 DAP properties frequency, specificity, and pathogenic intensity.

Pathogenic intensity is independent of frequency and specificity. Nevertheless, while the prioritisation of DAPs by pathogenic intensity is conceptually consistent, as in the case of

frequency, the current possibility of assigning a value to them is very limited, since it requires an estimate of the impact of DAPs at the population- and patient-level; meta-analyses of GWAS studies and lifestyle risk factors provide the best opportunity of quantifying pathogenicity scores for AD (15). However, homogenising different data types into a coherent scheme of AD risk remains a large conceptual and empirical obstacle, since there are currently no algorithms available to translate statistical conclusions into a risk factor for an individual AD patient. This is particularly difficult with ADAD patients with deterministic amyloidogenic mutations who represent a very small percentage of total AD cases. For example, observational data(*43*) suggest that physical activity may be even more protective in ADAD patients than in sporadic AD (sAD) patients. Both ADAD and sAD can be studied simultaneously in order to ascertain the differential effect of DAPs on these different patient groups(*44*).

[Figure 3]

Inspired by Herrup's important community-wide call to "choose them all" when studying DAPs, we have sought to offer properties of DAPs so as to avoid putting them all on the same footing. Before offering the first outline of our disease ontology, we shall offer a putative lexicon for terms used frequently in AD research articles derived from the primary properties that we have identified for DAPs (specificity, frequency, and intensity): cause, risk factor, and markers (Table 2).

[Table 2]

3 - The ADAPT ontology

The three DAP properties described–specificity, frequency, and pathogenic intensity–can be used to design an "ontology" of AD, where DAPs can be defined according to logical relationships in

a common framework to be completed with quantitative knowledge of pathogenic intensity and frequency in AD patients.

Briefly, in computer science, ontologies are resources that formalise concepts in relation to each other and produce controlled (natural language) vocabulary, thus reducing ambiguity for humans and computers. Today, there are many biomedical ontologies (bio-ontologies) (https://bioportal.bioontology.org). Once centralised, they are implicitly linked by "mapping" between common terms.

We have designed ADAPT[5] aimed at classifying DAPs according to our 3 properties for AD. This ontology is subdivided into 2 main types of classes: *Identified disease-associated process* and *classified disease-associated process*. *Identified disease-associated process* (iDAP,) is the branch of ontology in which the known DAPs for AD are classified according to their traditional biological identification. It is subdivided into 6 subclasses: *molecular DAP*, *physiological DAP*, *environmental DAP*, *gene-related DAP*, *pathological DAP*, and *other DAP*.

Classified disease-associated process (cDAP) is the branch of ontology that contains our three properties as the paradigm of hierarchisation. It is therefore divided into 3 sub-classes: *disease-associated process by specificity*, *disease-associated process by frequency*, and *disease-associated process by pathogenic intensity*. They are themselves subdivided into subclasses representative of the scale of the property (by specificity: *lifestyle DAP*, *pathogenic-type DAP*, *neurodegenerative DAP*, *AD DAP*, *AD-subtype DAP*, and *individual DAP*; as illustrated in **Figure 1** & **Table 1**). All of these subclasses aim to automatically integrate the DAPs previously listed in the branch iDAPs by computed inference, resulting in an ontological model that is functional, coherent, and flexible. While other bio-ontologies also focus on AD

[5] ADAPT is available at https://zenodo.org/record/4740141#.YJaJ3i3pMUs.

(ADO(*45*) and CADRO(*46*)), they aim to compile AD entities in order to index projects or data. ADAPT focuses on DAPs and aims to represent them according to their impact on AD.

ADAPT is best understood as a continuation of Herrup's community-wide call to "choose them all," i.e. not to reduce the scope of useful therapeutic targets in AD to one pathway, but we also provide three criteria to focus efforts and reduce ambiguity. It should therefore contribute to conceptual and therapeutic improvements. However, the long-term value of the model provided here will depend on concerted field-wide efforts to foster the convergence of efforts.

Concerning conceptual improvements, long-standing debates about DAPs' role in AD etiology should be resolved with the use of precise language about exactly which DAPs and sub-DAPs are under investigation in experimental investigation. One necessary condition for such debate will be data precision. The AD literature is a heterogeneous entity, a reflection of the different profiles working within it with different methods, theories, and objectives. Improving signal-to-noise within the literature—attaining "robust conclusions" which hold for different methodologies asking similar questions about the role of DAPs in AD etiology(*47*)—requires an end-to-end data quality approach. Thus, as data quantity increases exponentially, in order to not lose sight of a coherent, quantified and hierarchised picture of the relationships between DAPs and AD, the community should aim to improve the labelisation of published results, thanks to the existence of Medical Subject Headings (MeSH) terms in PubMed, meaning that there is a semantic framework which can be adapted to DAPs in order to improve their description of how they affect AD prognosis according to our criteria of specificity, frequency, and pathogenic intensity.

Those relationships between DAPs and AD etiology should be quantified and hierarchised, so as to improve precision. Where MeSH terms are not precise enough for molecular processes, the terminology of gene ontology (GO) consortium(*48*) for genes and gene products can be used.

While there are and certainly will be DAPs and sub-DAPs in AD which do not belong to either MeSH or GO terminology, existing resources with controlled vocabulary should be used as much as possible so as to avoid ambiguity in the literature, such as the Alzheimer's Disease Ontology (ADO). Thus, ADAPT has adopted and encourages the use of pre-existing terms. As community-wide efforts to improve homogenisation of conclusions within the literature improve, the automatic inclusion of standardised results (via MeSH/GO/ADO) into a quantifiable, hierarchised scheme like our ADAPT ontology, should be promoted.

However, the comparisons with other ontologies are limited, since ADAPT has been designed to play a very specific role to order DAPs to therapeutic ends following Herrup (2015), and should be assessed according to how satisfyingly it helps to achieve this end. Other ontologies are useful for annotations and researching information, whereas ADAPT is to be used for profiling DAPs as a function of their specificity, frequency or pathogenic intensity, thus adapting to the scientific literature.

While we have defined and highlighted specificity, there is arguably no more specific treatment for AD than anti-amyloid strategies. However, the last 20 years of unsuccessful anti-amyloid clinical trials have shown how difficult elaborating a specific treatment for AD is. Furthermore, for other indications, such as cardiovascular disease, non-specific treatments (e.g. statins) have indeed shown that important public health gains can be made despite treatments lacking specificity(*49*). Thus, every DAP property is important when choosing therapeutic targets for AD, and when considering treatments, further DAP properties could be elaborated, such as *in vivo* measurability of the DAP, the DAP's signal transience, current actionability against the DAP, and others. These might be considered "secondary" properties, since they do not define DAPs, but instead qualify their suitability in a therapeutic scheme. **Figure 2b** showed how DAPs with varying specificity interact (e.g. diet and autophagy). This could allow for non-

reductive discussion of how knowledge from different approaches to treatment (e.g. lifestyle interventions) can be both explored now for their disease-reducing potential(*50*), and also used to inspire pharmacology-based neurological approaches against specific DAPs thanks to study of mechanisms. But importantly, their therapeutic value at the community level should not be reduced to the latter strategy, since specificity should not be the only criterion used in developing treatments.

Finally, the notion of specificity can also be further analysed. Given that AD is defined as a clinico-pathological entity, it follows that the notion of specificity can also be separated along these two dimensions where the separability of clinical and pathological specificity becomes more apparent for highly specific DAPs. For example, amyloid and tau are highly pathologically specific for AD; while ADAD mutations suggest amyloid's high pathological specificity for AD, clinically speaking, however, tau pathology has better topographical clinical specificity for sporadic AD than amyloid-β depositions(*51*).

Beyond considering the separability of clinical and pathological dimensions of specificity, the suppleness of the term "associated" in "disease-associated process" also allows clinical manifestations of AD themselves to be considered as DAPs with different specificities, frequencies, and correlation with cognitive decline. For instance, hippocampal-type amnestic syndrome(*52*) is more specific than subjective cognitive decline(*53, 54*) and is a better predictor of future cognitive decline in AD(*55*). Future studies with comparisons of different symptoms of AD at different stages of the disease are required in order to clarify their respective weight as DAPs. Intra-cohort normalization of cognitive assessment(*56*) might serve this endeavour. Clinical DAPs can also be correlated with their biological(*57*), structural or functional(*58*) underpinnings in order to promote useful discussion about DAPs and their interactions, for

example, in the design and evaluation of clinical trials targeting specific DAPs and measuring specific clinical outcomes.

Conclusion

In the spirit of adaptation, we offer ADAPT as a collaborative platform for vital communication in the heterogeneous AD research community, in which different approaches might converge so as to favour fruitful discussion, information sharing, and strategy around priority-setting, thus speeding up therapeutic efforts against AD. If the dominant therapeutic model cannot provide treatments and adapt to new challenges facing AD research, then there is the risk of unproven, alternative remedies for dementia(*59*) creating confusion and false hope amongst the patient commnunity and further slowing down research into AD(*60*), the latter being supported by a fragile economic model(*27*) which may continue to struggle in the future.

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Table 1

Level	Description	Value
Life-determined	Chronological age and chromosomal sex.	1
Lifestyle	Generic DAPs linked to lifestyle habits (physical exercise, nutrition, etc.).	2
Pathological	DAPs associated with various pathologies affecting the whole body (obesity, autophagy dysfunction, herpes infection).	3
Neurodegenerative disorder	DAPs for neurodegenerative pathologies (tau aggregation, excitotoxicity, neuroinflammation).	4
Alzheimer's disease	DAPs defining AD (amyloid-β deposition, Tau hyperphosphorylation).	5
Alzheimer's disease (sub)type	DAPs differentiating AD subtypes (e.g. amyloid-β, Tau strains).	6
AD-determining	DAPs (e.g., ADAD mutations)	7

Table 1. Attributing DAP specificity values from 1 (Life-determined) to 7 (Individual mutations). The least specific DAPs for AD are chronological aging and chromosomal sex — determined risk factors for many chronic pathologies — whereas the most specific DAPs are specific aggregates of amyloid-β (senile plaques) and tau (tangles), these neuropathological hallmarks being part of this disease's definition. Individual-level specificity accounts for the existence of heritable forms of familial AD. It must be stressed here that the "value" attributed to specificity

here is a code to facilitate communication around classification with the computer in our disease ontology, and should not be understood as a measure of "importance."

Figure 1

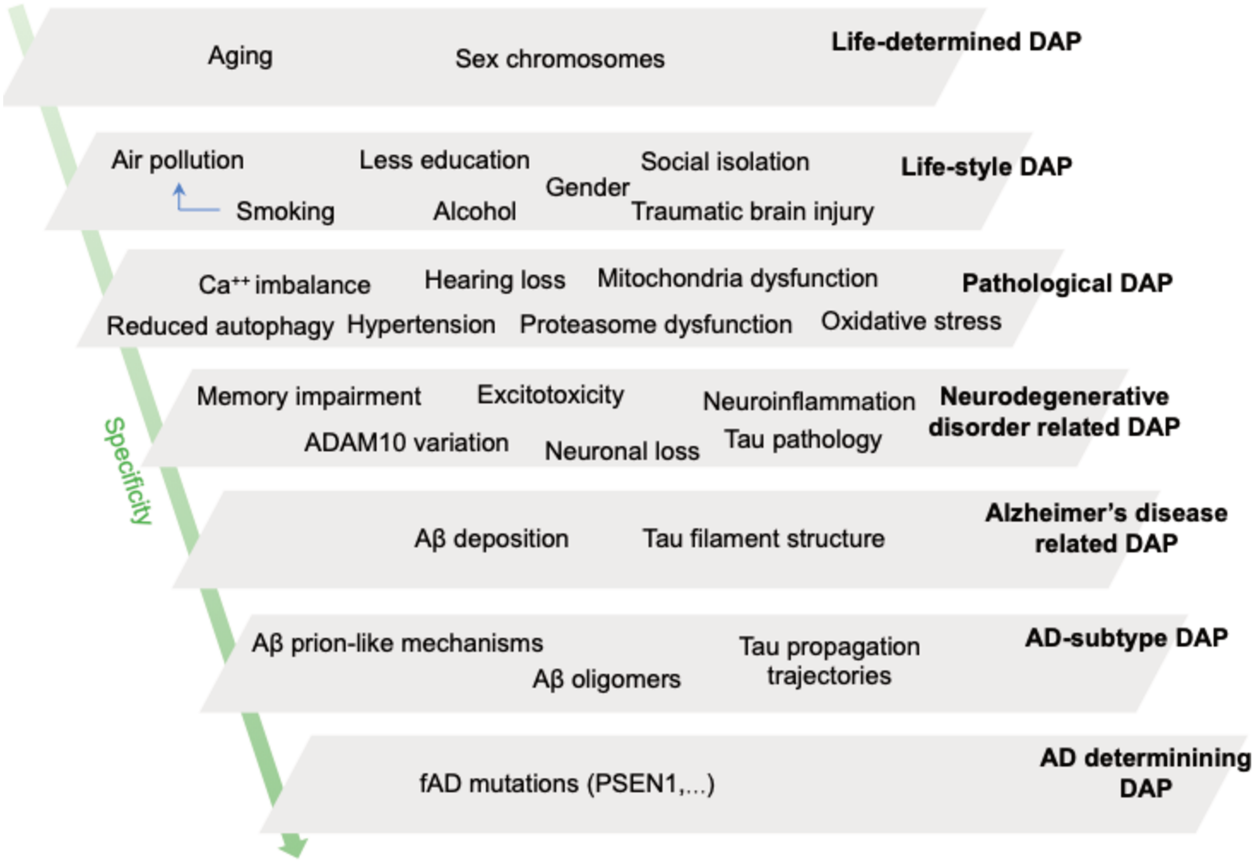
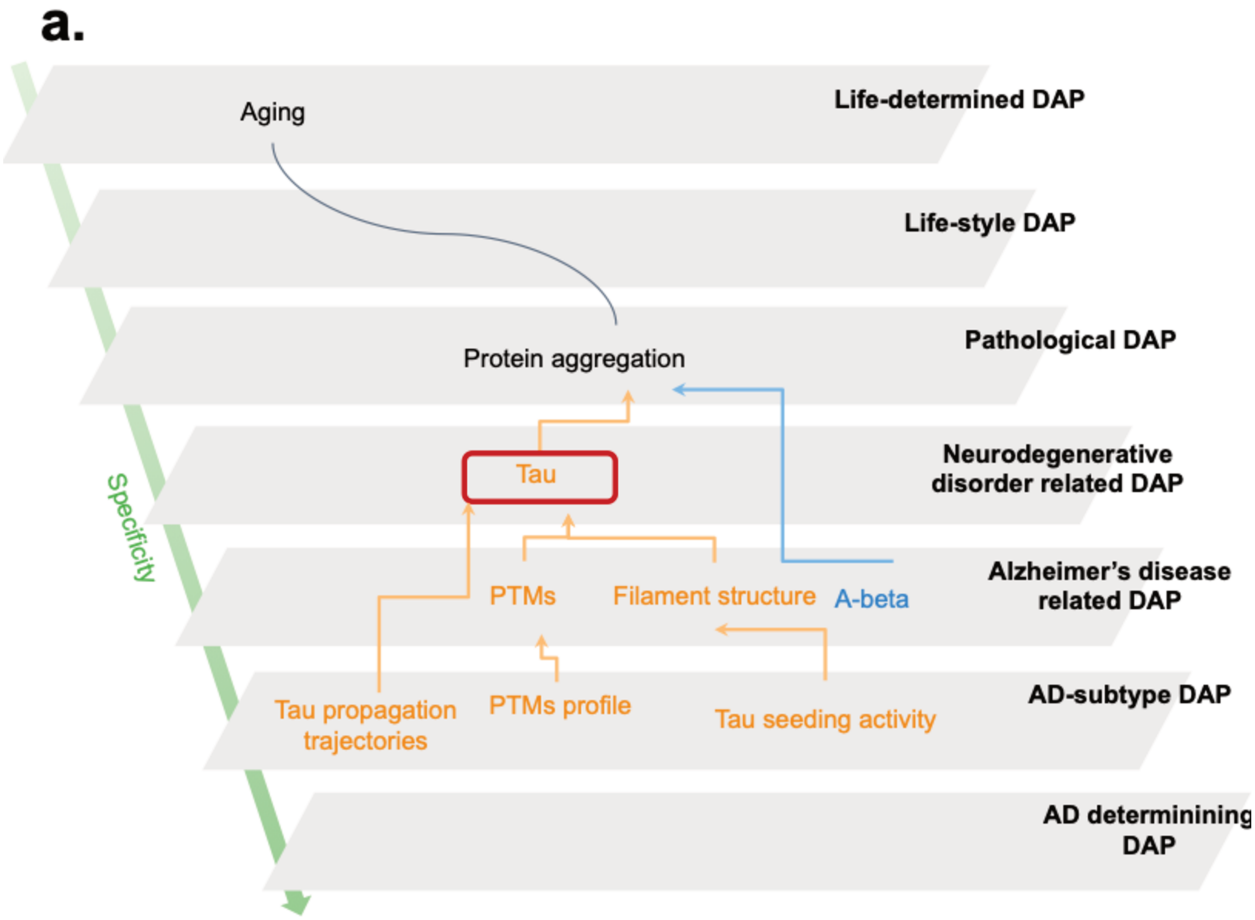
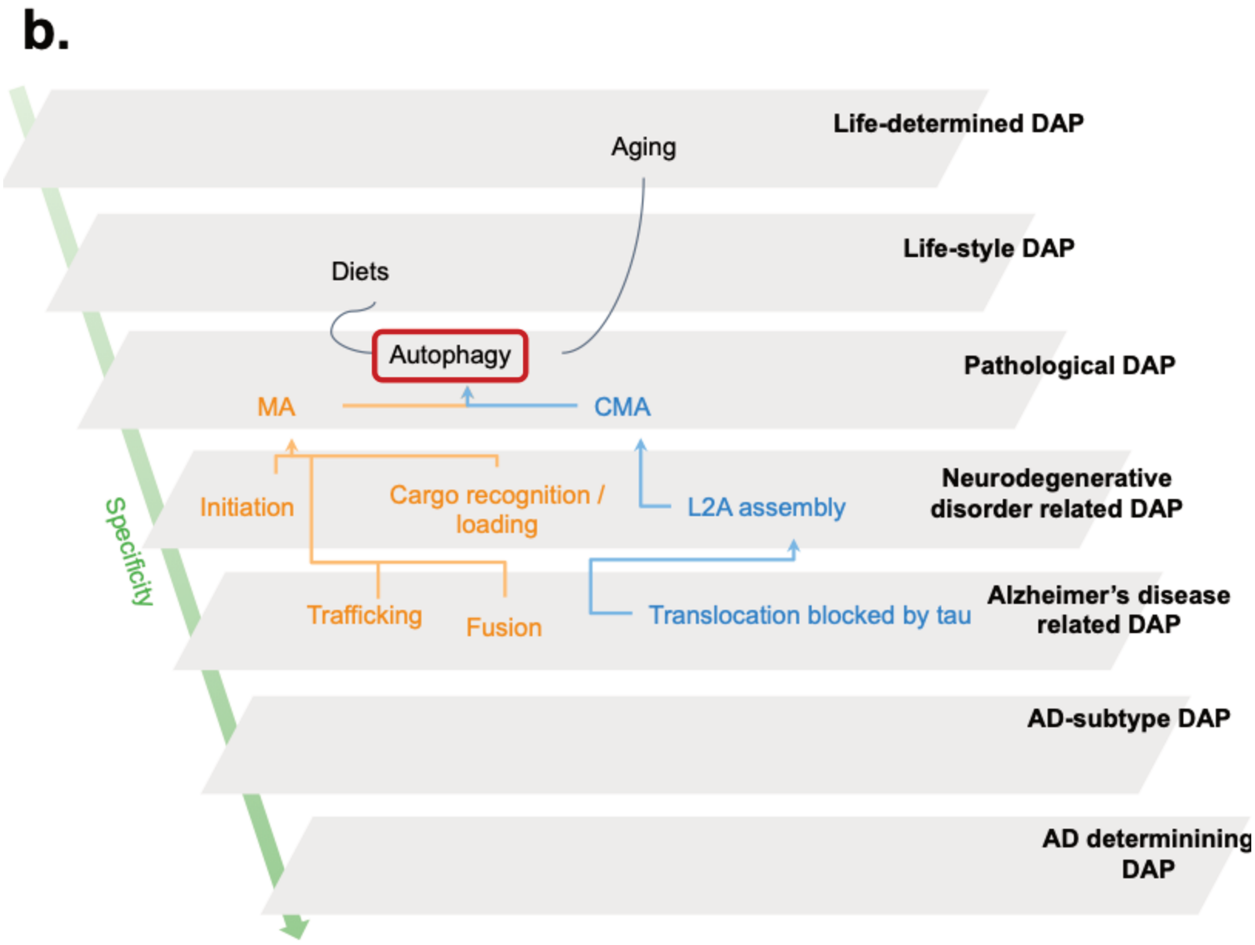


Figure 1. A schematic representation of our hypothetical model of disease associated processes (DAPs) for Alzheimer's Disease (AD) sorted by level of specificity. The schema allows for the understanding of why a specific patient or patient population may develop AD due to the converging pathological burden of several DAPs at different specificity levels. Life-determined DAPs cannot be changed (age, sex chromosomes). DAPs of lifestyle, such as smoking and alcohol use, are the next least specific DAPs. Pathological DAPs are those which clinicians use to define disease; DAPs involved in neurodegenerative disease contribute to cognitive decline in AD, but for non-specific reasons, e.g. cerebrovascular impairments. Amyloid-β accumulation and tau hyperphosphorylation are used to define AD-type impairments as per the literature. AD-determining DAPs are restrained to deterministic mutations affecting amyloid-β metabolism in familial autosomal dominant AD (ADAD). Aβ: Amyloid-β; fAD: familial AD.

Figure 2. Multi-level specificity analyses for tau-related pathology and autophagy. Arrows connect sub-parts (higher specificity) to part (lower specificity).



(a). Tau aggregation is a specific instance of protein aggregation, observed in many pathologies(*61*); "Tau" is neurodegenerative-level. Tau filaments are composed of different isoforms: AD filaments contain all six isoforms expressed in the human brain, while progressive supranuclear palsy filaments contain only four-repeat isoforms(*62*). Recent structural studies using cryo-electron microscopy have characterized tau filaments with unique structures associated with disease(*63-65*). Although a single conformer is described per disease for now, converging evidence suggests that tau strains could be unique to single patients or subsets(*66-68*). Likewise, the profile of post-translational modifications (PTMs) may be specific to AD and to certain subgroups of AD patients(*69*)(28). Tau seeding activity is different between subtypes of AD patients (slow and fast progressers)(*66*), and four distinct trajectories of tau deposition have been identified in Alzheimer's disease(*70*).



(**b**) Autophagy is influenced by aging and nutritional status(*71*), and autophagy dysfunction is observed in many pathologies, including AD(*72, 73*). Genetic alteration of murine autophagy alters neuronal proteostasis, resembling neurodegenerative conditions(*74, 75*). Mammals exhibit three coordinate and partially compensatory forms of autophagy, which differ in lysosomal cargo delivery mechanisms: macroautophagy, chaperone-mediated autophagy (CMA) and microautophagy. Because of more abundant literature on them, we consider only macroautophagy and CMA. Increasingly specific description of autophagy blockage by pathway (macroautophagy/CMA) or steps within a given pathway (induction, cargo recognition, autophagosome trafficking, autophagosome/lysosome fusion for macroautophagy or targeting, translocation complex assembly, LAMP-2A stability for CMA) allows for the identification of disease-specific signatures of autophagy impairments and targeted therapies in AD and other neurodegenerative diseases(*72, 76, 77*).

Figure 3

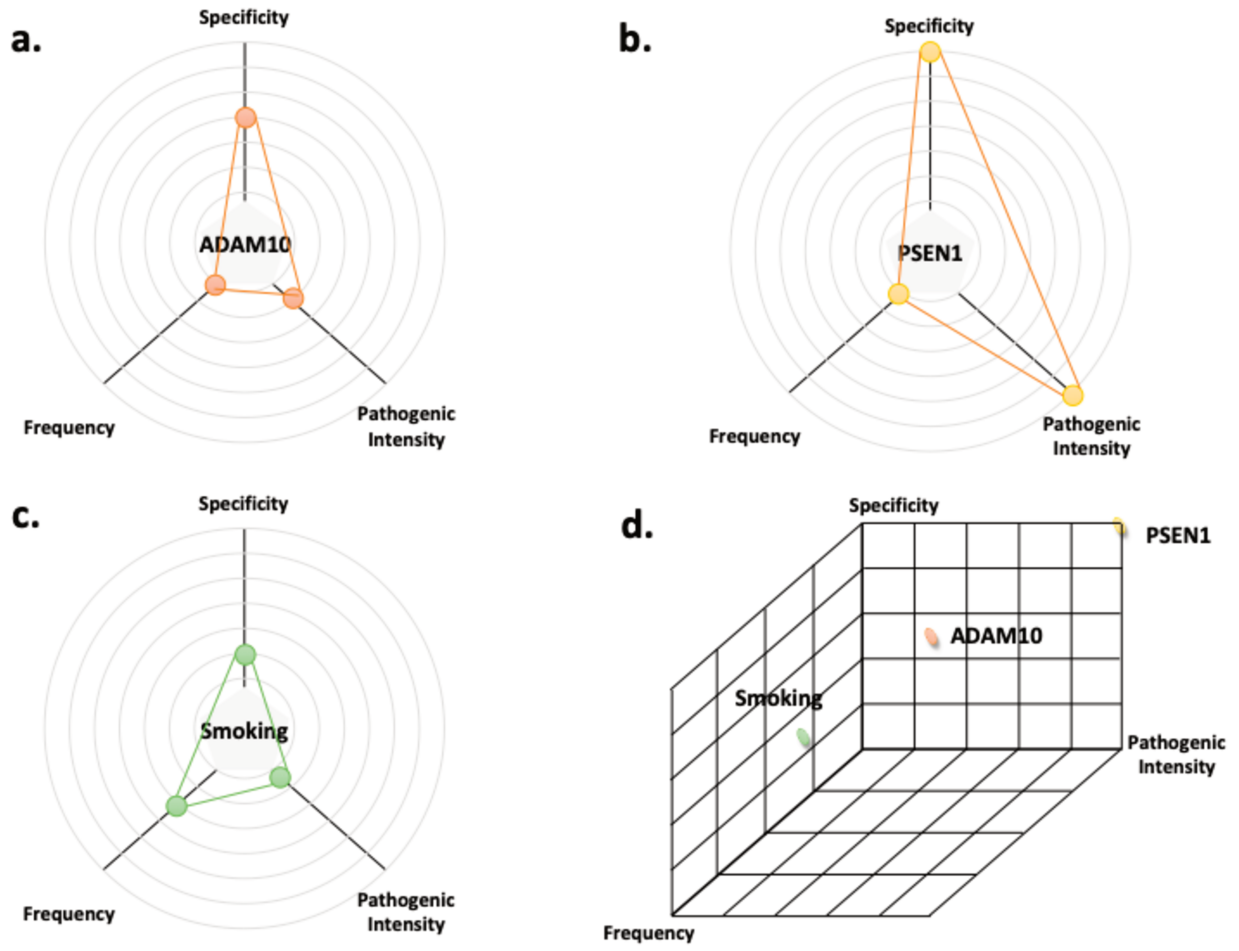


Figure 3 – Visualising specificity, frequency, and pathogenic intensity. Genetic examples confirm the intuition some DAPs are associated with greater pathogenicity in AD, yet frequency is expected to be important in therapeutic impact attained by DAP targeting. a) Genome-wide association studies (GWAS) demonstrating the variable pathogenic impact of single nucleotide polymorphisms (SNPs) for sporadic AD, such as *ADAM10(78)*. Yet these SNPs in sporadic AD are not deterministic. b) In contrast, deterministic AD mutations in familial AD (e.g. PSEN1) are nearly 100% penetrant, but they are exceedingly rare. c) The non-genetic factor of smoking provides a lifestyle DAP probably representing a small but significant contribution to the dementia burden at the population level. Table 1 of Livingston et al. (2020)(*36*) offers

population-level intensity scores for dementia. d) When these three properties are plotted together in three dimensions, estimates can be made about the expected therapeutic benefit to be gained from targeting the DAP.

Definition	**DAP property must satisfy the following minimal criteria in AD patients:**		
	Specificity for AD	**High frequency in AD patients**	**Pathogenic Intensity**
Risk factor	Low to intermediate	Not for all patients	Low to intermediate
Cause	High	Not for all patients (e.g., fAD mutations)	High
Marker	High	High	None needed

Table 2. A putative AD lexicon founded upon DAP properties: risk factor, cause, and marker. Risk factor: any DAP associated with AD onset and prognosis. A cause: a specific risk factor, i.e. be associated via both pathogenic intensity and specificity. ADAD mutations are low-frequency causes. A marker: both specific and high frequency in AD, in order to discriminate AD from non-AD states. However, markers themselves need not be associated with pathogenic intensity.

Chapter Four: Open-Peer Commentary to "Building clinically relevant outcomes across the Alzheimer's disease spectrum": A plea for simple tests of treatment

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Timothy Daly1, Ignacio Mastroleo2, Mathieu Bourdenx 3,4, Vincent Henry5, Stéphane Epelbaum5,6,7
1 Science Norms Democracy, UMR 8011 Sorbonne University, Paris, France
2 National Scientific and Technical Research Council (CONICET) and Programa de Bioetica, Buenos Aires, Argentina
3 Université de Bordeaux, Institute des Maladies Neurodégénératives, UMR 5293, Bordeaux, France
4 CNRS, Institute des Maladies Neurodégénératives, UMR 5293, Bordeaux, France
5 Inria Paris, Aramis Project Team, Paris, France
6 Sorbonne University, UPMC Univ Paris 06, Inserm U-1127, CNRS UMR-7225, Institut du Cerveau et de la Moelle Epinière, Hopital Pitié-Salpêtrière, Paris, France
7 AP-HP, Hôpital de la Pitié Salpêtrière, Institute of Memory and Alzheimer's Disease (IM2A), Centre of Excellence of Neurodegenerative Disease (CoEN), National Reference Centre for Rare and Early Dementias, Department of Neurology, Paris, France.

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Abstract

Rentz et al.'s report (*79*) of an Alzheimer's Association Research Roundtable (AARR) on clinical meaningfulness comes at a time when two major approaches to treating dementia are

being vigorously tested: the early targeting of the neuropathology of Alzheimer's Disease (AD), and multi-domain lifestyle interventions to promote resilience to neuropathology. The report argues that "a clinically meaningful outcome must produce a clear and sustainable benefit, while altering the disease trajectory." We apply the "web of information" model of clinical translation to argue firstly that tests of treatments aiming to achieve such outcomes should remain simple. Secondly, that building clinically-meaningful treatments should be kept separate from public health policy which means promoting wide-reaching action against risk factors now with available information.

1 Two major approaches to preventing dementia

Two international working groups argue that the early targeting of hallmark AD pathology (ADP)—including beta-amyloid (Aβ) and tau proteins—before the arrival of the symptoms of dementia may represent the best disease-modifying treatment option available [(*80, 81*). Conversely, members of two Lancet Commissions focus on the discrepancy between the accumulation of AD pathology and dementia and argue that 40% of cases of dementia might be preventable if society can take lifelong action against 12 risk factors involving physical, mental and social health across the lifetime (*36, 82*). Targeting Aβ has been the historically dominant approach to dementia prevention but a recent survey with researchers suggests that attitudes are shifting towards treatments such as tau protein and lifestyle interventions (*83*). Other approaches beyond targeting ADP and promoting resilience also exist within basic biology but there is a lack of expert consensus on how to choose between the "long list of disease-causing options" (*16*).

2 The concept of information applied to both approaches

Jeffrey Cummings regularly publishes updates on the "drug pipeline" for treatments of AD (*84*). But Kimmelman and London (*85*) argue that "the so-called drug pipeline is not really about drugs and is not much like a pipeline … [translation] is really about … information … a web ...

between exploratory studies, confirmatory studies, clinical practice, and theory" (pp. 27, 32, ibid) which requires finding the "*optimal values of various variables ... dose, timing of drug administration, or diagnostic scores ... at which [the intervention] achieves the most favorable risk-benefit balance ... [and] defining the boundaries on dimensions beyond which [treatment] ceases to be clinically useful ... clarifying the minimal effective and maximum tolerated doses, the earliest and latest a drug can be applied in disease course, and so on"* (p. 29, ibid).

This logic can be found in Rentz et al. who underline that meaningful endpoints involve necessarily different disease stages, stakeholders, and measures of meaningfulness, while recognising that major debates are still to be had about deciding between available options (*79*).

We understand a treatment producing a clinically meaningful outcome as a *setup* containing safety (*s*) and efficacy (*e*) instructions to make some thing (*t*) useful (*u*) with respect to some end point (*p*). We use the loose term "thing" because it can be applied to any*thing* in a proposed treatment (from treadmill running to taking aspirin) and because the same thing can have multiple clinical uses. (High-dose aspirin is used for alleviating pain and inflammation whereas low-dose aspirin is used as an antiaggregant agent for the secondary prevention of stroke. Same *thing*, different *treatment*.) This is why drugs have approved "labels" for use.

We apply this information model to both life-style interventions and drug strategies before discussing the prospects of combination therapies for dementia. Despite the optimism around aducanuab's accelerated FDA approval of aducanumab, there is uncertainty about its label as well as risk-cost-benefit (such as "Amyloid-Related Imaging Abnormalities" (ARIA) at high doses). For failed anti-amyloid trials, there are at least 3 sources of complications: right trial (target engagement, trial outcomes)? Right patients (diagnostic criteria, disease severity)? Right theory (targets, aspects of translation)? (*86*). Karran and Hardy (*87*) criticise the pernicious idea that anti-amyloid trials mean a failed amyloid theory by arguing that this interpretation is

informationally simplistic because of sparse preclinical data available for many drugs, often based on very limited animal models. Anti-amyloid antibodies may slow down the decline of cognitive or functional scores by up to 30% over an 18-month period with high doses, as suggested by clinical trials with the antibodies aducanumab and donanemab (*88*). Furthermore, a recent Phase II trial with an anti-tau monoclonal antibody showed approximately 40% slowing of the disease (NCT03828747). Whether or not these percentages are clinically meaningful remains to be seen. Other immunotherapies targeting ADP such as enzyme inhibition may well offer greater effect sizes.

The evidence for specific treatment setups is also scarce on the side of resilience promotion. "Little evidence exists for any single specific activity protecting against dementia" (p. 413, (*36*)). The Finnish Geriatric "FINGER" study which was a 2-year multi-domain physical and cognitive interventional trial led to "a small group reduction in cognitive decline" (p. 426, ibid) in a treatment group aged 60-77 of approximately 600 cognitively at-risk people vs. controls(*89*). It has not been replicated by other similar tests of multi-domain intervention.

Given the current failure of any one thing (drug or activity) to have some meaningful disease-modifying impact on AD, there are calls for combination therapies. In another AARR, Salloway et al. (*90*) offer biological, pharmacological and regulatory arguments to "support the development of combination disease-modifying therapies for AD" (Table 1, ibid). Karl Herrup (*16*) argues that there is a "long list of disease-causing options … choose them all … each treatment will make a difference" (p. 797, Ibid). His call is being heeded. There is a "more diversified" AD pipeline in 2021 than in previous years (*84*). Though Herrup indeed argues for "small and incremental" victories against this complex disease (p. 797, [7]), we are concerned that "choose them all …" might be interpreted as "simultaneously." For example, Guzman-

Martinez et al. (*91*) defend an "integrated approach ... preventive factors combined with novel pharmacological approaches … for the future control of the disease."

When simple treatments get combined they become a complex intervention ensemble, whose elements may interact. This is what Salloway et al. (*90*) cite as "additive or synergistic effects" (p. 2, ibid). There are famous instances of useful combination therapies like anti-retroviral therapy (ART) in HIV. But ART works so well because it employs improvements on therapies acting at already-validated targets, offering multi-pronged attacks on different aspects of the same virus (*92*). This is not the case for dementia research since even the most hopeful target (Aβ) may not deliver on its promise and most other targets are very diverse and not specific to AD (*16*). Just as drug interactions in the elderly are a major cause for concern, interactions between aspects of lifestyle intervention for the purpose of building and validating clinically meaningful treatments should be studied further. This is because individual risk factors may themselves be part of dementia, offer little direct therapeutic value, and also interact (*93*). We are concerned that for a disease with no currently-validated therapeutic targets, combining treatments may lead to interactions that may be more numerous and clinically significant than individual target engagement itself (Table 1). This would make interpreting the origin of treatment effects very difficult, with serious issues for generalisability for a disease with millions of sufferers waiting for a treatment.

3 Conclusion: Information vs. Action

For a complex disease with different stages, stakeholders, and outcome measures, providing a meaningful disease-altering benefit is a tall order. We argue to keep the tests of treatments simple, but also to distinguish research into treatments (building and validating them) from health policy which should be wide-reaching so as to maximise its impact. New platform trial

methodology should offer ways of accelerating the randomized controlled trial methodology with simple drug treatments (*94*). Conversely, policymakers must act on the best evidence available to them to promote health despite uncertainty and revise their decisions with new evidence. This involves encouraging wide-reaching action against risk factors, while being careful to respect individual autonomy and avoid stigmatising language of the sick (*95*). On the treatment side we must keep the stringent requirements of validation for full authorization and registration so as to avoid the propagation of unvalidated treatments for dementia (*60*). By keeping these activities separate, policymakers can act now while researchers make meaningful victories.

N. of items in the ensemble	Informational representation of the complex ensemble	Number of hypothetical interactions	Possible contributions to treatment effect
1	= Safety, Efficacy Instructions + Thing $(SET)_1$	0	1 item + 0 interactions = 1
2	= Set1 + Set2 + $Interaction_{1\text{-}2}$	1	2 items + 1 interaction = 3

3	= Set1 + Set2 + Set3 + I_{1-2} + I_{1-3} + I_{2-3}	3	3 items + 3 interactions = 6
4	= Set1 + Set2+ Set3 + Set4 + I_{1-2} + I_{1-3} + I_{1-4} + I_{2-3} + I_{2-4} + I_{3-4}	6	4 items + 6 interactions = 10

Table 1 – The informational complexity of complex treatments for diseases like Alzheimer's disease. Items in complex treatments may interact. In treatment-resistant dementia it is vital for the first therapies to be as informationally simple as possible. This same reasoning can be applied equally to drug cocktails and multi-domain lifestyle interventions.

Part Three — Neuroethics and innovation: the ethical stakes of a major unmet public health need

Part Two underscored the need for conceptual clarity in understanding the contribution of different processes to the worsening of disease prognosis, as well as the need for tests of treatments to function as sources of useful information for researchers and ultimately patients. This Part Three of the thesis explores the consequences of what the absence of treatments capable of slowing down dementia has meant for patients at an individual and societal level.

In his book on Pragmatic Neuroethics (2010), Racine (E. Racine 2010) defines neuroethics as "an interdisciplinary and collective response to ethical challenges in neuroscience and clinical care" (ix, ibid). Neurological and mental health disorders are characterised by

"*caregivers without appropriate support and resources; stigma and discrimination; lives that are shattered by illness and isolated suffering … diseases of the brain and mind now represent one of the greatest—and still increasing—public health burdens*" (ix–x, ibid).

Within those diseases, Alzheimer's disease (AD) is one of the most burdensome. AD is thought to be responsible for up to 70% of 55 estimated million cases of dementia in the world (WHO 2021). Dementia is thought to reach 78 million cases in 2030 and 139 million in 2050. The condition is still under-diagnosed and surrounded by stigma worldwide. Caregivers spend an average of 5 hours a day caring for patients, the total cost of the disease is thought to total over $1.3 trillion worldwide, and only 27 countries currently have national prevention plans, despite the condition representing a WHO priority.

Based on Racine's influential work and other definitions from the literature, (Dubljević, Trettenbach, and Ranisch 2021) argue for a tripartite understanding of related perspectives within neuroethics: knowledge-driven, technology-driven, and healthcare-driven.

Knowledge-driven neuroethics is an umbrella term for the ethics of neuroscience research as well as how neuroscientific knowledge can inform theories in ethics (Roskies 2002). Technology-driven neuroethics focuses on neurotechnologies such as brain enhancement, as well as their regulation (Farah and Wolpe 2004). The healthcare-driven perspective applies thinking from bioethics to the problems of neurological and mental illness with the aim of improving patient care (E Racine and Illes 2008). (Dubljević, Trettenbach, and Ranisch 2021) argue for a "fourth, socio-political perspective … [which] focuses on the interplay between the behavioural as well as the brain sciences and the socio-political system" (p. 5, ibid).

The final part of this doctoral thesis was motivated by the need to protect patients at a time when neither of the dominant approaches to the prevention of dementia—targeting the neuropathology of AD or promoting to resilience to dementia through action against risk factors—offers a fully-approved treatment avenue for them. The major burden represented by AD, and the lack of approved treatments, can create a context in which a lot of harm can be done.

Furthermore, there is a relatively large gap between research into dementia (for a cure) and medical practice (caring for patients). These two activities have historically been understood as the "dual mission" of the Alzheimer's Association: "to eliminate AD … and to enhance care," and the AA has been criticised as being "grossly unbalanced" in favour of cure research (Caspi 2019).

This dual mission has since been updated to a triple mission:

"accelerating global research, driving risk reduction and early detection, and maximizing quality care and support" (AA 2021).

The strategic placement of the goal of prevention (risk reduction in the form of multi-domain interventions, and early detection with the ensuing pharmaceutical strategies of neuropathology targeting) between cure and care is a reflection of the fact that as a goal for public health, prevention is preferable to both cure and care.

For as long as a disease-modifying treatment is not forthcoming, an obvious source of possible harm comes from non-validated treatments. (Hellmuth, Rabinovici, and Miller 2019) comment upon "The Rise of Pseudomedicine for Dementia and Brain Health", which they define as

"*supplements and medical interventions … promoted as scientifically supported treatments, but lack credible efficacy data. Practitioners of pseudomedicine often appeal to health concerns, promote individual testimony as established fact, advocate for unproven therapies, and achieve financial gains*" (p. 543, ibid).

They quote the value of the supplement industry at $3.2 billion USD, with what they term its "high-penetration consumer advertising" meaning that patients are frequently exposed to misleading claims about treatments with the possibility of being harmed by them.

Chapter Five builds on this starting point of the availability of non-validated treatments. The reflection in this part of the thesis is also influenced by another major industry: scientific and technical publishing, which is a $10.5 billion-dollar industry as of 2021. Major changes have been seen in the extent to which patients and their families can gain access to scientific

information. Access to scientific literature used to be almost entirely regulated by access to libraries. The Internet profoundly changed this model, making it much easier for scientists and patients to get direct access to scientific publications. There is a now a move from subscription-based fees where the library or reader pays (a few dozen dollars) for access to scientific articles, to "Open Access" where the researcher or their funder pays up to several thousands of dollars for their research to be made entirely available to anyone, without subscription.

Researchers working on theories guiding the quest for treatment do so in the context of academia, a fiercely competitive environment that puts major pressure on researchers to have their work published in specialist journals at the risk of becoming irrelevant and possibly jobless. The concept of "predatory publishing" has entered the debate on scientific integrity, and there are unfortunate examples where journals have not evaluated the scientific quality of submitted work and have published it in exchange for a hefty Open Access publication fee. Thus, there is a risk that non-scientific pressures on publishing harm the quality of science, and thereby, harm patients awaiting treatment.

Yet there is a large, international community of thousands of researchers working on AD. The Alzheimer's Association International Congress (AAIC) 2021 in Denver attracted over 11,000 attendees and saw over 3,000 scientific presentations given. Different countries have different degrees of scientific infrastructure. To deal with the problem of predatory publishing, librarians such as Jeffrey Beall have elaborated "lists of predatory and possibly-predatory publishers." Yet in the global context of AD research, such lists, elaborated by Western librarians, may have limited applicability (Raju, Nyahodza, and Claassen 2018). Instead, predatory publishing may best be understood as a practice to which individual publishers and researchers are more or less

vulnerable due to different pressures, rather than a sole feature of individual publishers in different parts of the world.

Chapter Five, placed squarely in the healthcare-driven perspective of neuroethics, is an attempt to combat what is identified as a possible problematic case of possible predatory publishing. This case has led to the promotion of a currently non-validated treatment for AD, that we call "metabolic enhancement protocols." According to Hellmuth et al. (2019), these protocols

"merely repackage known dementia interventions (eg, cognitive training, exercise, a heart-healthy diet) and add supplements and other lifestyle changes … " (p. 543, ibid).

It will be seen that the promotion of these protocols is characterised by a pseudomedicine approach described by Hellmuth et al. (2019): an appeal to the lack of available treatments, a reliance on individual testimony instead of rigorous science, and achieving financial gain. A further ethical dimension is the fact that these protocols are "promoted by medical professionals with legitimate credentials" (p. 544, ibid), raising questions about the extent to which patients with cognitive decline, and their desperate families, can be said to truly consent to participation in such therapies.

Conversely, the second and third chapters each address Dubljevic et al.'s "socio-political" neuroethics as it pertains both to the promotion of resilience to dementia and the targeting of AD neuropathology.

(Frisoni et al. 2020) offer a *Perspective* paper on both primary and secondary prevention of AD and related dementias. The perspective offered is that of European memory centres. They follow classical definitions of primary and secondary prevention of dementia:

Primary prevention may target cognitively normal persons with modifiable risk factors through lifestyle and multiple domain interventions (including general cardiovascular health) ... Secondary prevention will target cognitively normal persons at high risk of dementia due to Alzheimer's disease pathology with future anti-amyloid, anti-tau, or other drugs (pp. 1-2, Frisoni et al., 2020).

They close by arguing for "increased synergy among public health, general practice, and specialist care" (p. 10, Frisoni et al., 2020). It is likely that major public health gains could be made from exploiting this perspective. Chapter Six of this thesis should be understood as arguing for an extension of the responsible actors involved in dementia prevention. There are now campaigns to reduce dementia risk in 27 countries (WHO, 2021). The journal *Public Health Ethics* published a special issue on the concept of responsibility, asking *Who is responsible for prevention?* (Verweij and Dawson 2019). Underlying the various answers given to the question in that issue, an important theme is the idea of *sharing* responsibility for prevention between members of society and governments.

In Chapter Six, efforts have been made to protect current and future people from a moralising interpretation of the possibility of preventing dementia through action against risk factors, given the inexistence of strong evidence that individuals can act to definitively reduce their individual risk of developing dementia through lifestyle interventions. While dementia prevention programs should be ambitious, focusing only on lifestyle of the middle-aged population does not go far enough: lifelong study of risk looking at the social determinants of health such as socio-economic inequality will be needed to make society as resilient to dementia as possible.

In Chapter Seven, the controversial example of the FDA's accelerated approval of aducanumab is studied. It is first described as a complicated decision taking place in a time of crisis—disagreements about the future of research (as seen in Parts One and Two of this thesis), no fully approved treatment available, and the promotion of non-validated treatments (Chapter Five). Recent drug trials nevertheless support the possibility of treatments being found soon. An alternative model of funding drug development is proposed, which involves government co-operation with the pharmacological industry so that longer, more satisfying trials of anti-amyloid and other hopeful treatments can be kept afloat instead of being terminated for financial reasons before possible treatment effects are seen. Longer trials would also provide deeper feedback on the validity of the amyloid research agenda (as understood in the Introduction) by testing different disease scenarios by which hypothetical causes such as amyloid-beta lead to the development of AD and thereby contribute to the enormous burden of dementia (Hardy and De Strooper 2017).

Chapter Five: The ethics of innovation for Alzheimer's disease: the risk of overstating evidence for metabolic enhancement protocols

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Timothy Daly,[*] Ignacio Mastroleo,[†] David Gorski,[‡] Stéphane Epelbaum[§]

timothy.daly@paris-sorbonne.fr

Abstract

Medical practice is ideally based on robust, relevant research. However, the lack of disease-modifying treatments for Alzheimer's disease has motivated "innovative practice" to improve patients' well-being despite insufficient evidence for the regular use of such interventions in health systems treating millions of patients. Innovative or new non-validated practice poses at least three distinct ethical questions: first, about the responsible application of new non-validated practice to individual patients (clinical ethics); second, about the way in which data from new non-validated practice are communicated via the scientific and lay press (scientific communication ethics); and third, about the prospect of making new non-validated interventions widely available before more definitive testing (public health ethics). We argue that the authors of metabolic enhancement protocols for Alzheimer's disease have overstated the evidence in favor of these interventions within the scientific and lay press, failing to communicate weaknesses in their data and uncertainty about their conclusions. Such unmeasured language may create false hope, cause financial harm, undermine informed consent, and frustrate the production of generalizable knowledge necessary to face the societal problems posed by this devastating disease. We therefore offer more stringent guidelines for responsible innovation in the treatment of Alzheimer's disease.

Keywords Innovation; Alzheimer's disease; Dementia; Diffusion of innovation; Integrative medicine; Clinical ethics; Biomedical ethics

Introduction

[*] Sorbonne University, Paris, France | email: timothy.daly@paris-sorbonne.fr | ORCID: 0000-0003-1650-242X

[†] National Scientific and Technical Research Council, Buenos Aires, Argentina | email: ignaciomastro@gmail.com | ORCID: 0000-0002-8243-9943

[‡] Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA | email: gorskid@med.wayne.edu | ORCID: 0000-0002-9805-6699

[§] Institut du Cerveau et de la Moelle épinière (Brain and Spine Institute), Paris, France | email: stephane.epelbaum@aphp.fr | ORCID: 0000-0003-4059-2891

Research and practice in medicine are distinguished by their intention [1, 2]: the primary aim of research is to contribute to "generalizable knowledge," while the primary aim of practice is to "enhance the well-being of a particular individual or groups of individuals" [2, p. 3]. By providing medical practice with robust treatment data, biomedical research has reduced the burden of public health scourges such as cancer and HIV/AIDS. Yet despite decades of investment in and clinical trials of disease-modifying agents, research has so far not achieved disease-modifying therapeutic results for Alzheimer's disease (AD), the most common cause of the 50 million cases of dementia worldwide and a major source of disease burden. There is understandably huge demand for research solutions to AD, raising a number of ethical issues which result from long clinical trials with cognitively-declining AD patients [3].

Progress made in AD research has diminished centuries of prejudice and conceptual confusion surrounding so-called "senile dementia," and has separated AD from other contributing causes of dementia, allowing for earlier diagnosis and targeted treatments in AD patients [4]. Symptomatic AD patients are, however, a very treatment-resist population. Since it is well recognized that initiation of the disease process precedes symptom presentation by decades, scientists are pleading for earlier pharmacological interventions and for theories and treatments which take into account both genetic and lifestyle contributions to AD outcomes [5, 6].

Diagnosis of AD is currently confirmed via clinico-biological examination. Standard care practices include the prescription of pharmaceutical (acetylcholinesterase inhibitors or memantine) and non-pharmaceutical therapies (speech therapy, psychotherapy, mindfulness, physical exercise, art therapy, etc.). Comorbidities, such as depression or vascular disease, are also identified and treated. Finally, medico-social actions are undertaken as needed, and the

patient may be included in clinical trials to test disease-modifying agents. Existing "anti-dementia" drugs do not halt the disease; thus, AD-related cognitive decline is understood as currently irreversible.

Given the present lack of curative and preventative therapies, some clinicians engage in so-called "innovative practice" for AD patients without robust supporting evidence. Such interventions are ethically permissible if they address an unmet serious or life-threatening medical need and comply with ethical principles [7, 8].

The term "innovation" in medicine is confusing, since it can encompass both research and practice—discrete activities with different principles governing their ethical evaluation and harm–benefit analysis [9, 10, 11]. Moreover, an important distinction is made within health care between validated and non-validated practice, based on whether there is sufficient evidence of the safety or efficacy of a class of interventions to justify their regular use in the health care of millions of patients [11, 12]. To avoid this confusion, we follow the *Belmont Report* and others in identifying innovation with non-validated practice [1, 2, 11], a class of diagnostic, preventive, or therapeutic interventions, primarily to benefit patients, for which there is insufficient evidence of safety or efficacy to warrant regular use in medical practice. More specifically, what we term innovative practice refers to neither research nor validated practice, but to initial or recent usage of non-validated interventions with the aim of benefiting individual patients—or "new non-validated practice" (NNVP) [12]. While this definition is ethically neutral, there are at least three interrelated ethical dimensions along which to evaluate responsible NNVP.

First is the dimension of clinical ethics, which concerns the ethical utilization of innovative therapeutics and technologies to treat individual patients. Per paragraph 37 of the Declaration of

Helsinki, the unmet medical needs of AD patients present an opportunity for responsible NNVP use: “In the treatment of an individual patient, where proven interventions … have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering” [8].

Second is the dimension of scientific communication ethics, which involves the ethics of reporting NNVP data in the scientific and lay literature. Ethical frameworks stipulate that clinician-scientists should use their experience with innovative practice to contribute to generalizable research [7]. According to Helsinki paragraph 36, “Researchers … and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers … are accountable for the completeness and accuracy of their reports” [8]. Since the pathway from evidence generation to consumption contains many steps which can lead to misinformation [13], publishing the results of NNVP may generate undesirable consequences, accelerating the adoption of unvalidated practices by clinicians—known as “runaway diffusion” [9]—despite insufficient data to establish their safety and efficacy.

Third, and relatedly, is the dimension of public health ethics, which addresses the question of making new non-validated interventions widely available prior to testing with clinical trials. This question is particularly relevant during emergencies, when infrastructure for randomized controlled trials may not be in place for diseases with a high mortality rate (see [14]).

In this article, we evaluate a highly popularized NNVP for AD management, metabolic enhancement protocols, and argue that there are ethical issues with its current use and promotion along the three ethical dimensions identified—clinical ethics, scientific communication ethics,

and public health ethics. Recognizing that the ethical requirements mentioned in paragraph 37 of the Helsinki declaration seem insufficient for guiding responsible NNVP in the treatment of AD, we propose a provisional set of principles and benchmarks to address this gap in the literature.

Metabolic enhancement protocols as innovative practice

Recent observational studies reveal several modifiable risk factors for dementia: low education, physical inactivity, obesity, midlife smoking, depression, hypertension, and diabetes. It is thought that improving such risk factors could prevent or delay 40% of dementia cases [6, 15]. The US National Institute on Aging nevertheless recognizes that "the quality of evidence falls short" of supporting a full-blown public health campaign to promote such interventions [16]. Thus, any practice manipulating biological or lifestyle risk factors for AD is new and non-validated according to our definition above.

The most highly popularized innovative intervention for AD is the metabolic enhancement for neurodegeneration (MEND) protocol, a "personalized therapeutic program" that "involves multiple modalities" [17]: diet, supplementation, sleep, stress, and metabolic markers (e.g., heavy metals, oxidative stress, insulin, inflammation). MEND is based on papers published in 2014 and 2016 by Dale Bredesen and colleagues in the journal *Aging* [17, 18]. A subsequent study first-authored by Bredesen, published in 2018 in the *Journal of Alzheimer's Disease and Parkinsonism*, has apparently shown "documented improvement in cognition" for 100 patients following the reversal of cognitive decline protocol (ReCODE) [19], which "uses a specific set of 140+ factors, labs and cognitive and genetic testing" [20]. We collectively bracket MEND/ReCODE under the rubric of metabolic enhancement protocols for AD.

Clinical ethics: Can metabolic enhancement protocols be used responsibly to treat individual patients?

Paragraph 37 of Helsinki indicates that physicians may use non-validated interventions with individual patients only "after seeking expert advice" and "with informed consent" [8]. In 2011, Bredesen and colleagues "proposed the first comprehensive, double-blind, placebo-controlled trial for early Alzheimer's disease therapeutics," which, according to Bredesen, was rejected by both private and public institutional review boards (IRBs) for "being too complicated" (quoted in [21]). Thus, the expert advice sought seemed to suggest that his protocol was not suitable to test a meaningful therapeutic hypothesis with AD patients.

The journal *Aging*, which published Bredesen's protocol [17, 18], claims to adhere to guidelines elaborated by the Committee on Publication Ethics (COPE) and the recommendations of the International Committee of Medical Journal Editors (ICMJE) [22]. Additionally, the journal welcomes editorials, research papers, theory articles, research perspectives, reviews, and mega-reviews and books, stipulating:

> All research involving humans and animals must have been approved by the authors' institutional review board or equivalent committee and that board named by the authors. In the case of human participants, informed consent must have been obtained and all clinical investigation must have been conducted according to the principles expressed in the Declaration of Helsinki. Authors should submit a statement from the ethics committee or institutional review board indicating their approval of the research. [23]

Yet it seems that in Bredesen's case, *Aging* has published a research paper without mention of its IRB rejection or any statement about consent. For contrast, one might refer to the "ethical and regulatory considerations" offered in Eliane Gluckman and colleagues' landmark paper on an innovative practice case study involving the transplantation of umbilical-cord blood to induce hematopoietic reconstitution in an anemic patient [24]. In publishing metabolic enhancement protocols for AD, the authors and platform are equally guilty of neglecting guidelines regarding interventions with human subjects.

Given both the apparent lack of precursory expert support for metabolic enhancement protocols in the form of IRB approval and the absence of any explicit demonstration of informed consent, these new non-validated interventions cannot, under the Declaration of Helsinki, be responsibly used to treat individual AD patients in clinical settings.

Communication ethics: Have authors and platforms responsibly reported the results of metabolic enhancement protocols?

In the lay press, Bredesen's 2017 published book *The End of Alzheimer's: The First Program to Prevent and Reverse Cognitive Decline* [25] is a *New York Times* and *Wall Street Journal* bestseller, with over 1500 positive reviews on Amazon.com. Within it, Bredesen claims that "progression to severe dementia has until now been inevitable, with nothing but bad news from every expert. The anti-Alzheimer's protocol my colleagues and I developed consigns that bleak dogma to the dustbins of history" [25, p. 11]. He claims to provide "scientific evidence" that supports his conclusions [25, p. 13]. The headline of a *CBN News* interview with Dr. Bredesen professes that "new research proves Alzheimer's symptoms can be reversed naturally" [26]. Bredesen is now Chief Science Officer of brain health at Apollo Health LLC, which "provides the only Bredesen-approved protocol for preventing, treating, and reversing Alzheimer's disease and cognitive decline" [27]. Their description credits him with showing the "first successful reversals of cognitive decline in Alzheimer's disease, published in 2014, 2016, and 2018" [28].

Within the scientific press, Bredesen et al. (2016) claim in their abstract that the magnitude of cognitive improvement using MEND is "unprecedented, providing additional objective evidence that this programmatic approach to cognitive decline is highly effective," and maintain that such results "have far-reaching implications for the treatment of Alzheimer's disease" [18]. Bredesen et al. (2018) echo the claim of "unprecedented improvements in cognition" using ReCODE [19].

We would expect to see robust, generalizable data supporting these strong claims; this is not so for the "scientific evidence" Bredesen quotes in his book. Given the risk of spreading misinformation, communication of results from NNVP is highly delicate. We argue that authors and platforms have overstated evidence in favor of metabolic enhancement protocols for AD.

For context, these protocols are based in functional medicine, whose proponents claim to address "root cause, rather than symptoms" with treatment that "targets the specific manifestations of disease in each individual" [29]. Unfortunately, functional medicine requires ordering several expensive, unvalidated diagnostic tests and measuring serum levels of dozens of micronutrients and cofactors, as well as prescribing "corrective" supplements. The American Academy of Family Physicians found that "a lack of accompanying evidence existed to support the practice of Functional Medicine" and observed some treatments to be "harmful and dangerous" (quoted in [30]). Proponents of functional medicine dismiss such criticism, contending that research models are unable "to test each individualized, patient-centered therapeutic plan that is tailored to a person with a unique combination of existing conditions, genetic influences, environmental exposures, and lifestyle choices" [31]. Bredesen et al. (2018) in turn criticize failed "monotherapeutic" pharmaceutical strategies for AD for "targeting the mediators (e.g., Aβ peptides) instead of the root causes (e.g., pathogens, toxins, and insulin resistance)," defending their "very different approach" that involves "addressing the many potential contributors to cognitive decline for each patient"—the apparent success of which "implies that the root cause(s) of the degenerative process are being targeted, and thus the process itself is impacted" [19].

However, the "each patient" individualism touted in the studies by Bredesen and colleagues [17, 18, 19] undermines their ability to demonstrate improvements. To begin with, all

evaluations in medicine require a basis for comparison: a treatment is better or worse than another or no treatment. Since the authors do not have a non-treatment (control) group and also use a radically individualized methodology, the only comparisons possible are between the same patients before and after their study. Yet the three papers provide only sparse descriptions of patients' cognitive decline. They do not convey how radical the changes due to the protocol were in patients' lives; all they allege is that the protocol helped them improve. Given the difficulty of establishing improvement using before-and-after longitudinal evaluations, contemporary medical method uses cross-sectional comparisons between treatment and non-treatment control groups in randomized controlled trials (RCTs) in order to infer causal claims about hopeful treatments and overcome uncertainty about their safety and efficacy [32].

Another problem is the lack of published selection criteria: the authors do not explain why certain patients' data were published and not others, and so a bias to publish data from patients who improved cannot be ruled out. The absence of controls also means that placebo/enrollment effects may be partly responsible for the improvements. Finally, there is no evidence that the studies were blinded so as to avoid bias when collecting or interpreting data. For these reasons, we do not agree that the authors have demonstrated the protocols to halt cognitive decline.

However, supposing patients did improve, making generalized claims requires some measurement consistency, which all three studies appear to lack. In Bredesen's 2014 study, only three out of ten patients' improvements from MEND are described in detail: patient 1 "noted that all of her symptoms had abated"; for patient 2, "his wife, co-workers, and he all noted improvement"; patient 3 "no longer needed her iPad for notes, and no longer needed to record conversations" [17]. While clinically relevant, such improvements are vague. The "status" of the rest of the patients is summarized primarily using one to three words: normal, improved, or

working (except patient 9 who also had "negative amyloid PET" and patient 10 whose status is "decline").

In their 2016 paper, Bredesen et al. describe ten patients' improvements from MEND and identify their apolipoprotein E (ApoE) genotype, a genetic risk factor for Alzheimer's [18]. However, in tabulating their treatment outcomes, each participant is described in terms of "subjective improvement," "marked subjective improvement," or (in one case) "clear subjective improvement," without any explicit operational distinction drawn between the descriptors (e.g., "marked" vs. "clear"). Moreover, the objective treatment outcomes listed are inconsistent and at times vague: patient 1 had "hippocampal volume increase"; patients 6 and 7 had improved mini-mental state exam (MMSE) scores; patient 9 had improved Montreal cognitive assessment (MoCA) scores; and patients 2–5, 8, and 10 all had general "neuropsychological testing improvement."

Similar issues surface in Bredesen and colleagues' 2018 presentation of 100 patients' results with ReCODE [19]. While only three cases are described in detail, the authors ostensibly tabulate participants' ApoE genotype, symptoms, diagnosis, evaluation, follow-up, and comments. Yet a closer look reveals that their table has numerous blanks—ApoE genotyping is not performed for twenty patients, symptoms are omitted for patient 50, twenty-eight patients have no reported evaluation, and patients 87 and 93 have no reported follow-up. Moreover, different evaluation and follow-up methods are used across individual patients without justification: for example, why are qEEG and MoCA used with patient 27, MRI and SLUMS used with patient 44, and FDG-PET and MMSE used with patient 76?[6] Additionally, the table

[6] For reference, the methods are respectively abbreviated as follows: quantitative electroencephalogram (qEEG), Montreal cognitive assessment (MoCA), magnetic

shows unexplained discrepancies between objective follow-up results and subjective assessments. In particular, patient 61 has a very low MoCA score which is seen to decrease ("MoCA 5 → Declined"), and yet the comment describes him as "vastly improved, conversing again, dressing himself, calling grandchildren by name, working again." That a patient with such a low MoCA score could be "working again" seems improbable without further explanation. It does not follow from individualized *treatment,* potentially justified by AD's complexity, that there is good reason for individualized *evaluation* of cognitive outcomes.

Ultimately, these functional-medicine–style individualized measures mean that patient improvements as a result of metabolic enhancement protocols cannot be generalized. Descriptions of subjective outcomes are opaque, and the reasons for use of different objective measurements are not made explicit. Furthermore, reliance on "subjective improvement" may skew the results insofar as decreasing awareness of cognitive decline is recognized as a marker of worsening early AD [33]. Finally, none of the papers contains statistical significance tests or a methods section, making the findings more difficult to reproduce and thereby undermining the principle that NNVP should be validated through research [7].

We therefore consider the claims made by Bredesen et al. [17, 18, 19] to be overstatement, given the paucity of supporting data consisting in case studies without selection/exclusion criteria, controls, blinding, consistent metrics, or significance tests. These statements violate paragraph 36 of Helsinki [8]. A further ethical dimension of the overstatement is its intention, which we cannot fully establish here [34].

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resonance imaging (MRI), Saint Louis University Mental Status (SLUMS), fluorodeoxyglucose-positron emission tomography (FDG-PET), and mini-mental state examination (MMSE).

Additionally, Bredesen and colleagues' 2018 paper was published in the *Journal of Alzheimer's Disease and Parkinsonism* [19], which is part of OMICS Publishing Group. OMICS has been recognized by Jeffrey Beall as a predatory Open-Access publisher [35], with PubMed Central blacklisting many OMICS publications [36]—indeed, the 2018 paper by Bredesen et al. is not indexed on PubMed. Regarding the other two papers [17, 18], *Aging* was listed by Beall as possibly predatory [37].

For an example of more balanced language with innovative interventions, take Tiia Ngandu and colleagues' 2015 Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER), in which 591 at-risk elderly individuals underwent a two-year multidomain intervention to prevent cognitive decline compared to a 599-person control group [38]. Finding statistically significant differences in cognition between these groups, the authors claim in their abstract that "findings from this large, long-term, randomised controlled trial *suggest* that a multidomain intervention *could* improve or maintain cognitive functioning in at-risk elderly people from the general population" [38] (our emphasis). This RCT was designed specifically to overcome uncertainty regarding treatment outcomes [32], allowing for synchronic comparisons and using consistent measures. Ngandu et al. used their protocol with 591 patients, in contrast to the 10 patients treated with MEND [18], and employed statistical methods to draw conclusions; and yet their language is still far more restrained than that of Bredesen and colleagues, whose 2016 claim to have findings of "unprecedented" magnitude is, incidentally, undermined by this study's existence.

Guidelines for more balanced communication already exist. For authors of observational studies, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative provides a twenty-two-item checklist concerning the title, abstract, methods, results,

and discussion of manuscripts before submission to journals [39]. We call on *Aging* and the *Journal of Alzheimer's Disease and Parkinsonism* as scientific platforms to respect the guidelines laid out by COPE and the recommendations of the ICMJE, both of which (as mentioned above) *Aging* already purports to adhere to [22]. For lay platforms, the Code of Ethics for the Society of Professional Journalists offers four principles: Seek truth and report it, minimize harm, act independently, and be accountable and transparent [40]. In table 1, we offer an example of an alternative to overstatements made by Bredesen [25] and one of his platforms in lay press (CBN News) [26].

Table 1. Improving overstatements for innovation in AD treatment.

Overstatement	**Suggested non-overstatement**
Source: Bredesen 2017 [25]	
Let me say this as clearly as I can: Alzheimer's disease can be prevented, and in many cases its associated cognitive decline can be reversed. For that is precisely what my colleagues and I have shown in peer-reviewed studies in leading medical journals—studies that, for the first time, describe exactly this remarkable result in patients.	Let me say this as clearly as I can: Alzheimer's disease could eventually be prevented, and in many cases its associated cognitive decline could be improved. I believe this because my colleagues and I have reported instances of cognitive improvement in patients adhering to a metabolic enhancement protocol in published observational studies.
Source: CBN News 2019 [26]	
New research proves Alzheimer's symptoms can be reversed naturally	Observational studies suggest complex protocol might improve Alzheimer's symptoms

Public health ethics: Should metabolic enhancement protocols be made widely available based on current evidence?

We cannot support widespread use of metabolic enhancement protocols in the regular health care of AD patients for reasons that are evidential, financial, and informational.

To start, useful treatments are "intervention ensembles"—that is, not only materials (e.g., a drug), but also information (e.g., dose, scheduling, secondary effects) about the practices that make them safe and efficacious [41]. Given the number of variables involved in these protocols, confecting a useful intervention ensemble—via diet, fasting, rigorous exercise, dozens of supplements—for each AD patient is a colossal undertaking. Bredesen recognizes its complexity, calling it a "silver buckshot" approach [21]. These exacting lifestyle changes could be justified by their potential to deliver therapeutic fruits, but we argue that the current evidence base does not support the likelihood of such outcomes for this treatment-resistant population.

Bredesen nevertheless claims in chapter 1 of his book that "if enough people adopt ReCODE, the consequences would ripple across the nation and the world, cutting medical costs by many billions of dollars a year, preventing Medicare's bankruptcy, reducing the global burden of dementia, and enhancing longevity. All of these are feasible" [25, p. 15]. While we recognize the importance of general lifestyle interventions for overall health and improvement of disease prognosis, these specific claims are unfounded. There are an estimated 5.8 million people over 65 living with AD in the United States in 2020 [42], and Bredesen speculates that there are around 75 million Americans at risk of AD by virtue of having the ε4 version of the ApoE gene [25, p. 100], a gene involved in cholesterol metabolism. The basic cost of procuring an initial one-time ReCODE report runs between $1,090 (at a laboratory facility) and $1,245 (for a mobile blood draw) [20]. For every at-risk patient to receive such a report would therefore cost approximately $82–$93 billion, around 13–14% of the $644 billion Medicare budget in 2019 [43, p. 19]. The cost of dietary supplements alone "may range from $150 to $450 per month" [20]. At a $300 average, that would cost $22.5 billion per month, over 40% of the monthly 2019 Medicare budget. Furthermore, a preliminary look at the online customer reviews of Bredesen's

book suggests the possibility for greater individual financial harm, with a one-star review reading: “We paid 30k [to] be part of the official immersion training program and have spent thousands more implementing the protocol. We have not had success and none of the other patients we are in touch with have either” [44].

Even correcting the above figures to take into account economy of a scalable protocol, these measures still have a serious potential for financial harm at the individual and federal levels, while also exploiting the hope of patients and their families with low probability of success. We consider multidomain AD interventions using RCT methodology, such as those in the World-Wide FINGERS network [45]—whose US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER) is led by the Alzheimer’s Association [46], the largest non-profit organization funding AD research—to present a superior alternative.

Furthermore, we argue that it is unreasonable to expect patients or legal representatives to evaluate the data supporting claims made by a neurologist, so metabolic enhancement protocols cannot currently be used with informed consent insofar as overstatements by their authors have given rise to misinformation. The way that terms like “innovation” are deployed has been shown to affect participants’ understanding of experimental treatments and thereby their ability to offer informed consent [47].

Due to the potential for financial harm and false hope, granting individual patients responsible access to the interventions advanced by Bredesen and colleagues would require extensive communication of these protocols’ evidential limitations to the different stakeholders. Eligible patients should also be made aware of alternative programs, specifically actively recruiting RCTs, so that widespread NNVP does not crowd out more generalizable research [10,

11, 14]. Notably, the ReCODE clinical trial registered in ClinicalTrials.gov in March 2019, which is slated for completion in December 2020 (NCT03883633), is another case-only observational study [48]. In its current state, we would consider widespread adoption of the protocol by clinicians an unfortunate instance of what Jake Earl calls "runaway diffusion" [9], leading to the frustration of generalizable knowledge based on RCTs [14].

Conclusion and guidelines for responsible innovation in treating AD

Generalizable therapeutic interventions are desperately needed for AD, for which no disease-modifying treatment currently exists. Solutions may well come from multidomain interventions addressing the multifactorial nature of AD; however, individualized metabolic enhancement protocols, an innovative practice we examined, do not have robust evidence to support their use in general health care. Nevertheless, despite the protocols' having ostensibly been rejected for RCT testing by IRBs, their authors have published data from observational studies and made overstatements about their efficacy in the scientific and lay press, which has led to interest towards the approach from lay platforms and non-experts [49]. We call upon authors and platforms (both scientific and lay press) to adhere to ethical codes regulating communication within their field.

Furthermore, there are more generalizable alternatives: multidomain FINGER prevention studies are recruiting, and many hopeful pharmacological treatments are in the AD pipeline. Further promotion of metabolic enhancement protocols risks deceiving hopeful stakeholders, causing financial harm, undermining informed consent, and crowding out sound research pathways.

We conclude by proposing more stringent criteria for innovation than those laid out in the Declaration of Helsinki, which attempt to address the risks that we have identified in this article

(table 2). Our proposal is inspired by a narrow selection of ethical works on the use of innovative practice [7], unproven interventions outside clinical trials [50], and first-in-human use [51]. As a disclaimer, our proposed modifications are a limited and incomplete attempt to capture important criteria in an alternative way. In this way, they are meant neither to replace paragraph 37 of the Declaration of Helsinki nor to be used in real-world ethical evaluation of innovative practice. For this, the relevant authorities and medical associations should develop a complete set of ethical guidelines for responsible innovative practice. It is our hope that the criteria we advance here will add impetus to such development, while encouraging critical examination of new non-validated practice in the treatment of Alzheimer's disease and other diseases that presently lack disease-modifying therapies.

Table 2. Proposed adaptations to paragraph 37 of the Declaration of Helsinki regarding "use of unproven interventions in clinical practice" for responsible innovative practice for Alzheimer's disease treatment

Original	In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.
Proposed modifications	**1. Priority of research over innovative practice** In the treatment of an individual patient with Alzheimer's disease, where proven interventions do not exist or other known interventions have been ineffective, the physician, recognizing the need for generalizable solutions for this large treatment-resistant patient population, should first (i) suggest enrollment in actively recruiting randomized controlled trials (RCTs) or (ii) seek institutional review board (IRB) approval for an RCT of a hopeful but non-validated treatment, adhering to classical research pathways and guidelines. **2. Independent regulatory and ethical oversight** However, if an IRB rejects RCT testing of the non-validated treatment, and it is impossible or infeasible to enroll the patient in other RCTs (e.g., no ongoing eligible trials, prohibitive distance to trial site), then relevant national regulatory agencies (or other appropriate health authorities) and IRBs (or other appropriate ethics committees without conflicts of interest and with the capability to evaluate scientific evidence and perform a benefit–harm assessment of the intervention) may nevertheless approve the treatment's use in a monitored protocol of practice with unproven interventions. This use should not foreseeably hinder or interfere with the initiation, conduct, or completion, of present or future clinical AD research. The evaluative capacities of appropriate authorities and committees should be proportional to the degree of uncertainty or risk and previous experience with the use of the proposed intervention: higher uncertainty and risk, and less experience with an unproven intervention, will require that reviewers have greater and more nuanced capacities for evaluating pre-clinical and scientific data. **3. Risk minimization** This activity should be performed in an institutional context with appropriate resources to ensure that risks can be minimized. **4. Consent process**

	With informed consent from the patient and a legally authorized representative, or with only the legally authorized representative's consent where national regulations allow it, the physician may use an unproven intervention if in the physician's judgement—if and only if not contradicted by an IRB or appropriate independent committee—it offers hope of saving life, re-establishing health or alleviating suffering. The informed consent form should communicate at least the intervention's and protocol's evidential limitations and main therapeutic intention, the existence of validated interventions or available recruiting RCTs as alternatives, risks and potential benefits, the patient's right to discontinue or refuse the intervention, anticipation of new evidence that may require the intervention to be paused or stopped, and whether patient insurance coverage is unaffected or the patient knowingly chooses self-payment, as well as additional consent for use of data for future research, measures to protect patient privacy, and any other relevant information needed for a valid consent process according to the IRB or appropriate ethics committee. The consent process should be continuous, and patients and representatives should be informed of any change in the evidence that significantly affects the relative risk and potential benefit profile of the intervention. **5. Registry, data gathering, transparency, and good publishing practices** Data from monitored protocols of practice with unproven interventions, along with IRB or other appropriate independent committee decisions (e.g., rejection of research but approval of practice), should be registered, documented, and subsequently published as observational research, respecting guidelines for observational studies (such as the STROBE initiative) to minimize the risk of overstatement in the scientific press. In all cases, new information must be recorded, and an accountable third party should approve lay press publication. National research registries or other appropriate registries should allow for registration of monitored protocols of practice with unproven interventions, and such protocols should clearly be distinguished from generalizable AD research protocols. **6. Transition to research** Finally, if the observational data appear promising (e.g., if the treatment outcomes are statistically significant), a new IRB review can be sought in order to undertake generalizable research designed to evaluate the treatment's safety and efficacy.

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Chapter Six: Health, wealth, and responsibility in dementia prevention post-Covid-19

Timothy Daly[1], Raffaella Migliaccio[2,3,4], Stéphane Epelbaum[2,4,5]

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1 – Sorbonne Université, Science Norms Democracy, UMR 8011, Paris, France. Corresponding e-mail: timothy.daly@paris-sorbonne.fr.
2 Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, Inserm, CNRS, APHP, Hôpital de la Pitié Salpêtrière, Paris, France
3 FrontLab, ICM, Paris, France.
4 AP-HP, Hôpital de la Pitié Salpêtrière, Institute of Memory and Alzheimer's Disease (IM2A), Centre of Excellence of Neurodegenerative Disease (CoEN), National Reference Centre for Rare and Early Dementias, Department of Neurology, Paris, France.
5 Inria, Aramis project-team, Inria-APHP collaboration, Paris, France.

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Abstract

There is a move within dementia research and government policy in many countries to increase individuals' resilience to dementia by taking action against modifiable risk factors. But the available evidence suggesting that individuals who decide to undertake healthy lifestyle actions can significantly reduce their individual risk is weak. So we cannot say that it is their moral responsibility to undertake them. Focusing only on lifestyle interventions may detract from social determinants of health and growing health disparities exacerbated by the Covid-19 pandemic. A "resilience-friendly" society should encourage not only lifestyle actions but also wide-reaching research into and action against barriers to resilience across the lifetime.

Introduction

It is becoming increasingly accepted that drug interventions for Alzheimer's disease (AD), the leading cause of dementia, will need to be used early to be effective. But doing so in people without the symptoms of dementia poses a number of ethical issues (*96*). There is a corresponding shift in dementia research away from targeting AD pathology (ADP) to the study of what makes people resilient to ADP and other lesions to be found in the aging brain.

Authors of a large meta-analysis of observational studies propose that resilience to dementia might depend on modifiable risk factors and that 40% of dementia cases might be prevented by taking action against 12 of them across the lifetime (*36*): early life (less education), midlife (hearing loss, brain injury, hypertension, alcohol consumption, obesity), late life (smoking, depression, social isolation, physical inactivity, diabetes, air pollution).

According to the World Health Organization's Global Dementia Observatory, there are now 27 countries with national dementia risk-reduction campaigns as of August 2021. Action against risk factors represents a major potential public health opportunity but there is a need for ethical reflection so as to respect individual autonomy and reduce stigmatization (*95*). Here, we continue this reflection by offering a broad understanding of contributors to resilience to dementia and identifying obstacles on the way to a "resilience-friendly" society following the Covid-19 pandemic that has exacerbated health disparities.

1 Resilience depends on lifelong physical, mental and social health

Resilience describes the finding that tissue damage and/or biological indicators of it do not always correlate directly with clinical disease severity (*97*). Resilience to dementia is understood as the phenomenon that some individuals with significant brain pathology (particularly ADP) maintain cognitive function in spite of it. The elderly brain contains many different, concurrent lesions which affect the clinical presentation and progression of different diseases. AD itself progresses in a very heterogeneous manner between patients and there are also phenotypes with

different aggressiveness including “atypical focal variants” where patients often present with isolated disturbances of language or visuo-spatial functions and a less aggressive clinical profile (*98*).

Dementia was until quite recently called “senility” which stigmatized the elderly and framed cognitive decline as inevitable (*34*). The emphasis placed on later life also detracts from findings suggesting that development and later degeneration are closely related. While there is genetic risk for AD including aggressive deterministic mutations involving ADP which run in families and the Apoe4 lipoprotein involved in cholesterol metabolism (*99*), we will argue that resilience to dementia depends on broader aspects of physical, mental, and social health.

“Less education” is cited by Livingston et al. (2020) as an early-life modifiable risk factor for later dementia. There are different reasons as to why young individuals may have lower education or reap less rewards from it. Having better cognitive abilities in early life makes for more resilience to dementia later (*100*). This may partly be determined by the richness of the environment to which children are exposed (*101*), including the amount of words they hear on a daily basis (*102*). People with learning disabilities and dyslexia have a higher risk of developing atypical language-heavy variants of AD later in life (*103*).

Beyond early-life cognitive function, Livingston et al. identify aspects of physical (e.g. midlife obesity and hypertension) and mental health (e.g. late-life depression). The three dimensions of social health (*104*) have also been applied to dementia: “(1) capacity to fulfil potential and obligations; (2) ability to manage life with some degree of independence; (3) participation in social activities” (*105*). The late-life risk factor of social isolation identified by Livingston et al. (2020) suggests that the concept of social health applies not just to people diagnosed with dementia but is also a key component of resilience.

Taken together, to improve lifelong brain health and thereby build resilience to dementia, aspects of physical, mental, and social health should be considered, as should identifying specific learning disabilities and also ensuring access to rich environments.

2 Responsibility and wealth in reducing dementia risk

"Little evidence exists for any single specific activity protecting against dementia" (p. 413, (Livingston et al., 2020)). Evidence in favour of specific activities comes from multi-domain lifestyle interventions. The Finnish Geriatric "FINGER" study was a 2-year multi-domain physical and cognitive interventional trial with people aged 60-77 (*89*). The intervention consisted of nutritional guidance; exercise; cognitive training and social activity; and management of metabolic and vascular risk factors. Controls received regular health advice only. The intervention led to "a small group reduction in cognitive decline" (p. 426, Livingston et al. 2020) in the approximately 600 cognitively at-risk people vs. controls. However, it has not been replicated by similar studies: the French Multi-domain Alzheimer's Prevention Trial ("MAPT") with omega-3 supplementation and lifestyle intervention and the Dutch "Prevention of dementia by intensive vascular care" (PreDIVA) studies did not find significant beneficial effects on cognition of these interventions in people of similar ages.

Taken together, the available evidence suggesting that individuals who decide to undertake healthy lifestyle actions can significantly reduce their individual risk is weak. So we cannot say that it is their moral responsibility to do so or that they are blameworthy if they do not. Yet they might decide to take part based on a responsibility they have towards *themselves*. This has been called prudential responsibility: "to the extent that health is instrumental for well-being … maintenance of a certain level of health is (all-things-considered) rational for many agents, given their pleasures and plans" (pp. 120-121, (*106*)).

Focusing only on individuals' participation in lifestyle interventions for reducing dementia risk may distract from a huge determinant of health: wealth. It is well documented that worse health outcomes are much more common amongst the poor (*107*). It is not clear whether the protection against dementia offered by wealth depends on aspects of lifestyle or not (*108*) but lifestyle activities may "play a minimal role as mediators between low socio-economic status (SES) and dementia" (*109*). Actually reducing dementia risk may require improving SES. Returning to education, a recent study of educational reform "that extended primary education by 1 year for 70% of the population between 1936 and 1949" in a sample of over a million Swedish concluded that "without mediation through adult socioeconomic position, education cannot be uncritically considered a modifiable risk factor for dementia" (*93*). And "in an English nationally representative sample … the association between SES and dementia incidence in a contemporary cohort of older adults may be driven by wealth rather than education" (*110*).

The wealth-brain health link makes sense if low SES leads to an impoverished physical, mental, and social environment for individuals. However, there is an unfortunate trend mentioned in the public health literature towards what is known as "lifestyle drift" which describes "how broad policy initiatives for tackling inequalities in health … start off with social determinants (upstream) … [and] drift downstream to largely individual lifestyle factors" (*111*).

Governments promoting dementia risk reduction should be careful to avoid shifting responsibility to individuals through the convenient locus of lifestyle factors. The wealth-brain health link suggests that more efforts should be directed towards social determinants of health.

3 The post Covid-19 world could create a perfect storm for dementia.

(*112*) argue that "Post covid-19, we must build back fairer" to reduce major and growing health disparities. In the case of dementia, a society with reduced social interaction, growing wealth disparities, and an overly individualistic view of responsibility for one's health could make a physically, mentally, and socially healthy society a far-off objective. We echo a recent Lancet Neurology editorial which argues that, "Amid competing priorities, dementia must not be forgotten … Governments need to do more

to prevent dementia, and to tackle inequalities that are potential barriers to prevention (eg, ensuring people have access to affordable, healthy food, rather than just encouraging them to eat healthily)" (p. 685, (*113*).

Conclusion

We argue that for dementia risk-reduction campaigns to ethically promote resilience to dementia they must go beyond promoting healthy lifestyles to identifying and overcoming barriers to physical, mental, and social health of members of society. There has been significant government involvement in making a "dementia-friendly" society a reality (*114*). The momentum gained from these efforts could be extended to the promotion of a "resilience-friendly" society.

This would require elected leaders encouraging research to identify and overcome barriers to resilience in a society with growing health disparities. Governments should encourage and facilitate access to enriched environments to maximise physical, mental, and social health across the lifetime. This would require building and adapting more parks, community centres for all age groups with mentally and socially stimulating activities, campaigns against lifelong loneliness, and making affordable, healthy food available in schools, supermarkets and residential centres.

Finally, risk reduction is not absolute, and so there must be continued funding into pharmacological and non-pharmacological treatments for dementia to ensure that those who already have and those who will develop the condition are not left behind.

Chapter Seven: The accelerated approval of aducanumab invites a rethink of the current model of drug development for Alzheimer's disease

Timothy Daly1, Stéphane Epelbaum2,3

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1 Sorbonne Université, Science Norms Democracy, UMR 8011 Paris, France
2 Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, Inserm, CNRS, APHP, Hôpital de la Pitié Salpêtrière, Paris, France
3 AP-HP, Hôpital de la Pitié Salpêtrière, Institute of Memory and Alzheimer's Disease (IM2A), Centre of Excellence of Neurodegenerative Disease (CoEN), National Reference Centre for Rare and Early Dementias, Department of Neurology, Paris, France.

It is a tale of two Pfizers. In 2018 they abandoned research into the leading cause of dementia, Alzheimer's Disease (AD) (*27*). In 2021, they developed the first vaccine for Covid-19 to receive full approval from the United States Food and Drug Administration (FDA) only 530 days after the World Health Organization declared Covid-19 a pandemic. Fernandez Lynch et al. (2021) argue that three factors have made for such rapid progress in the prevention and treatment of Covid-19 as compared to other serious diseases: beyond massive societal impact, there is also high perceived personal risk, and actionable biology (*115*). Nevertheless, in this historic year for medicine, on June 7th 2021, Biogen/Eisai's Aduhelm (aducanumab) received controversial FDA accelerated approval. This is not the first time a drug for AD has received some form of FDA approval. But previously approved drugs only treat the symptoms of AD by altering neurotransmission in the already degenerating brain. And the last one to be approved—Memantine—was approved in 2003. Aducanumab is the first potential disease-modifying treatment (DMT) for use in mild AD following decades of unsuccessful trials with similar therapies.

We will argue that the complexity of AD calls for a new economic model of drug development for AD. The current model for AD is short-term, high risk, and high reward. It costs

approximately 5.7 billion USD to bring a drug to market for this condition (*26*). The pharmaceutical company that brings the first DMT to market stands to make an astronomical return on this investment through monopolised patents for use in millions of potential patients. The dominant strategies for finding a cure for AD are supported by a therapeutic model using precision drugs funded by short-term investments, with the hope that the target will deliver therapeutic rewards. But when the clinical trial of a highly anticipated AD treatment fails, the stock market value of the pharmaceutical company that developed it loses up to 40% overnight (*15*).

Like many other hopeful trials before it, aducanumab is directed at the protein beta-amyloid that accumulates in the brains of AD patients but also in healthy elderly people. The therapeutic value of targeting amyloid is still disputed 20 years after the first trials started in the early 2000s. The fact that dozens of anti-amyloid trials have taken place in AD patients despite the lack of disease-modifying effect is a testament to the dominance of the "amyloid cascade hypothesis" (ACH) (*37*). According to the ACH, the protein beta-amyloid accumulates in the brain and triggers a cascade of pathophysiological events leading to neurodegeneration and later dementia.

Given the lack of progress in finding a DMT with anti-amyloid treatments, some researchers advocate a shift to other molecular targets, none of which has however been validated despite an increasingly diverse "drug pipeline" for AD (*84*). This means that AD can be understood in a multiplicity of ways as a growing list of contributions to dementia is discovered by researchers (Herrup, 2015). There is a particularly strong shift towards the promotion of lifestyle interventions based on observational evidence suggesting that certain activities and diets might protect the ageing brain (*36, 83*). In the meanwhile, patients are left without any DMT, and are

resorting to the use of non-validated “alternative” therapeutic protocols which may be causing harm (*60*).

It is therefore a context of crisis in which the FDA accelerated approval of aducanumab has taken place. However, unfortunately the data on aducanumab do not provide a definitive answer to the validity of anti-amyloid strategies and only seem to be further dividing the community.

Two phase III trials of aducanumab in AD patients—“ENGAGE” and “EMERGE”—were halted in March 2019 because of the apparently futile results they provided. Aducanumab clearly reduced levels of beta-amyloid but it did not appear to meaningfully slow down cognitive decline in patients. Yet later that year Biogen researchers undertook another analysis in which they excluded participants with a very aggressive disease progression from the ENGAGE trial data. This made it look like high-dose aducanumab could slow down mild AD. They made a case for FDA approval and got accelerated approval for use in mild AD on June 7th, 2021. Whether or not the Biogen data are convincing or overly massaged is a major point of controversy.

Many fingers are pointed at the FDA and patient association groups such as the Alzheimer’s Association for the pressure they put on approval. Yet the FDA’s accelerated approval programme was designed to "allow for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint … that is thought to predict clinical benefit, but is not itself a measure of clinical benefit" (*116*). What seems central to the debate around the soundness of the FDA’s decision amongst scientists is whether lowering beta-amyloid is thought to predict clinical benefit.

But solving the relationship between beta-amyloid and clinical benefit is a quest going back centuries. Before the neuropathology of AD could be targeted, pathologists such as Dr. Alzheimer in the late 19th century studied correlations between post-mortem “senile plaques”

made up of beta-amyloid and the severity of dementia the plaques were thought to cause. The question still rages on today with the use of in vivo biomarkers which can measure AD neuropathology. But while these markers may be useful for deciding who gets enrolled in an anti-amyloid clinical trial for research purposes, they do not provide a perfect predictor of who will develop AD, leading to a host of ethical problems in clinical practice (*117*).

In short, is lowering beta-amyloid thought to predict clinical benefit? It depends on who you ask in a diverse, divided research community. The results of a recent survey with AD researchers suggests that as of 2019, 22% were still "pro-ACH" and therefore in favour of strategies lowering levels of beta-amyloid in the brain (*83*).

Here we do not attempt to assess the validity of the FDA's complex decision, nor argue that the AD field should prioritise such and such a theory or therapy. Instead, we seek to propose an alternative model of funding drug development which might offer several benefits.

The model relies on increased collaboration between governments and industry, which is one of the lessons that Fernandez Lynch et al. (2021) argue can be applied from the Covid-19 pandemic to other serious diseases. The reason there is need for such a model is due to the mismatch between the disease course of AD and the economic time course of current drug development. The disease sets in silently over decades before being diagnosed. Yet the current economic model only allows for 12-18 month short-term trials, most of which have historically taken place in patients who already have symptoms of dementia, which is thought to represent a later disease stage where irreversible damage has already been done to the brain.

Risk and reward are factors at play in motivating industry to develop drugs for AD. One ethical problem resulting from the FDA accelerated approval is the idea that Biogen reap economic rewards without Aduhelm having therapeutic impact (*32*). So unearned reward might be an issue.

Furthermore, if too much risk is what dissuades industry from drug development for AD then public funds could be used to alter the risk-reward profile of drug development for AD. So instead of high-risk, high-reward, then lower-risk, lower-reward.

In this model, the state would help cover the costs of research and development for a hopeful drug to be tested long-term in the right patients, as early as ethically possible (*96*). The developer of the drug would then agree to offer the drug at a reduced price following validation of its safety and efficacy. If the drug doesn't work, then it is the state who foots the bill. If the drug does work, then it is the developer who sacrifices profits.

Given the fact that AD appears to be very resistant to treatments, many trials would need to take place. This would inevitably require more government—and thus taxpayer—funding of AD drug development. But AD is already a growing health problem that costs up to 1% of global GDP and the majority of the care and financial burden falls on sufferers' families to bear (*118*).

Despite its costs, the model could provide clear benefits for drug approval in AD. The pressure of this devastating disease with unmet need and the use of imperfect surrogate endpoints will always make for complicated decisionmaking in the accelerated approval pathway. But this model would reduce pressure on this pathway to act as an investment magnet to dissuade companies from following Pfizer's exit example. Concurrently, the trials themselves would provide much more useful feedback for researchers to know whether a target delivers on its therapeutic promise and therefore narrow down more valuable targets.

There is promising work being done in this direction. The Alzheimer's Clinical Trials Consortium (ACTC) is a cooperative agreement between the National Institute of Aging (NIA) and academia which funds innovative trials into AD in partnership with industry. Alongside the pharmaceutical company Eisai, the ACTC is involved in running the the AHEAD 3-45

randomised clinical trial (NCT04468659). This trial will go on for 216 weeks and will use Lecanemab (BAN2401) which targets beta-amyloid. The study will compare the effects of Lecanemab vs. placebo on cognition and beta-amyloid levels in people with early *in vivo* signs of beta-amyloid accumulation in their brain.

This kind of arrangement is a necessary first step to getting useful feedback on targeting amyloid. It is not perfect: trials may need to go on even longer than 4 years to decades so as to better reflect the disease time-course (*119*). Furthermore, a more democratic view of AD research which better reflects the popular vote of researchers may require concerted efforts to move beyond the dominance of amyloid as a therapeutic target for AD (*83*). But what is essential to the point made here is not so much the target as the trial testing it. More collaboration between governments and industry could help to free the power of pharmaceutical innovation from economic short-sightedness, allowing for promising, expensive trials to be undertaken long enough so that real efficacy and safety profiles can be established for much-needed treatments for a growing number of patients.

Conclusion

The title of this PhD is *Alzheimer's disease: Epistemology, ethics, innovation.* It was was inspired by the PhD of the French philosopher Fabrice Gzil, *Philosophical Problems Raised by Alzheimer's Disease: History of science, Epistemology, Ethics* (Gzil 2008). Epistemology and ethics have been key to understanding contemporary research. The history of science has played a more modest role in this thesis in identifying key concepts to understand contemporary issues. The introduction first sought to establish that this once rare clinicopathological entity is now seen as a major threat to public health. Secondly, that the amyloid research agenda is the dominant approach to explaining the disease and finding a disease-modifying treatment. Finally, that issues arising from recent definitions of the disease and the failure of anti-amyloid strategies have led to disease-modifying approaches being mostly split between the targeting of AD neuropathology and the promotion of resilience to dementia. Beyond the title, the approach adopted in which Gzil studied the complex object of Alzheimer's disease from several philosophical angles was necessary inspiration for me to undertake this thesis in the way I have done.

Part One provided two different empirical perspectives on the dominance enjoyed by the amyloid cascade hypothesis (ACH) in biomedical research into Alzheimer's Disease (AD). Their differences are suggestive of the complexity of the broader landscape of AD research that goes well beyond the published scientific literature.

The bibliometric study suggests that citation practices of the ACH are nuanced, with no problematic positivity in citations of the original formulation of the ACH to be found in Hardy & Higgins (J.A. Hardy and Higgins 1992) (HH92). Scientists tended to cite this version neutrally as they recognised the evolving nature of the "research agenda" based on the ACH which posits a central role for amyloid-beta in the pathogenesis of AD. Those newer versions of the agenda were indeed cited more favourably than the original formulation found in HH92.

This suggests that research into amyloid and Alzheimer's disease can indeed be usefully understood in light of the auxiliary hypotheses of the amyloid research agenda as a Lakatosian research programme as defended in the Introduction. The "amyloid-beta --> AD" relationship is still taken to guide research, although the specifics of that relationship are subject to being updated in the light of empirical investigation, such as elucidating which chemical species of amyloid are involved, via what mechanism, and with details of the disease's complex time course still under active investigation (J. Hardy and Selkoe 2002; Selkoe and Hardy 2016).

Moreover, the finding that 89% of our sample of empirical articles (N=110) came to a pro-ACH conclusion based on testing the ACH's claims or related observations suggests that pro-ACH citations in those articles are justified. Claims of "herd-like behaviour" are not substantiated by empirical investigation of citation practices carried out amongst scientists themselves. These findings indicate that the community-level ethos of scientists working on AD appears to be intact according to this bibliometric study. However, this does not mean that there is no "herd-like" behaviour to be found elsewhere in the larger AD community, nor cases of individuals violating professional codes of ethics (see the Higgins example in the Discussion of Chapter One, and see Part Three).

This community is indeed large - over 33,000 people from over 160 countries attended the Alzheimer's Association International Congress (AAIC) in 2020, and it seems reasonable to posit that there are complexities within such a community that go well beyond the published scientific literature and citation practices within it. When 173 researchers in 2019 answered questions about theories and therapies of AD, only 22% appeared to be "pro-ACH". There are several ways of interpreting this finding, however it is not surprising in view of the proportion of clinical trials testing anti-amyloid agents compared to those trials testing agents based on other

hypotheses. Figure 1 of Liu et al.'s "History and progress of hypotheses and clinical trials for Alzheimer's disease" (Liu et al. 2019) shows that 22.3% of trials up to 2019 had been based on the ACH, the hypothesis attracting most funding. Interestingly, the survey indicated that some researchers were more optimistic about anti-tau therapies and lifestyle interventions than anti-amyloid treatments. The majority of study participants—even the majority of pro-ACH responders—argued that there was problematic adherence to the ACH to be found in parts of the AD research community. This has implications for the level of publishing and funding policies that might unduly influence priority setting in the biomedical AD research community. This survey is however only reflecting the 2019 opinions of researchers. Those who filled out the survey did it before the accelerated approval of Aducanumab by the FDA and original results with Lecanemab and Donanemab were available. In this evermoving field of biomedical research it is somewhat difficult to keep track of the AD research community attitude towards the pathophysiology and best therapeutic venue against AD.

The use of these two empirical tools to study the place of the ACH was limited by both the small sample of articles in the bibliometrics study, as well as the number of researchers approached in the survey. Nonetheless, the study shows how complex the question of reliance on the ACH theory is, while offering avenues for further research into this theory and others. Indeed, this study has shown the potential of using empirical tools, such as bibliometrics and surveys, to garner information from researchers and to analyse their behaviour. Interestingly, researchers at University College London (UCL) have joined with the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) to promote a survey among current and former Early Career Researchers (ECRs) in dementia research to identify barriers facing such ECRs.

The approach in Part Two was inspired by what Pradeu et al. (2021) (Pradeu et al. 2021) term "Philosophy in Science" ('PinS') in which researchers "use philosophical tools to address scientific problems and to provide scientifically useful proposals." The scientific problem is as follows: Since targeting amyloid deposition in AD patients—the most hopeful DAP—has not yet proven entirely fruitful (aducanumab's recent accelerated approval by the FDA notwithstanding), and there is no other validated disease-modifying treatment for AD, how can decisions around priority setting be made with the "long list of disease-causing options?" The conceptual analysis of association offered here is the tool we propose to provide one answer.

Herrup (Herrup 2015)'s case for rejecting the ACH can be summarised as follows: there is good reason to believe that the linear model linking amyloid and AD (i.e. the "driver" disease scenario from (Karran, Mercken, and De Strooper 2011) has been refuted. Thus, we should reject the ACH. What is meant in heuristic terms is as follows. As for the positive heuristic, amyloid-centric thinking should no longer be used as a prism through which to understand other associations: perhaps other DAPs work via amyloid-independent mechanisms to contribute to a worsened disease prognosis. As for the negative heuristic, so the argument goes, all of the auxiliary hypotheses in the agenda have been refuted, and the problem facing the community is that there is no longer a central event to AD, and certainly not "amyloid deposition" (J. Hardy and Allsop 1991) (Hardy & Allsop, 1991).

The shift in the last 15 years of AD research from the heuristic value of finding mutations to the broader study of association (via GWAS and lifestyle) can be understood in light of the Lakatos research programme and the findings of Part One of this thesis. The future of research is less about a fork in the road (i.e. to reject or not to reject), and more about the *relevance* of the

original and later formulations of those hypotheses attributing a central role to amyloid in AD in light of the increasing complexity of AD revealed by the most recent experimental findings.

A more piecemeal therapeutic scheme is becoming increasingly likely, given this complexity. When basing treatments on the long-list of possible disease-causing options for AD—as identified in Herrup (2015), GWAS (Bellenguez et al. 2020), and lifestyle risk factors (Livingston et al. 2020)— it may indeed be necessary to "choose them all" (p. 797, Herrup, 2015) but we argue that if we "choose them all," it should be "one at a time." Simple tests mean minimising the number of auxiliary hypotheses about why a treatment does or does not work. By minimising the number of auxiliary hypotheses, more information can thus be garnered about treatment effects. Focusing too much on "hardware" (i.e. the *thing* in the treatment rather than the treatment setup as a whole) might lead to certain otherwise promising treatment avenues not being explored. It would be better to be more agnostic towards the source of treatment effect (whether pharmacological or non-pharmacological) and more rigorous about getting useful information to understand treatment effects and their absence.

A key theme in Part Three of the thesis was protecting the autonomy of people—at risk of, or already suffering from, dementia—from misinformation, moralisation, and less useful clinical trials. A major stake for a complex disease without treatment is how it is represented to the patient population. There are different sources of information about dementia—one's general practitioner, specialised neurologists and geriatricians, the media, and the Internet being major sources. The existence of the "Bredesen" protocol has certainly changed the representation of AD, since there is at least one world-renowned neurologist claiming that AD is reversible, that the "First Survivor's of Alzheimer's" (Bredesen 2021) already exist and the commercial success of his books and ever-evolving protocols stands in stark contrast to drug "failures" in more

conventional biomedical research. But unfortunately, these claims are based on testimony rather than science, and are examples of overstatement with major potential costs for the patient community. The promotion of these protocols for AD suggests the "need to revise the Helsinki Declaration" (Asplund and Hermerén 2017). Our proposal to update this declaration is based on the need for external review before offering experimental treatment, particularly if a clinician stands to make profit from it. But in the case of AD, increasing participation in rigorous research via randomised controlled trials is preferable to widespread use of non-validated treatments given the need for generalizable solutions for millions of patients. In his Open Peer Commentary on our article in *Theoretical Medicine and Bioethics*, Helgesson (Helgesson 2020) argues that waiting for external review in the cases of rare diseases is more ethically complicated.

The arrival of the Covid-19 pandemic has offered many lessons for the study of other diseases (Fernandez Lynch et al. 2021). Though Lynch and colleagues' argument focuses on drug access and development, the pandemic also saw the arrival of an 'infodemic' with various sources of misinformation about disease severity, transmission, and treatments, causing possible and actual harm to individuals and groups. The example of Dr. Bredesen's success shows that misinformation is a current and future problem facing dementia research.

The Covid-19 pandemic has also brought to the surface the prejudice to be found in attitudes towards the sick. This clearly happened in the case of HIV, labelled as a disease of the "other" (Brandt 1988). There have also been unfortunate cases of stigmatisation of those suffering from serious forms of Covid, as part of a mechanism of 'othering' the victim. For example, despite official figures showing the possible mortality associated with SARS-CoV-2 infection, Schmidt et al. (Schmidt et al. 2020) found "misconceptions of being protected against the virus or having low or no risk" in a qualitative survey. Such discourse could emerge in the context of dementia.

If there is widespread belief that dementia is fundamentally preventable and depends merely on lifestyle, this could lead to "blaming the victim" (p. 1379, (Steyaert et al. 2021). Chapter Six was an attempt to show that there are no good evidential grounds for moralising attitudes to dementia prevention. Stigmatisation, which is already rife towards diseases of the mind and brain, is a major barrier to better public health.

Finally, as Lynch et al. (2021) note, there are important lessons to be learnt from the Covid-19 pandemic for drug access and development. We argue in Chapter Seven that one possible lesson for AD drug development could be the use of government–industry partnerships to create a more stable economic model in which longer drug trials can take place. This could encourage necessary investment, ease pressure on the accelerated approval pathway for a disease with such complex biology, and in the case of anti-amyloid trials, provide better feedback on the disease scenarios offered by Karran et al. (2011). They would therefore be much more useful to the patient community.

There is no denying that a silver bullet-style approach to medicine focusing on local pathology has allowed humanity to make huge strides in public health, such as antibiotics, surgical interventions, and anticancer therapy. Yet such a targeted approach using "specific pharmacological strategies to lower amyloid β-protein levels as a way of treating or preventing all forms of the disease" (Selkoe 2007) has not yet seemed to fit well with the chronic, complex etiology of dementia. Lock (Lock 2013) argues that AD's complexity is such that it cannot be "wiped out" akin to an infectious disease and that we should favour a global political change to engage with the reality of aging (p. 242, ibid). In other words, solving the public health problem of dementia requires moving away from silver-bullet approaches to therapeutics (Caspi 2019). This can be applied both to the targeting of neuropathology and resilience promotion. For

example, despite the promise of the data and arguments from the Lancet commissions, lifestyle risk factors should not be seen as the next "silver bullet" for dementia, as the problem of lifestyle drift may distract away from studying health disparities which increase dementia risk and which also reduce participation in those lifestyle interventions designed to reduce it (Coley et al. 2021). One way of overcoming such thinking would be to focus on realigning research priorities away from pharmaceuticals and toward wide-scale social interventions (Stegenga 2018). But a broader approach cannot exclude those specific pharmacological strategies which may have as-yet untapped therapeutic potential.

In conclusion, there are three arguments to summarise this thesis on biomedical research into Alzheimer's disease (AD).

Firstly, since the initial formulation of the amyloid cascade hypothesis (ACH), scientific publishing and the problems associated with publishing norms has been a major contemporary influence on the generation and interpretation of information about Alzheimer's disease. Secondly, the alleged crisis in obtaining clinically-meaningful information should prompt a re-think about clinical translation. Thirdly, and finally, the image of Alzheimer's disease brought about by this situation should lead to a more democratic vision of dementia in science and society at large.

Scientists are the generators of scientific articles, as individuals or in groups. Certain published articles possess great influence, both within the research community and outside it. Since the original formulation of the ACH by Hardy and Higgins in 1992, there has been an explosion of research activity, as it provided the impetus for fruitful testing of predictions made about the role of beta-amyloid in AD and therapeutic attempts based upon it. Though these clinical trials are still on-going, the ACH still holds significant sway in the opinions' of researchers. The two

major approaches to preventing dementia—the targeting of AD neuropathology, and the promotion of resilience to dementia through multi-domain interventions—are based on highly-cited expert papers offering consensus definitions of their object of study and methods for how to take meaningful action in their approach. The publication of such research within basic science could be an important step towards a more coherent conceptual framework. Publishing norms may be stifling explanations of this complex disease by restricting the use of language used to "associate" biological processes and disease. Furthermore, publishing practices and editorial decisions are arguably playing a role in epistemic injustice against researchers working on more fringe theories. Nevertheless, the protocols of Dale Bredesen, while being a testament to the power of the published article (and misinformation), serve as a reminder of the need for researchers to respect the norms of publication within biomedical science, despite them being imperfect. There is also need to educate the general public and the lay press as to what constitutes genuine rigorous research and the problem of predatory publication practices. Education should also be extended to policymakers, who are not specialists in Alzheimer's disease research. For example, since 2018 in France, anticholinesterase inhibitors are no longer reimbursed by state healthcare, but most of the French specialists of the disease with whom I have spoken have criticised this decision.

The epistemology of the future of AD should be conducted in a global way by using data from all over the globe, be it published article or surveys. Even if the tools for such global analyses exist, there is still a great heterogeneity in the geographic origin of data in the AD community with a large predominance of it coming from the USA, followed by Europe and with a relatively smaller amount from Asia. Meanwhile, data from Africa on this research topic are still sparse. Efforts should be made by high income countries to promote research is lower income countries

to produce generalisable scientific claims for men and women everywhere. Furthermore, the spread of misinformation on dementia in other countries, particularly as they move towards national dementia plans sheet(WHO 2021), is a major stake.

There are many promising targets for discovering a disease-modifying therapy for Alzheimer's disease, providing many sources of therapeutic optimism for multiple researchers. But in general the last 20 years of research has been promising in theory but has not been shown to be promising in therapeutic trials. The explosion of research interest in beta-amyloid stands in stark contrast to the negative results obtained from clinical trials testing various anti-amyloid agents, though admittedly, these generally negative results may be changing with currently-tested antibodies, and better trials are being proposed to test disease scenarios and provide better feedback. The number of auxiliary hypotheses being tested in therapeutic trials for Alzheimer's disease underscores the need for experimental rigour, and fundamentally, this is the basis for the critique of Dr. Bredesen's protocol. Furthermore, it is likely that the disease's complexity will necessitate the gradual combination of different therapies. Just as drug trials are moving towards less optimistic endpoints (slowing down cognitive decline instead of stopping or reversing it), it is also apparent that multi-domain lifestyle interventions will also not be a 'silver bullet' and should not distract from the health disparities contributing to dementia risk.

The state of research into Alzheimer's disease is currently very dynamic but its image is fragile. Within research, clinical trials are a major source of controversy, and while there is disagreement about the extent to which they can be said to refute the claims of the amyloid research agenda, the recent accelerated approval of aducanumab is seen as an affront to scientific norms by some researchers (Karlawish and Grill 2021), and a necessary boost to research by others (Selkoe 2021). There is also a conceptual crisis: for defenders of resilience promotion, the importance of

Alzheimer's disease as a biologically-defined specific entity with an established biological definition is seriously questioned by the mixed nature of dementia in the elderly. Unfortunately, misinformation only serves to harm research into this major source of societal fear, whereas the complexity of the disease ought to make for greater collaboration. While it is essential to protect patients' autonomy from non-validated treatments and moralising interpretations of current evidence around interventions based on lifestyle risk factors, a more ambitious democratic vision of dementia is needed, both within research and in larger society. Research should be structured so as to avoid injustices against researchers working to find alternative cures for this disease based on different approaches, with the values of rigour and pluralism being respected. In addition, the role of dementia in larger society also needs to change, and recent research on lifestyle risk factors and health disparities should be regarded as evidence enough to show that society should not be viewed as a passive agent waiting for change from within the biomedical research community. Debates around priority setting with members of the patient community and representatives of larger society are sorely needed to determine how public money should be used to fund action against recognised health disparities and risk factors, and to fund more alternative trials of possible disease-modifying treatments. Trials should be designed in ways that reflect the reality of those who suffer from dementia, representative of people from all over the world and different societies (Manly and Glymour 2021).

In conclusion, the biological and societal complexity of Alzheimer's disease ought to mean that there should be no monopolies on approaches, and that the population at large, all potentially affected by this growing burden on public health, should be made agents of change to influence the direction of future research and policy changes.

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Introduction

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Maladie d'Alzheimer : Epistémologie, Ethique, Innovation

Résumé
La maladie d'Alzheimer (MA) est une source majeure de peur et d'incompréhension et est devenue une priorité de santé publique. Mais la recherche biomédicale menée sur elle a été marquée ces dernières décennies par des déceptions et des débats acharnés. Cette thèse en trois parties mobilise différentes méthodes pour étudier les controverses, explorer leurs conséquences et proposer des solutions.
La première partie est une étude empirique qui interroge la dominance de l'hypothèse amyloïde par le biais d'une analyse bibliométrique des pratiques de citation et un sondage international auprès des chercheurs promue par l'*Alzheimer's Association*. La deuxième partie emploie une approche conceptuelle pour envisager les recherches au-delà de l'hypothèse amyloïde—nous y proposons un modèle holistique visant à maximiser la qualité et la quantité d'informations utiles à la recherche et aux patients. La troisième partie explore l'éthique de l'inexistence de traitements validés et l'existence de traitements non validés avec l'objectif de protéger l'autonomie des personnes contre les traitements non-validés, les attitudes moralisatrices à l'égard de la prévention, et un modèle économique fragile qui sous-tend le développement des médicaments.
Nous soutenons que la complexité tant biologique que sociétale de cette maladie échappe à tout réductionnisme et monopole, et que la population dans son ensemble, toutes potentiellement affectées par les nombreux problèmes posés par la MA pour le bien-être et la justice, devrait devenir des agents du changement afin d'influencer la direction des recherches et politiques futures.

Mots-clés : philosophie ; alzheimer ; maladie d'Alzheimer ; épistémologie ; éthique ; innovation ; prévention ; philosophie des sciences ; philosophie de la médecine ; Karl Popper ; Imre Lakatos

Alzheimer's Disease: Epistemology, Ethics, Innovation

Summary
Alzheimer's disease (AD) is a major source of fear and misunderstanding and has become a public health priority. But biomedical research on AD has been marked by disappointment and fierce debate in recent decades. This three-part thesis mobilises different methods to study the controversies, explore their consequences, and propose solutions.
The first part is an empirical study that questions the dominance of the amyloid hypothesis through a bibliometric analysis of citation practices and an international survey of researchers promoted by the Alzheimer's Association. The second part uses a conceptual approach to consider research beyond the amyloid hypothesis and we propose a holistic model to maximise the quality and quantity of information useful to research and patients. The third part explores the ethics of the non-existence of validated treatments and the existence of non-validated treatments with the aim of protecting people's autonomy from non-validated treatments, moralistic attitudes towards prevention, and a fragile economic model underpinning drug development.
We argue that the biological and societal complexity of this disease defies reductionism and monopoly, and that the population as a whole, all potentially affected by the many problems AD poses for welfare and justice, should become agents of change to influence the direction of future research and policy.
Keywords : philosophy ; Alzheimer's disease ; epistemology ; ethics ; innovation ; prevention ; philosophy of science ; philosophy of medicine ; Karl Popper ; Imre Lakatos

UNIVERSITÉ SORBONNE UNIVERSITÉ
ÉCOLE DOCTORALE :
ED 5 – Concepts et langages Maison de la Recherche, 28 rue Serpente, 75006 Paris, FRANCE
DISCIPLINE : Philosophie