Descriptif du projet de recherche interdisciplinaire / Description of the interdisciplinary research project

SUR 5 PAGES MAXIMUM/ ON A MAXIMUM OF 5 PAGES

1. Titre de la thèse / Thesis title

Is Alzheimer's disease unique to the human species? Analysis of proteomic data through the lens of the evolution of human aging.

2. Directeur-s Directrice-s de thèse / Thesis director

Vincent Planche (Neurologist, associate professor, IMN)
Maël Lemoine (Philosopher, professor, ImmunoConcept)

3. Résumé / Abstract

Présenter le contexte, l'état actuel des connaissances sur le sujet, les objectifs du projet / Provide the context, the current state of the art on the subject, the objectives of the project

Alzheimer's disease (AD) is a huge public health problem in our aging Western societies. Surprisingly, more than a century after its initial description, there is still no consensus on the nosology of AD. Indeed, a very biological view of the disease proposes that the mere presence of extracellular deposits of amyloid proteins and intracellular aggregates of tau proteins in the brain is sufficient for its definition (Jack et al, 2018). These biological abnormalities are deemed to be "causal" in the development of neuronal death and the onset of symptoms, according to the amyloid cascade hypothesis. For other authors, biology is insufficient in the definition of the disease and must be accompanied by clinical signs suggestive of a future evolution towards dementia (Dubois et al, 2021). Indeed, it is now known that biological abnormalities in AD can precede the onset of symptoms by 10 to 20 years and many healthy elderly subjects with diffuse amyloid deposits in the brain will never develop the disease. This thorny nosological issue has a major impact on the measurement of the global prevalence of the disease, from 32 million people with AD defined by the presence of a dementia syndrome to 315 million if a "biological only" definition is considered (Gustavsson et al, 2023). This will also have an impact tomorrow in the redefinition of diagnostic and therapeutic strategies with the arrival of plasma biomarkers of the disease and the arrival of anti-amyloid immunotherapies (two are now approved in the US by the FDA). In AD, the borderline between the normal and the pathological seems to be blurring.

This nosological problem also has an impact on the representation of AD in the animal kingdom. Indeed, zoologists and ethologists have been able to show the presence of certain lesions characteristic of AD in certain species of rodents (Inestrosa et al, 2015), cetaceans (Vacher et al, 2022) and primates (Heuer at al, 2012) in advanced age. However, although these animals develop an amyloidopathy very similar to humans, they do not develop all the characteristics of human tauopathy. Also, the impact of these lesions on their cognitive functions remains uncertain. Finally, the very definition of dementia (i.e. cognitive disorders significantly affecting an individual's autonomy: grooming, dressing, ...) simply does not exist in animals, and remains an anthropocentric definition. AD would thus exist in animals in its

minimalist biological definition centered on amyloid (AD continuum), but would not exist according to a clinico-biological definition.

Finally, it appears that the definition of Alzheimer's disease articulates (explicitly or not) complex notions of biology, anthropology, and psychology. In this thesis, we propose to interrogate all these aspects through a transdisciplinary approach. We will first address the conceptual and cultural dimension of the question, drawing largely on evolutionary theory, anthropology and philosophy of science. We will then attempt to compare our findings through proteomic analysis of brains of healthy elderly subjects, subjects suffering from biological or clinico-biological Alzheimer's disease. In the same way, we will analyze brains of aged rhesus macaques having received or not injections of pathological proteins (tau +/- amyloid).

In the conceptual part of this thesis, we will start from three hypotheses. According to the first hypothesis, Alzheimer's disease is the effect on specifically human functions of biological abnormalities that are probably found in all mammals. Thus, if we cannot study the symptoms of the disease in animals, we can study its fundamental mechanisms. This is the hypothesis proposed by Maël Lemoine in the case of depression (Lemoine 2017). According to the second hypothesis, human cultural evolution has made possible an extreme longevity without example in other species, without natural gene selection having had the time or evolutionary opportunity to adapt the human organism to the possibilities of this extreme longevity. The "evolved learner" model (Sterelny 2012) emphasizes the convergence of a multitude of factors toward a pattern of social evolution that transforms the human "niche" through learning-centered interactions. This would be underpinned by increasing cognitive demands (with equal genetics), increasingly interdependent social organization, and increased longevity enabled by both extensive collaboration and group selection (see the embodied capital model proposed by Kaplan 2000 and the so-called "grandmother hypothesis" proposed by Hawkes 2013, 2020a and 2020b). This hypothesis was developed by Maël Lemoine (in collaboration with Nora Abrous and Muriel Koehl) concerning mental disorders linked to dysfunctions of hippocampal neurogenesis (Abrous et al. 2021). This hypothesis also explains why it is difficult to find examples of AD in other species: it is simply as difficult as finding cases of early AD in a random sample of a human population (less than 1 case per 1000 before 60 years of age). Some mammals (e.g., rodents) would not live long enough to develop this brain pathophysiology because of other earlier vulnerabilities (e.g., neoplastic, immune, or cardiovascular). Other mammals (e.g., whales) would have had time to adapt their brain physiology to their extreme longevity. The third hypothesis is that a specifically human variation that arose through genetic drift is the cause of a specific vulnerability to which human longevity gives the opportunity to express itself in the form of this late-onset disease. Indeed, genetic hypotheses about human evolution have recently been proposed to explain longevity and AD risk, at least in some humans (Raichlen et al. 2014). These three hypotheses conflict on the nature of the specific mechanism - specifically human impact of a biology common to aging in all mammals, originality of human cultural evolution, or human-specific molecular variation - but could as well co-exist in explaining the human specificity of AD. It will be a question of specifying them, of articulating them, and of defining more specifically how they can be separated.

In the experimental part of this thesis, we propose to test our conceptual hypotheses by a dedicated bioinformatics analysis of numerous raw data from proteomic analyses (mass spectrometry, LC-MS/MS). First, we will study data from the brains of healthy elderly subjects, subjects suffering from biological Alzheimer's disease (without cognitive

impairment) and subjects suffering from clinico-biological Alzheimer's disease. These data, from different cohorts, are available in open access for the scientific community (Bai et al., 2020). On these data, "traditional" network analyses have highlighted the differential expression in AD of proteins involved in phosphorylation, lysosomal functions, mitochondrial metabolism, cytosquellete organization... We propose to go beyond these "agnostic" or "data driven" analyses by a "hypothesis driven" approach born from our conceptual reflections in order to better identify the molecular vulnerabilities of elderly subjects developing this disease.

In particular, to discuss our evolutionary hypotheses, we will rely on primate proteomics data unique to the Bordeaux area and recently acquired by Vincent Planche in Erwan Bezard's team at the Bordeaux Institute of Neurodegenerative Diseases (Neurocampus, IMN, Univ. Bordeaux and CNRS UMR 5293). This team is indeed working to model AD and other neurodegenerative diseases (Darricau et al., 2022) by injecting pathological proteins from patients' brains into the aged rhesus macaque (the animal species phylogenetically closest to humans on which it is ethically accepted to experiment). In the context of AD, we will focus on monkeys that have received injections of pathological tau proteins (+/- co-injection of oligomeric Abeta proteins). We hypothesize that differential analysis of human and primate proteomes in response to the presence of pathological tau and amyloid proteins will help us identify mechanisms of vulnerability specific to humans. These cross-species proteomic analyses are possible here because of the close phylogenetic distance between macaque and human. The main results will be confirmed in a second step by Western-Blot or Immuno-histochemistry. These experimental data will be able to feed our conceptual reflections in order to refine them. If we identify mechanisms of "resistance" to neurodegeneration in the macaque (or mechanisms of vulnerability in humans), our results could eventually lead to the identification of new therapeutic approaches for AD.

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4. Dimension interdisciplinaire et répartition et contribution

Indiquer la dimension interdisciplinaire du projet et la répartition et contribution de chaque encadrant dans les 2 unités / Describe the interdisciplinary dimension of the project and the distribution and contribution of each supervisor from both units

The conceptual part will be conducted under the direction of Maël Lemoine (philosopher of science, specialist in aging), but will strongly involve the clinical expertise of Vincent Planche (neurologist, specialist in Alzheimer's disease). It will be developed in interaction with the laboratory De la Préhistoire à l'Actuel : Culture, Environnement et Anthropologie (PACEA) and, in particular, with Mathilde Lequin (CR CNRS), philosopher assigned to this laboratory. Mathilde Lequin leads a working group on human development, which could also cooperate in this project on human aging.

The experimental part will be done under the responsibility of Vincent Planche, in close collaboration with Maël Lemoine for the discussion of the hypotheses.

5. Originalité et pertinence du projet

Décrire l'originalité et la pertinence du projet, les objectifs et l'intérêt pour la collaboration, et spécifier les résultats attendus. / Describe the originality and relevance of the project, the objectives and value of the collaboration, and specify the expected results.

To our knowledge, there is no collaboration that mobilizes conceptual expertise in philosophy of biology and medicine, expertise in clinical neurology and neuroscience, and expertise in anthropology and human evolutionary biology.

We believe that the agnostic nature of proteomics data collection quickly shows its limits if it cannot be interpreted within the framework of clear and strong hypotheses. The synergy between the power of -omics biology and the conceptual clarity of the philosophy of biology, in the context of precise anthropological and clinical insights, should yield major results for

the entire field. We hope to establish, at least in the form of proof of concept, 1) the value of this method and 2) strong hypotheses about the human specificity of AD.

6. Intérêt du projet

Présenter l'intérêt du projet et les applications éventuelles/ Describe the relevance of the project and possible applications

We expect this project to provide new insights into the framework traditionally used to interpret translational studies of AD in mammals. It should both reinterpret data from the literature in a new light, and inspire innovative hypotheses about more specific mechanisms involved in AD.

7. Profil du doctorant

Décrire le profil du doctorant et les compétences à acquérir (ex : programme de formation disciplinaire ou transverse à suivre). / Describe the doctoral student's profile and the skills to be acquired (e.g.: disciplinary or cross-functional training program to be followed).

The doctoral student may come from philosophy, anthropology, neurobiology or bioinformatics. In any case, he/she should have been trained in database exploitation, or at least be able to quickly extend his/her skills to the exploitation of -omic databases, and present a strong interest for conceptual issues.