

A venture into the epigenetics of aging and Alzheimer's Disease

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VALORIZATION

As society becomes more critical about what science feeds it, it is a logical requirement to dedicate a chapter to the societal impact of my research. However, before I present my view, let us first take a look at what 'non-scientists' think the impact of my research is. When someone asks me what I do, I usually just say "I do research into aging and Alzheimer's disease". For this chapter, I asked a few people what they think the societal impact of my research is (admittedly, they have not much to go on):

"Immense. You are able to scientifically show how many people get Alzheimer's in these times with many elderly. More years to live; live longer at home, economic target, save money on healthcare; people are able to live longer independently, etc."

"I have no knowledge of the actual content of your research, but I myself have no urge to further extend the lifespan, something many strive for. Your research seems part of this and I think it may eventually contribute to this in the future."

"I think it has a positive influence, as our careers get longer these days. Additionally, the quality of life can, especially at advanced ages, be drastically improved for many people when aging can be slowed and Alzheimer's can be detected/treated earlier."

"The research will lead to a better understanding of Alzheimer's disease, and because of this a better treatment can be provided or the symptoms can be managed better."

"If you succeed, you will profoundly increase the quality of life for the elderly, but especially for those close to the otherwise affected individuals."

Now, how do the findings of this thesis compare with these steep expectations? In short, unfortunately there still is no cure for Alzheimer's disease and our life expectancy remains the same. On the one hand, it should be recognized that, especially the first chapters of this thesis involving animal research, are very fundamental and exploratory in nature. The research presented in this thesis will likely not have a direct impact on society in the short run, but mainly offers insights important for other scientists and is able to guide future studies. On the other hand, the research covered in **CHAPTER 4** offered new insights into caloric restriction, which is known to prolong life in rodents. As a life-long reduction in calorie intake may not sound attractive to many people to extend their lifespan a bit, my research and that of others in our group, investigated the mechanisms behind the effects of caloric restriction so

that these processes may in the (far) future be targeted through e.g. pharmaceutical intervention instead of reducing calorie intake. Although most responses above do not address aging directly, promoting healthy aging, or even ‘curing’ aging would have the largest impact on society imaginable (only one responder seems to realize this!).

The research of **CHAPTER 5** may be the furthest from society. Comparing different animal models, its main conclusions are about how to tackle future studies in the field of epigenetics¹ and Alzheimer’s disease. Useful for fellow researchers, but not so much for society at large. Or is it? It is easy to diminish the usefulness of a single study when viewed separately, but it may play a pivotal role in directing future research into more fruitful avenues. As the study in **CHAPTER 5** indicates, current animal models do not capture Alzheimer’s disease very well, and findings are not easily translated to the human situation. Indeed, while Alzheimer’s disease has been cured over and over again in animal models (see e.g. [1] for an overview), it should not be forgotten the end goal is to treat human patients. Thus, although animal models are extremely important for fundamental research (see e.g. [2]), it needs to be complemented with human-oriented studies to ensure the clinical validity of the observations.

Starting from **CHAPTER 7**, the research focuses on humans and gets closer to society. In this chapter, we offer novel insights into epigenetic dysregulation associated with Alzheimer’s disease, comparing brain tissue from patients and healthy controls. While for this type of study replication is crucial, the affected markers identified can be further investigated as potential diagnostic markers or treatment targets in future studies. Note that many of the findings of epigenome-wide association studies (i.e. covering the epigenetic regulation of most known genes), such as those described in Chapters 7 through 9, are often not easily replicated, making the selection of viable targets for mechanistic and functional follow-up studies a major challenge. Nevertheless, expanding our knowledge of the disease is already a merit on itself, as a greater understanding is crucial for the development of effective treatment strategies, whereas a lack of knowledge may explain why there currently is no cure for Alzheimer’s disease.

¹ Wonder what epigenetics is? In short, epigenetic regulation supervises gene expression; it dynamically determines which genes are expressed (and to which extent) and which are not in response to your diet, physical activity and other environmental factors. For a more detailed, but still accessible explanation of epigenetics see: <http://www.whatisepigenetics.com/what-is-epigenetics/>.

The final scientific efforts described in this thesis, in **CHAPTERS 8 AND 9**, are similar in nature to **CHAPTER 7**, but focus on the blood instead of the brain. While it may seem strange at first, to investigate the blood in relation to a neurodegenerative disease, this actually makes the findings much more relevant for clinical purposes in the shorter run. Brain tissue can in most cases only be obtained postmortem, but blood can be easily obtained from patients, and importantly, possible future patients. Even though blood markers may thus indirectly represent

what happens in the brain, they can be directly used for diagnostic and prognostic applications. In fact, this is what my future research will focus on ; using machine learning to make predictions about the development of Alzheimer's disease based on blood markers and identify novel candidates for therapy, such as oxytocin. Even though the identification of Alzheimer's disease at a pre-clinical stage has currently, without the availability of an effective treatment, not much clinical use, it may be fundamental for the development of such treatments, as it is thought past clinical trials have focused on a disease stage where damage to the brain is too advanced to reverse [3]. Furthermore, to fully grasp the etiology of complex diseases like Alzheimer's disease it will be necessary for future research to embrace advances in computer modelling and systems biology to integrate genomic, epigenomic, transcriptomic, proteomic, and other data modalities. This will also allow for a better informed development of treatment strategies.

Looking again at what others think the impact my research has on society, it seems many people² think of what the impact could be. This is indeed what is traditionally described in, say, a grant proposal, as this is perhaps what people want to hear. Therefore, I decided to write about the toned-down, in my view more realistic impact my research may have on society, as you see above. Notably, apart from the societal impact of the research performed by PhD students, it is in my opinion extremely important to look at the societal impact of successful PhD students themselves (i.e. the most important outcome of a PhD project is not the research, but the researcher). While I cannot speak for all PhD students, going through the PhD trajectory has allowed me to explore a field of research in depth, identify gaps and weaknesses in the current body of knowledge and related approaches. During the latter part of my project, I have expanded my capabilities in my specific field of study beyond the strong foundation provided by my supervisors to meet the requirements to advance this field. I now feel ready and confident to design my own studies, write my own grant proposals, and supervise my own team. In short, now, I am ready to make a real impact on society.

² Please forgive me the crude extrapolation of 5 people's opinion to that of many.

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