

# Epigenetics in mental and neurodegenerative disorders

## Citation for published version (APA):

Iatrou, A. (2018). *Epigenetics in mental and neurodegenerative disorders: The unusual suspects*. Maastricht University. <https://doi.org/10.26481/dis.20180712ai>

## Document status and date:

Published: 01/01/2018

## DOI:

[10.26481/dis.20180712ai](https://doi.org/10.26481/dis.20180712ai)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

## General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

[www.umlib.nl/taverne-license](http://www.umlib.nl/taverne-license)

## Take down policy

If you believe that this document breaches copyright please contact us at:

[repository@maastrichtuniversity.nl](mailto:repository@maastrichtuniversity.nl)

providing details and we will investigate your claim.

## 9 Valorization

“What is your research about?” they ask me.

“Alzheimer’s disease” I respond.

“Ah great! We will definitely need you in a couple of years!” they say in a tone mingling excitement and fear for the future.

This is one of the most common reactions I receive once I try to explain what I do for a living to my relatives.

My relatives: middle-aged common people with mostly office jobs receiving input of a wide gamut of diseases that might affect them in the coming years, and amidst them Alzheimer’s disease, the seemingly most terrifying one. These people put their hope in individuals like me in order to treat a disease that could gradually erase their lifetime memories and their timeline thus far.

Me: a researcher on my 4th year of working experience attempting to gain a little more insight in the widely undiscovered world of epigenetics and complex diseases through a computer screen and huge datasets or animal experiments. The aforementioned reaction does not put me at ease, as I am aware that should any of them develop Alzheimer’s disease in the next decades, there may be nothing we can do; the time bomb has most likely been set to go off already and although help is on the way, it may be too late for them.

Currently, on average, for every day of an Alzheimer’s disease researcher’s life, 16,437 people are being diagnosed with the disease, which translates in a devastating sum of 6 million new cases annually, worldwide, adding an immense burden on families, caregivers and financial costs for society [1]. Should Alzheimer’s disease get eradicated, annual savings from payments for all American dementia patients could pay off the Greek government debt [2]. Similarly, burdensome is the scourge of mental illnesses with almost 40% of the developed countries population being diagnosed with a mental disorder, which corresponds to approximately 164.8 million people affected [3]. The need for a therapy is imperative. Nevertheless, this intense global scientific scouting around for treatment strategies has not reported back that many encouraging results.

While it is a fact that the lack of effective therapeutics is mainly due to the overly complicated nature of such disorders, one could also claim that the majority of research lines are restricted to pathological observations made decades ago and researchers seem rather skeptical to leap towards more innovative hypotheses. Scientists supported that their arsenal was lying within the genetic code, and expected that upon decoding the whole human genome in 2003, answers concerning causality and aetiopathogenesis would emerge. However, they soon realized that complex disorders, such as Alzheimer's disease, schizophrenia, bipolar disorder, are not of genetic origin only, but to a big extent depend on the impact of the environment, which plays an important role in their onset and progression. From then on, the field of epigenetics burgeoned and, thus, empirical basis was set for the speculative nature of the implication and mechanisms of epigenetic modification on disease pathogenesis. Therefore one might wonder: "could it be that for the last 4 decades the scientific world has been fighting the wrong adversaries?".

The work presented in this dissertation attempts to respond to this question by examining "unusual suspects" among players of disease pathology and pathogenesis. These "unusual suspects" are not only restricted to epigenetic mechanisms, but also extend to brain structures with previously underrecognized roles in disease pathogenesis and pathology. Most possibly this book will not have a directly observable impact on society or economy, but it is highly relevant for the academic enterprise. The majority of the chapters represent an exploratory body of work applied on human tissue specimens that could serve as pillars and thus maneuver future studies towards novel directions.

To this end, the research presented in **CHAPTER 3** is an interrogation of specific epigenetic modifications associated with Alzheimer's disease. The impact of this work on the scientific world lies in two levels. Firstly, being among the first of its kind to simultaneously examine three cytosine states, it does indicate that methylation and hydroxymethylation marks highly differ even in the same genetic locus and thus advocates that previously reported studies on methylation which looked into the combined signal of methylation and hydroxymethylation should be reviewed with caution. Secondly, in retrospect, one could claim that the conception of this study is highly relevant for society due to the novel view in a different brain structure. In contrast to the majority of the hippocampus/memory deficits-targeted research lines, the hypothesis driving this project is tailored to the most incipient preclinical disease manifestations that a patient experiences, and therefore considers the understudied brainstem structures [4]. While such study requires replication in order to highlight the validity of the outcomes, it might nominate novel targets, relevant to earlier stages of the disease, that can be used for diagnostic or treatment alternatives in future studies.

Similarly, the work presented in **CHAPTER 5** is an effort to define epigenetic signatures associated with mental disorders, namely schizophrenia and bipolar disorder. The novelty of this study lays in the interrogation of epigenetic marks in the understudied cerebellum. And indeed its impact is rather big as, regardless the small sample size of the cohort, the most differentially methylated regions were replicated in an independent cohort. Further mechanistic approaches are required in order to functionally characterize the meaning of this epigenetic signature at a systems level as well as cross-regionally in the brain with the ultimate goal of using the identified markers as preventive or diagnostic tools.

In the interim, the stature of epigenome-wide studies like the ones presented in **CHAPTER 3** and **5** is the broadening of knowledge until a more holistic understanding of the pathological underpinnings of these diseases is reached. Novel approaches covering previously underrecognized brain areas while employing internationally used methodologies, namely the Illumina arrays, add one more brick to this global effort to comprehend the width and depth of the biological mechanisms making an individual susceptible to Alzheimer's disease, schizophrenia or bipolar disease.

The project presented in **CHAPTER 4** does not solely focus on brain material, but on blood as well, which makes it more clinically relevant as well as more possible to have a societal impact. The blood is an easy accessible platform to study epigenetic changes throughout the lifespan and thus attempt to model epigenetic marker fluctuations during the onset and progression of a disease. Furthermore, blood markers could also be indicative of central events related with the outbreak of the pathology. To this end, changes in the i.e. methylation state of a genetic locus, or, to be more realistic, a combination of them, could indicate the conversion of a healthy person to an AD patient and therefore a simple blood test could serve as a diagnostic and/or prognostic tool.

The scientific work concluding this dissertation in **CHAPTER 6** tackles the main clinical symptom of Alzheimer's disease, memory loss, with the assistance of animal models. Excitingly, the administered compound that targets the BDNF/TrkB signaling system, managed to restore the memory impairment in a transgenic mouse model of Alzheimer's disease. However, what is the impact of this outcome? Perusing the literature, every week, another article gets published suggesting to have cured Alzheimer's disease in animal models. Still, regardless this tremendous 'success' rate, no effective, disease-eradicating treatment has been introduced to the market yet [5]. Under no circumstances should the importance of animal models be undermined, as they are the impetus of fundamental research, but yet again, the current animal models fail to portray the disease in an accurate and global manner, crashing the hopes for the successful translation to the human

situation. At this point I would like to clarify that intervention studies like this one cannot provide a shortcut to the cure. However, the significance of this research line lies in the fact that modulation of a fundamental signaling pathway seems to have beneficial effects in memory performance and therefore adds one more piece to the puzzle of the pathophysiology of Alzheimer's disease.

So upon reflection of the impact my work will have in various levels, I stay puzzled. The environmental stimuli that could influence the vulnerability of our genome increase per decade, with the ever-changing pace of life. Worldwide, people of similar disciplines make a change for the humankind by finding cures for the most common disorders. The lifespan thus is extended; but is the quality of the 30-40 prolonged years optimal? What society demands from scientists is a solution for all these three disorders, in the form of cure or prevention, as soon as possible. Eventually, holistic knowledge of epigenetics will offer novel alternatives to therapeutic approaches and/or fast and accurate diagnosis close enough to the onset of each disease. Hopefully by that time, personalized medicine will have progressed to the point that e.g. targeted epigenetic engineering will allow for an intervention that could cure the disease. Will this dissertation yield any therapeutic candidates? Wishfully yes. Of course it will not happen from one day to the next. Fundamental research is vital to set the pillars for applied research and to inspire researchers, generate novel ideas that eventually will lead to scientific breakthroughs. And for now, the fact that my research offers another stepping-stone towards better understanding of the complex nature of the disorders makes all the efforts worthwhile.

## References

1. Association, A.s., 2018 ALZHEIMER'S DISEASE FACTS AND FIGURES, in *Alzheimers Dement.* 2018. p. 367-429.
2. Statista. Greece: National debt from 2012 to 2022 (in billion U.S. dollars). 2018, April; Available from: <https://www.statista.com/statistics/270409/national-debt-of-greece/>.
3. Wittchen, H.-U., et al., The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European neuropsychopharmacology*, 2011. 21(9): p. 655-679.
4. Simic, G., et al., Does Alzheimer's disease begin in the brainstem? *Neuropathol Appl Neurobiol*, 2009. 35(6): p. 532-54.
5. Franco, R. and A. Cedazo-Minguez, Successful therapies for Alzheimer's disease: why so many in animal models and none in humans? *Frontiers in pharmacology*, 2014. 5: p. 146.