SEXUAL DIMORPHISMS IN ALZHEIMER'S DISEASE

An overview of what we know about one of nature's most interesting sex-related dichotomy

Abstract

The existence of sexual differences in development and progression of Alzheimer's Disease (AD) is supported by a growing body of scientific evidence. The causes of these dimorphisms are, however, largely unknown. This paper aims to examine the exact differences between sexes and to what extent the physiological mechanisms behind them have been defined already.

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Chapter 1. Introduction

Alzheimer's disease (AD) is an irreversible and progressive brain disorder that slowly destroys brain functions such as memory and thinking. Eventually, patients are unable to carry out the simplest tasks and depend completely on others for basic activities of daily living. Alzheimer's is the most common cause of dementia among seniors. Dementia can be defined as the loss of cognitive functioning and behavioural abilities, the cause varying dependent on the brain changes that are taking place. For Alzheimer's, this concerns the development of abnormal clumps and tangled bundles of fibres; Amyloid Beta Protein (ABP) plaques and fibrillary tangles of hyperphosphorylated Tau protein (depicted in figure 1). These abnormalities interfere with the biological mechanisms in the brain and do fatal damage to surrounding neurons and neural messaging, thereby disrupting the functioning of essential processes. Typically, symptoms first appear in the mid-60s, with an average life expectancy of 8-10 years after diagnosis (National Institute of Ageing, 2018).

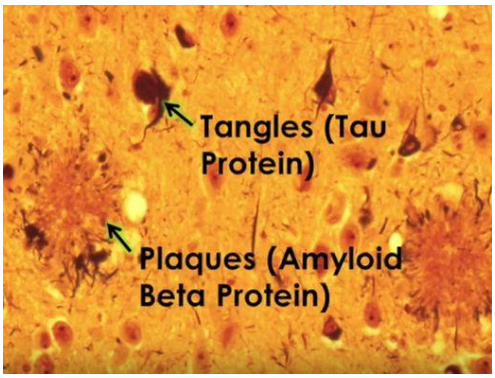

Figure 1: tangles and plaques, respectively formed by Tau protein and Amyloid-Beta Protein (ABP) in Alzheimer patients (Health Hub, 2015).

AD is one of the leading causes of death in the world, currently ranked sixth. Every 65 seconds, someone in the United States develops AD. Approximately 5.7 million Americans suffer from Alzheimer's, of which almost 2/3 are women. This number is expected to rise to 14 million by 2050, as shown in figure 2. In the US, 1 in 3 seniors die with Alzheimer's or another form of dementia. This is more than breast cancer and prostate cancer combined (Alzheimer's Association, 2018). The severity and extent of Alzheimer's are evident. Naturally, research on this topic is abundant. The past decades, we have learned a lot about causes and progression of Alzheimer's and factors that influence susceptibility. Despite this extensive knowledge, we are not able to stop the disease from becoming fatal, but merely slow it down (Alzheimer's Association, 2018).

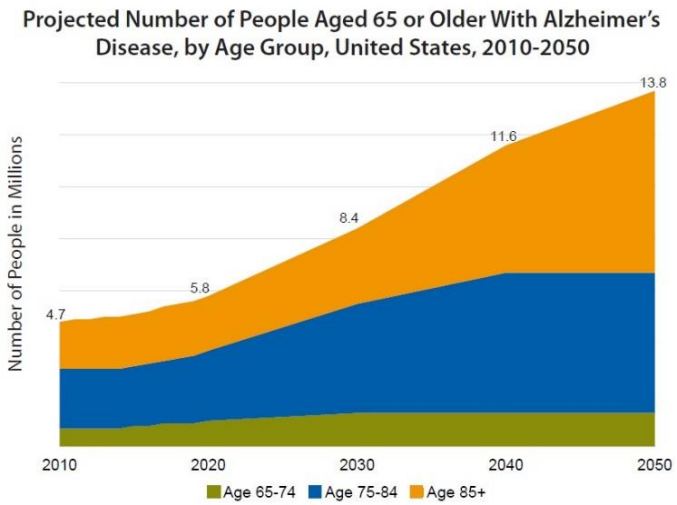

Figure 2: projected number of people with Alzheimer's in the United States 2010-2050 (Herbert, et al., 2013).

Besides the decrease in mortality, an early and accurate diagnosis of Alzheimer's could also save up to 7.9 trillion dollars in medical and care costs, in the US alone (Alzheimer's Association, 2018). Therefore, it is of great importance that prevention and treatment methods are improved. This could be accomplished by further identifying key molecular mechanisms to target, but also by identifying factors that are influencing susceptibility towards and progression of the disease. The past years, research has shown for example that sexual dimorphisms in disease risk, progression and susceptibility are evident. Discovering the cause of these dimorphisms and the exact difference between sexes would provide valuable information for the optimization of prevention and treatment method.

Knowledge on the biological mechanisms causing and affecting these dimorphisms is scarce, however. Several groups have hypothesized that sexual divergence in AD is likely to be caused by the known differences in longevity between men and women (Edland, et al., 2002) (Bachman, et al., 1993) (Fiest, et al., 2016) (Hebert, et al., 2001) (Rocca, et al., 1998). Nonetheless, recent research has presented mounting clinical and preclinical evidence that supports the presumption that women also have intrinsic susceptibilities towards the disease (Fisher, et al., 2018) (Podcasy & Epperson, 2016). Discovering the exact extent and causes of these intrinsic sexual dimorphisms would be of enormous value to the development of individual-adjusted therapy.

Therefore, the aim of this thesis is to critically examine existing knowledge on sexual dimorphisms in AD and the biological mechanisms that are causational to them. The central question that is attempted to be answered could be formulated as such: "what are the factors that cause sex differences in the susceptibility towards AD and disease progression?" In the first section, the sexual dimorphisms in susceptibility, symptoms and disease progression will be examined by analysing the regular pathophysiology and then elucidating on the sexual differences. This way, a clear image of the exact extent of sexual dimorphisms in AD will arise. In the second section, an analysis of underlying biological mechanisms of AD in general and sexual dimorphisms in specific is performed. This way, a clear image of existing knowledge on the causal role of several actors is created. By combining the insights provided in both sections, it is expected that a thorough and scientifically-based answer to the central question can be formulated.

Chapter 2. Sexual dimorphisms in susceptibility towards AD

Data shows that the population of women with AD is significantly larger than the male population, thereby suggesting that women might be more susceptible towards AD. The Alzheimer's Association reports a total patient population of 5.7 million in 2018 the United States, of which 2/3 are women (Alzheimer's Association, 2018). Alzheimer Nederland reports a total patient population of 189.000 in 2015 in The Netherlands, with female incidence being 1/3 and male incidence being 1/7 (Alzheimer Nederland, 2015). Global prevalence rates per gender are shown in table 1, based on data presented in the Alzheimer's Disease International (ADI) report on the global impact of dementia (including AD) that was published in 2015.

		AGE GROUPS						
REGION	**GENDER**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**85-89**	**90+**
ASIA	M	1.4	2.2	3.4	5.7	9.5	15.4	28.9
	F	1.5	2.5	4.2	7.3	13.0	22.4	45.7
EUROPE	M	1.4	2.1	3.1	4.8	7.6	11.6	20.1
	F	1.9	2.9	4.6	7.5	11.3	19.6	36.1
AMERICAS	M	1.4	2.3	4.0	7.1	12.5	21.6	44.5
	F	1.2	2.2	4.0	7.7	14.5	27.0	61.1
AFRICA*	M	1.0	1.5	2.3	3.8	5.7	9.2	17.5
	F	2.0	3.0	4.6	7.5	11.5	18.6	35.8

*Table 1: global prevalence of Dementia, generated from Poisson random effects models. * = data based on Sub-Saharan Africa only (Alzheimer's Disease International, 2015).*

Higher prevalence rates amongst women are visible across all regions and age groups, the difference between both genders increasing with age. Due to these differences in prevalence, the question whether factors influence that susceptibility differ between sexes inevitably arises. To assess this, sexual differences in the factors that are assumed to have the largest influence on susceptibility are analysed in detail below.

§2.1 Longevity

Often, it has been hypothesized that prevalence of AD is larger in women due to the longer life-expectancy compared to men (Edland, et al., 2002) (Hebert, et al., 2001) (Bachman, et al., 1993). Even though longevity influences the total patient population and gender-specific population, it does not account for the prevalence rates that have been adjusted to total population. This suggests that other factors must be involved. A broad of range of research has shown indications of intrinsic biological differences between men and women that cause a difference in risk of development of Alzheimer's. These intrinsic biological differences are discussed in chapter 4.

§2.2 Genetics

Besides the direct effects of intrinsic mechanisms, several factors have been identified to increase susceptibility towards AD. Age remains the leading risk factor for AD, with studies showing that the incidence of AD exponentially rises after the sixth decade of life (Kukull, et al., 2002) (Masters, et al., 2015). Family history and heritability have also proven to be important risk factors for AD, with the amount of risk that can be attributed to genetics being estimated at 70% (Ballard, et al., 2011). Both risk genes and deterministic genes for AD are known.

§2.2.1 Risk gene: APOE-E4

Risk genes increase the likelihood of developing a disease, deterministic genes directly cause AD, thereby guaranteeing that anyone who inherits one will develop the disorder. Apolipoprotein E-E4, or APOE-E4, is the most important risk gene for AD (Alzheimer's Organization, 2018). Involvement of APOE on the pathology of AD includes deregulation of ABP clearance, Tau phosphorylation, blood-brain barrier integrity, inflammatory responses, cerebrovascular permeability and synaptic maintenance. This leads to both loss-of-function and gain-of-toxic-function effects, that are listed in table 2 (Fisher, et al., 2018).

Loss-of-function effects	Gain-of-toxic-function effects
(-) Synaptic function	(+) Brain atrophy
(-) Glucose metabolism	(+) Neuronal toxicity
(-) Neurogenesis	(+) ABP aggregation
(-) ABP clearance	(+) Tau hyperphosphorylation
(-) Vascular function	(+) Aberrant brain activity
(-) Mitochondrial function	
(-) Cholesterol metabolism	

Table 2: effects of APOE-E4 induced biological changes in regulation of several biological processes, leading to an increased risk of development of AD. (-) indicates a decreased intensity of the biological process, whilst (+) indicates an increased intensity of the biological process.

Recent studies demonstrate that women that possess the APOE-E4 allele are at greater risk than age-matched men, especially when comparing heterozygous individuals carrying the APOE-E4 allele (Riedel, et al., 2016). In fact, women who are heterozygous for the APOE-E4 allele were found to be diagnosed with AD five years earlier than heterozygous men (Poirier, et al., 1993). Similarly, the odds radio for AD in APOE-E4 heterozygous women is 4-fold greater than in men (Altmann, et al., 2014).

It is plausible that this increased risk is primarily caused by the decreased ABP clearance and increased aggregation of ABP, leading to plaque formation, and hyperphosphorylation of Tau, leading to tangle formation. Both characteristics are central to the pathophysiology of AD, as discussed before. Moreover, other effects of APOE-E4 (such as decreased neurogenesis, mitochondrial dysfunction and increased neuronal toxicity) contribute to vulnerability of the brain, thereby making it more susceptible to the development of AD in general (Corder, et al., 2006) (Bu, 2009). The biological causation of the sexual differences that are observed remains unknown, however. Further research into the general interaction between APOE-E4 and AD is therefore needed to ensure an increased understanding of the discussed sexual dimorphism in susceptibility towards AD.

§2.2.2 Blood Derived Neurotrophic Factor (BNDF)

Blood Derived Neurotrophic Factor (BDNF) has frequently been reported as a biomarker of neuropsychiatric diseases, especially mood disorders (Yeh, et al., 2015). It is known to regulate synaptic plasticity in the central nervous system (CNS), thereby changing in disease pathogenesis and treatment. Similar to APOE, studies have shown increased risk of AD for women that possess certain BDNF polymorphisms compared to men. This is the case for the BDNF Val66Met polymorphism for example, which increases risk of AD in women solely (Li, et al., 2017). Interestingly, a link between BDNF and APOE in AD pathogenesis has been frequently demonstrated. It has been suggested that APOE-E4 directly regulates BDNF expression and secretion, by stimulating translocation of histone deacetylase 4 and 6 (HDAC4/6) to the cell nucleus. HDAC4 and HDAC6 deacetylate the transcription site of BDNF, thereby decreasing expression and subsequent secretion (Sen, et al., 2015).

Given the fact that APOE might affect BDNF levels and that certain APOE and BDNF alleles may predispose women to develop AD more easily than men, a sexually divergent interaction between these AD effectors is plausible. Again, further investigation of sex differences in BDNF's effect on susceptibility towards AD would be very valuable to our understanding of sexual dimorphisms in AD.

§2.2.3 Deterministic genes

Deterministic genes for AD are variations of genes that normally encode amyloid precursor protein (APP), presenilin-1 (PS-1) and presenilin-2 (PS-2). Besides these well-known deterministic loci, more have been identified to be related to an increase of risk of AD (Marioni, et al., 2018). When Alzheimer's is caused by deterministic variations, we speak of autosomal dominant Alzheimer's disease (ADAD). In 0,1% of the patients with AD, ADAD is diagnosed as cause of development. Individuals with ADAD develop symptoms in an earlier stage of life, usually in their 40s or 50s (Alzheimer's Organization, 2018). There is no evidence of sexual dimorphism in these deterministic variations, although the biological mechanisms affecting them might be differentially regulated in men and women.

§2.3 Lifestyle

Lifestyle is also increasingly regarded as influential on susceptibility towards AD. Lifestyle characteristics such as sufficient physical activity, balanced dietary intake (both in calories and macronutrients), no smoking and low cholesterol are assumed to have a positive influence on the risk of AD (Vos & Visser, 2018) (Reitz & Mayeux, 2014) (Imtiaz, et al., 2014). Logically, the effect of these factors on susceptibility towards AD is extremely individual-specific. Epidemiologic analysis is therefore irrelevant. However, given the fact that differences in lifestyle response between sex are prevalent, this could contribute to the sexual dimorphism in susceptibility towards AD. For example, recent studies show that differences in prevention of Type 2 Diabetes Mellitus (T2D) are visible (Harreiter & Kautzky-Willer, 2018). Given the fact that T2D appears to negatively influence the risk of AD, these differences could diverge risk development between males and females.

Similar results are shown for dietary balance (Södergren, et al., 2013) and body fat percentage (Wu & O'Sullivan, 2011), two examples of lifestyle factors that are also presumed to influence the risk of AD development. Therefore, it could be hypothesized that these sex differences in lifestyle factors contribute to sexual dimorphism in risk of AD.

§2.4 Education

Interestingly, a low level of education has repeatedly been identified as key risk factor of developing AD. Better education has even shown to protect against clinical manifestation of AD in individuals with an unfavourable genetic background i.e. APOE-E4 carriers (Imtiaz, et al., 2014). Several population cohorts reported that higher education reduces the risk of AD due to an increase in the threshold at which pathological changes can manifest themselves clinically (EClipSE Collaborative Members, 2010). These findings were supported by structural magnetic resonance imaging (MRI) analysis for cortical thickness and brain volume, that found more years of education to increase the threshold before which brain atrophy manifested clinically in patients with AD (Liu, et al., 2012). This phenomenon is hypothesized to be caused by an increased cognitive reserve for individuals with better education. Although the majority of individuals receives alike forms of education during childhood, there are considerable gender disparities in the level of educational attainment in some countries. This suggests educational exposure also contributes to sexual differences in susceptibility towards AD (Podcasy & Epperson, 2016).

Fundamental sexual differences in cognitive reserve, so those characteristic for the sex, are also supported by several studies. Due to the strong relevance of brain reserve to progression of AD, this subject will be discussed in further detail in §3.2.

§2.5 Summary

In summary: higher prevalence rates of AD in women compared to men suggest sexual differences in susceptibilities. Hypotheses involving longevity fail to account for these sexual differences, thereby suggesting other factors might be of influence. Genetics factors such as APOE-E4 and BDNF show significant sexual differences, thereby influencing sexual differences in susceptibility towards AD. More research on the exact relation between extrinsic lifestyle factors and AD development is needed to make definitive assumptions regarding their influence on risk of AD in general and sexual differences specifically.

Chapter 3. Sexual dimorphisms in progression of AD

Progression of AD is typically divided into three phases that can be identified: mild, moderate and severe AD. Symptoms of the disease differ in characteristics and severity per phase. These phases are precedented by a preclinical mild cognitive impairment (MCI) phase, also known as pre-dementia. MCI is not regarded as part of the pathophysiology of AD, but as a transition stage from normal ageing to Alzheimer's due to the fact that no additional assistance is needed to carry out standard tasks (UCSF Memory and Ageing Center, 2018). Table 3 describes characteristics of every stage.

STAGE	PHASE	AVERAGE DURATION	AREA(S) AFFECTED	SYMPTOMS INCLUDED	LEVEL OF ASSISTANCE
MCI (-)	Very early	7 years	Medial temporal lopes	▪ Short-term memory loss ▪ Mood swings	No
Mild (I)	Early	2 years	Lateral temporal lobes Parietal lobes	▪ Reading problems ▪ Poor object recognition ▪ Poor direction sense	Minimal
Moderate (II)	Middle	2 years	Frontal lobes	▪ Poor judgement ▪ Impulsivity ▪ Short attention span ▪ Long-term memory loss ▪ Motoric problems ▪ Speech difficulties	Complex daily tasks
Severe (III)	Late	3 years	Occipital lobes	▪ Visual problems ▪ Aggressiveness ▪ Incontinency ▪ Loss of speech	Daily tasks

Table 3: characteristics of the specific stages of Alzheimer's disease (Alzheimer Nederland, 2018) (Förstl & Kurz, 1999).

The mentioned symptoms are consequences of the atrophy of brain tissue. As mentioned before, intracellular tangles (formed by hyperphosphorylated Tau) and extracellular plaques (formed by accumulation of ABP) characterize the causative pathophysiology of AD. Both abnormal processes do damage to the surrounding tissue in a distinctive way, eventually leading to massive cell death. The circumference of this cell death is incremental, as depicted in figure 3, thereby worsening symptoms as the disease progresses.

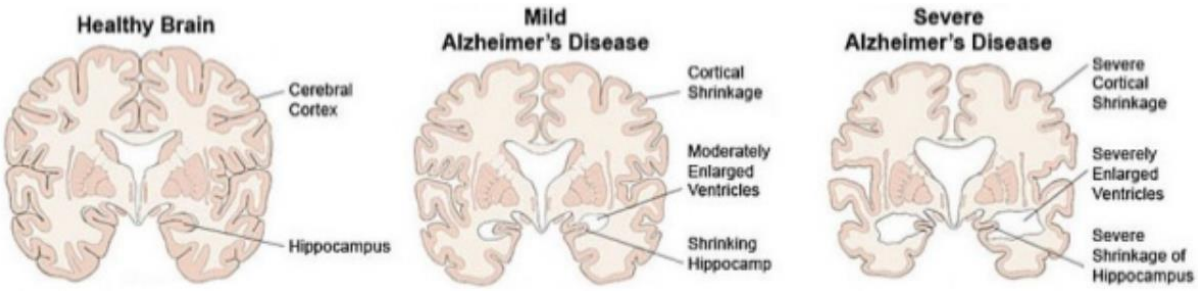

Figure 3: progression of Alzheimer's disease (Morreale, 2018).

A considerable amount of literature has been published on sex differences in the time course and characteristics of disease progression. In general, sex differences in ageing processes are significant (Beeri, et al., 2006). Women perform better on verbal memory tasks, for example, while men perform better on visuospatial tasks with age (Van Exel, et al., 2001) (Proust-Lima, et al., 2008). Apart from the differences in the trajectory of the normal ageing process, cognitive decline in pathological ageing defined as AD also seems to vary between sexes.

§3.1 Sexual dimorphisms in disease progression

An extensive body of research brings forth sexual dimorphisms that are visible in disease progression of AD. For instance, the Mayo Clinic Study of Aging recently reported that risk of progression of MCI to AD was increased in women after age 80 compared to men. For younger age groups, this rate of progression was similar (Roberts, et al., 2014). Comparatively, Li et al. found progression of MCI to be more robust in women (Lin, et al., 2015). Moreover, several studies have found the time course of disease progression to be accelerated in men (Stern, et al., 1997) (Lapane, et al., 2001). Overall, more brain regions are affected and ABP depositions are more extensive throughout the brain (Corder, et al., 2006). Barnes et al. reported that each additional unit of AD pathology was associated with a 3-fold increase in risk of AD in men, compared to a 22-fold increase in women.

This difference seems to be primarily caused by a larger proportion of neurofibrillary tangles in women compared to men (Barnes, et al., 2005). A recent meta-analysis by Irvine et al. compared performance of male and female individuals with AD in all cognitive domains: verbal, non-semantic, memory, visuospatial and semantic performance. This comparison showed that men modestly but significantly outperform women in all domains. Differences in disease severity and age did not explain this male advantage, thereby indicating that cognitive functions are both more severely and widely affect in women with AD compared to men with AD (Irvine , et al., 2012). So, in general; women show more robust progression from MCI to AD and higher severity of AD pathology compared to men.

Several hypotheses have been proposed as possible explanation of this sexual dimorphisms in progression of AD pathophysiology. Theories that are regarded as the most plausible current day are discussed.

§3.2 Brain reserve hypothesis

First of all, Katzman et al suggest sexual dimorphisms are given rise by the concept of 'brain reserve'. This theory posits that individuals with higher reserve have a greater capacity to cope with pathological developments, which would explain why cognitive decline is sometimes initiated at different times in relation to the onset of pathology for each specific individual. In other words, individuals with larger brains are better able to withstand pathological developments at the same level of cognitive performance (Katzman, et al., 1988). Men are expected to therefore be able to withstand more pathology compared to women, given the larger head size and cerebral brain volume in men of approximately 10% (Giedd, et al., 2012). This supports the beforementioned findings that risk and speed of progression of MCI to AD are increased in women compared to men (Roberts, et al., 2014) (Skup, et al., 2011). Comparatively, studies show that men have more pronounced cerebral metabolic deficits compared to women at the same level of cognitive impairment (Perneczky, et al., 2007) (Perneczky, et al., 2007). Again, this suggests that greater brain reserve may be helping men to withstand more pathology at an equal level of pathological severity.

§3.3 Brain connectivity hypothesis

Another theory offered as explanation for sexual differences in behaviour in general and AD specifically is brain connectivity. Typically, neural activity is constrained by brain connectivity. By affecting cerebral metabolism, brain connectivity is crucial to the way neurons and neural networks process information. It has drawn the attention of researchers primarily due to the interesting functional hemispheric specializations that are observed (Hsieh, et al., 2011). The fact that local activity differs per area, situation and individual suggests that unravelling brain connectivity increases our understanding of the functioning of our brain. It has therefore been a popular topic of research for decades, first being discussed by Cajal in 1909.

Brain connectivity includes several levels of scale: individual synaptic connections that link individual neurons (microscale), networks connecting neuronal populations (mesoscale) and brain regions linked by fibre pathways (macroscale). Anatomical connections are both specific and variable at all levels of scale. Specificity is primarily found in arrangement of synaptic connections between distinct neuronal types, in spatial extent and branching patterns of axonal arborizations and in long-range connectivity between neural structures. Variability is found in the shape, size and placement of individual neurons within large-scale structures. Both characteristics vary within the same individual with ageing, as a result of developmental processes of growth, plasticity and repair. This affects neural dynamics and behavioural performance, relating to cognitive decline (Sporns, 2007).

Besides age-related differences in connectivity, a broad body of research on sexual differences is also available. Functional imaging measurements of brain connectivity have shown significant differences between men and women, due to their direct linkage resulting in similar changes in brain connectivity and metabolism. The most important ones include a higher cerebral blood flow in parietal association cortices and overall connectivity for women, and higher connectivity and cerebral blood flow for men in visual and motor cortices (Hsieh, et al., 2011) (Gur, et al., 1995). Structural connectivity of the female and male brain is depicted in figure 4. The connections between the front and back of the same brain hemisphere are abundantly present in the top images, depicting the male brain. Strong interhemispheric connections are clearly visible in the bottom images, that depict the female brain. These sex differences in structural connectivity are likely to account for the behavioural differences that have been discussed in chapter 3. In short, these include men's better visuospatial and motor skills, in contrast to women's better verbal skills and intuitive abilities.

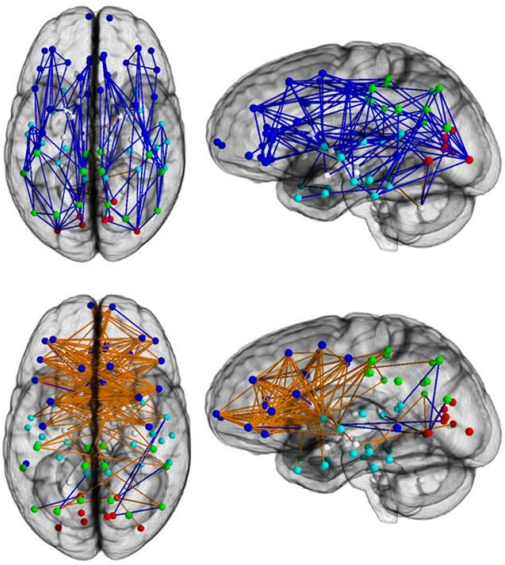

Figure 4: connectivity in the male (top left & right) and female (bottom left & right) brain (Ingalhalikar, et al., 2014).

For AD specifically, the sexual differences in brain connectivity are addressed related specifically to regional amyloid deposition. Recent research has hypothesized that regions of high connectivity harbour amyloid deposition. In other words, brain regions with high connectivity show higher plaque formation compared to brain areas with lower connectivity (Hsieh, et al., 2011). This finding is extremely interesting for further understanding AD pathophysiology. As explained in the paragraphs before, certain brain areas are affected more severely in men compared to women with AD and vice versa. This could be explained by the fact that connectivity in these areas differs between sexes. Research that specifically compares plaque formation with connectivity in certain areas between sexes is however missing. Given the enormous relevance, it would be very interesting to further investigate the relation between brain connectivity, sex and AD progression.

§3.4 Summary

In summary, several studies have shown that sexual dimorphisms in disease progression of AD are ubiquitous. The brain reserve hypothesis of Katzman et al. posits that larger brain reserve increases capacity to withstand pathological development. This theory is in accordance with the described sexual dimorphisms and therefore poses as interesting and valuable explanation. Another factor that could be of influence is brain connectivity, that might affect disease progression by influencing amyloid deposition. Further research into this specific interaction is necessary.

Chapter 4. Biological explanations for sexual dimorphisms in AD

Due to the extremely complex interactions involved in both healthy ageing and pathological ageing, numerous biological mechanisms can be and are of influence on the development and progression of AD. This increases the difficulty of identifying direct causes of disease development, thereby making assumptions regarding these causes precarious. Only in a limited amount of patient cases, for example those with ADAD, a direct cause can be identified. Besides the limitations that this lack of causative identification induces for the development of effective treatment and medication, it also complicates the identification of causative mechanisms for sexual dimorphisms specifically. However, dozens of studies have investigated interactions between AD and certain biomarkers and mechanisms in both animal models and humans. Three major interaction themes can be identified, which will be elucidated on below.

§4.1 Sex hormones

Sex hormones or gonadocorticoids are hormones that mediate slow genomic and non-genomic mechanisms related to development of primary and secondary sex organs. Release of sex hormones is regulated by the neuroendocrinological system, that consists of several integrators and effectors. In general, internal and environmental stimuli (such as weight loss) induce release of Gonadotropin-Releasing Hormone (GnRH) by the hypothalamus to the anterior pituitary, which in its turn releases FSH and LH. In males, FSH is important for spermatogenesis. In females, it is important for maintaining follicles. LH acts on the cells of Leydig in males, thereby aiding in testosterone production. In women, LH contributes to estrogen production. Estrogen and testosterone function as long negative feedback loop for GnRH release, whilst LH and FSH function as short negative feedback loop for GnRH release (Silverthorn, et al., 2016). This pathway is depicted in figure 5.

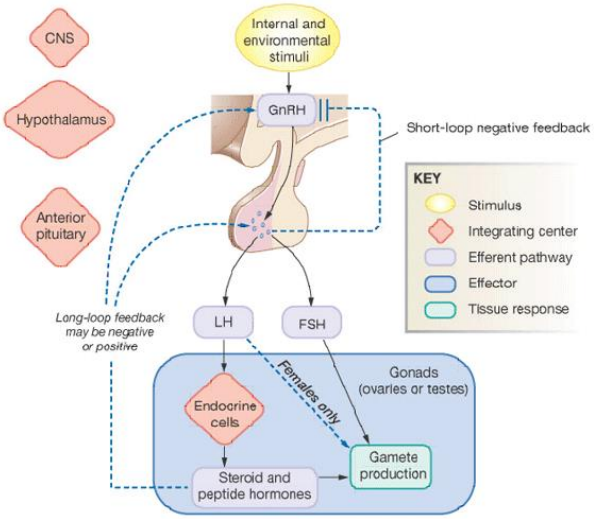

Figure 5: overview of gonad hormone signalling pathways (Silverthorn, et al., 2016).

Recent reports show that high levels of gonadotropins are associated with cognitive decline that is observed with age (and in AD). LH has recently been reported to modulate ABP precursor processing and ABP generation, suggesting that age-related increases in gonadotropins are a relevant signal for neurodegeneration in the ageing brain (Rosario, et al., 2010) (Pike, et al., 2009) (Overk, et al., 2013). By assessing the impact of testosterone and gonadotropins on plasma ABP levels and brain amyloid burden (measured as Pittsburgh Compound B (PiB retention)), Verdile et al. detected that PiB retention was associated with decreased free testosterone and increased LH levels. This does not only suggest a potential progressive involvement of LH and testosterone in development of AD, they could also be considered as AD predictors in early stages of the disease (Verdile, et al., 2014).

Involvement of sex-specific steroids would suggest a possible influence on sexual dimorphisms in AD pathophysiology. In general, the alleged neuroprotective role of sex hormones is often mentioned as major influence in the age-related increase in risk of AD. All groups of sex steroids are discussed in general and specifically focusing on their neuroprotective role and related mechanisms. An overview of the causative mechanisms that are discussed is depicted in figure 6.

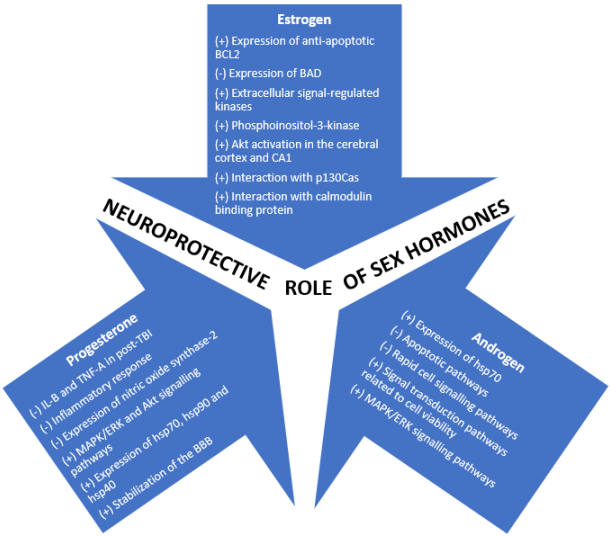

Figure 6: overview of the neuroprotective mechanisms of action of progesterone, estrogen and testosterone. (+) indicates an increased intensity, (-) indicates a decreased intensity of the biological process (composed by author).

§4.1.2 Estrogens

General introduction on estrogen

Estrogens are a group of primary female sex hormone, responsible for development and regulation of female reproductive system and secondary sex characteristics. They are synthesized from cholesterol and primarily produced by the ovaries. Estradiol is the major estrogen, outperforming others in quantity and potency. Estrogens diffuse across the cell membrane and either bind to nuclear or membrane estrogen receptors (ERs/mERs). Their biological effects are primarily genomic (Silverthorn, et al., 2016).

Neuroprotective role of estrogen

It has been hypothesized that the rapid decrease in estrogen during menopause functions as trigger for the development of AD in women due to these neuroprotective abilities (Paganini-Hill & Henderson, 1994). Estrogen appears to slow down injury progression, to diminish cell death by suppressing apoptotic pathways and to enhance cell survival by stimulating expression of survival genes. It also shows protective effects on dorsal hippocampal neurons in the CA1 region specifically, by decreasing oxidative stress, glucose deprivation and the promotion of cell survival (Siddiqui, et al., 2016).

Several clinical studies have supported this potentially protective link between estrogen and AD. The Mayo Clinic published results that showed a 2-fold increase in risk of AD in women who underwent bilateral oophorectomy before menopause (Rocca, et al., 2011). Another study by Zandi et al. demonstrated that women who used hormone replacement therapy in the perimenopausal period had fewer cases of AD later on in life (Zandi, et al., 2002). Bove et al. further supported the possible neuroprotective role of estrogen by publishing that surgical menopause appears to be associated with a faster cognitive decline and more Tau hyperphosphorylation (Bove, et al., 2014).

Mechanisms of action of estrogen's neuroprotective role
Mechanisms through which these neuroprotective effects are assumed to be initiated includes, amongst others, the estrogen receptor (ER) dependent signalling pathway, that is reported to overexpress the anti-apoptotic BCL2 gene. It also inhibits the BAD gene, which is the antagonist of BCL2, thereby further promoting cell survival. Estrogen also induces certain other pathways, such as the MAPK/ERK signalling cascade that is known to play an important role in neuroprotective action. Moreover, ERs have been reported to interact with striatin in vascular cells, which is essential for estrogen-mediated Akt and endothelial nitric oxide synthase (eNOS) activation leading to enhanced neuroprotection (Siddiqui, et al., 2016).

§4.1.3 Androgens

General introduction on androgen
Androgens are a group of hormones that regulate development and maintenance of male characteristics, inducing embryological development of the primary male sex organs and development of secondary male sex characteristics during puberty. They are synthesized from cholesterol and primarily produced in the testicles. Testosterone is the major androgen in males, outperforming other androgens in quantity and potency. Even though androgens are often regarded as only present in males, low levels are produced by the ovaries and adrenal glands as well. In both males and females, androgens function as precursor to estrogen and in libido and sexual arousal. Androgens bind to both nuclear and membrane androgen receptors (ARs) to mediate their biological effects. These effects are primarily genomic (Silverthorn, et al., 2016).

Neuroprotective role of androgen
Testosterone is assumed to have a neuroprotective role through the activation of androgen pathways and its antioxidant and anti-apoptotic potential. Androgens are positive regulators of neuronal plasticity, excitability and density in certain regions. They also appear to prevent retraction and increase the length and size of motor neurons (Siddiqui, et al., 2016).

Mechanisms of action of androgen's neuroprotective role
The mechanism through which these neuroprotective actions are assumed to be activated is, amongst others, the general AR-dependent pathway. This pathway includes members of heat-shock protein families (hsp70) that provide cellular protection during stress. Moreover, AR-dependent signalling appears to inhibit apoptotic signalling pathways and activate cell viability pathways in both neuronal and non-neuronal cells (Siddiqui, et al., 2016). In addition to these effects, androgen-mediated activation of the MAPK/ERK signalling cascade has also been suggested as contributing factor to the neuroprotective role of androgens. As mentioned before, MAPK/ERK signalling is known to play an important role in neuroprotection. Inhibition of MAPK/ERK signalling with MEK inhibitors decreased androgen-activated neuroprotection, thereby confirming this role (Siddiqui, et al., 2016).

§4.1.3 Progestogens

General introduction on progestogen
Progestogens are a group of sex hormone involved in the menstrual cycle, pregnancy and embryogenesis. The major progestogen is progesterone, which is both an important factor in these processes, as well as a crucial metabolic intermediate in the production of other sex hormones and corticoids. Progestogens are synthesized from cholesterol and are produced by the ovaries. Via both genomic and non-genomic signalling, progesterone has several key physiological effects (Silverthorn, et al., 2016).

Neuroprotective role of progesterone
Progesterone is assumed to have a broad range of neuroprotective effects in several diseases. These include AD, traumatic brain injuries (TBI), spinal cord injuries, diabetic neuropathy, seizures and epilepsy. These effects might collectively be important for the neuroprotective role of progesterone against neurodegeneration as observed in AD (Siddiqui, et al., 2016).

Mechanisms of action of progesterone's neuroprotective role
The mechanisms through which these neuroprotective effects are assumed to be induced are mainly centred around the nuclear progesterone receptor (PR). PRs need a chaperone molecule for hormonal binding, which then expresses its action by dissociating from the chaperone, dimerizing and finally interacting with the progesterone response element at the promotor region of the target gene. PRs have been localized in several brain regions, including the hippocampus, hypothalamus, cortex and cerebellum. PR-dependent pathways seem to cause reduction of interleukin-B (IL-B) and tumor necrosis factor A (TNF-A) and inhibit inflammation cytokines in certain cortex areas in post-TBI. As well as estrogen and androgen, progesterone is known to activate the MAPK/ERK pathway, which' role as contributing factor to the neuroprotective role of sex hormones has been supported by recent research. Progesterone is also assumed to be related to upregulation of BDNF, which is known to enhance learning and memory processes (Siddiqui, et al., 2016).

§4.2 Immune function

The interaction of ABP and hyperphosphorylated Tau with the immune system is increasingly investigated. Besides their functioning as pathogenic intermediates, this interaction might play a central role in the development and progression of AD. Evidence of important and specific interactions between the immune system and AD development is strongly accumulating. Of these interactions, microglial regulation of synapses may be of biggest importance for AD. It has been demonstrated that the degree of synaptic degeneration outperforms ABP levels as predictor of cognitive decline in AD, as this degeneration is in closer synchronization with symptom development and precedes neuronal loss (Hong, et al., 2016) (Mucke & Selkoe, 2012). This in line with the hypothesis that persistent ABP toxicity primes microglia, directly causing them to respond to local changes in a state of inflammation by means of cytokine release and enhanced pruning of synapses (Heneka, et al., 2015) (Perry & Holmes, 2014).

Sexual differences that could cause sexual divergence in the effect of the immune system on AD development and progression are abundant. Males have a higher tendency to develop infections compared to females (Klein, 2000). In contrast, females tend to have a stronger immune response by means of greater antibody production and a greater propensity toward T-Helper cell 1 (TH1) responses (Hanamsagar & Bilbo, 2016). Moreover, estrogen generally enhances the immune system at low doses. Androgen tends to be more immunosuppressive (Hanamsagar & Bilbo, 2016). Males tend to have more microglia early in development, while females tend to have more microglia from early adulthood onward (Lenz & McCarthy, 2015).

While influence of the immune system on AD development and progression is plausible and sexual differences in inflammatory response are widely supported by research, it remains unclear whether these divergent responses lead to significant differences in susceptibility towards AD. Further investigating the interaction between the immune system and sex in AD pathogenesis is highly necessary to confirm if risk of AD is indeed diverged due to sexual differences in immune response.

§4.3 Stress and sex-specific CRF1 signalling

Clinical evidence suggests that changes in the hypothalamus-pituitary-adrenal (HPA) axis occur in correlation with the severity of cognitive decline, where a stress-related increases in plasma cortisol level seems linked to stronger cognitive decline (amongst others showing increased brain atrophy) (Csernansky, et al., 2006).

Due to this negative correlation between plasma cortisol and cognitive decline, sexually dimorphic stress responses could account for the sexual dimorphisms in AD development and progression. Rasmuson et al. interestingly demonstrated that women with AD have significantly higher levels of cortisol compared to age-matched males, which would support the increased cognitive decline in females with AD compared to men with AD that has been discussed before (Rasmuson, et al., 2011). Further human studies on this topic are scarce, unfortunately. Preclinical studies have however shown a strong sex-specific difference in AD pathogenesis under psychosocial stress. Sotiropoulos et al. for example show that environmental stress triggers memory impairments in female but not in male P301L-tau mice and that stress-related increases in caspase-3-truncated tau and insoluble tau aggregate exclusively in the hippocampus of females (Sotiropoulos, et al., 2015). These promising preclinical results invite for further research into this topic as possible causative mechanism of sexual dimorphisms in AD pathophysiology.

Besides increased plasma cortisol levels, other mechanisms involved in stress regulation are also assumed to affect AD pathogenesis. Corticotropin-releasing factor 1 (CRF1) signalling has repeatedly been suggested as causative mechanism to the detrimental effects of stress on AD in preclinical studies. Increased CRF1 signalling is generally associated with multiple stages of APP proteolysis, regulation of ABP generation and ABP-mediated toxicity, leading to the stress-related increase in cognitive decline as mentioned before (Csernansky, et al., 2006) (Thathiah, et al., 2013). Interestingly, sexual differences in CRF1 signalling are also observed. As depicted in figure 7, male CRF1 signalling is biased towards B-catenin activated Rho, Akt and Src signalling pathways. Female CRF1 signalling, however, is biased towards Gs-PKA signalling (leading to downstream CREB and GSK3 signalling). Gs-PKA signalling plays a vital role in the formation of ABP aggregates and hyperphosphorylation of Tau. This further supports the hypothesis that intrinsic biological mechanisms cause the higher AD susceptibility observed in women with AD compared to men (Valentino, et al., 2013) (Fisher, et al., 2018).

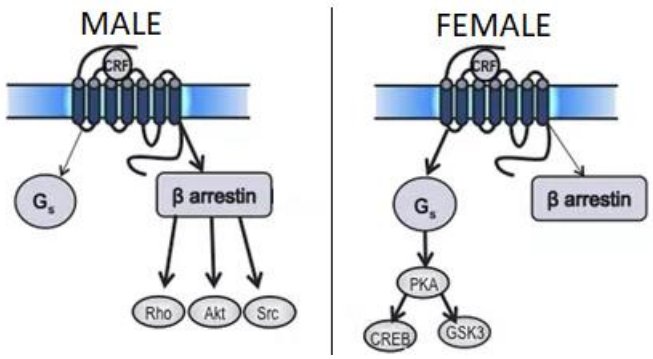

Figure 7: sex biased CRF1 signalling pathways ((Valentino, et al., 2013), edited by author).

§4.4 Summary

Biological mechanisms underlying the sexual differences in development and progression of AD are extremely diverse. Most important and evident to be interacting with AD pathogenesis are sex hormones, the immune system and sex-biased stress response CRF1 signalling. The sexual differences in each of these systems are very likely to explain the sexual dimorphisms that are observed in susceptibility towards and progression of AD.

Chapter 5. Conclusion

This study set out to discover what factors are causing sex differences in the development and progression of AD by critically examining existing knowledge on sexual dimorphisms in AD and the biological mechanisms that are causational to them. An extensive literature review was performed, that focused both on regular pathology of AD and sex-related differences in pathology. Intrinsic and extrinsic mechanisms that might be underlying these sexual differences were extensively analysed. This way, a clear overview of all sex-related differences and their possible causative mechanisms has been created.

The results of this investigation show that sexual differences are significantly present in AD. This includes both differences in inclination towards development of AD and speed and severity of cognitive decline. In general, women are more likely to develop AD, especially at age 80 and over. Moreover, the disease seems to progress at a faster rate and with higher severity in women compared to men.

Overall, several factors of essence have been identified. Intrinsic genetic factors such as APOE-E4 and BDNF are presumed to be involved in sexual differences in development of AD, as well as intrinsic biological mechanisms such as immune response and sex-biased CRF1 signalling. Sex hormones are also increasingly mentioned as plausible to be at least partially explanative for the observed sexual dimorphisms. Numerous mechanisms of action are suggested as influential on AD pathogenesis through increase or decrease of the neuroprotective role of sex hormones. Further research on the involvement of extrinsic lifestyle factors is needed to assess the exact extent of their effect on the risk of developing AD. Differences in disease progression are likely to be caused by structural differences in brain reserve and enhanced brain connectivity in certain brain regions. A definitive explanation for the apparent difference in AD development and progression remains elusive, however, which further underlines the importance of further research.

This comprehensive investigation adds to the growing body of research that indicates that sexual differences in AD are evident and possibly of greater importance than we are currently assuming. The findings are of enormous interest to our further understanding of the pathogenesis of AD and improvement of diagnosis and treatment.

Chapter 6. Discussion

Since this study was limited to a very small timeframe, it is beyond the scope of the thesis to examine the discussed biological mechanisms on a more molecular level. As stated in the introduction, the aim is to create a clear overview of the factors that cause sex differences in the susceptibility towards AD and disease progression. Therefore, despite of its exploratory nature, the study offers insights in an annotative way.

It should also be noted that studies denying the increased incidence of AD for women compared to men are also prevalent. It is remarkable, to say the least, that many studies have suggested the presence of female-specific risk and severity-increasing factors, whilst so few have uncovered a significant difference in incidence between sexes. Difficulties in classification of AD remain one potential driving force of ambiguity. Often, reported differences in incidence are equivocal for younger age groups, but are consistent for individuals after the age of 80 years. This way detected differences fail to reach statistical significance (Fisher, et al., 2018). Nonetheless, it is important to consider that sex differences in incidence of AD are not undisputed when interpreting findings.

Furthermore, the better part of studies that are referred to are limited by their retrospective design. Hypotheses that attempt to explain sexual dimorphisms in disease progression argue that structural differences are responsible for the sexual differences that are observed in disease risk, symptoms and progression rate. However, due to the retrospective design, factors that also influence regional brain functioning (such as handedness, occupation, physical damage) are not eliminated. These could affect individual results and therefore average outcomes per sex. Hypotheses supported by retrospective studies will therefore remain of questionable certainty to some extent.

Also, clinical trials involving estrogen replacement therapy (ERT) have resulted in inconclusive data, that sometimes contradicts the neuroprotective role of estrogen that is suggested by the mentioned preclinical evidence (Asthana, et al., 2001) (Henderson, et al., 2000). These findings are unexpected, but the possibility that ERF confers other risks that interact with AD pathology to worsen cognition should be considered. Moreover, it remains unclear if estrogen combined with progesterone or progesterone alone may have different neuroprotective properties in postmenopausal women compared to those who received ERT. Evidently, further research is needed to clarify this inconclusive data and to understand the exact interaction of estrogen with AD.

For clinical applications, it is also important to bear in mind that progesterone has a potential antagonistic relationship with estrogen. Studies have shown that progesterone could block the estrogen-induced increase in spine density and reverses estrogen-induced enhancement of spatial memory. This would diminish the neuroprotective role of estrogen and increase neurodegeneration (Siddiqui, et al., 2016). Application of progesterone in AD treatments should therefore be closely monitored in correlation to estrogen-related effects.

In addition, it is interesting to mention that pathways identified as promising and suitable to be targeted in trials for AD treatments do not always show the clinical results that are expected. A large multicentre randomized and placebo-controlled phase III trial, for example, with progesterone as contradictor for AD, ischemic stroke and multiple sclerosis showed disappointed results. Despite promising results in earlier phases, failure in phase III continues to take place (Siddiqui, et al., 2016). It is hypothesized that this is caused by faulty extrapolation of preclinical animal studies data, but it is safe to say that further research into this discrepancy between expectation and reality is needed. Future studies might prevent these overenthusiastic estimations of effect sizes by pooling preclinical data and using more coordinated phase II trials using standardized outcomes, so potential findings can be replicated.

Besides being discussed as direct actors within the causative mechanisms of sexual dimorphisms in AD, sex hormones and APOE-E4 as risk gene are likely to also be related. As mentioned in table 2, APOE-E4 deregulates cholesterol metabolism. Since sex hormones are synthesized with cholesterol as precursor, this typically leads to decreased sex hormone levels. As extensively discussed in chapter 4.1, decreased sex hormone levels are associated with an increased risk of development of AD due to the loss of the neuroprotective role of sex hormones. Therefore, it is plausible that besides the direct negative effects of APOE-E4 on susceptibility towards and progression of AD, it also indirectly worsens AD pathophysiology through the decrease of sex hormones. This interaction between two factors that are discussed separately in this thesis is likely to not be the only one. It is for example also mentioned that sex hormones have differences on immune function, besides the direct effect of the immune system on AD. Due to the extreme complexity of the discussed mechanisms and their enormous range of biological effects, it is highly probable that discussed mechanisms exercise numerous reciprocal effects as well. This increases difficulty of identifying direct effects of the discussed mechanisms on AD risk and progression, which should be considered when interpreting findings.

As mentioned in summaries of the separate chapters, leads for future research are abundant. Even though our understanding of involved processes and mechanisms is increasing rapidly, the majority remains unknown. Given the enormous clinical relevance, it is of the utmost importance that research on these topics is proceeded and, if possible, intensified. Considerably more work will need to be done to determine the exact effects of lifestyle factors, such as smoking, physical activity, diabetes and cholesterol levels. Comparatively, research on the interaction between androgen levels and AD is extremely scarce. More broadly, epidemiologic research is needed to further determine sex differences in incidence and prevalence of AD on a global scale and eliminate any ambiguity regarding it.

Implications for treatment of AD could be enormous. A recent meta-analysis performed by Canevelli et al. describes the lack of attention on sexual differences in cohort trial studies. This creates an extreme paucity of data on essential characteristics, that otherwise could be used to analyse treatment efficacy per sex. Only a minority of these trial studies (2/48) explores if and how sex-related factors affect the observed efficacy and tolerability of the tested pharmacological interventions (Canevelli, et al., 2017). Creating awareness of the importance of generation of data on this topic and stimulating the processing of it, is essential if we desire to improve AD diagnosis and therapy.

Chapter 7. References

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Chapter 8. Appendices

§8.1 List of abbreviations

AD	Alzheimer's Disease
ABP	Amyloid Beta Protein
APP	Amyloid Precursor Protein
AR	Androgen Receptor
APOE-E4	Apolipoprotein E-E4
ADAD	Autosomal Dominant Alzheimer's Disease
BAD	BCL2 Associated Death (gene)
BCL2	B-Cell Lymphone 2 (gene)
BDNF	Blood Derived Neurotrophic Factor
CNS	Central Nervous System
CRF1	Corticotropin Reacting Factor
eNOS	Endothelial Nitric Oxide Synthase
ER	Estrogen Receptor
ERT	Estrogen Replacement Therapy
FSH	Follicle-Stimulating Hormone
GnRH	Gonadotropin-Releasing Hormone
HDAC4/6	Histone Deacetylase 4/6
HPA axis	Hypothalamus-Pituitary-Adrenal axis
IL-B	InterLeukin-Beta
LH	Luteinizing Hormone
MRI	Magnetic Resonance Imaging
MCI	Mild Cognitive Impairment
PR	Progesterone Receptor
PS-1	PreSenilin 1
PS-2	PreSenilin 2
TH1	T-Helper Cell
TBI	Traumatic Brain Injury
TNF-A	Tumor Necrosis Factor Alfa
T2D	Type 2 Diabetes

§8.2 Assignment description (source: Ocasys)

Bachelorscriptie levenswetenschappen
De bachelorscriptie vormt een onderdeel van de afsluiting van de bachelorfase van de opleiding. Samen met het bacheloronderzoek vormt de bachelorscriptie het bachelorproject. In het geval van een onderzoek laat de student door het schrijven van een bachelorscriptie zien dat hij/zij in staat is weliswaar onder begeleiding, maar toch in hoge mate zelfstandig, tot het uitvoeren van een literatuuronderzoek op een academisch niveau. In de bachelorscriptie wordt op basis van een probleemstelling, doelstelling en onderzoeksvragen literatuuronderzoek gedaan.

Eindtermen:
De student…

- is er in getraind om met een kritische werkhouding informatie op waarde te schatten;
- is in staat om een duidelijke argumentatie te ontwikkelen ter ondersteuning van een standpunt of visie die op relevante en effectieve wijze wordt ondersteund door wetenschappelijke literatuur.
- kan een helder, kritisch en logisch gestructureerde wetenschappelijke tekst van substantiële omvang schrijven in duidelijke, doelmatige en academisch taal.
- is in staat kritisch te reflecteren op eigen academisch handelen en kan indien noodzakelijk zijn of haar handelswijze aanpassen.

De student…

- kan een eigen vraagstelling afbakenen, formuleren en motiveren op basis van relevante wetenschappelijke literatuur en heeft zich daartoe geoefend in het snel en doelgericht verzamelen van informatie door het raadplegen van personen dan wel van geschreven bronnen
- kan grenzen van een literatuur search aangeven
- is in staat om informatie te documenteren, herstructureren, analyseren en relateren aan andere informatie.

De bachelorscriptie bestaat uit een literatuuronderzoek binnen het onderzoeksgebied van de gevolgde major. De scriptie wordt geschreven in combinatie met het bacheloronderzoek en sluit hier inhoudelijk bij aan. De student dient onder begeleiding van een docent…

- op een wetenschappelijk verantwoorde manier een vraagstelling te formuleren
- literatuuronderzoek te verrichten
- bevindingen en conclusies te presenteren door middel van een wetenschappelijke tekst
- een beargumenteerd standpunt of visie in te nemen en deze te verantwoorden

§8.3 General outline

Student: Sem Foreman (S2887436)
Supervisor: prof. U. Eisel
Field of research: Alzheimer's disease

General description of thesis:

- Outlined according to academic standards
- Approx. 5000-6500 words
- Including figures and tables wherever necessary
- Reviewed by supervisor + second evaluator

Topic: sexual dimorphism in risk, progression and symptoms of Alzheimer's disease.
Background & aim: the existence of sexually-based differences in risk of Alzheimer's, its progression rate and outline and symptoms of the disease has been largely proved in several pieces of research. The causes of this dimorphism are, however, largely unknown. In this paper, I aim to examine the exact differences between sexes and to what extent the physiological mechanisms behind them have been defined already.

Global outline of subtopics:

- Introduction
  - Background
  - Previous research
  - Relevancy of the topic
  - Aim & objective (incl. central question)
- Literature review
  - Prevalence (risk dimorphism)
  - Disease progression dimorphism
  - Symptoms dimorphism
  - Causes of dimorphism
- Conclusion
  - Summary of findings
  - Answering of central question
- Discussion
  - Remarks on findings & research used
  - Implications for prevention/treatment & future research
- References & appendices

Global outline of planning

- **Start**: 4-6-2018
- *Writing 1st version*: 4-6-2018 until 22-6-2018
- **Deadline** - *1st version*: 22-6-2018
- *Feedback processing*: 22-6-2018 until 29-6-2018
- **Deadline** – *2nd/End version*: 29-6-2018