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The impact and limitations of bilingualism as a generalized protective factor against neurodegenerative diseases on the basis of Alzheimer's disease

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Abstract

The study examined the effect bilingualism on maintaining cognitive functioning and delaying the onset symptom not only of Alzheimer's but also the following three most common neurodegenerative diseases to verify, whether bilingualism can be identified as a generalized protective factor. The strengthening of the neural networks, leading to cognitive reserve, increases the resistance of the brain against mental deterioration and eventual brain damage. In this case the linguistic capability stands in direct correlation with the progression of neurodegenerative diseases with the potential of changing its progression. The use of a second language correlates with the activity in key neural networks and allows better coping with damage before the onset of symptoms of the disease, although the varying efficiency along the bilingualism gradient must be considered. The stronger the cognitive reserve, the longer it could compensate for the cognitive decline caused by the initial onset symptoms, allowing a longer life period unaffected by the disease. Bilingualism has already been proven by previous studies to effectively delay onset symptoms of Alzheimer's, which serves as a basis but this study attempts to expand its sphere of action to all neurodegenerative diseases in general. As aside from Alzheimer's disease, also Huntington's, Parkinson's disease and multiple sclerosis have been studied regarding their connection with cognitive reserve, which strongly correlates with bilingualism. Therefore, to support the universal nature of bilingualism as a protective factor against neurodegeneration the respective underlying mechanisms was analysed as well.

The result depicts the expected outcome by initially verifying the effectiveness of bilingualism against the onset of symptoms of Alzheimer's disease, as well Parkinson's disease, Huntington's disease, and multiple sclerosis. The mitigation of the progression rate could only be partially confirmed regarding multiple sclerosis in two of the six studies included.

For a universal outcome, further long-term research is required.

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1. Medical and terminological foundation

The link between neurology and linguistics have been focusing on the brain areas reserved for the linguistic ability and their relevance regarding the different types of diseases caused by damage to these specific parts.

The aim of this study is to establish the interference of a general improvement through bilingualism, when facing neurodegeneration. Based on the derivation that bilingualism does not only strengthen the specific neuronal regions responsible for Alzheimer's and dementia related diseases, but can also be confirmed as a beneficial factor against Parkinson's and Huntington's disease, partly even multiple sclerosis and amyotrophic lateral sclerosis, which results in the majority of neurodegenerative diseases, the inference of a general improvement of cognitive reserve can be drawn, leading to bilingualism being an effective general factor against most neurodegenerative diseases.

Therefore, the medical and terminological foundation must be established to comprehend the underlying mechanisms and analyze the interconnection not only between the neurological components of bilingualism and Alzheimer's disease but also between the different forms of neurodegeneration. Accordingly, not only the diagnostic aspects as well as the progression of Alzheimer's disease but also the definitional approach as well as significance of cognitive reserve must be described in detail beforehand.

1.1 Diagnosis, progression and genetic predisposition of Alzheimer's disease and neurodegeneration in general

Dementia and dementia related diseases can be described as a disorder of the nervous system, where the loss of nerve cells leads to decreased mental performance. Alzheimer's disease is the most common cause of dementia, leading to a significant reduction of quality of life, but still not curable. According to "the European Collaboration on Dementia, co-ordinated by Alzheimer Europe, […] there were [..] 8.45 million people in Europe with AD"[1] in 2010, and their numbers "are set to double in the next 30 years."[2] An early onset of AD, before the age of 65, can point to a greater genetic predisposition, resulting in a more aggressive course.[3] The numbers show great significance, which is the main cause for great interest in curing or at least delaying the onset of symptoms and therefore allowing patients to enjoy a longer life period without limitations.

[1] J. Hort, J. T. O'Brien; G. Gainotti et al. (2010) EFNS guidelines for the diagnosis and management of Alzheimer's disease. In: European Journal of Neurology Vol. 17. URL: doi:10.1111/j.1468-1331.2010.03040.x. pp. 1236-1248, here p. 1237

[2] Ibid. p. 1237

[3] Cf. ibid. p. 1237

Diagnosis

In attempt to diagnose Alzheimer's disease, a series of different steps are taken. The assessment of onset symptoms is often initiated, either due to a previously known occurrence in the family due to a genetic predisposition, or because initial symptoms begin to surface requiring an examination of the underlying condition. The problem when accessing Alzheimer's disease (AD) is that there are no definite criteria and indicators for a definitive diagnosis, which leads to a delayed assignment of the symptoms, especially since memory loss and forgetfulness can be caused by many different diseases resulting in possibly contrasting treatment.

Shortly Alzheimer's disease can be described as a

> "brain disorder characterized by a progressive dementia that occurs in middle or late life. The pathologic characteristics are degeneration of specific nerve cells, presence of neuritic plaques, and neurofibrillary tangles."[4]

Exactly these specific "abnormal amounts of amyloid proteins forming plaques and tau proteins forming tangles"[5] were used only to confirm the diagnosis at the autopsy.

The initial guidelines for a clinical diagnosis of AD were established in 1984 and revised, supported by the NIA (National Institute of Aging), part of the NIH (National Institutes of Health) and the Alzheimer's Association in 2011, to reflect the evolving research results by incorporating the scientific advances in the field. The addition of the guidelines in 2011 concludes the "incorporation of biomarkers of the underlying disease state and [the] formalization of [three] different stages of disease in the diagnostic criteria" [6] allowing the incorporation of the full spectrum of the disease including the gradual changes over the years, the recognition of other symptoms beyond memory loss, a more distinct differentiation between Alzheimer's and other forms of dementia and finally the potential using biomarkers.[7] "Biomarkers are parameters (physiological, biochemical, anatomic) that can be measured *in vivo* and that reflect specific features of disease-related pathophysiological processes."[8]

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[4] McKhann, Guy; Drachman, David; Folstein, Marshall et al. (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group unter the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. In: Neurology. July Issue, pp. 939-944, here p. 939

[5] Vaughn, Peggy (2011) Alzheimer's diagnostic guidelines updated for first time in decades. Website of National Institute on Aging. URL: https://www.nia.nih.gov/news/alzheimers-diagnostic-guidelines-updated-first-time-decades

[6] Cf. Clifford, Jack Jr. R. & Albert, Marylin S. et al. (2011) Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. In: Alzheimer's & Dementia. Volume 7, Issue 3, May. Pp. 257-262, here p. 259

[7] Cf. Alzheimer's Disease Diagnostic Guidelines. Website of the National Institute on Aging. URL:https://www.nia.nih.gov/health/alzheimers-disease-diagnostic-guidelines.

[8] Cf. Clifford & Albert et al. (2011) Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. p. 260

The clinical diagnosis of Alzheimer's disease consists of four major components. The medical history, laboratory, neurological and physical examination. The medical history is collected from the patient and often close friends or relatives. Furthermore, blood tests regarding vitamin B12, folate, thyroid stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function abnormalities[9] can be useful to exclude co-morbidities.

The early signs of Alzheimer's disease are often misdiagnosed due to their similarity to other dementia related diseases, therefore an early diagnosis is rather rare, although essential for an accurate assessment of the symptoms and further progression.

> "Of individuals aged 70 years or older, 20% to 40% without cognitive impairment have biomarker or autopsy evidence of AD pathology; therefore, pathologic AD findings are not sufficient for symptoms."[10]

Nevertheless, it is more frequent for symptoms to manifest years before a sufficient clinical diagnosis, which includes.

> "Changes in mood, anxiety, and sleep [but also] heightened anxiety, depressive symptoms, apathy, and withdrawal are highly prevalent in preclinical or early stages of AD. Progression to later-stage symptoms, such as impaired judgment, disorientation, and confusion; major behavioural changes, such as aggression and agitation; and neuropsychiatric symptoms, such as delusions and hallucinations, can go unrecognized and undertreated until diagnosis."[11]

Additional symptoms can also include difficulties with finishing daily tasks, social isolation, and problems with speech production.[12]

The diagnostic spectrum for AD includes a comprehensive evaluation complemented by the pathological biomarkers, primarily from the cerebrospinal fluid and through a PET scan, although the latter is often an addition, when the comprehensive evaluation is inconclusive. The cerebrospinal fluid (CSF) is a clear fluid surrounding the brain and spinal cord functioning as a cushion, protecting the brain. Proteins that are made in the brain are released into the CSF, which can be collected by a spinal tap and analysed for potential indicators.[13] These biomarkers are still being in their experimental phase and therefore not adequate for general practice.[14]

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[9] Cf. Hort & O'Brien et al. (2010) EFNS guidelines for the diagnosis and management of Alzheimer's disease. p. 1237

[10] Atri, Alireza (2019) The Alzheimer's Disease Clinical Spectrum. Diagnosis and Management. In: Medical Clinics of North America. Volume 103, Issue 2, March. URL: https://doi.org/10.1016/j.mcna.2018.10.009. pp. 263-293, Here p. 266

[11] Ibid. p. 266

[12] Cf. Mayo Clinic Staff (2022) Diagnosing Alzheimer's: How Alzheimer's is diagnosed. Website of Mayo Clinic. URL:https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048075.

[13] Cf. Dobrowolska Zakaria, Justyna (2021) Cerebrospinal Fluid (CSF) Biomarkers and Alzheimer's Disease. Website of Bright Focus Foundation. Expert Advice. URL: https://www.brightfocus.org/alzheimers/article/cerebrospinal-fluid-csf-biomarkers-and-alzheimers-disease.

[14] Cf. Vaughn (2011) Alzheimer's diagnostic guidelines updated for first time in decades.

The neuropathological hallmarks of AD consist of "extracellular amyloid plaques that are composed of Aβ40 and Aβ42 and intracellular neurofibrillary tangles (NFT), which is composed of hyperphosphorylated protein tau."[15] "The biomarker abnormalities such as low CSF β-amyloid 42 (Aβ42) and cerebral amyloid deposits precede elevated CSF tau cerebral injury."[16] The amyloid buildup can be detected through cerebrospinal fluid analysis and with positron emission tomography (PET) scans.[17] A positron emission tomography (PET) scan uses a radioactive substance, most commonly fluorodeoxyglucose (FDG), to identify brain regions with decreased glucose metabolism and according to the pattern of metabolic impairment different types of degenerative brain disease can be distinguished. In this case by detecting clusters of amyloid proteins (plaques) or tau (neurofibrillary tangles) indicating with Alzheimer's dementia.[18] The accumulation of amyloid can start as early as 15-20 years before the onset of symptoms. At the same time, the relation of the proteins in the CSF show that while $A\beta_{42}$ decreases, the tau level increases.[19] This is due to the "opposite relationship between the $A\beta_{42}$ levels in the brain and in the CSF: when $A\beta_{42}$ is being trapped in plaques, less of it leaves the brain to enter the CSF and thus CSF $A\beta_{42}$ measurements in AD patients are generally lower than for healthy patients."[20] Although also possible with other dementias, the three core CSF biomarkers for AD are $A\beta_{42,}$ total tau and phosphorylated tau.[21]

Although AD is not a deadly disease it decreases the life expectancy by 7-10 years with an increasingly high susceptibility for infections and even though individual differences must be considered, the average life expectancy after the diagnosis lies between 4 to 8 years.

Progression

The progression of Alzheimer's disease can vary strongly based on the individual's ability to maintain cognitive abilities, which can be modified by factors that will be elaborated further in the following chapters. Primarily AD was described as a one stage disease, Alzheimer's dementia. Although the pace of progression varies individually, according to recent research results, three distinct stages of AD can be differentiated, first preclinical, then mild cognitive impairment and finally dementia.

[15] A. Anoop; Pradeep K. Singh; Reeba S. Jacob & Samir K. Maji (2010) CSF Biomarkers for Alzheimer's Disease Diagnosis. URL: doi: 10.4061/2010/606802; p. 1

[16] Jill Rasmussen & Haya Langerman (2019) Alzheimer's Disease – Why We Need Early Diagnosis. In: Degenerative Neurological and Neuromuscular Disease, pp. 123-130, URL: DOI: 10.2147/DNND.S228939 Here p. 124

[17] Cf. Vaughn (2011) Alzheimer's diagnostic guidelines updated for first time in decades.

[18] Cf. Mayo Clinic Staff (2022) Diagnosing Alzheimer's: How Alzheimer's is diagnosed.

[19] Cf. Dobrowolska Zakaria, Justyna (2021) Cerebrospinal Fluid (CSF) Biomarkers and Alzheimer's Disease.

[20] Cf. ibid.

[21] Cf. ibid.

A more detailed and accurate description of the progression of AD offers the 7-Stage model from 1982 (Table 1).

Table 1: 7-stage model of AD progression

Stage	Level of Impairment
1	No impairment
2	Very mild cognitive decline
3	Mild cognitive decline
4	Moderate cognitive decline (early-stage dementia)
5	Moderately severe cognitive decline (early mid-stage dementia)
6	Severe cognitive decline (late mid-stage dementia)
7	Very severe cognitive decline (late-stage dementia)

[22]

The early preclinical stage is often without cognitive symptoms, yet the first changes, including the amyloid buildup, are possibly already in process and can be detected on brain imaging with PET scans and CSF analysis.[23] An early diagnosis can be made often up to 8 years before the onset of dementia begins, when mild cognitive impairment (stage 2 or 3) is perceptible, but the independence is still intact.[24]

As a second and preliminary stage before AD follows the Mild Cognitive Impairment (MCI), where the patient experiences noticeable and even measurable cognitive decline, still not severe enough to impede activities of daily living (ADL). [25] It is not imperative for patients with MCI to progress to AD.[26]

The final and medically most relevant stage is Alzheimer's dementia. It is marked by symptoms such as memory loss, cognitive decline, word-finding and vision issues, impaired reasoning, or judgment, while being severe enough to cause difficulties with ADL and compromise independence. [27] Biomarkers at this stage can be used indicate the level of certainty and contribute to the distinction from other dementias.[28]

Genetic predisposition

[22] Rasmussen & Langerman (2019) Alzheimer's Disease –Why We Need Early Diagnosis. here 124 – citing - Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. Am J Psychiatr. 1982; 139:1136–1139

[23] Cf. Vaughn (2011) Alzheimer's diagnostic guidelines updated for first time in decades.

[24] Cf. Rasmussen & Langerman (2019) Alzheimer's Disease – Why We Need Early Diagnosis. p. 124

[25] Cf. Hort & O'Brien et al. (2010) EFNS guidelines for the diagnosis and management of Alzheimer's disease. p. 1237

[26] Cf. Vaughn (2011) Alzheimer's diagnostic guidelines updated for first time in decades.

[27] Cf. Alzheimer's Disease Diagnostic Guidelines. Website of the National Institute on Aging. URL:https://www.nia.nih.gov/health/alzheimers-disease-diagnostic-guidelines.

[28] Cf. Vaughn (2011) Alzheimer's diagnostic guidelines updated for first time in decades.

The most frequent and effective risk factor to develop AD, being the most common form of dementia, is due to ageing. But beside several risk factors, including age, gender, education, lifestyle among others, the most significant influence on the emergence of AD is caused by the genetic predisposition due to additional genes or gene mutations within the familial medical history. This rare type of AD is called Early-Onset Alzheimer's Disease (EOAD) occurs with a certainty of 20% regarding relatives for first grade and 10% for second grade, which depicts a notable difference in contrast to genetically unaffected individuals. As for the affected genes and underlying mechanisms,

> "in the familial disease, the three genes implicated are all autosomal dominant [genetic trait passed down from parent to child] and include the amyloid precursor protein gene on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1. Presenilin 1 gene mutations are most common among familial AD mutations. Mutations in these genes lead to an overproduction of beta-amyloid (Aβ) peptides (Aβ40 and Aβ42), which give rise to synaptic dysfunction, neurotoxicity, and Aβ deposits in the brain called neuritic or senile plaques."[29]

Apolipoprotein E (APOE) ε4 allele, the most significant genetic, and therefore unmodifiable, risk factor for AD.[30] In these cases, the genetic testing is common and often suggested to undertake delaying measures regarding the early onset of symptoms. It is important to state that at this point biomarkers although widely used in research setting, the application in general practice cannot be approved without further validation.[31]

1.2 Definition approach, structure, and significance of cognitive reserve

A linear relationship between chronological age and cognitive decline can be assumed generally, although not without exception. Cognitive reserve (CR) has been discussed to be an effective preventative concept against cognitive decline as it has proven to delay neurodegeneration. Several similar terms such as brain reserve, neuronal reserve, compensation, and cognitive reserve have been used interchangeably to describe the same concept, although with minor differences. A definition of the concept of cognitive reserve has been often approached, reaching similar descriptions with the question of the discrepancy as

[29] LW Chu (2012) Alzheimer's disease: early diagnosis and treatment. In: Hong Kong Medical Journal, Volume 18, No. 3, pp. 228-237, here p. 228

[30] Giovanna Viticchi, Lorenzo Falsetti & Laura Buratti et al (2015) Framingham risk score can predict cognitive decline progression in Alzheimer's disease. In: Neurobiology of Aging, Volume 36, Issue 11, pp. 2940-2745. URL: https://doi.org/10.1016/j.neurobiolaging.2015.07.02, here p.

[31] Cf. Vaughn (2011) Alzheimer's diagnostic guidelines updated for first time in decades.

the common denominator. It has been found to be the accounting factor for the different outcomes due to a same degree of brain damage.[32]

Defining characteristics

Cognitive reserve (CR) has been explained by Stern (2002) and Barulli and Stern (2013)[33] as the absence of direct relationship between the degree of brain pathology, such as with Alzheimer's disease, and its clinical manifestation negatively impacting among other factors the activities of daily living in form of symptoms, leads to the assumption of a concept responsible for this discrepancy.[34] Due to the fact that the neurodegenerative changes do not reflect the "disconnect between preserved function and neurodegeneration is the hallmark of reserve and expressed through the specific concepts of brain reserve, brain maintenance and cognitive reserve."[35] The concept of cognitive reserve is also often used to explain the discrepancy when neurodegenerative changes, similar in nature and extent, vary strongly regarding the severity of brain damage. [36]

Cognitive reserve also describes the ability of a person to compensate for cognitive decline, based on the individual neuronal pathways and cognitive processes. Its active process includes

> "several mechanisms, such as the increase of synapses and dendritic endings, as well as other neural factors, allow for greater efficiency of the brain's networks and/or the recruitment of alternative nets or strategies."[37]

Cognitive reserve is mainly the minds and brain's resistance to damage. It is also understood as the maintenance of cognitive abilities despite healthy aging, neurodegeneration, or acute damage.[38] It is with this cognitive reserve that, if strong and extensive enough, the brain can brace against neurodegenerative diseases by either preventing its early emergence or by decelerating its progression offering a longer lifespan without the impairment by symptoms.

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[32] Cf. Yaakov Stern (2002) What is cognitive reserve? Theory and research application of the reserve concept. In: Journal of the International Neuropsychological Society, 8(3). pp. 448-460. URL: DOI: 10.1017.S1355617701020240. here p. 448

[33] Cf. Yaakov Stern & Daniel Barulli (2019) Chapter 11 – Cognitive reserve. In: Handbook of Clinical Neurology, Volume 167. pp. 181-190, here p. 182

[34] Cf. Stern (2002) What is cognitive reserve? Theory and research application of the reserve concept. p. 448

[35] Berkes, Matthias & Bialystok Ellen (2022) Bilingualism as a Contributor to Cognitive Reserve: What it Can do and What it Cannot do. In: Intervention and Prevention of Neurodegenerative Disease Building Resilience – Review. Vol. 37. p. 2

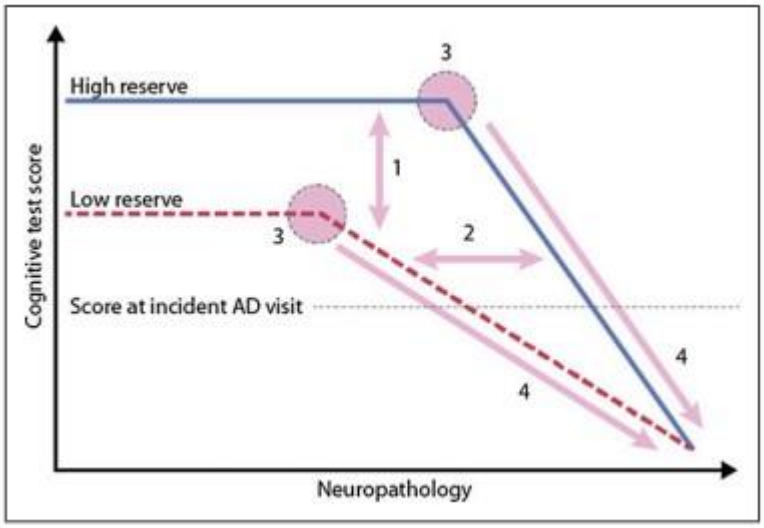
[36] Cf. Lawrence J. Whalley & Ian J. Deary et al. (2004) Cognitive reserve and the neurobiology of cognitive aging. In: Ageing Research Reviews, Volume 3, Issue 4. Pp. 369-382, here p. 372

[37] Ana Martins da Silva; Sara Cavaco & Inês Moreira et al. (2015) Cognitive reserve in multiple sclerosis. In: Multiple Sclerosis Journal, Volume 21, Issue 10 pp. 1312-1321, here p. 1312

[38] Ladan Ghazi Saidi (2019) Bilingual speakers postpone symptoms of cognitive deficit in Parkinson's disease – Innovation in Aging. Volume 3, Issue 8, November (Suppl 1). p. 661. doi: 10.1093/geroni/igz038.2447. PMCID: PMC6846036.

Cognitive reserve, being the capacity of the brain to sustain injuries or diseases and its effects, can be supported by the general improvement of the cognitive abilities achieved through and influenced by high quality education, intelligence (IQ) and occupational complexity.[39]

The hypothesis of cognitive reserve also includes the individual differences of task processing mechanisms, which can also contribute to reserve against brain pathology allowing a greater neural efficiency as well as capacity and most significantly the recruitment of other brain regions to compensate for the existing damage.[40] According to cognitive reserve, cognitive processes are adaptable, which is responsible for individual inconsistencies regarding cognitive functioning when faced with neurodegeneration. As an active process, cognitive reserve uses compensatory mechanisms or other functional brain processes to cope with or adjust to cognitive decline. Therefore, despite similar levels of neuropathology high cognitive reserve allows in a better cognitive performance. This again indicates that patients with higher cognitive reserve, at a similar level of cognitive performance, should show a greater level of neuropathology, as a result of more adequate coping mechanisms. This also results in the delayed surfacing of symptoms due to cognitive decline and a faster progression once the initial impairments set in (figure 1).[41]



[42]

Figure 1: Correlation between cognitive test score and neuropathology

[39] Cf. Lawrence J. Whalley; Ian J. Deary; Charlotte L. Appleton & John M. Starr (2004) Cognitive reserve and the neurobiology of cognitive aging. In: Ageing Research Reviews, Volume 3, Issue 4. Pp. 369-382, here p. 372-73

[40] Cf. M. Tucker, A & Stern, Y. (2011) Cognitive Reserve in Aging. In: Current Alzheimer Research, Volume 8, Number 4. Pp. 354-360. URL: https://doi.org/10.2174/156720511795745320.

[41] Cf. Matthias Berkes & Ellen Bialystok (2022) Bilingualism as a Contributor to Cognitive Reserve: What it Can do and What it Cannot do. In: American Journal of Alzheimer's Disease & Other Dementias. Volume 37(0). p. 1-9. - In: Intervention and Prevention of Neurodegenerative Disease: Building Resilience – Review, here p. 2

[42] Ibid. p. 2

Although it seems counterintuitive, as the result of the disease is inevitable and patients with higher cognitive reserve were coping firstly with greater neuropathology and second for a longer period, once the shielding threshold is breached, the decline occurs more rapidly.[43]

Structure

As presented by Stern (2002, 2007), within the concept of reserve, a subdivision into two interrelated concepts. The passive model refers to brain reserve, designated to brain size and neuronal count, focusing on the amount of brain damage that can be compensated before clinical symptoms start to surface. The active model, on the other hand, describing cognitive reserve, where the brain is actively attempting to compensate for or cope with the damage by "by using pre-existing cognitive processing approaches or by enlisting compensatory approaches". [44] Although the two models are not mutually exclusive, cognitive reserve (CR) represents the active approach of the brain in order to protect the brain against damage and cognitive decline and is more effective as it can withstand a more extensive brain damage without showing symptoms.[45]

Despite the similar conclusions regarding the description, the active and passive factors cannot only be applied to the differentiation between brain and cognitive reserve, but also within the components of cognitive reserve itself. A high level of education as well as complex occupations are regarded as active components, while the brain structure responsible for the efficient processing of information, memory retrieval or problem solving represents the passive components. An exception, as it is of anatomical nature, yet classified as an active component of cognitive reserve, are presented by the enhanced "efficiency of cortical circuits sub-serving specific cognitive tasks" [46], which can be achieved through repeated use.

Cognitive reserve as such is not sufficient to prevent neurodegenerative diseases but can improve its course depending on its efficiency regarding the different levels of cognitive reserve. The various factors that can have an impact on the brain's resistance against damage include various activities as well as environmental factors.

Therefore the hypothesis also includes that, when facing neurological diseases or cognitive decline due to aging, an additional protection can be achieved through enriching life experiences, as they lead to an increased capacity and efficiency of the neural networks.[47] This

[43] Cf. ibid. p. 4
[44] Yaakov Stern (2007) Cognitive reserve: Theory and Applications, p. 1
[45] Cf. Yaakov Stern (2007) Cognitive reserve: Theory and Applications, p. 1
[46] Whalley & Deary et al. (2004) Cognitive reserve and the neurobiology of cognitive aging. p. 373
[47] Cf. James F. Sumowski (2015) Cognitive reserve as a useful concept for early intervention research in multiple sclerosis. In: Frontiers in Neurology. Volume 6, Article 176. doi: 10.3389/fneur.2015.00176. here p. 2

is also supported by the reduced risk for dementia of older adults that received a more sophisticated education and intellectually challenging occupation, often in combination with cognitively stimulating leisure activities. A similar conclusion can be drawn according to the findings of Perani et al. (2017), where the significance of cognitive activities and environmental factors, including stimulating activities, cognitive, social, and physical, complemented by a high socioeconomic status and intellectual achievements in education and occupation, even suggest its potential as a delaying factor regarding the onset of dementia.[48]

Significance and adjacent concepts

The complex mental activity and continual engagement of cognitive control abilities[49], coherent with the regular usage of more than one language, over the lifespan aid the building of a capacity to compensate, when facing pathological neural changes and decline. It is due to the robust connectivity in the neuronal system resulting in an increased cognitive reserve that leads to a more effective resilience against impairment.

The benefits of a higher cognitive reserve offer advantages even after the diagnosis by providing a slower progression of the decline in some cognitive areas[50] due to the more efficient cognitive networks.

The analysis of the cognitive reserve of the patient, enables earlier detection of dementia related diseases. A crucial key point of cognitive reserve that must be established is that it continues to change and evolve throughout the lifespan. This allows the conclusion that cognitive reserve can still be improved later in life offering an overall improvement of the quality of life by reducing the emergence and slowing down the progression of Alzheimer's disease and other cognitive problems.[51]

In connection with cognitive reserve the notion of maximal lifetime brain growth (MLBG), belonging to the genetic factors, must be considered as well. A larger MLBG also implies that the loss of more brain volume can be endured before reaching cognitive impairment, being

[48] Cf. Daniela Perani; Mohsen Farsad & Tommaso Ballarini et al. (2017) The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia. In: The Proceedings of the National Academy of Sciences, Volume 114, No. 7, pp. 1690-1695, here p.

[49] Keera N. Fishman et al. (2021) Bilingualism in Parkinson's disease: Relationship to cognition and quality of life. In: Journal of Clinical and Experimental Neuropsychology. Volume 43, Issue 2. pp. 199-212. doi: 10.1080/13803395.2021.1902946. Epub 2021 Apr 8. PMID: 33827353. p. 1

[50] Cf. J. H. Barnett; C. H. Salmond; P.B. Jones & B.J. Sahakian (2006) Cognitive reserve in neuropsychiatry. In: Psychological Medicine, Volume 36. pp. 1053-1064. URL: doi:10.1017/S0033291706007501, here p. 1054

[51] Cf. M. Tucker, A & Stern, Y. (2011) Cognitive Reserve in Aging. In: Current Alzheimer Research, Volume 8, Number 4. Pp. 354-360. URL: https://doi.org/10.2174/156720511795745320.

directly proportional to the brain's resistance against damage.[52] MLBG in combination with environmental factors contribute to reserve in to delay cognitive decline.[53]

Cognitive reserve is claimed to be directly proportional to its effectiveness in coping with more severe or prolonged neuropathological damage.[54] Bilinguals, although at a similar stage in Alzheimer's disease as monolinguals, are on an average older, when the initial symptoms begin to surface and the cognitive impairment becomes noticeable, which indicates a better compensation in case of a neurodegenerative damage.

The individual descriptions for each concept clarify the differences between their mechanisms, the context to each other and their impact regarding neurodegeneration.

Brain reserve can be apprehended as the 'neurobiological capital', referring to cortical thickness including the total brain volume and quantity of neurons at a given time. It supports the brain to withstand ageing and neurodegeneration longer due to the increased amount of neural matter that can be lost before symptoms of cognitive decline can be detected. This passive model of reserve has however no significant influence once the initial threshold of brain decline is overstepped. Brain reserve is potentially impacted by brain maintenance and cognitive reserve, which again are impacted by genetic and lifestyle factors.[55]

Brain maintenance is a complementary concept to brain reserve, refers however to the reduced neural degeneration over time, which can be related to age or the disease. It can lead to a slower buildup of neuronal plaques and grey matter shrinkage. Therefore, in contrast to brain reserve, brain maintenance should be measured longitudinally to depict its development. To put both concepts into context, brain reserve aims to protect against the effects of pathology, contrary to brain maintenance, where focus lies primarily on the prevention itself. The latter can be influenced by genetic factors, like allelic variation in genes, as well as lifestyle factors including stimulating leisure activities.[56]

The correlation between cognitive reserve and bilingualism will be elaborated in the following chapter.

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[52] Cf. James F Sumowski and Victoria M Leavitt (2013) Cognitive reserve in multiple sclerosis. In: Multiple Sclerosis Journal, Volume 19, No. 9. pp. 1122–1127, Here p. 1123

[53] Cf. ibid. p. 1123

[54] Fishman et al. (2021) Bilingualism in Parkinson's disease: Relationship to cognition and quality of life. p. 1

[55] Matthias Berkes & Ellen Bialystok (2022) Bilingualism as a Contributor to Cognitive Reserve: What it Can do and What it Cannot do. In: American Journal of Alzheimer's Disease & Other Dementias. Volume 37(0). p. 1-9. - In: Intervention and Prevention of Neurodegenerative Disease: Building Resilience – Review, here p. 2

[56] Cf. Matthias Berkes & Ellen Bialystok (2022) Bilingualism as a Contributor to Cognitive Reserve: What it Can do and What it Cannot do. In: American Journal of Alzheimer's Disease & Other Dementias. Volume 37(0). p. 1-9. - In: Intervention and Prevention of Neurodegenerative Disease: Building Resilience – Review, here p. 2

1.3 Research question and thesis structure

The active usage of more than one language brings neurological benefits and also provides protection against cognitive impairment. The positive impact of bilingualism in delaying the onset symptoms of Alzheimer's and most dementia related illnesses has already been proven by previous research studies conducted in the field of neurolinguistics. An additional aspect of this research papers consists of the differentiation and thorough consideration whether different degrees of bilingualism, summarized as the bilingualism gradient, also result in varying resistance or whether it primarily can be found when comparing bilinguals with monolinguals. Therefore, it is to be determined whether a certain degree of bilingualism is necessary for a significant neuroprotective benefit4 although it is supposed that with increasing proficiency in multiple languages, the neuroprotective advantage improves as well.

The initial thought for the hypothesis of this study is based on the theory, that if bilingualism can prevent the early expression of neurodegeneration in Alzheimer's and other dementia related diseases, that its sphere of action probably is not limited to the diseases mentioned above but can be applied to other neurodegenerative diseases including Parkinson's or Huntington's disease in general. Direct research results in this field are limited and less common but exist. Based on this derivation, as bilingualism does not only strengthen the specific neuronal regions responsible for Alzheimer's and dementia related diseases, but leads to a general improvement of cognitive reserve, bilingualism could be an effective general factor against most neurodegenerative diseases.

2. Theoretical framework

Following the medical and terminological foundation, the individual connections between bilingualism and cognitive reserve as well as Alzheimer's disease will be elaborated further.

2.1 The correlation between bilingualism and cognitive reserve

From a linguistic perspective the knowledge of a certain language has mostly been analysed regarding its elements within a language system or its sociolinguistic effects. The interesting aspect of this study is however that it focuses on the correlation between bilingualism and its impact on the neurological mechanisms, especially the cognitive reserve. A difference between bilinguals and monolinguals were first discovered by Saer in 1923.[57] Cognitive reserve explains the individual differences in cognitive level including the variation in functional abilities, when

[57] Cf. Liu H and Wu L (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. In: Frontiers in Psychiatry Volume 12, Article 696015. URL: doi: 10.3389/fpsyt.2021.696015, p. 2

showing signs of continuous decline due to ageing or disease. Although an important presupposition of this study, the positive correlation between CR and bilingualism is not without controversy. To delay neurodegeneration in general and preserve cognitive performance, a combination of neuroprotective mechanisms, factors aiming to prevent cognitive decline, and compensatory mechanisms, concluding factors allowing the adaptation to declining neural functioning, are necessary. Since the factors can work combined but also alone and the concepts of cognitive reserve and brain reserve have different underlying mechanisms, the hypothesis, whether it is possible to have one but not the other, emerged. [58]

The defining characteristics of bilingualism are not without controversy as there are no absolute and universal criteria that must be fulfilled. Bilingualism can be understood as the regular use of two or more languages with a native language, referred to as L1, and a second acquired language, L2. Around 50% of the world's population speaks more than one language. Due to the strongly varying levels of proficiency, the tendency to include bilinguals can lead to significant discrepancies between its effectiveness against cognitive decline. It is important to note that the neurocognitive profile of bilingualism is significantly susceptible to the different factors determining the second language such as level of proficiency, context of use or age of acquisition.[59]

To provide a positive correlation between bilingualism and neurodegeneration, the beneficial influence on cognitive reserve must be established. Bilingualism has been established as a significant contributor to cognitive reserve as it can be described as the most used activity in the daily life. According to psycholinguistic research, in bilingual individuals both languages are jointly activated, therefore the monitoring and attentive selection of the respective languages is necessary for a successful language production. This process of selection to access the required languages but also language use in general activates the whole brain, apart from a few posterior regions, which, due to its scope, contributes significantly to reserve. It can even as extensive as resulting in changes in the brain structure and the cognitive ability, including brain regions and processes unrelated to language processing or production as far as nonverbal

[58] Cf. Berkes & Bialystok (2022) Bilingualism as a Contributor to Cognitive Reserve: What it Can do and What it Cannot do. p. 1-2

[59] Cf. Liu H and Wu L (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. In: Frontiers in Psychiatry Volume 12, Article 696015. URL: doi: 10.3389/fpsyt.2021.696015, p. 2

domains.[60] The daily use of two, or more, languages improves the attention and cognitive control skills resulting in a strengthened cognitive reserve.[61]

The research results support the presupposition that on average, bilingual individuals show better results in cognitive tests investigating executive functions. Its scope however cannot yet be applied to young adults and children as research, challenging these findings, has not been able to reach the same results. The tendency that bilinguals outperform monolinguals in cognitive tasks is nevertheless often also the case in younger adults. The different aspects that can lead, such as the age of language acquisition, type and period of use and context are also of relevance. There is also the hypothesis, that the different forms and degrees of bilingualism can result in a varying efficiency[62] regarding neurodegeneration, which will be elaborated further in chapter 2.2.

Bilingualism can be regarded as cognitive reserve-enhancing factor aiding the resistance to avoid or cope with brain damage and cognitive decline. The impact of bilingualism on cognitive reserve as well as brain reserve and neural connectivity unfolds its impact evenly, not being restricted to the brain areas responsible for speech production and comprehension.

Long term active bilingualism can contribute to improved mental capacity and performance beyond the areas of language production and comprehension potentially offering an overall protection against cognitive decline.

To maintain cognitive functions aiding the protection against neuropathology, the efficient application and distribution of brain resources is necessary and can be provided by lifelong bilingualism. This can be achieved through the early acquisition of or proficient use of the L2.[63]

Through the examination of the "higher axial diffusivity in the left superior longitudinal fasciculus" in healthy older bilinguals in contrast to monolinguals, based on the comparison of seven specific factors including the "verbal and spatial intelligence quotient (IQ), age, education, Trail-Making Test (TMT), Mini Mental State Examination (MMSE), and gender,

[60] Cf. Matthias Berkes & Ellen Bialystok (2022) Bilingualism as a Contributor to Cognitive Reserve: What it Can do and What it Cannot do. In: American Journal of Alzheimer's Disease & Other Dementias. Volume 37(0). p. 1-9. - In: Intervention and Prevention of Neurodegenerative Disease: Building Resilience – Review, here p. 3

[61] Cf. Maurits Van den Noort; Katrien Vermeire & Peggy Bosch et al. (2019) A Systematic Review on the Possible Relationship Between Bilingualism, Cognitive Decline, and the Onset of Dementia. In: Behavioural Sciences 9(81). URL: doi:10.3390/bs9070081, Special Issue Individual Variation and the Bilingual Advantage - Factors that Modulate the Effect of Bilingualism on Cognitive Control and Cognitive Reserve. pp. 201-237, here p. 2

[62] Cf. Matthias Berkes & Ellen Bialystok (2022) Bilingualism as a Contributor to Cognitive Reserve: What it Can do and What it Cannot do. In: American Journal of Alzheimer's Disease & Other Dementias. Volume 37(0). p. 1-9. - In: Intervention and Prevention of Neurodegenerative Disease: Building Resilience – Review, here p. 3

[63] Cf. Liu H and Wu L (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. In: Frontiers in Psychiatry Volume 12, Article 696015. URL: doi: 10.3389/fpsyt.2021.696015, p. 2

and their interactions",[64] the delay of cognitive decline in bilinguals and the positive contribution of L2 to neural reserve has been proven.[65]

Among other factors, bilingualism is a significant "enriching exercise contributing to neuroplasticity"[66].

Part of the underlying mechanisms of bilingualism ensuring its protective effects can be ascribed to the adaptation of the brain to an increased effort caused by the coordination of multiple languages. The central cognitive mechanism called the language control mechanism, being part of the executive control system, can through its increased use support brain plasticity, mostly within the related cognitive control network.[67]

The relation between bilingualism and cognition is potentially bidirectional, a higher cognitive reserve leads to a resistance against neuropathology and therefore can delay cognitive decline. The active use of more than one language implicated neuroplastic changes. An element of bilingualism is an increased functional connectivity that compensates for, mostly disease-related, cognitive decline.

The analysis of brain structure through MRI scans showed that while cognitive reserve correlates with an increased volume of grey and white matter in the frontal and temporoparietal cortices, cognitive impairment can be detected by the decrease of grey matter in the prefrontal cortex.[68] The contribution of bilingualism to cognitive reserve is through two brain mechanisms, neural reserve and neural compensation.[69] It can be understood as the brains ability to either withstand cognitive impairment or actively recruit alternative brain networks to replace the damage. This can be also deducted from the comparison of the structural integrity of white matter, which on the same level is associated with cognitive impairment only in monolinguals, again supporting the beneficial contribution of bilingualism to cognitive reserve.[70] Consistent to the increase in grey matter and integrity of white matter due to bilingualism, according to neuroanatomic research, it also counteracts the decrease of grey matter volume in the left

[64] Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 4

[65] Cf. 3389/fpsyt.2021.696015, p. 2

[65] Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 4

[66] Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 4

[67] Cf. Perani & Farsad et al. (2017) The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia. p. 1690

[68] Cf. Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 4

[69] Cf. ibid. p. 4

[70] Cf. Matthias Berkes & Ellen Bialystok (2022) Bilingualism as a Contributor to Cognitive Reserve: What it Can do and What it Cannot do. In: American Journal of Alzheimer's Disease & Other Dementias. Volume 37(0). p. 1-9. - In: Intervention and Prevention of Neurodegenerative Disease: Building Resilience – Review, here p. 3

temporal lobe due to age. Within the scope of bilingualism, the proficiency in L2 also positively correlates with the density of grey matter in the left inferior parietal region.[71]

As bilingualism contributes to neural reserve and compensation, it could also lead to a greater tolerance for neuropathology following the manifestation of the disease. This is proven by neuroimaging showing greater brain pathology in bilinguals than monolinguals at the same cognitive level.[72]

The underlying mechanisms of bilingualism compensating for cognitive impairment include the recruitment of alternate brain networks when facing brain damage. Through the constant switching between multiple languages, at least one must be supressed. With the aim to counteract the surfacing of symptoms, this process prepares the brain to use alternate connections and pathways, which is essential to secure neural compensation in the case of cognitive impairment. It is important to note that while bilingualism delays the symptoms of Alzheimer's and other dementia related diseases, it does not prevent the onset of the disease itself.

2.2 Positive connection between Alzheimer's disease and bilingualism

As described previously, the active usage of more than one language brings neurological benefits and provides protection against cognitive impairment. The positive impact of bilingualism in delaying the onset symptoms of Alzheimer's and most dementia related illnesses has already been proven by previous research studies conducted in the field of neurolinguistics.

Cognitive reserve is the ability to cope with brain pathology[73], in other words the brain's resistance to damage. The emphasis in this case is not on the brain areas, mostly the Broca's and Wernicke's area primarily responsible for language control, but instead on the stronger neurological connections. This can be concluded from the aspect of double memorizing, where bilingual speakers have the possibility to resort back to a certain concept with either one of the languages learned. The emphasis in this case lies on the improved neurological structure and

[71] Cf. Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 4

[72] Cf. Victor Costumero; Lidon Marin-Marin; Marco Calabria; Vicente Belloch; Joaquín Escudero; Miguel Baquero; Mireia Hernandez; Juan Ruiz de Miras; Alber Costa; Maria-Antònia Parcet & César Ávila (2020) A cross-sectional and longitudinal study on the protective effect of bilingualism against dementia using brain atrophy and cognitive measures. In: Costumero et al. Alzheimer's Research & Therapy 12:11. URL: https://doi.org/10.1186/s13195-020-0581-1. p. 2

[73] Franzmeier, N., Caballero, M. Á. A., Taylor, A. N. W., Simon-Vermot, L., Buerger, K., Ertl-Wagner, B.; Mueller, C.; Catak, C.; Janowitz, D.; Baykara, E.; Gesierich, B.; Duering, M. & Ewers, M. (2016) Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment. In: Brain Imaging and Behavior. Springer Science+Business Media New York 2016. URL: DOI 10.1007/s11682-016-9599-1

resistance of the brain to withstand cognitive decline. Cognitive stimulation is the keyword, when researching and debating the efficiency of bilingualism as it is due to the acquired cognitive reserve requiring multiple aspects of brain activity that bilingualism contributes to the onset delay of dementia symptoms "by approximately 4-5 years as compared with monolingual patients."[74]

Yet it is crucial to differentiate between the two forms of the disease as dementia occurs principally significantly earlier than Alzheimer's, therefore the absolute age of the patients alone is not sufficient but has to be regarded separately in coherence with the respective disease.

> "[…] bilingual patients who have been diagnosed with probable Alzheimer's report symptom onset up to five years later than monolingual patients. Post-mortem examinations of 137 elderly bilinguals revealed that, in some, Alzheimer's neuropathology had been quite advanced although, in life, they had evinced no symptoms whatsoever (Moore, 2010) because lifelong bilingualism contributes to cognitive reserve and to the consequent delay of symptom onset (Roger, 2014);"[75]

It is also a certain "enhanced executive functioning and plasticity that is assumed to lead to more cognitive reserve […]. Accordingly, bilingualism has been suggested to delay the clinical manifestation of […] Alzheimer's disease (AD)."[76] A strengthened condition of the brain is the most significant indicator, whether brain degenerative diseases have slighter chance at manifesting early on or progressing at a rapid pace. This reasoning can also be confirmed in a recent article from 2019 exploring this topic further, whereas it is stated that "bilingualism evokes brain-stimulation because it requires more neural processing than monolingualism (Marian and Shook, 2012)."[77] The neurological process to have access to two languages at any given time requires a long term enhanced brain activity, which again leads to a strengthened cognitive reserve being more resistant against a degenerative decline or dysfunction. "Sustained exposure to a complicated activity such as bilingualism maintains adult neurogenesis [the growth and development of nervous tissue] at a higher level and improves learning (Kramer et al., 2004)."[78] The theory that this complicated activity and an enhanced brain functional

[74] Kim Sujin & Jeon Seong Gak et al. (2019) Bilingualism for Dementia: Neurological Mechanisms Associated With Functional and Structural Changes in the Brain. Front. Neurosci. 13:1224. doi: 10.3389/fnins.2019.01224, p. 1

[75] Guillermo Albán-González & Teresa Ortega-Campoverde (2014) Relationship between bilingualism and Alzheimer's. In: Suma de Negocios 5(11). p. 126-133, here p. 128-129

[76] Woumans, Evy; Santens, Patrick; Sieben, Anne; Versijpt, Jan; Stevens, Michaël & Duyck, Wouter (2015) Bilingualism delays clinical manifestation of Alzheimer's disease. In: Bilingualism: Language and Cognition 18 (3), p. 568–574 C Cambridge University Press, here p. 569

[77] Kim Sujin & Jeon Seong Gak et al. (2019) Bilingualism for Dementia: Neurological Mechanisms Associated With Functional and Structural Changes in the Brain. p. 2

[78] Ibid. p. 2

connectivity could also be reached by acquiring a foreign language instead of long-term bilingualism, is refuted by the fact that it is

> "experience-dependent brain activity [that] provokes the formation of neural connections and structures in order to respond to the demands of managing multiple elements of numerous language systems […]. In addition, bilingualism extends to memory tasks (Wodniecka et al., 2010)."[79]

As it is mainly the memory loss that most dementia and Alzheimer's patients struggle with and is therefore seen as the most noticeable symptom of these degenerative diseases, the fact that bilingualism seems to improve the retrievability of information is the predication that through this access the delay of the onset timing as well as a certain deceleration of further progression can be confirmed. This aspect is not restricted in its success by factors such as language learning age as it showed "no difference in brain activation between L1 and L2 use in multilingual individuals (Briellmann et al., 2004)."[80] The fact that the learning age is irrelevant, when analysing the benefits of bilingualism leads to the conclusion that it is the proficiency and continuity in usage of both languages as it can only manifest and change the brain structure permanently if the sufficient time needed for these adaptation is ensured. Bilingualism also increases the grey matter density leading to the improvement of functional connectivity and preservation of brain structure, which results in the delay of the onset of dementia.[81] Yet the epoch-making discovery regarding the coherence of bilingualism and its influence on dementia and Alzheimer's is that

> "bilingualism recruits alternative brain networks to compensate for those that become damaged during aging and dementia (Marian and Shook, 2012), and the efficient utilization of brain networks to enhance brain function during aging increases cognitive reserve (Schroeder and Marian, 2012)."[82]

This finding was also reached by Stern in 2002 cited in an article by Albán-González and Ortega Campoverde from 2014 stating that

> "cognitive reserve appears to allow the brain to compensate for pathology by recruiting alternate brain networks, in the face of brain damage (Stern 2002)."[83]

Both statements converge to the assumption that bilingualism enables the brain to compensate a great number of diseases and symptoms affecting brain tissue. This concludes a universal

[79] Kim Sujin & Jeon Seong Gak et al. (2019) Bilingualism for Dementia: Neurological Mechanisms Associated With Functional and Structural Changes in the Brain. p. 2
[80] Ibid. p. 8
[81] Ibid. p. 8
[82] Ibid. p. 3
[83] Albán-González & Ortega-Campoverde (2014) Relationship between bilingualism and Alzheimer's. p.129

regenerative ability not only to delay the onset timing of dementia and Alzheimer's but also decelerating the progression past the manifestation of the first symptoms. The sphere of action of bilingualism enabling brain cells and networks to be multifunctional or even change their function and replace, or act as a substitute for, the area in the brain affected by the disease suggests a superior healing mechanism against almost all diseases. This multifunctionality not only allows the delay of onset symptoms but is also very likely to be beneficial during the progression of the illness once the first symptoms start to surface.

Although it could not be confirmed in MCI patients, in contrast to monolinguals, bilingual AD patients had a greater level of hypometabolism, which is a common characteristic of neurodegenerative diseases referring to the decreased brain glucose consumption,[84] in the left parietal, temporal, and frontal areas.[85] The status of bilingualism can also result in differing structural developments in the brain and therefore alter the effectiveness against cognitive decline. In the stage of Mild Cognitive Impairment (MCI), before the onset of AD or dementia, bilingual patients reported the occurrence of clinical problems approximately 7.4 years later than monolinguals.[86] Regarding the underlying mechanisms due to MCI, in contrast to passive bilinguals, the active use of multiple languages resulted in a "lower white matter integrity in the fornix but higher integrity in the parahippocampal cingulum and uncinate fasciculus"[87]. This indicates that the decomposition of white matter does not occur evenly but shows a differential pattern.[88]

To complement the description of bilingualism above, the criteria by which bilingualism can be defined includes an early acquisition of a second language, high level of proficiency, frequent switching, and overall balanced use of the languages.[89]

The use of multiple languages results in a constant strengthening process and a greater executive control caused by the necessary coordination and eventual suppression of the languages,

[84] Cf. Zilberter Y, Zilberter M. The vicious circle of hypometabolism in neurodegenerative diseases: Ways and mechanisms of metabolic correction. J Neurosci Res. 2017 Nov;95(11):2217-2235. doi: 10.1002/jnr.24064. Epub 2017 May 2. PMID: 28463438. Here p. 2217

[85] Cf. Victor Costumero; Lidon Marin-Marin; Marco Calabria; Vicente Belloch; Joaquín Escudero; Miguel Baquero; Mireia Hernandez; Juan Ruiz de Miras; Alber Costa; Maria-Antònia Parcet & César Ávila (2020) A cross-sectional and longitudinal study on the protective effect of bilingualism against dementia using brain atrophy and cognitive measures. In: Costumero et al. Alzheimer's Research & Therapy 12:11. URL: https://doi.org/10.1186/s13195-020-0581-1. p. 2

[86] Cf. Liu H and Wu L (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. In: Frontiers in Psychiatry Volume 12, Article 696015. URL: doi: 10.3389/fpsyt.2021.696015, p. 2

[87] Ibid. p. 4

[88] Cf. ibid. p. 4

[89] Cf. ibid. p. 3

especially due to frequent switching between the languages, offering improvement even in areas unrelated to language.

To emphasize the positive correlation between bilingualism and Alzheimer's disease empirically, five initial studies will be elaborated briefly. The Baycrest Research (2005) by Bialystok, as well as the Hyderabad Research (2006-2012) by Dr. Bak were both longitudinal studies to determine effectiveness of bilingualism to delay the onset symptoms of AD. Both results could confirm a delay in bilinguals by 4.5 to 5 years in contrast to monolinguals. The conclusions included the constant activation of two languages even in monolingual settings and the independence of education, however modified by the age of L2 acquisition.[90] The study by Tom Schweizer and Michael Weiner (2007) focuses on the interaction of the cerebellum with the frontal loves performing executive functions, using cognitive paradigms and neuroimaging, allowing the understanding of the effects of brain damage, often caused by AD or a head injury. The comparison between a monolingual and a bilingual groups of probable AD patients with equal education resulted in similar results despite the double amount of brain damage in bilinguals. Schweizer referred to the use of alternate pathways due to the suppression of one language and frequent switches as the logical conclusion.[91]

Within the Swedish Experiment (2012) Army veterans either learned a new language at a fast pace in about one year or were equally mentally challenged except language learning. The results were conducted by comparing the final MRI scans, which showed structural brain changes improving overall cognitive control and therefore demonstrate that the benefits are not restricted to lifelong bilingualism.[92] Finally, Brian Gold's studies (2013) focused on task switching abilities, that tend to decrease with age, comparing bilinguals with monolinguals, resulting in bilinguals outperforming their monolinguals peers in executive functions at the same age. The results were also supported by MRI scans of monolinguals showing a greater effort to complete the tasks.[93]

Clear clinical evidence, as for the delay and therefore effectiveness of bilingualism to protect against AD, are the findings regarding abnormal levels of amyloid plaques, a definite biological proof of AD, during the brain autopsy, in contrast to a symptom free life. This is also derived from the progression of AD, during which after the initial amyloid buildup the formation of

[90] Cf. Albán-González & Ortega-Campoverde (2014) Relationship between bilingualism and Alzheimer's. p. 128-129
[91] Cf. ibid. p. 129
[92] Cf. ibid. p. 130
[93] Cf. ibid. p. 130

tangles and loss of neurons signal further deterioration leading to the perceptible clinical symptoms.[94]

Although the effectiveness might not be identical, the beneficial effect of bilingualism is not limited to lifelong bilingualism resulting from a second language acquisition in early infancy, in form of a parallel first language acquisition, but can be detected in individuals, who became bilingual in adulthood.

The detailed analysis of the research results regarding the similarities and differences between monolingual and bilingual AD patients will be elaborated in chapter 4 and 5.

2.3 Causes, symptoms and progression of Parkinson's disease, Huntington's disease, and Multiple sclerosis

Parkinson`s disease

Parkinson's disease (PD) is after Alzheimer's disease the most common neurodegenerative disease. PD can be described as a chronic progressive neurodegenerative movement disorder. It is defined by "severe pars-compacta nigral-cell loss, and accumulation of aggregated α-synuclein in specific brain stem, spinal cord, and cortical regions"[95]. PD is a deadly disease and results in a shortened life span, but also significantly reduces the quality of life.

The central characteristics include the loss of nigrostriatal dopaminergic neurons in the substantia nigra of the midbrain with Lewy bodies in the remaining neurones.[96] The clinical manifestation includes motor impairments such as resting tremor, bradykinesia, postural instability, gait difficulty and rigidity. The decrease of dopaminergic neurons cannot be prevented but with the proper medication the symptoms can be relieved. The risk factors include genetic susceptibilities, that are linked to rare familial forms and include α-synuclein, leucine rich repeat kinase 2 (*LRRK-2*), and glucocerebrosidase (*GBA*)[97], and environmental factors. The dopamine neuronal function is compromised by mitochondrial dysfunction, oxidative damage, protein accumulation and phosphorylation.[98]

Although the direct cause of Parkinson's disease is unknown, a genetic predisposition with a greater sensitivity to toxic substances is an important causal factor. Other possible risk factors

[94] Cf. Vaughn (2011) Alzheimer's diagnostic guidelines updated for first time in decades.
[95] Andrew J. Lees, John Hardy & Tamas Revesz (2009) Parkinson's disease. In: Volume 373, Issue 9680, pp. 2055-2066. URL: https://doi.org/10.1016/S0140-6736(09)60492-X, here p.
[96] A. H. V. Schapira (1999) Parkinson's disease. In: BMJ 318:311. URL: https://doi.org/10.1136/bmj.318.7179.311, here p. 320
[97] Lees & Hardy et al. (2009) Parkinson's disease. p. 2056
[98] Bobby Thomas & M. Flint Beal (2007) Parkinson's disease. In: Human Molecular Genetics, 2007, Vol. 16, Review Issue 2, pp. 183-194. URL: doi:10.1093/hmg/ddm159, here p. 185

include the exposure to well water or pesticides, mostly in rural environments,[99] yet with only one identified environmental neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), even within 14 days of exposure.[100]

Among the early symptoms is the for Parkinson's disease characteristic tremor affecting about 70% of patients. The symptoms can however vary strongly, including numbness or muscle pain, often in the limbs, without an identifiable cause. The difficulty with standard repetitive tasks such as writing, brushing teeth, or eating with cutlery can be the sole reason for initial complaint. It is followed by fatigue, depression, and often significant weight loss.[101] Due to the general nature of the symptoms an early diagnosis often leads to other diseases. The diagnosis is difficult as there is no specific test or list of criteria to be fulfilled, remains therefore on the clinical level. To establish the clinical criteria, Hughes et al proposed bradykinesia and additionally either classic rest tremor, unilateral onset, progressive persistent asymmetry, excellent response to levodopa, levodopa induces dyskinesias, continued response to levodopa for at least five years.[102]

The therapeutic approaches include dopamine replacement therapy to reduce motor handicap as well as embryonic stem cells and gene therapy.[103] Nevertheless the timing for an effective treatment is extremely difficult at the time of sufficiently perceptible symptoms, the majority, 70-80% of the dopaminergic neurones are likely dead. This is also caused by the length of presymptomatic or incubation phase, which can also vary depending on the cause. Therefore, an effective treatment consists of the protection of dopaminergic neurones, focusing on prevention or slowing the progression, but also of the preservation of risked neurones.[104]

Even the hypothesis that PD is not necessarily one but a combination of several,[105] has been proposed. The pathological overlap with other neurodegenerative diseases, also AD,[106] supports the reasonable comparison regarding their underlying mechanisms in correlation with bilingualism.

Huntington's disease

Huntington's disease is an "autosomal-dominant, progressive neurodegenerative disorder with a distinct phenotype, including chorea and dystonia, incoordination, cognitive decline, and

[99] Cf. C. D. Marsden (1994) Parkinson's disease. In: Journal of Neurology, Neurosurgery, and Psychiatry, Volume 57, Issue 6, pp. 672-681. URL: 10.1136/jnnp.57.6.672. here p. 672
[100] Cf. Schapira (1999) Parkinson's disease. p. 321
[101] Marsden (1994) Parkinson's disease. p. 672
[102] Ibid. p. 673
[103] Lees & Hardy et al. (2009) Parkinson's disease. p. 2058
[104] Schapira (1999) Parkinson's disease. p. 322
[105] Ibid. p. 323
[106] Ibid. p. 323

behavioural difficulties"[107] affecting mostly the striatum. It is the most common hereditary neurodegenerative disease including progressive uncontrolled motor movements as well as cognitive and psychiatric deficits. Therefore, genetic testing can be essential for an early diagnosis.

HD affects the extrapyramidal motor system as well and contributes significantly to dementia.[108]

The underlying mechanisms are not yet investigated sufficiently, however the identification of the mutant protein 'huntingtin', resulting from an expanded CAG repeat causing a polyglutamine strand of carriable length at the N-terminus, has been conducted successfully. [109]

Since a genetic mutation does not trigger the development of HD instantly, an underlying biochemical event is presumed, which is either the nucleation of a misfolded form of polyQ-expanded HTT or the accumulation of protein deposits, sufficient to start the progress, needing decades to occur.[110]

The cause of HD is an expanded CAG trinucleotide repeat of no determined length in the gene HTT, which encodes the protein huntingtin. A mutation exists when huntingtin has abnormally long polyglutamine sequences that lead to toxicity and speeds up the decomposition of the protein, resulting in neuronal dysfunction and death of the patient.[111]

Assessing the relevance of alleles of HTT with CAGs accurately, the number is crucial. Lower than 35 CAGs equal no risk, between 36-40 CAGs it is ambivalent, but possible and over 40 CAGs, the disease is inevitable, yet possibly not surfacing within the lifetime. The number of alleles, with the same CAG extension, as such however does not have an impact on the onset timing of symptoms. Merely the homozygosity of the CAG mutation, being extremely rare, can cause an increase in severity.[112]

The main areas suffering from atrophy due to HD are the caudate nucleus, putamen, globus pallidus and the cerebral cortex, especially large neurones in layer VI. This is complemented by receptor changes in the basal ganglia, varying according to the different stages of HD.[113]

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[107] Francis O. Walker (2007) Huntington's disease. In: The Lancet, Volume 396, Number 9557, pp. 218-228. URL: https://doi.org/10.1016/S0140-6736(07)60111-1. Here p. 218

[108] S. Davies & D. B. Ramsden (2001) Huntington's disease. In: Journal of Molecular Pathology, Volume 54, Issue 6, pp. 409-413. URL: 10.1136/mp.54.6.409, here p. 409

[109] Walker (2007) Huntington's disease. p. 218

[110] Cf. Steven Finkbeiner (2011) Huntington's Disease. In: Cold Spring Harbor Perspective in Biology 3:a007476. pp. 1-24. URL: 10.1101/cshperspect.a007476. here p. 3 [citing Chen et al 2002]

[111] Gillian P. Bates, Ray Dorsey & James F. Gusella et al (2015) Huntington disease. In: Nature Reviews Disease Primers 1, Article 15005. URL: https://doi.org/10.1038/nrdp.2015.5,

[112] Finkbeiner (2011) Huntington's Disease. p. 2

[113] Cf. Davies & Ramsden (2001) Huntington's disease. p. 409

Although age is not a requirement, the age of onset of symptoms on average is around 40 years, not excluding juvenile and senior variants. [114] This is mostly because the HD alleles (40-50 CAGs) produce symptoms around this age. [115]

Early symptoms include loss of balance, chorea, sudden, unintended, and uncontrollable movements of the arms, legs, and facial muscles,[116] and often also previous personality changes,[117] which become more severe as the disease progresses.

In the absence of a cure and effective disease-modifying therapies against HD at the moment, the application of targeted huntingtin-lowering drugs in the trial stage and the development of biomarkers, as a basis for future research are the only prospect resembling a therapy.[118]

Multiple sclerosis

The autoimmune disease multiple sclerosis (MS) is the most common neurological disease in young adults. Due to the diverse clinical manifestations and unpredictable course, the diagnosis is difficult. It is generally and overtly progressive disease causing the cumulation of severe neurological deficits such as brain atrophy and neuronal decline, lasting from onset until the death of the patient. The susceptibility consists of hereditary and environmental factors, including infections, nutrition, smoking, low vitamin D levels and a higher prevalence in women. The Epstein-Barr virus (EBV), being a prerequisite for increased neurofilament light chain levels and potentially increases the risk of MS by 32-fold.[119]

The central causes for MS are elevated levels of neurofilament light chain, a biomarker for neurodegeneration, in the cerebrospinal fluid (CSF) that be detected up to 6 years prior to the onset of symptoms. Additionally, the HLA complex contains the greatest genetic susceptibility to developing MS, with HLA class II alleles driving disease risk.[120] The genetic susceptibility for MS is also linked to the genes in the major histocompatibility complex (MHC) on chromosome 6.[121]

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[114] Cf. Marianne J. U. Novak & Sarah J. Tabrizi (2010) Huntington's disease. In: BMJ 340(c3109). URL: https://doi.org/10.1136/bmj.c3109

[115] Finkbeiner (2011) Huntington's Disease. p. 4

[116] Chorea. Website of National Institute of Neurological Disorders and Stroke. URL: https://www.ninds.nih.gov/health-information/disorders/chorea#:~:text=Chorea%20is%20a%20movement%20disorder,%2C%20legs%2C%20and%20facial%20muscles.

[117] Cf. Marianne J. U. Novak & Sarah J. Tabrizi (2010) Huntington's disease. In: BMJ 340(c3109). URL: https://doi.org/10.1136/bmj.c3109

[118] Gillian P. Bates, Ray Dorsey & James F. Gusella et al (2015) Huntington disease. In: Nature Reviews Disease Primers 1, Article 15005. URL: https://doi.org/10.1038/nrdp.2015.5,

[119] Cf. Kathrine E. Attfield, Lise Torp Jensen & Max Kaufmann et al (2022) The immunology of multiple sclerosis. In. Nature Reviews Immunology 22, pp. 734-750. URL: https://doi.org/10.1038/s41577-022-00718-z, here p. 734

[120] Ibid. p. 735

[121] Cf. Lawrence Steinman (2001) Multiple sclerosis: a two-stage disease. In: Nature Immunology 2, pp. 762-764, here p. 762

Aside from the genetic factors, the greatest environmental risk factor for MS are gamma herpesviruses, especially EBV and human herpesvirus 6 (HHV-6) as both EBV and HHV-6 have been found in the CSF and brain tissue of patients with MS.[122]

Aside from the genetically vulnerable immune system, the timing is crucial regarding the risk beard by viruses, [123] as an infection before the age of 10 is often asymptomatic or resembles a simple acute infection, while in adolescence and young adulthood it can cause infectious mononucleosis and other serious complications such as anaemia and other neurological conditions. Furthermore, it does not only result in a greater risk for MS, but also shorten the time until reaching disease development. Generally, after EBV, the average time to disease onset after seroconversion is about of 7.5 years, with no neurodegeneration present prior to the EBV infection, which can be measured with the neurofilament light chain levels.[124] It is also important to note that the individual immune system including metabolism, diet, obesity, and especially the gut microbiome can either contribute to the risks or acting as a mitigating component against MS. The common symptoms include paralysis, sensory disturbances, lack of coordination as well as visual impairment.[125]

After the diagnosis, fluctuations in symptoms within the first few years are common and referred to as relapsing-remitting MS (RRMS).[126]

The clinical assessment of MS is problematic as different aspects of nervous system are involved and the course is strongly variable. The development of Disease Steps is an approach to evaluate disease progression. The Disease Steps combined with the Expanded Disability Status Scale (EDSS) often behave similarly and correlate strongly with each other, offering a useful and reliable tool for initial therapeutic decision making.[127]

In the early stages, new waves of inflammatory cells cause new lesions entering the central nervous system and elevate the demyelinated plaques in the white and grey matter. In contrast, in later stages the inflammation decreases, yet the susceptibility of the largest tissue for

[122] Kathrine E. Attfield, Lise Torp Jensen & Max Kaufmann et al (2022) The immunology of multiple sclerosis. In. Nature Reviews Immunology 22, pp. 734-750. URL: https://doi.org/10.1038/s41577-022-00718-z, here p. 737
[123] Ibid. p. 737
[124] Ibid. p. 736
[125] Lawrence Steinman (2001) Multiple sclerosis: a two-stage disease. In: Nature Immunology 2, pp. 762-764, here p. 762
[126] Attfield & Jensen et al (2022) The immunology of multiple sclerosis. p. 734
[127] Cf. M. J. Hohol; E. J. Orav & H. L. Weiner (1999) Disease steps in multiple sclerosis: a longitudinal study comparing Disease Steps and EDSS to evaluate disease progression. In: Multiple Sclerosis Journal Volume 5, Issue 5. Pp. 349-354. URL: https://doi.org/10.1177/135245859900500508. here p. 349

neurodegeneration increases. The mitochondrial injury is the central element leading to brain damage.[128]

The beginning is often ascertainable by the autoimmune inflammatory 'strike' against the myelin sheath, an insulating layer, or sheath that forms around nerves, including those in the brain and spinal cord. This initial attack can last up to weeks, followed by a longer period of remission, even for years, with the risk of entering a secondary chronic-progressive state, where the disease progresses subliminally without distinct attacks yet result in the patients inability to walk.[129] The functional stages of MS are not clearly distinguishable, resulting in the Development of Disease Steps to ease the assessment, complemented by the Expanded Disability Status Scale (EDSS). The Disease Steps range from "0 = Normal; 1 = Mild disability, mild symptoms or signs; 2 = Moderate disability, visible abnormality of gait; 3 = Early cane, intermittent use of cane; 4 = Late cane, cane-dependent; 5 = Bilateral support; 6 = Confined to wheelchair; and U = Unclassifiable."[130] This continuous sequence also depicts the simplified progression of this disease.

Although not specific to autoimmune cells and acting as global immunosuppressants, a potential treatment approach to reduce relapse frequency is the suppression or elimination of central nervous system (CNS)-homing autoreactive immune cells. [131] Another treatment approach, based on genetic associations, involves the repurposing or development of drugs.[132]

3. Bilingualism as a generalized protective factor against neurodegenerative diseases

In the following chapters the specific characteristics of cognitive decline, bilingualism as well as the chosen methodology is elaborated further, followed by the detailed evaluation of previously conducted studies obtained from the literature review.

3.1 Primary process, indicators, and progression pace of cognitive decline

The process of cognitive decline can vary strongly according to the respective disease and the resistance of the patient against decline. Although there is no certain pattern that can be applied to cognitive decline in general, there are similarities that can be established and offer an overview of the progression. To analyse the different types and forms of cognitive decline not

[128] Cf. Hans Lassmann (2013) Pathology and disease mechanisms in different stages of multiple sclerosis. In: Journal of the Neurological Sciences, Volume 333, Issue 1-2. Pp. 1-4. URL: https://doi.org/10.1016/j.jns.2013.05.010. Here p. 1

[129] Cf. Steinman (2001) Multiple sclerosis: a two-stage disease. p. 2

[130] M. J. Hohol, E. J. Orav, H. L. Weiner (1995) Disease Steps in multiple sclerosis. A simple approach to evaluate disease progression. In: Neurology 45(2). Pp. 251-255. URL: https://doi.org/10.1212/WNL.45.2.251, here p. 251

[131] Attfield & Jensen et al (2022) The immunology of multiple sclerosis. p. 734

[132] Ibid. p. 735

only the pace of deterioration, but also the pattern of distribution must be considered. The combination of these factors can determine the variety of cognitive impairment and offer reference points for further research.

A clinical method to potentially determine the progress rate of deterioration if offered by the comparison of regional cerebral blood flow (rCBF) through single-photon emission computed tomography (SPECT) in rapidly and slowly progressing AD patients. This method is complimented by the Mini Mental State Examination (MMSE), applied to assess the decline rate. In this case higher score results were found in the more rapidly progressing group in contrast to the slower progressing group, which supports the correlation of the MMSE score and the pace of the progression. Low levels of rCBF in the right posterodorsal anterior and superior prefrontal cortices and in the inferior parietal cortex could be found in rapidly progressing patients. Furthermore, rapid deterioration, determined in the MMSE, correlates lower perfusion in the previously described regions. Concluding, the rCBF values can indicate the pace of cognitive decline.[133]

Subjective cognitive decline (SCD) is a specific form of cognitive decline as it describes the self-perceived impairment of cognitive functions over time. The criteria for SCD are the self-experienced continuous decline regarding the cognitive capacity, not directly caused by a certain event, and regardless of the symptoms, normal performance on cognitive tests. Although the two criteria are fairly defined, the self-experienced cognitive decline in itself is a common concomitant of the ageing process. The causes for an SCD vary strongly. An additional study focusing on the progression from SCD to MCI by comparing two groups, one randomly recruited and one actively seeking help in a clinical setting. The prediction suggested a higher progression in the clinical setting, in correlation with the presence of *APOE* ε4 allele, which increased the prediction accuracy of progression for SCD in a clinical setting.[134]

In studies investigating the correlation between the Framingham cardiovascular risk profile (FCRP), an added consisting of the presence and severity of vascular factors. and the cognitive impairment in AD patients can also contribute to the overall determination the effectiveness of bilingualism. The FCRP score for the 284 participants was calculated at the beginning and complemented by a follow-up after one year to determine the cognitive changes according to the Clinical Dementia Rating score. The overall results show, that, although a genetic

[133] Cf. Yasuhiro Nagahama; Hidehiko Nabatame & Tomoko Okine et al. (2003) Cerebral Correlates of the Progression Rate of the Cognitive Decline in Probable Alzheimer's Disease In: European Neurology, 50 (1) pp. 1-9. URL: https://doi.org/10.1159/000070851, here p. 1

[134] Cf. Beth E. Snitz; Tianxiu Wang & Yona Keich Cloonan (2018) Risk of progression from subjective cognitive decline to mild cognitive impairment: The role of study setting. In: Alzheimer's & Dementia, Volume 14, Issue 6, pp. 734-742. URL: https://doi.org/10.1016/j.jalz.2017.12.003, here p. 736

predisposition and an advanced vascular impairment can increase the risks as well as the accuracy of these findings, the FCRP score is equally reliable and can predict the progression of cognitive decline in all AD patients.[135]

Apolipoprotein E (APOE) ε4 allele, the most significant genetic, and therefore unmodifiable, risk factor for AD. Vascular impairment also increasing cognitive decline as a potential contributor to AD was speculated to be modifiable, but several following studies showed, that it is the aggregation of multiple vascular risk factors that have an impact on cognitive decline. Therefore, therapeutic measures show no significant effect regarding the deceleration of progression. There is however a strong correlation between FCRP and atherosclerosis markers, detected by an increase in the carotid intima-media thickness (IMT).[136]

Cognitive decline due to AD is a progressively deteriorating process that can be measured by key events. AD causes a continuously increasing dependence in ADL, which include the inability to dress, eat and wash often leading to an institutionalization and result in death around 8-10 years after the diagnosis. Although the key events are clearly defined, the pace of their occurrence is completely individual, therefore they cannot offer universal predictions, but can improve the long-term planning and care.[137]

SCD can also stand for subtle cognitive decline in preclinical Alzheimer's disease. A study from 2018 focused the early detection of the risk to decline rapidly with the integration of neuropsychological (NP) test scores. AD patients were classified either early, late or no SCD according to their test scores in the SCD criteria. These criteria included the frequency of wordlist intrusion errors, the correct use of retroactive interference and the efficiency to complete tasks. In this case the scores defining the process rate were integrated into the SCD criteria to provide an earlier identification of risk to cognitive decline before the indication is presented by the NP scores.[138]

Another study from 2020 investigated the relationship between the ATN classification, referring to amyloid, tau and neurodegeneration, cognitive decline, and the risk of dementia in SCD patients. The determination according to the ATN model is based on a PET scan or CSF

[135] Cobb & Wolf et al. (1995) The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. Neurology 45, pp. 1707–1712. URL: doi: 10.1212/wnl.45.9.1707, here p. 1710

[136] Giovanna Viticchi & Lorenzo Falsetti et al (2015) Framingham risk score can predict cognitive decline progression in Alzheimer's disease. In: Neurobiology of Aging, Volume 36, Issue 11, pp. 2940-2745. URL: https://doi.org/10.1016/j.neurobiolaging.2015.07.02, here p.

[137] Cf. Massimo Musicco & Katie Palmer et el. (2009) Predictors of progression of cognitive decline in Alzheimer's disease: the role of vascular and sociodemographic factors. In: Journal of Neurology, 256, pp. 1288-1295. URL: DOI 10.1007/s00415-009-5116-4, here p. 1288

[138] Kelsey R. Thomas & Emily C. Edmonds et al. (2018) Using Neuropsychological Process Scores to Identify Subtle Cognitive Decline and Predict Progression to Mild Cognitive Impairment. In: Journal of Alzheimer's disease, Volume 64, No. 1, pp. 195-204. URL: DOI: 10.3233/JAD-180229, here p. 195

β-amyloid for the amyloid levels (A), CSF p-tau for the tau levels (T) and an MRI-based medial temporal lobe atrophy to verify neurodegeneration (N). To ensure the credibility also a control group without SCD was among the participants. In the results, the control group showed no correlation between ATN and the cognitive abilities. Overall, the A+ profiles depicted a stronger decline in cognitive and executive functions, as well as an increased risk for dementia in general. Patients with the biomarker profile "A–T+N+, A+T–N–, A+T+N–, and A+T+N+" showed not only a greater risk for dementia but also a more rapid cognitive decline in contrast to the patients with a A–T–N– profile. Therefore, the methodology of biomarker profiles can be established as a reliable source for initial assessment to predict the risk and progression of cognition.[139]

A study from 2017 focused on establishing a correlation between abnormal cerebrospinal fluid (CSF) biomarkers of AD and the progression of decline in SCD patients. The abnormal CSF biomarkers were compared between two groups with the same age, one with SCD and the other with MCI. To have referential data, the progression was assessed during the 3-year follow-up with Cox-Proportial-Hazard models, based on the hypothesis that hazard ratio between two groups stays constant over time. According to the results, the CSF markers were significantly higher in MCI than in SCD, in contrast to amyloid deposition. In both groups, the combined abnormality of amyloid and tau was the most significant predictor of the clinical progression of cognitive decline.[140]

The prognostic predictors of cognitive decline progression, severity and duration cannot only be of biological but also of sociodemographic nature. Withing the scope of the longitudinal study conducted in 2009 by Musicco & Palmer et al. AD patients, with mild to moderate symptoms, the time-dependent probability of cognitive decline was evaluated and results in a 5-point decrease in the Mini Mental State Evaluation (MMSE) score. The factors included to determine their significance for AD progression were age, education, severity and duration of the disease, family history of dementia, hypertension, hypercholesterolemia, and type 2 diabetes. Age and education act counterintuitive and result in a more rapid progression.

Hypertension and hypercholesterolemia did not affect the progression significantly. A surprising finding is the reduced risk of rapid progression by 65% caused by diabetes, which

[139] Cf. Jarith L. Ebenau; Tessa Timmers & Linda M.P. Wesselman et al. (2020) ATN classification and clinical progression in subjective cognitive decline. The SCIENCe project. In: Neurology 95 (1). pp. 46-58. URL: https://doi.org/10.1212/WNL.0000000000009724. Here p. 46

[140] Steffen Wolfsgruber, Alexandra Polcher & Alexander Koppara et al. (2017) Cerebrospinal Fluid Biomarkers and Clinical Progression in Patients with Subjective Cognitive Decline and Mild Cognitive Impairment In: Journal of Alzheimer's disease, Volume 58, No. 3, pp. 939-950. URL: DOI: 10.3233/JAD-161252, here p. 939

offers an essential factor for the deceleration of disease progression and the foundation for further research.[141]

A contradictory effect of bilingualism was found between non-clinical patients, who are yet without symptoms, and clinical patients, already showing signs of cognitive impairment. The former did only experience an overall positive effect regarding their cognitive functions, but the rate of progression remained the same. Among the latter group, cognitive reserve has a wider scope and expedites the progression of decline.[142] This can be attributed to the presence of a stronger threshold, which can effectively prevent the onset of symptoms, when crossed however, does not offer a significant protection from further decline.

3.2 Efficiency determination process of bilingualism

Although bilingualism has been proven to improve the cognitive abilities, the full extent, and the underlying mechanisms, including the affected brain areas and their significance in correlation with bilingualism and cognitive decline are yet to be analyzed in detail. Previous research studies with the aim to assess the remaining cognitive abilities and determine the degree of impairment, manifesting in form of onset symptoms, mostly included tasks involving the executive control system. As a result, the relationship between the executive control system of the brain and the language control system could be established.

3.2.1 Underlying mechanisms of and brain altering changes due to bilingualism

The intensity of the language learning process, even for a short period of time, significantly contributes to the increase of hippocampus volume and "hippocampus volume and cortical thickness in the left middle frontal gyrus, inferior frontal gyrus, and superior temporal gyrus"[143]. There is also a close correlation between the left inferior frontal gyrus and the proficiency in the acquired language.[144]

A central sign of cognitive decline, that also allows the clinical measurement of the extent, is the accumulation of amyloid β (Aβ) and neurofibrillary tangles, enabling the early diagnosis of AD. In accordance with this finding, there is no or less correlation between the plasma Aβ-42/40 level and the loss of cognitive abilities. The loss of episodic memory due to ageing, the

[141] Cf. Massimo Musicco, Katie Palmer & Giovanna Salamone et al. (2009) Predictors of progression of cognitive decline in Alzheimer's disease: the role of vascular and sociodemographic factors. In: Journal of Neurology, 256, pp. 1288-1295. URL: DOI 10.1007/s00415-009-5116-4, here p. 1288

[142] Cf. Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 6-7

[143] Ibid. p. 6

[144] Cf. ibid. p. 6

executive functions as well as the perceptual speed are based on the dopamine (DA) system. The noradrenergic system can offer a neuroprotective effect through its repeated activation and therefore also contribute to cognitive reserve against AD. The activation mechanism of noradrenergic signalling pathway is potentially linked to the onset delaying effects of bilingualism in AD. The scope of bilingualism to ensure the protection against cognitive decline includes many neural factors such as the "nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), and brain-derived neurotropic factor (BDNF)"[145]. To include the biochemical mechanisms in the determination process regarding the effectiveness of bilingualism, brain metabolism and connectivity has been measured by using fluorodeoxyglucose (FDG)-positron emission tomography (PET). The results in bilinguals show a severe pattern of cerebral hypometabolism, previously established as a common feature of neurodegeneration, in several posterior brain regions as well as hypermetabolism, referring to elevated resting energy expenditure (REE), in the orbitofrontal, inferior frontal, and cingulate cortex. The connectivity between the posterior cingulate, subcortical regions and anterior cingulate indicate a compensation against neurodegeneration and has been associated with probable AD in bilinguals. Bilinguals with probable AD also show enhanced connectivity in the executive control and default mode networks. According to neuropathological research even early bilingualism can contribute to the executive and visual-spatial functions and cognitive reserve, based on lower levels of the CSF AD biomarker tau and fewer occurrence of preclinical AD.[146]

When analyzing the contributing effects of bilingualism to cognitive and brain reserve, according to Valenzuela and Sachdev (2006), the distinction between neurological and behavioral brain reserve can be of relevance. Neurological brain reserve, presumably biological and of genetic origin, is based on the theory that peak brain volume improves the effects on cognitive abilities and signs of dementia caused by brain pathology. Behavioral brain reserve, referring to cognitive reserve, determines the protection against the occurrence of dementia as well as slower progression rate of cognitive decline based on the sustained complex mental activity.[147]

In comparison to monolinguals, bilinguals show increased functional connectivity, unrelated to the state of health. Regarding the structural differences, the conclusion that bilingualism

[145] Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 5
[146] Cf. ibid. p. 5
[147] Cf. Ellen Bialystok; Fergus I.M. Craik & Morris Freedman (2007) Bilingualism as a protection against the onset symptoms of dementia. In: Neuropsychologia 45. p. 459-464

contributes to brain reserve was drawn according to the more severe age-related atrophy in areas of the frontal, parietal, and temporal lobules in monolinguals, as they are linked to cognitive performance. These results contribute additionally to the assumption that bilingualism is an effective counteracting mechanism against neurodegeneration by enhancing neural compensation and brain reserve.[148]

In studies based on structural neuroimaging, bilingual patients show an increase in the grey or white matter densities in "the anterior cingulate cortex (ACC), the left prefrontal cortex, the left inferior parietal lobule, and the left caudate"[149], which are linked to executive control and therefore strengthen the resistance against damage. Furthermore, a long-term second language use can also increase the white matter integrity as well as grey matter volume in the anterior temporal loves, the orbitofrontal cortex and inferior parietal lobules, contributing to neural reserve and therefore offering protection against cognitive decline. Bilinguals show increased neural efficiency in the prefrontal and ACC regions as well as in the frontoparietal network for executive control (ECN) and in the default mode network (DMN).[150]

The positive correlation between CR and increased grey and white matter volumes in the associated frontal and temporoparietal cortices has been assessed through MRI studies. The results also showed reduced diffusivity in the bilateral hippocampi. Although of no universal nature yet, the protective effect of cognitive reserve (CR) in neurodegenerative diseases was evaluated by using fluorodeoxyglucose and PET (FDG-PET). FDG-PET allows the measurement of the cerebral metabolism, which is an indicator for neuronal activity and viability, but also the resting-state brain metabolism, associated with synaptic function and density.[151]

Neural compensation contributes to brain reserve and can be described as the maintenance of cognitive function despite brain atrophy by using alternative networks effectively, which can also lead to a brain size increase of certain areas, which contributes to brain plasticity and the resistance against atrophy.[152]

Bilingual AD patients show more significant brain atrophy in the areas linked to AD, such as the left middle temporal lobes, than monolinguals. The results were informative in that the two

[148] Cf. Victor Costumero & Lidon Marin-Marin et al. (2020) A cross-sectional and longitudinal study on the protective effect of bilingualism against dementia using brain atrophy and cognitive measures. In: Costumero et al. Alzheimer's Research & Therapy 12:11. URL: https://doi.org/10.1186/s13195-020-0581-1. p. 2

[149] Perani & Farsad et al. (2017) The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia. p. 1690

[150] Cf. ibid. p. 1690

[151] Cf. ibid. p. 1690

[152] Cf. Costumero & Marin-Marin et al. (2020) A cross-sectional and longitudinal study on the protective effect of bilingualism against dementia using brain atrophy and cognitive measures. p. 2

groups experienced the same level of cognitive decline and therefore lead to the conclusion that, to obtain similar cognitive functions as the monolingual group, the tolerance of neuropathology and atrophy is stronger in bilinguals.[153]

Multilingual AD patients in the early phase of the disease have a thicker cortex in the frontal and related areas, associated with episodic memory, and therefore indicate effective memory compensation, based on the increased executive control abilities. Bilinguals uphold white matter connectivity between the frontal and posterior areas more effectively than monolinguals. Bilingualism can also increase neuronal connections in general, deducting from the finding that, compared to monolinguals, bilinguals have higher neocortical grey and white matter lobar volumes as well as grey matter structure in the temporal lobe. L2 acquisition and training can also result in structural changes in the inferior frontal gyrus, including its thickness. The proficiency in L2 is also related to a greater temporal pole volume in bilinguals. The changes in the brain structure caused by bilingualism include even the left inferior parietal lobule, the anterior cingulate and the subcortical structures, composing together the executive control network, clarifying the basis of enhanced performance of bilinguals in executive tasks.

The concept of neural compensation refers to the need to maintain cognitive functions, in case of brain damage, which can be achieved by increasing the use of the brain network. This process also results in the improvement of neural reserve, identifiable by the size increase of specific brain areas.[154]

Based on neuroimaging studies, bilingualism is also presumed to influence white matter (WM) structure, leading to the conclusion that high proficiency bilinguals show higher axonal density or myelination in WM tracts. These tracts connect among others the bilateral inferior frontal gyrus (IFG), the left superior temporal gyrus (STG), and the caudate nucleus, which are critical regions for bilingual language processing.[155]

Limitations

It is important to note that although this study focuses on the positive correlation between bilingualism and the delay of neurodegeneration, there are certain limitations that cannot be

[153] Cf. Costumero & Marin-Marin et al. (2020) A cross-sectional and longitudinal study on the protective effect of bilingualism against dementia using brain atrophy and cognitive measures. p. 2

[154] Cf. Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 4

[155] Cf. Simone Sulpizio; Nicola Del Maschio & Gianpaolo Del Mauro et al. (2020) Bilingualism as a gradient measure modulates functional connectivity of language and control networks. In: NeuroImage, Volume 205 Article 116306, pp. 1-10 URL: https://doi.org/10.1016/j.neuroimage.2019.116306. here p. 1

crossed, as, regardless of the effectiveness of the counteractive factors, neurodegenerative disease without a cure can only be delayed to a certain point, but not avoided completely.

Although effective in the initial stage, the impact of bilingualism decreases rapidly once the clinical symptoms of dementia have surfaced, even as far as allowing bilinguals to decline at a faster pace than the monolinguals. Bilingualism increases cognitive reserve complemented by the enhanced executive control as well as neural reserve, improving the left frontal and related areas. Therefore, the compensatory factors allow the delay of the onset, cannot however prevent the disease itself.[156]

Active bilingualism can contribute to the maintenance of brain activities in the posterior areas, producing more efficient memories, yet when comparing the scores in long-term memory tasks, active bilinguals did not perform better than monolinguals.[157]

In the course of dementia, when the frontal language control is affected, the risk of asymmetrical language impairment is higher in bilinguals. As the suppression of L1 becomes to straining, it results in the reversion to L1. At comparable clinical stages, the temporal neuropathology is more advanced in bilinguals, which points to a stronger resistance despite cognitive impairment. Another unexpected result offers the Boston naming test, used to assess the word retrieval abilities in patients with aphasia, AD, or other similar diseases, where bilinguals perform lower than monolinguals. Although the overall knowledge in L2 decreases significantly faster than the L1 performance, they tend to balance out as the disease progresses.[158]

The protective effect of bilingualism could not be confirmed by enhanced executive functions, measured with MMSE scores, which leads to the conclusion that it is the active use of languages that contributes to cognitive reserve rather than bilingualism itself. [159] This finding supports the previous results presupposing the active use of multiple languages to strengthen the neural connections and contribute to cognitive reserve.

The controversial research results investigating the correlation between bilingualism and neurodegeneration are often based on the inconsistent definition of bilingualism, including the irregular specification of L2 proficiency as self-perceived knowledge assessments are often inaccurate. Another difficulty is caused by the inconsistencies based on the variety and different types of bilinguals, often due to the timeline regarding the language acquisition, differentiating simultaneous or sequential bilinguals. Furthermore, the variety of remaining contributing

[156] Cf. Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 6
[157] Cf. ibid. p. 3
[158] Cf. ibid. p. 6
[159] Ibid. p. 6

variables such as education acculturation, native language or family structure are endless, which complicates the establishment of consistent conditions for research in this area. Lastly, the most significant factor, which can hardly be incorporated accurately in bilingualism studies are the cultural, emotional associations as well as social standing of the respective language. Although the positive effect of bilingualism is proven, it does not modify the progression rate of cognitive decline. Several studies concluded that cognitive reserve could differ in its efficiency according to the APOE genotype and show a stronger correlation in patients with the ε4 allele. A significant difference was discovered between the ε4- group and the ε4+ group, where in the latter group, cognitive reserve was identified as a risk factor increasing the progression ratio from MCI to AD dementia.[160]

3.2.2 Stages along the bilingualism gradient as an indicator for effectiveness

The conclusion that the active use of multiple languages offers neurological benefits as well as protection from cognitive impairment has been already established. The efficiency however, in the overall correlation between bilingualism and neurodegeneration, can vary according to the different levels of proficiency in L2. To determine, whether there is a threshold that must be reached to allow the significant neuroprotective benefit[161] of bilingualism, the several stages of the bilingualism gradient will be analyzed in detail.

The increased beneficial effect of lifelong bilingualism contributing to cognitive reserve and delaying the onset of cognitive decline for 4 to 5 years in AD patients and 7.4 years in MCI patients.[162] This concludes that although studies primarily focus on the delaying effect of bilingualism against Alzheimer's disease, it is even more effective in its preliminary state due to a milder impairment.

The difference between high- and low-proficiency bilinguals can be described based on the memory system, as the former engages the procedural memory system by using L2 implicitly, while the latter is more susceptible to AD.[163] According to this derivation, L2 proficiency is crucial for the effectiveness in delaying onset symptoms of cognitive decline.

[160] Cf. Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 6-7

[161] Cristina Sáez (2020) Actively speaking two languages protects against cognitive impairment. URL: https://www.uoc.edu/portal/en/news/actualitat/2020/360-bilingualism-alzheimer.html#ot-pc-content – access date: 09.03.2023 17:46

[162] Cf. Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 6-7

[163] Cf. ibid. p. 6

The proficiency degree of bilingualism can be regarded as the antidote against dementia. The exact relation regarding the dosage is not determined yet, however research results so far recommend a threshold 5 hours per week for L2 learning. To accomplish the maximal range of benefits, the lifelong exposure to both languages as well as their active use is necessary. The efficiency of bilingualism is based on the ability to use alternative networks enabling the maintenance of cognitive functions for longer.[164]

Despite the effectiveness of bilingualism against AD and dementia, the same impact could not be confirmed for MCI patients. This contradiction however is ascribed to the variety in methodology, samples, and possible inconsistencies regarding the evaluation.[165]

High proficiency in L2 can result in more convergent neurofunctional mechanisms. To investigate the differences in brain structures between high and low proficiency bilinguals, the Multilingual Naming Test (MINT) was conducted. The results of high proficiency bilinguals correlated with cortical thickness of the entorhinal cortex and middle temporal gyrus. In contrast, low proficiency bilinguals produced results correlating with the thickness of the left caudal anterior cingulate cortex, linked to error monitoring and task switching.[166]

Aside from the structural differences, the determination of effectiveness of late bilingualism, when L2 is acquired in adulthood, is difficult due to the inconsistency in motivation and frequency of use.[167]

The hypothesis of a bilingualism gradient allows the inclusion of inter-individual variables in brain functioning based on language experience. The continuum concept offers two main advantages. On one hand it portrays the specific nature of bilingualism including the heterogeneity between bilinguals but also the individual dynamic course over time. On the other hand, the various effects of bilingualism can be detected and interpreted more precisely. According to the Adaptive Control Hypothesis (Green and Abutalebi 2013), lifelong bilingualism can form the resting state of functional connections, presupposing the continuity of active language use as well as cognitively stimulating activity. The modifying factors on plasticity based on individual variability include linguistic distance between languages or cultural diversity aspects. When analysing bilingualism regarding the neural impact, socio-linguistic factors can be of significant character, determining the correct allocation of research

[164] Cf. Liu & Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. p. 6
[165] Cf. ibid. p. 3
[166] Cf. ibid. p. 4
[167] Cf. ibid. p. 6-7

results. Bilingualism modifies functional connectivity within language and control networks as well as between, and therefore contributes to brain plasticity.[168]

The stages along the bilingualism gradient begin with individuals, who only speak one language actively and are exposed passively to another and end with bilinguals with excellent proficiency in both languages and use them alternately daily. The conception of the bilingualism gradient was concluded including the age of acquisition (AoA) of L2, the activity of usage and the frequency of switching between the languages, primarily within the same context. Calabria attempted to determine the degree of bilingualism that has a neuroprotective effect by evaluating the difference between bilinguals by examining the population of Barcelona, as a highly bilingual group speaking Catalan and Spanish.

The study was conducted with 266 participants in total, 63 healthy individuals, 135 MCI and 68 AD patients. According to a questionnaire, the proficiency in each language was assessed and the results were correlated with the onset of symptoms and the age of neurological diagnosis. The resulting cognitive advantage was investigated further with various cognitive tasks, focusing on executive tasks including memory and cognitive control tests.

The results show that a high degree of bilingualism in active bilinguals delays the diagnosis of MCI, in contrast to passive bilinguals. The regular switching between languages trains the brain and enhances cognitive functions such as the executive control, which is responsible for the switching between tasks. The executive control system is also responsible for the switching between the languages supressing the one not actively in use. Therefore, with increasing proficiency and switching frequency in bilingual language use, the efficiency to resist brain damage improves as well.[169]

A neuroanatomical analysis shows that L2 learning, and use contribute to volume increase in multiple grey matter (GM) regions associated with language processing and bilingual language control. Accordingly, early L2 learners and high proficiency bilinguals have greater GM density than monolinguals.[170]

Along the bilingualism gradient, three main factors can aid to determine the effectiveness of bilingualism, the age of L2 acquisition (L2 AoA), L2 proficiency, and the relative frequency between L1 and L2. The determination process was based on the resting-state functional

[168] Cf. Simone Sulpizio & Nicola Del Maschio et al. (2020) Bilingualism as a gradient measure modulates functional connectivity of language and control networks. In: NeuroImage, Volume 205 Article 116306, pp. 1-10 URL: https://doi.org/10.1016/j.neuroimage.2019.116306, here p. 9-10

[169] Cf. Cristina Sáez (2020) Actively speaking two languages protects against cognitive impairment. URL: https://www.uoc.edu/portal/en/news/actualitat/2020/360-bilingualism-alzheimer.html#ot-pc-content – access date: 09.03.2023 17:46

[170] Sulpizio & Del Maschio et al. (2020) Bilingualism as a gradient measure modulates functional connectivity of language and control networks. p. 1

connectivity (rs-FC), measuring "spontaneous correlations in fluctuations of the BOLD signal during task-independent neural activity".[171] Despite of a still unclear universal agreement, the two factors contributing to brain plasticity most effectively are, first the L2 AoA, based on the malleable state of the brain in early years, and second the combination of L2 proficiency and use frequency. Both approaches correlate in that an early L2 AoA results in a more long-term bilingual language use, essentially ensuring the beneficial impact of bilingualism.[172]

3.3 Literature review as research methodology and data analysis

The arrangement of data and the following analysis will be gathered primarily in form of a systematic review of previously conducted neurolinguistic research studies. To determine the hypothesis as stated above and to establish a tendency or initial verification, the methodology of literature review the most adequate in this case as the personal collection of neuropathological data and evidence would exceed the frame and specific area of expertise of this study. In addition to this fact, the previously conducted studies were executed in strictly observed clinical environments and are therefore considered accurate enough to offer a basis for further derivations.

3.3.1 Data acquisition, structure, and realization

The research studies that have been executed so far, have aimed to confirm the positive correlation between bilingualism and the delay of onset symptoms of Alzheimer's and other dementia related diseases. The empirical data collection and possible verification in this study will consist of the detailed elaboration and analysis of these previously conducted studies focusing on the underlying mechanisms and the similarities between the results. To be able to extend the positive correlation between bilingualism and most neurodegenerative diseases and therefore analyse the hypothesis in detail a selection of other neurodegenerative disease, where the beneficial effect of bilingualism has already been initially assessed, such as Huntington's and Parkinson's disease, will be included as well. The inclusion of further diseases allows the initiation of a more general impact, although not all degenerative diseases have been investigated yet regarding their correlation with bilingualism, which only allows an initial conclusion.

[171] Sulpizio & Del Maschio et al. (2020) Bilingualism as a gradient measure modulates functional connectivity of language and control networks. p. 2
[172] Cf. ibid. p. 2

The structure follows a chronological path incorporating each study, summarizing the results, and considering, depending on the individual emphasis, the different side aspects of each research. The chronological structure allows the correct allocation of data and results as well as the composition of a logical comprehensive overview of the research developments over time. It is essential that potential links across the different neurodegenerative diseases and the respective research studies are highlighted to establish certain consistencies and possible patterns to offer a definite direction for further investigations. After reviewing the relevant literature regarding Alzheimer's disease in correlation with bilingualism the extension of the sources to the other two neurodegenerative diseases Parkinson's and Huntington's disease, already examined in relation with bilingualism, will follow. The similarities between the research results will be collected and subdivided into different categories, according to their effectiveness and frequency, to determine and compare their significance in the overall proportion. The extraction of analogies regarding the affected brain areas and underlying mechanisms of cognitive decline, caused by these diseases, and the different ways bilingualism aides in the maintenance of the cognitive connections and abilities, are the type of data that is provides the essential foundation for the conduction of this study. Along the analysis of the various neurodegenerative diseases, bilingualism remains as the one mutual component and therefore the mitigating results can be attributed to its efficiency. According to the derivation above, the foundation for the focus of this study is ensured by the comparative analysis of correlation studies between bilingualism and the 4 main neurodegenerative diseases and enables the determination whether bilingualism in fact can be ascertained as a generalized protective factor when facing neurodegeneration.

The research results dates included in this study range from 1984 to 2022. The focus lies on the studies from the early 2000s, but especially from the 2010s. The confirmation of the acute significance of this study is provided by the increasing number of studies focusing on dementia related diseases and possible counteracting factors as it reflects the difficulties of an aging society and its enhanced interest in searching for remedies.

This study will be conducted through the inclusion and analysis of studies, where first the relevant medical specifics of Alzheimer's disease as well as of Parkinsons's disease, Huntington's disease and multiple sclerosis are described to comprehend the basic underlying mechanisms and establish the groundwork for the following analysis. Second, the concept of cognitive reserve as its correlation between bilingualism and the individual neurodegenerative diseases, mentioned above, is elaborated. To understand the progression of cognitive decline, which is to be mitigated or delayed through bilingualism, the first initial signs and the primary

progress will be described concisely, allowing the identification of the initial symptoms contributing to an earlier diagnosis and therefore contributing to the development of effective therapeutic treatment measures. It is also essential to consider the different forms, types and therefore also varying effects of bilingualism, as the frequency in use as well as switching can be of crucial significance when determining the beneficial contribution of bilingualism in delaying neurodegeneration. After a short description and explanation of the literature review as the chosen methodology, the central element and main empirical contribution follows in form of a detailed and chronological analysis of previously conducted studies regarding the correlation between bilingualism and the individual neurodegenerative diseases as well as the collection and comparison of diverse similarities and differences. Finally, the conclusion of all results allowing the initial conclusion regarding the universal nature of the benefits provided by bilingualism completes the scope of this study.

The data collection and selection of literature was conducted in the span from April 2023 to September 2023 by evaluating the search results in the database of Google scholar to obtain the latest and most frequently cited research papers, which include the terms “bilingualism”, “cognitive reserve”, “Alzheimer's disease”, “Parkinson’s disease”, Huntington’s disease”, “Multiple sclerosis” and various combinations thereof.

The selection of literature was conducted based on various inclusion criteria such as the inclusion of both, bilingual and monolingual groups complemented by a healthy control group in contrast to the diagnosed patients as well as exclusion criteria such as the lack thereof.

The studies included differ strongly in the methods, the number and composition of the participants and the amount and quality of additional variables bearing noticeable effect on the outcome. The heterogeneous composition of sources leads to a brief analysis of each study individually instead of a summarizing overview complemented by a statistical meta-analysis.

According to the analysis of the retrospective literature review the positive correlation between bilingualism and Alzheimer’s disease has already been established the central aim of this study is to provide a narrowed down yet sufficient overview of research conducted in this field presented in a chronological order to look over the evolvement of research results over time. This offers the opportunity to summarize the research findings so far and point out a likely tendency in the future.

3.3.2 Critical evaluation of data obtained from the literature review

This study aims to include the latest research results based on the current linguistic and neurological evaluations to avoid out-of-date conclusions and allow for the incorporation of critical reviews.

Although it is a common practice and reliable methodology to build on existing academic knowledge and evaluate it in relation to these previous research results, it must be regarded critically. As most studies do not remain on the general level, their specific topic of interest can be fragmented, not offering an overall evaluation of results for further interdisciplinary studies. Literature review can be an utmost effective methodology, as it is conducted in form of a systematic collection and synthesis of previous research results, and therefore significantly contribute to theory development. It can also detect yet uncovered areas, that are needed to complete theoretical foundations or establish new concepts.

A common flaw of literature review is the incomplete scope or unsystematic structure, which can lead to either inaccurate conclusions or, based on the selection of evaluated literature, ignore certain contradicting facets, and therefore only offer a selective view on the respective subject. A literature review can be conducted according to different guidelines and depend strongly on the intended contribution, when selecting an approach. In this study the semi-systematic review will be applied. Although initially defined and analyzed within the respective fields, bilingualism, cognitive reserve, and the different neurodegenerative disease, due to the divergent specifics of linguistics and neurology, cannot be concluded to a full systematic review. It is not the aim of this study to critically review and compare the contradicting approaches and research results, but to establish the correlating factors, synthesize the similarities and filter out the underlying universal conclusions. The inclusion of development of research results over time can enlighten possible inconsistencies but also point out the constant elements, establishing fundamental groundwork for future research.

A significant intermediate level is established by the inclusion of review or meta-analysis articles. The additional analysis of articles, already critically reviewing the previously conducted studies within clinical conditions, allows the correct allocation of the results, attempting to prevent one sided conclusions.

On one hand, the main disadvantage of literature review as research methodology is presented by its increased susceptibility to bias. The exclusive inclusion of literature and research results validating the established hypothesis and the exclusion of contradicting arguments can lead to incorrect conclusions, which can again serve as a foundation for further research. The

continuation of such aftereffects can have a lasting harming effect on the accuracy of the resulting conclusions.

On the other hand, literature review, especially when conducted systematically, can offer a reliable source for further interpretations and extension of research, when the realization of a clinical study regarding the respective hypothesis is not achievable within its scope.

The latter is the main argument leading to the decision for this methodology, allowing the inclusion of relevant research results without presupposing the conduction of a new study. It is also an opportunity, by collecting the significant supporting and contradicting arguments regarding a new hypothesis, to identify research gaps, additionally contributing to the further development and investigation of yet unexplored or so far not proven research fields.

3.4 Chronological review and analysis of previous neurolinguistic studies evaluating the impact of bilingualism in neurodegenerative diseases

The aim of the present study is to determine whether the beneficial effect of bilingualism on Alzheimer's disease and other dementia related diseases, especially regarding the onset timing, can be extended to other neurodegenerative diseases such as Parkinson's and Huntington's disease. A repeated positive correlation would implicate a general counteractive outcome, according to which, bilingualism can be for the present identified as universal protective factor against neurodegeneration. This will be ensured by providing an overview of the studies that have been conducted either in the field of neurodegeneration and related diseases or in the field of bilingualism. The general interest in delaying or finding protective factors cognitive decline or neurodegeneration became increasingly relevant due to a continually ageing society. The particular interest in this case lies on the similarities of the underlying mechanisms regarding cognitive decline caused by neurodegenerative diseases while analysing the correlation to the structural peculiarities and changes caused by bilingualism.

The discrepancy between the slightly differing results regarding the effectiveness of bilingualism is caused by two main aspects. First, the benefits of bilingualism are significantly higher if acquired in and maintained since childhood, as the base for executive functions are formed and peek simultaneously at this time, therefore its benefits are mostly detectable later in life. According to this conclusion, a study conducted with young bilinguals as participants can hide or deform the impact and effectiveness of bilingualism. Second, the use of the second language is a reliable determinant of effectiveness. It significantly strengthens and improves the executive control mechanisms, as the time an individual spends using the second language

as well as a highly bilingual environment, securing a frequent use, including the presupposed frequent code-switching, thus improving structural brain connectivity.[173]

Research regarding the underlying mechanisms of Alzheimer's disease focused on standardizing biomarkers for amyloid and other possible signs of injury to the brain, including elevated levels of tau or decreased levels of beta-amyloid in the CSF, reduced glucose uptake in the brain as determined by PET, and atrophy of certain areas of the brain as seen with structural magnetic resonance imaging (MRI).[174] These strategies however are not sufficient to identify general mechanisms of cognitive impairment.

The studies regarding the correlation between Alzheimer's disease and bilingualism have been conducted primarily over the course of two decades. The overall number of articles included in this study concludes to 22, 11 for AD, two for PD, 3 for HD and 6 for MS.

The first significant research with this focus, included in this study, was conducted in 2007 by Bialystok & Craik et al. with 184 dementia patients, of whom 51% were bilingual. In the 5 years following the diagnosis, participants with higher education showed a faster deterioration in cognitive decline as they arrived at a comparable cognitive stage at a similar time. This result initiated the examination of the progression in bilingual patients. A subset of the participants showed similar results according to the Mini-Mental State Examination (MMSE) measuring the rate of decline over 4 years after the diagnosis, which indicates that although bilingualism contributes to the delay of onset symptoms, there is no change in the progression. Overall, the results showed a significant difference between the language groups as bilinguals experienced onset symptoms on average 4 years later than monolinguals, although all other parameters were equivalent, which is a prerequisite for the analysis of the correct interpretation of the results.

A summarizing article offering an initial overview of research regarding the positive inference of bilingualism and cognitive reserve was elaborated in an article written by Albán-González and Ortega-Campoverde from 2014 including various experiments and studies, such as The Baycrest Research from 2005, the Hyderabad research of Dr. Bak between 2006 and 2012, Tom Schweizer & Michael Weiner from 2007, The Swedish Experiment from 2012 and the studies of Brian Gold from 2013. All these studies are listed with their results supporting the viewpoint that bilingualism in fact can provide a significant improvement combating Alzheimer's. A detailed description regarding their conduction follows.

[173] Cf. Fraibet Aveledo, Yolanda Higueras & Theodoros Marinis et al. (2021) Multiple sclerosis and bilingualism. Some initial findings. In: Linguistic Approaches to Bilingualism, Volume 11, Issue 4, pp. 551-577. URL: https://doi.org/10.1075/lab.18037.ave, here p. 569

[174] Cf. Vaughn (2011) Alzheimer's diagnostic guidelines updated for first time in decades.

The Baycrest Research (2005)[175]

This research has been conducted with 184 patients supported laboratory tests, neuropsychological evaluation, and a Magnetic Resonance Image (MRI) scan.

After the probable diagnosis of AD, bilingual patients the report of onset symptoms of bilingual patients is delayed by up to five years. The comparison between bilinguals and monolinguals was conducted with a variety of cognitive tasks. This has been also supported by the findings of post-mortem examinations, revealing advanced neuropathology without the occurrence of any symptoms. The study was conducted over a span of one year, during which the onset timing was determined, acknowledging the higher age of bilinguals at the time of onset. The conclusion in this case was drawn due to the contribution of bilingualism to cognitive reserve and therefore also delaying the onset symptoms. According to Bialystok the constant activation of both languages even in monolingual settings is responsible for the increased resistance against decline, does not however offer protection against the disease itself.

Dr. Bak and the Hyderabad Research (2006-2012) [176]

This longitudinal study included the different subtypes of dementia and was the largest, conducted in this field, working 853 participants in comparison between 1947 and 2008. The results show that general intelligence and later-life cognition were positively affected by bilingualism despite L2 acquisition in adulthood and unrelated to the level of education. The overall conclusion leads to a delay of onset symptoms by an average of 4.5 years in bilinguals in contrast to monolinguals, conforming the research results of Bialystok.

Tom Schweizer & Michael Weiner (2007)[177]

This study focuses on the interaction of the cerebellum with the frontal loves performing executive functions, using cognitive paradigms and neuroimaging, allowing the understanding of the effects of brain damage, often caused by AD or a head injury. The comparison occurred between two groups with identified probable AD of similar education, but only one group being bilingual. According to the MRI scans, bilinguals has twice as much brain damage, yet both groups reached similar test results. The results allow the conclusion that bilinguals are better equipped to resist brain damage as through the switching between and suppression of languages trains the brain to use alternate pathways in the case of atrophy.

[175] Cf. Albán-González & Ortega-Campoverde (2014) Relationship between bilingualism and Alzheimer's. p. 128-129
[176] Cf. ibid. p. 129
[177] Cf. ibid. p. 129-130

The Swedish Experiment (2012)[178]

This experiment aimed to examine the benefits of adult bilingualism compared with lifelong bilingualism. The results show that L2 with AoA in adulthood expands the brain as well, however not exactly to the same extent.

The study was conducted with Army recruits as participants learning a new language, without prior knowledge, aiming to accomplish proficiency within 13 months, forcing a strict learning pace. The control group of civilians was also instructed in cognitively challenging activities, except language learning. The analysis of MRI scans showed structural brain changes in the language learning group in contrast to the civilian group, debunking the presumption that the benefits of bilingualism can only be achieved if maintained throughout a lifetime. The comparison of the MRI scans taken before and after the study showed a high variability in development, depending on the performance and degree of effort. The acquisition of more elaborate language knowledge, depending on performance, resulted in changes in the growth of the hippocampus, associated with new material learning and spatial navigation, the necessity of increased effort to obtain the same level of knowledge however resulted in the growth of the middle frontal gyrus, the motor region of the cerebral cortex. The results show that bilingualism, even if achieved in adulthood, contributes beneficially to cognitive control increasing its resistance to impairment.

Brian Gold's studies (2013)[179]

Brian Gold composed his study with older lifelong bilinguals to perform attention-switching tasks, as it is one of the abilities gradually decreasing with age. His findings confirmed that bilinguals can uphold their executive abilities longer as they age. The MRI scans showed an increased effort in monolinguals to complete the tasks, which leads to the conclusion that bilinguals are able to cope more efficiently with cognitive decline and therefore experience the restricting impact of brain atrophy and therefore confirm the beneficial contribution of bilingualism.

Manchon & Colombo et al. in 2015 investigated the impairment of both languages in late bilingual AD dementia patients, presupposing an increased impairment in the second language (L2) in comparison to the first language (L1). The difference in performance was compared according to language comprehension and production skills in both languages in late proficient

[178] Cf. Albán-González & Ortega-Campoverde (2014) Relationship between bilingualism and Alzheimer's. p. 130
[179] Cf. ibid.p. 130

bilinguals in a group of 13 AD dementia patients and a healthy control group of 12. The results showed that AD dementia affected all aspects of language and furthermore both languages, similarly, not allowing for a clear differentiation between L1 and L2. The impairing impact of AD could therefore not be primarily restricted the L2. The final conclusion reports that because late bilinguals show similar impairments in both languages, a shared language network can be assumed,[180] which contributes to a decreased effectiveness of bilingualism against AD, as patients cannot rely on the L2 skills and network to compensate for the impairment in L2.

Another research from 2015 by Woumans & Santens et al. confirms the previous findings of the beneficial contribution of bilingualism to delay AD. The study was conducted with 69 monolinguals and 65 bilinguals with a diagnosis of probable AD. The results showed that, after considering the potential influence of other variables, among others education or social background, bilinguals display a significant delay of 4.6 years in manifestation and 4.8 years regarding the diagnosis of AD. Therefore, the cognition that bilingualism contributes to cognitive reserve and therefor aids to postpone the symptoms of AD can be verified.[181]

The following study by Perani & Farsad et al. in 2016 investigated the impact of lifelong bilingualism as CR regarding its neuroprotective effect against AD. To determine the hypothesis, various tests such as the investigation of brain metabolism, analysing the synaptic function and density, and neural connectivity was included. Overall, 85 probable AD patients participated of which 45 were bilingual and 40 monolingual, with a significant variance in age as the bilingual group was on average 5 years older than the monolingual group. The results showed that, in congruent to the hypothesis, cerebral hypometabolism was more severe in the group of bilingual AD patients. The analysis of the brain metabolism showed an increased connectivity in the executive control and default mode networks in bilingual AD patients in comparison with the monolinguals. As previously stated, the degree of bilingualism also resulted in a distinctive protection of crucial neural networks, including neural reserve and compensatory mechanisms. In this case bilingualism is postulated as an equally successful proxy against neurodegeneration as cognitive reserve.[182]

The underlying neural mechanisms of cognitive reserve in Alzheimer's disease were also analysed in the dissertation by Nicolai Franzmeier in 2017. The study focused primarily on the

[180] Cf. Mélanie Manchon & Francoise Colombo et al. (2015) Impairment of both languages in late bilinguals with dementia of the Alzheimer type. In: Bilingualism: Language and Cognition, 18(1), pp. 90-100. URL: doi:10.1017/S1366728914000194, here p. 97

[181] Evy Woumans & Patrick Santens (2015) Bilingualism delays clinical manifestation of Alzheimer's disease. In: Bilingualism: Language and Cognition 18(3), pp. 568-574. URL: doi:10.1017/S136672891400087X, here p. 571

[182] Cf. Perani & Farsad et al. (2017) The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia. here p. 1690

resting-state functional networks, especially the fronto-temporal control network, which strongly correlates with cognitive reserve and was able to identify a resting state fMRI index of the fronto-parietal control network connectivity as a marker of cognitive reserve,[183] to promote a more defined identification of cognitive reserve.

In 2017, the study by Klimova & Valis et al. allows an insight in the specificity of the research methodology as it reviewed 14 studies with the focus on bilingualism as a delaying strategy regarding the onset of Alzheimer's disease, including 6 prospective and 8 retrospective studies. Despite the same focus, the findings differed as the retrospective studies confirmed a positive association between bilingualism and the delay of AD onset, the prospective studies stated the opposite.[184] Therefore, to determine a universal result in this case, further research is required.

According to an article by De Leon and Grasso from 2020, about the context between bilingualism and Alzheimer's, "it has been postulated that individuals with high cognitive reserve can sustain a greater degree of pathological burden before displaying clinical symptoms."[185] According to this statement, it is not necessarily the ability to speak more than one language that can contribute to the delay in onset timing with dementia and Alzheimer's, but rather a more clear-cut cognitive reserve. The study was conducted between 2005 and 2017, where the participants disclosed their complete clinical history and were tested neuropsychologically as well as neurologically by a multidisciplinary team. The exact speaker status was determined with a four-step procedure. First, the division of the participants into the basic categories of in a bilingual, monolingual, and an inconclusive group as was conducted according to the constructed chart indicating a bilingual language history. The participants divided into the last category were excluded from the study. In the second step, the identification of any form of AD was used to exclude further participants not meeting the requirements. In the third step, the remaining participants underwent a more in-depth review, overviewing eventual incorrect classifications. The last step was set to gather more detailed information about the linguistic personal background of the bilingual AD patients, including the age at which first symptoms appear, defined by the observation of family members or the participants themselves. The initial classification was followed by the comparison of

[183] Nicolai Franzmeier (2017) Neural Mechanisms of Cognitive Reserve in Alzheimer's Disease. Dissertation of the Graduate School of Systemic Neurosciences of the Ludwig-Maximilian-University of Munich, p. 77-78

[184] Blanka Klimova & Martin Valis (2017) Bilingualism as a strategy to delay the onset of Alzheimer's disease. In: Clinical Interventions in Aging, Volume 12, pp. 1731-1737. URL: https.//doi.org/10.2147/CIA.S145397, here p. 1735-1736

[185] De Leon, Jessica; Grasso, Stephanie M.; Welch, Ariane; Miller, Zachary; Shwe; Wendy; Rabinovici, Gil D.; Miller, Bruce L.; Henry, Maya L. & Gorno-Tempini, Maria Luisa (2020) Effects of bilingualism on age at onset in two clinical Alzheimer's disease variants. In: Alzheimer's & Dementia. The Journal of the Alzheimer's Association. (Issue 16) p. 1704-1713, here p. 1704

demographic variables and neuropsychological assessment scores. Although the results of both groups, monolingual, and bilingual, did not show significant differences either in the neuropsychological assessment scores nor based on demographic data, test results of episodic memory tasks showed a lower performance of the group with amnestic AD than patients with lvPPA (logopenic variant primary progressive aphasia). In this study, the results of an ANCOVA (covariates = sex, immigrant status and years of education)[186] showed no difference between monolingual and bilingual speakers in AD variants, however in the lvPPA group bilinguals were approximately 5.4 years older at the of the diagnosis than monolinguals.[187] Although these findings confirm the presupposed hypothesis of a beneficial correlation between bilingualism and AD, the inconsistencies indicated by different results from various studies can be caused by the missing incorporation of patterns within the varying patterns and premature diagnostic criteria for AD. This study by De Leon and Grasso however aims to dissolve contradictions by including different behavioural phenotypes, implicating varying underlying brain networks.

The correlation between bilingualism and different types of primary progressive aphasia (PPA) resulted in the conclusion that the beneficial effect of bilingualism is potentially network-specific and delays the age of onset in lvPPA variants, where the word-retrieval and repetition abilities are impaired caused by un underlying phonological deficit.[188] This leads to the inference that bilingualism shows enhanced effectiveness against impairment in the phonological network but less in the networks involving semantic or syntax and motor speech impairment. Bilingualism affects cognitive reserve in AD, primarily by increasing the grey matter volume and white matter connectivity in phonological networks.[189] According to the results from voxel-based morphometry (VBM), a neuroimaging technique to investigate focal differences in brain anatomy by differentiating between grey matter, white matter and cerebrospinal fluid,[190] "increased grey matter in the left inferior parietal cortex, Heschl's gyrus, [being the first cortical structure to process incoming auditory information,] the superior temporal gyrus, [which includes Wernicke's area,] and inferior frontal regions."[191] Additionally

[186] De Leon, Jessica; Grasso, Stephanie M.; Welch, Ariane; Miller, Zachary; Shwe; Wendy; Rabinovici, Gil D.; Miller, Bruce L.; Henry, Maya L. & Gorno-Tempini, Maria Luisa (2020) Effects of bilingualism on age at onset in two clinical Alzheimer's disease variants. In: Alzheimer's & Dementia. The Journal of the Alzheimer's Association. (Issue 16) p. 1704-1713, here p. 1708
[187] Cf. ibid. p. 1708
[188] Cf. ibid. p. 1709
[189] Cf. ibid. p. 1710
[190] Kiyotaka Nemoto (2017) Understanding Voxel-Based Morphometry. In: Brain Verve 69 (5), pp. 505-511. URL: DOI: 10.11477/mf.1416200776, here p. 505
[191] De Leon & Grasso (2020) Effects of bilingualism on age at onset in two clinical Alzheimer's disease variants. p. 1710

diffusion-weighted MRI (DWI) determined greater connection density in the left frontal and temporo-parietal network as well as in the left occipital, temporo-parietal and right superior frontal network in bilinguals in contrast to monolinguals.[192] This indicates increased grey matter volume and white matter integrity in regions overlapping with the impaired networks due to lvPPA, counteracting its symptoms, but not in medial temporal and anterior default mode networks, which are associated with amnestic AD, suggesting restricted effectiveness.[193] An additional aspect to be considered regarding the affecting scope of bilingualism is the later age of onset of amnestic MCI, the preliminary stage of AD, in bilinguals compared to monolinguals, implicating the same effect in AD, which could not be confirmed. This finding however indicates a faster progression in decline of bilinguals AD patients. De Leon and Grasso additionally support this conclusion with the results of Berkes et al.[194] reporting a similarly faster progression from MCI to AD in bilingual patients, verifying the theoretical framework of cognitive reserve ensuring a stronger threshold against decline, however, when crossed allowing for a more rapid deterioration.[195] The contribution of this article is essential in this study as it incorporates the different AD variants displaying the high variability within the same disease, and at the same time points out the complexity of this matter. Nevertheless, as the extent of this study does not allow for the inclusion of all MCI, AD and neurodegenerative disease variants, the focus remains on the correlation between bilingualism, AD, Parkinson's disease, Huntington's disease, and Multiple sclerosis to draw further conclusions and identify the gaps and direction of research required to achieve universality. The by De Leon and Grasso (2020) criticized low availability of objective data regarding L2 proficiency levels and the suggested view of bilingualism as a continuous variable were elaborated in chapter 2.2 along the bilingualism gradient, primarily investigated by Liu H and Wu L (2021). Another variant, only partly included in bilingualism studies correlating with AD is the immigrant status despite its significance for the beneficial impact based on the age and manner of L2 acquisition. The overall conclusion of the study by De Leon and Grasso documents a 5-year delay of symptom onset in lvPPA but not in AD patients, which indicates a beneficial impact of cognitive reserve, strengthened by bilingualism, is primarily restricted to the language variant of AD. [196]

[192] Cf. ibid. p. 1710
[193] Cf. ibid. p. 1710
[194] Cf. Berkes, Matthias & Bialystok Ellen (2020) Conversion of Mild Cognitive Impairment to Alzheimer Disease in Monolingual and Bilingual Patients. In: Alzheimer Disease & Associated Disorders, 34(3):225-230. URL: doi:10.1097/wad.0000000000000373.
[195] Cf. De Leon & Grasso (2020) Effects of bilingualism on age at onset in two clinical Alzheimer's disease variants. p. 1710
[196] Cf. De Leon & Grasso (2020) Effects of bilingualism on age at onset in two clinical Alzheimer's disease variants. p. 1711-1712

In the study conducted by Mendez & Chavez in 2020 the delaying effect of bilingualism regarding the clinical expression of AD was evaluated. The 253 participants, of which 74 were bilingual and 179 monolingual, were evaluated regarding among other language retrieving abilities, their demographic variables, native language, onset age and MMSE. The results showed a significant delay of onset of the mean of 4 years in bilinguals despite having worse MMSE scores, when other variables stayed without mentionable difference. Therefore, this study again confirms the beneficial delaying effect of bilingualism regarding the onset timing of AD. Overall, it was ascertainable that bilinguals regressed to their L1 gradually. However, a distinctive realization of this study that despite a general presupposition could not be verified in all studies with similar focus, is the frequent reversion to L1 can be interpreted that the L1 language networks can function as a supporting system, which contributes to the compensation of cognitive impairment and therefore delays the emergence of early symptoms.[197]

The dissertation study conducted by May at the University of South Dakota in 2020 focuses not only on the beneficial contribution of bilingualism to cognitive reserve to delay onset symptoms of AD, but also multilingualism as a part of a systematic review. After the anatomical, physiological, and behavioural assessment, the results showed that although there is no significant direct evidence of bilingualism or multilingualism providing cognitive reserve. Nevertheless, the benefits of bilingualism can be detected by the structural contribution to neural reserve increasing the compensatory neural networks, which aid to resist brain structure impairment without behavioural symptoms.[198]

The same conclusion was reached by Liu & Wu in their study in 2021, identifying bilingualism as a significant contributing factor to cognitive reserve and therefore effective element to delay the onset of AD, but not sufficient in itself.[199]

Parkinson's disease

Regarding the correlation between bilingualism and Parkinson's disease has already been assessed initially, and two significant ones in chronological order will be included in this study.

[197] Mario F. Mendez & Diana Chavez (2019) Bilingualism Delays Expression of Alzheimer's Clinical Syndrome. In: Dementia and Geriatric Cognitive Disorders, 48(5-6), pp. 281-289. URL: DOI: 10.1159/000505872, here p. 285-286

[198] Kirsten L. May (2020) Bilingualism/Multilingualism to Protect Against Cognitive Decline in Alzheimer's Disease and Other Forms of Dementia: A Systematic Review. Dissertation at the University of South Dakota, p. 49-50

[199] Haiqing Liu & Longhuo Wu (2021) Lifelong Bilingualism Functions as an Alternative Intervention for Cognitive Reserve Against Alzheimer's Disease. In: Frontiers in Psychiatry, Volume 12. URL: https://doi.org/10.3389/fpsyt.2021.696015, here p. 2-4

The study of Hindle & Martin-Forbes et al. in 2015 focused on cognitive reserve in Parkinson's disease and especially how bilingualism can affect executive function. The study was conducted with 57 monolingual English speakers and 46 Welsh/English bilinguals with Parkinson's disease comparing their performance in executive function (EF) tests. Mental generativity and speed were assessed with the Design Fluency and Verbal Fluency, subtests from the Delis-Kaplan Executive Function System (D-KEFS), combined with Raven's Coloured Progressive Matrices (RCPM). The working memory could be evaluated with the Wechsler Memory Scale, especially the Backwards Spatial Span, backwards Digit Span, and the Keep Track task. The Test of Everyday Attention (TEA) Elevator Counting with Distraction, Simon task, Stroop colour word naming and Go No-Go task were used to determine inhibition and management response, sustained attention as well as set-shifting and switching. The results showed that in this case the difference in performance between monolinguals and bilinguals are not significant, except for the correlation between the bilingual index, the high score being equivalent to a high degree of bilingualism, and an enhanced performance on the Raven's Coloured Progressive Matrices test, for nonverbal reasoning, as well as the Keep Track test, for working memory. These findings do not confirm the hypothesis of the study by Hindle and Martin-Forbes et al. nor the hypothesis of this study. The reasons for this divergence, as it has been proven successful for AD and the underlying mechanisms contributing to cognitive reserve are among other to achieve a more intact executive function when facing neurodegeneration through compensation, is yet to be determined. The probable underlying problem has been presumed to be caused by the similar disease severity and age of the participants in contrast to the comparison of similar disease severity and varying age or cognitive abilities. Additionally, the nonlinear rate of cognitive decline in PD could contribute to a difficult determination of the effectiveness of bilingualism. It is presumed however that bilingualism can delay the first inflection point of cognitive decline, causing the initial stable period to convert to dementia, but not advances deterioration.[200]

The second and most significant study so far regarding the correlation between bilingualism and Parkinson' s disease conducted by Fishman & Roberts in 2021 aims to determine the effectiveness of bilingualism by assessing the cognitive state of bilingual PD patients using neuropsychological tasks, among others, evaluating attention and working memory, language, executive function, and visuospatial ability. The results in this case are contradictory to the

[200] John V. Hindle, Pamela A. Martin-Forbes and Alexandra J. M. Bastable et al. (2015) Cognitive Reserve in Parkinson's Disease: The Effects of Welsh-English Bilingualism on Executive Function. In: Parkinson's Disease, Volume 2015 Article ID 943572. URL: http://dx.doi.org/10.1155/2015/943572, here p. 2-8

expected outcome as not only did bilingual PD patients not perform better than monolinguals with PD on attention and working memory and language measures, but a higher degree of bilingualism even correlated with lower scores in these measures.[201] The overall conclusion of this study depicts that bilingualism in PD is not associated with a better cognitive performance and is therefore of no confirming value to the hypothesis of this study.

Huntington's disease

The number of studies focusing on the correlation between bilingualism and Huntington's disease is of no significant amount. The two studies that will be presented in this section can be regarded as the initial foundation to include Huntington's disease to the neurodegenerative diseases benefiting from bilingualism. The focus lies on one hand on the structural changes in the brain caused by bilingualism and on the other hand on language reconfiguration abilities in bilingual Huntington's patients to determine its significance and effectiveness when facing neurodegeneration. The number of studies investigating the correlation between cognitive reserve and Huntington's disease are also limited and of which two will be elaborated further to establish the indirect connection with bilingualism as through the contribution of bilingualism to cognitive reserve and the beneficial impact of cognitive reserve against neurodegeneration, therefore the conclusion can be drawn that bilingualism aids the delay of neurodegeneration through its contribution to cognitive reserve.

Chronologically the first article by Bonner-Jackson & Long et al. from 2013 examined the relationship between cognitive reserve and longitudinal changes in cognitive functioning as well as brain volumes in prodromal Huntington's disease patients.[202] As a potential biomarker for HD, longitudinal changes in striatal, especially in the caudate and putamen, volumes, a critical component of the motor and reward system, have been proposed. Caudate atrophy has been detected as early as 14 years before the motoric symptoms result in a diagnosis. Therefore, the participants were selected based on their genetics confirming prodromal, gene expansion-positive, HD. To examine the longitudinal changes, four cognitive measures and three brain volumes were observed and assessed annually over approximately 6 years. The results showed that higher cognitive reserve contributed to a slower rate of change regarding the cognitive measure Trail Making Test, used to determine continued safe driving ability, as well as a slower

[201] Cf. Fishman et al. (2021) Bilingualism in Parkinson's disease: Relationship to cognition and quality of life. p. 1

[202] Aaron Bonner-Jackson, Jeffrey D. Long, Holly Westervelt, Geoffrey Tremont, Elizabeth Aylward, Jane S. Paulsen AND The PREDICT-HD Investigators and Coordinators of the Huntington Study Group (2013) Cognitive Reserve and Brain Reserve in Prodromal Huntington's disease. In. Journal of the International Neuropsychological Society 19, pp. 739-750. URL: 10.1017/S1355617713000507

rate of volume loss in the caudate and putamen brain structures, which are closely related to disease onset. These findings verify a beneficial impact of cognitive reserve, executive brain functioning and certain brain structure integrity in HD patients. [203] Through the contribution of bilingualism to cognitive reserve, these results are regarded as an indirect confirmation of the positive impact of bilingualism delaying the onset symptoms and even to a certain extent slow down the progression.

In the study of Calabria, Pérez Pérez, and Martínez-Horta et al. in 2018 the effects of Huntington's disease were analysed regarding the two mechanisms of bilingual language control (BLC), language inhibition and cross-language interference. Two experimental tasks, including a Stroop tack and a language switching task, were used to assess the performance of the two study groups of pre-symptomatic and early-stage HD patients. The differing results showed that in contrast to language inhibition, cross-language reference is not related to the HD pathology and is therefore not affected by bilingualism.[204]

The most important contribution so far regarding the correlation between bilingualism and Huntington's disease has been established by the article by Martínez-Horta and Moreu from 2019, where the study was conducted with early-stage bilingual HD patients assessing not only the degree of use and competence in the languages but also its impact on clinical parameters, brain structure and metabolism by applying not only grey-matter volume measures but also 18F-fluorodeoxyglucose (18F-FDG) metabolic uptake (SUVr).[205] The participants included thirty Catalan-Spanish bilinguals being carriers of the gene mutation (CAG≥39). Their classification based on the Unified Huntington's Disease Rating Scale's total motor score (UHDRS-TMS) resulted in two categories assessing either early or mild-stage HD.[206] Frequent lifelong bilingualism correlates with changes on 18F-FDG metabolic uptake in certain brain regions and contributes to an increase in GMV in a single frontal region, according to which the enhancement of inhibitory control and cognitive flexibility can be established. This concludes that a higher use of bilingualism decreases the clinical expression of symptoms.[207] The results showed that a high use of bilingualism correlated with higher grey-matter volume

[203] Cf. Bonner-Jackson & Long (2013) Cognitive Reserve and Brain Reserve in Prodromal Huntington's disease. p. 739

[204] Cf. Marco Calabria, Jesús Pérez Pérez & Saúl Martínez-Horta et al. (2018) Language reconfiguration in bilinguals: a study with Huntington's disease patients. In: Linguistic Approaches to Bilingualism 11 (6), pp. URL: DOI:10.1075/lab.18022.cal, Here p. 2

[205] Cf. Martínez Horta, Saul; Moreu, Andrea; Perez-Perez, Jesús et al. (2019) The impact of bilingualism on brain structure and function in Huntington's disease. In: Parkinsonism & Related Disorders, Volume 60, pp. 92-97, here p. 95

[206] Cf. ibid. p. 95

[207] Cf. Martínez Horta & Moreu et al. (2019) The impact of bilingualism on brain structure and function in Huntington's disease. p. 96

(GMV) in the inferior frontal gyrus. The significant effect of bilingualism also included significant changes in the fronto-temporal regions, especially in the dorsal anterior cingulate cortex, the anterior insula, and the ventromedial orbital prefrontal cortex, which was concluded based on 18F-FDG data. These regions contribute significantly to an increased inhibitory control and set shifting, but also aid the preservation of motor and functional capacity.[208] The final conclusion allows to state that lifelong bilingualism contributes to structural and metabolic brain changes improving cognition, movement, and functionality in HD patients.[209]

In the study from 2022 by Migliore & D'Aurizio et al. cognitive reserve was investigated in early HD patients to determine the influence of lifetime intellectual enrichment. Cognitive reserve was assessed with the Cognitive Reserve Index questionnaire (CRIq) consisting of the three sections education, working and leisure activities. The progression of HD was assessed at the beginning of the study and then annually for two years with the Unified Huntington's Disease Rating Scale (UHDRS) based on motor, cognitive, functional, and behavioural evaluations. The study consisted of 75 participants, whose clinical stage was determined according to the Total Functional Capacity (TFC) scale. To determine the efficiency of cognitive reserve, and therefore indirectly also of bilingualism against HD, the association between CRIq leisure time (CRIq_LA), the longitudinal functional impairment, being the differential TFC score between the initial HD assessment and after two years, and the progression of HD according to the UHDRS was evaluated. The results show that CRIq_LA positively correlates with an enhanced cognitive performance, which leads to the conclusion that it also contributes to a milder progression of HD.[210]

Multiple sclerosis

Multiple sclerosis is the most researched neurodegenerative disease after Alzheimer's regarding the correlation with bilingualism as well as cognitive reserve.

The first study included in this thesis by Sumowski and Chiaravalloti in 2009 is also the first research focusing on cognitive reserve as a protective option to retain cognitive functioning despite multiple sclerosis. The cognitive reserve of 58 participants with MS and 43 participants of the healthy control group was assessed with the Wide Range Achievement Test-Third

[208] Cf. ibid. p. 96-97
[209] Cf. ibid. p. 97
[210] Cf. Simone Migliore; Giulia D'Aurizio & Eugenia Scaricamazza et al. (2022) Cognitive Reserve in Early Manifest Huntington Disease Patients: Leisure Time Is Associated with Lower Cognitive and Functional Impairment. In: Journal of Personalized Medicine 12(1), pp. 36-48. URL: https://doi.org/10.3390/jpm12010036, here p. 36

Edition (WRAT-3) requiring the participants to read a specific list of words sorted from higher to lower frequency within the language. With this test, the premorbid verbal intelligence can be established. The overall results showed an increased efficiency in complex information processing and verbal learning and memory due to higher cognitive reserve and therefore indirectly due to bilingualism as well.[211]

Another study, also in 2009, by Sumowski and Chiaravalloti et al. postulates the positive impact of cognitive reserve when facing brain atrophy due to multiple sclerosis and is evaluated based on information processing (IP). The cognitive abilities of the 38 participants with MS were assessed with the Wechlser Vocabulary test and the Symbol Digit Modalities Test and Paced Auditory Serial Addition Task measuring IP efficiency. The state of brain atrophy was approximately determined by measuring the third ventricle width with high-resolution anatomical brain magnetic resonance imaging. The evaluation of the results showed that cognitive reserve contributed to a better IP efficiency. High cognitive reserve was even determined to mitigate the negative effect of brain atrophy on IP efficiency and therefore withstand MS neuropathology with a lower degree of cognitive impairment.[212] According to the results cognitive reserve is an efficient and significant methodology to counteract the cognitive impairment and brain atrophy caused by MS.

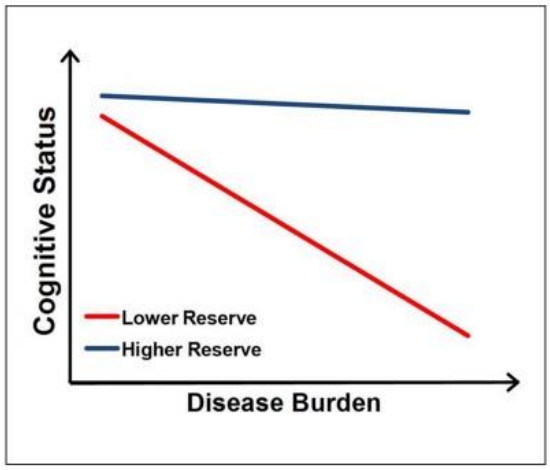
The next study was conducted in 2013 by Sumowski and Leavitt focusing on the ability of MS patients to withstand significant brain atrophy, often due to white matter lesions or cerebral atrophy without showing experiencing cognitive impairment. According to the reviewed literature regarding cognitive reserve in MS, the source of resistance are primarily based on heritable factors such as a larger maximal lifetime brain growth (MLBG) as well as environmental factors such as the amount of intellectual enrichment mostly in form of cognitively challenging leisure activities over a lifetime.[213] According to the results, higher cognitive reserve, often combined with brain reserve, does not only provide an effective coping

[211] James F. Sumowski & Nancy Chiaravalloti et al. (2009) Cognitive reserve protects against cognitive dysfunction in multiple sclerosis. In: Journal of Clinical and Experimental Neuropsychology, 31(8), pp. 913-926. URL: https://doi.org/10.1080/13803390902740643, here p. 914-923

[212] Ibid. p. 607-610

[213] James F. Sumowski & Victoria M. Leavitt (2013) Cognitive reserve in multiple sclerosis. In: Multiple Sclerosis Journal 19(9), pp. 1122-1127. URL: DOI: 10.1177/1352458513498834, here p. 1122

strategy to withstand MS without cognitive impairment longer but contributes a slower deterioration process as well, as seen in the figure below.

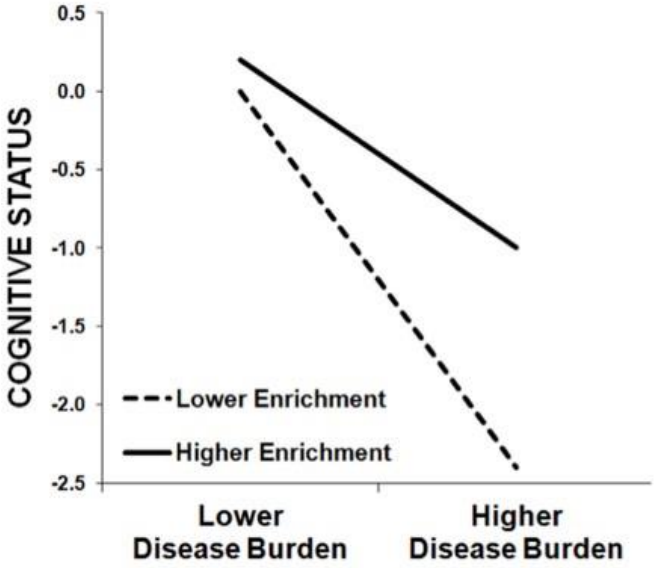


[214]

Figure 2: Correlation between cognitive status and disease

In this study, the correlation between bilingualism and MS can be established through the intermediate concept of cognitive reserve, among other factors, contributed by bilingualism.

The fourth relevant study included in this thesis was conducted by Sumowski in 2015, which, based on Sumowski (2013), proposes cognitive reserve as an effective concept for early intervention in MS. Similar to the previous study, a comparable diagram was also depicted in this study (see below) confirming the beneficial impact of cognitive reserve against MS, including the mitigation of progression rate.



[215]

Figure 3: Correlation between cognitive status and disease burden

[214] Sumowski & Leavitt (2013) Cognitive reserve in multiple sclerosis. p. 1123

[215] James F. Sumowski (2015) Cognitive reserve as a useful concept for early intervention research in multiple sclerosis. In: Frontiers in Neurology. Volume 6, Article 176. doi: 10.3389/fneur.2015.00176. here p. 2

The diagram (figure 3) shows that a higher enrichment, including intellectual leisure activities as well as bilingualism contributing to an increased cognitive status, even when facing a higher disease burden in form of brain atrophy continuously deteriorating in direction of and past the certain threshold, cognitive reserve can be identified as the main factor slowing the progression of further deterioration.

According to Sumowski (2015) additionally to cognitive reserve, brain reserve capacity plays a significant role as cognitive impairment is identifiable if brain volume reduction reaches a certain threshold, even allowing the conclusion that a larger head circumference and intracranial volume, related to MLBG, can contribute to a lower risk for dementia. MLBG is strongly associated with neuronal or synaptic count[216] strengthening the brains ability to resist atrophy by enabling alternate neural networks for compensation. Presupposing a high education and increased vocabulary, mostly achieved through lifelong bilingualism, cognitive reserve offers protection against cognitive deficiency and memory problems. Further contributing elements include cognitive leisure activity, not correlating with lifetime enrichment.[217]

Again, in this study, the correlation between bilingualism and MS is accomplished by the contribution of bilingualism to the intermediate concept cognitive reserve, nevertheless confirming its efficiency.

The fifth study by Martins da Silva & Cavaco et al. in 2015 investigates if, aside from demographic, clinical and genetic factors, education is an equally significant factor contributing to cognitive reserve. The study was conducted with 419 MS patients and a healthy control group consisting of 159 participants, whose cognitive state was assessed by comprehensive neuropsychological (NP) evaluation, the Hospital Anxiety and Depression Scale questionnaire complemented by the Mini-Mental State Examination (MMSE). Regarding the biological information, the human leucocyte antigen HLA-DRBI as well as the apolipoprotein E (ApoE) genotypes were included in the overall analysis. The results showed that, even considering other covariates, a higher education can mitigate the amount of cognitive deficit an MS patient experiences. These other relevant factors include age, Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Severity Scale (MSSS). The biological covariates HLA-DRBI and ApoE ε4 alleles did not have significant impact on the progression of MS. As bilingualism is an essential part of education, it is also a crucial contributor to cognitive reserve and therefore a counteracting mechanism against MS.

[216] Sumowski (2015) Cognitive reserve as a useful concept for early intervention research in multiple sclerosis. p. 2-3

[217] Cf. ibid. p. 2

The last, for this study relevant, article, written by Aveledo & Higueras et al. in 2020[218], investigated the correlation between bilingualism and multiple sclerosis focusing initially on the impact of bilingualism on executive, monitoring and inhibitory, control in multiple sclerosis patients. The participants were divided into four groups bilinguals with and without MS and monolinguals with and without MS. The linguistic abilities were determined by the Language and Social Background Questionnaire, assessing information about language background, including the proficiency, engagement period and spoken languages, as well as the social and educational background, including among others the profession and country of origin. The MS patients were diagnosed with relapsing remitting MS, based on the McDonald criteria. The physical state of the patients was assessed with the Expanded Disability Status Scale (EDSS), which did not determine a difference between bilingual and monolingual MS patients either regarding the average age of onset, the mean years with MS nor the degree of physical disability. The cognitive abilities were assessed with a neuropsychological evaluation, which included the Symbol Digit Modality Test (SDMT) for information processing speed, the Test of Verbal Learning España-Complutense (TAVEC) for verbal memory, the Brief Visual Memory Test Revised (BVMT-R) for visual memory, the Paced Auditory Serial Addition Test (PASAT) für attentional control and executive functioning and a verbal fluency task for executive function.[219] The results showed no cognitive impairment in the two groups without MS and no significant differences between the monolingual and bilingual groups of MS patients.

According to the hypothesis, bilingual MS patients are expected to show an enhanced performance in contrast to monolingual MS patients and therefore perform similarly than healthy monolinguals. This effect is attributed to the underlying beneficial mechanisms of bilingualism to enhance frontal-posterior attentional control mechanisms due to the consequent joint activation of two languages. Another aspect of the overall evaluation is the monitoring mechanism as part of the attentional network, which can be measured in form of monitoring costs. An increased monitoring costs indicated a poorer performance of monolinguals, which again confirms the effectiveness of bilingualism when facing MS.[220] The same advantage of bilinguals in contrast to monolinguals could not be confirmed regarding the inhibitory control mechanisms, as of 25 studies that have been reviewed by Aveledo & Higueras, only 6 could confirm a positive impact of bilingualism on inhibition.[221] Similarly to the studies introduced

[218] Cf. Aveledo & Higueras et al. (2021) Multiple sclerosis and bilingualism. Some initial findings. p. 567
[219] Ibid. p. 558
[220] Cf. Aveledo & Higueras et al. (2021) Multiple sclerosis and bilingualism. Some initial findings. p. 567
[221] Cf. Aveledo & Higueras et al. (2021) Multiple sclerosis and bilingualism. Some initial findings. p. 568-569

and analysed in this chapter, the factor between bilingualism and the prevention of neurodegenerative diseases.

Although the direct beneficial contribution of bilingualism to cognitive reserve is

Limitations

The heterogeneous nature of bilingualism regarding the degree of balance between the two languages, language dominance, and the proficiency regarding the different domains of expression and comprehension[222] does not allow a homogenous use of the term. The differentiation between lifelong bilingualism and acquiring a second language later in life is not in every case but often of importance in this matter.

> "Factors such as socioeconomic status (SES), social network, and leisure activities all seem to contribute to behavioural brain reserve and a delay in incident dementia (Fratiglioni, Winblad & von Strauss, 2007; Scarmeas, Levy, Tang, Manly & Stern, 2001; Valenzuela & Sachdev, 2006)."[223]

There are a few other significant factors that can contribute to a later emersion or development of dementia and Alzheimer's and therefore must also be considered according to the individual situation of the patients. Any abnormality influencing the significance of a certain element can be of great importance, when evaluating the effect and efficiency of bilingualism.

> "[…] older people who engage in brain-stimulating activities, such as reading books and playing board games, are less likely to experience memory loss associated with dementia than those who do not engage in these activities (Akbaraly et al., 2009). Cognitive stimulation strengthens the connections between neurons and promotes healthy cognitive aging (Valenzuela and Sachdev, 2006)."[224]

Nevertheless, the positive coherence of bilingualism has already been shown by various research teams and demanded awareness with its convincing results. Furthermore dementia is a broad concept as it can take different forms and is often a concomitant phenomenon to other degenerative neurological diseases such as Parkinson's disease or Creutzfeldt–Jakob disease, all of these with undefinable causes.[225] This can lead to an uncertain outcome as even if bilingualism is so far clinically proven to delay onset symptoms of dementia and Alzheimer's

[222] Gasquoine, Philip Gerard (2016) Effects of Bilingualism on Vocabulary, Executive Functions, Age of Dementia Onset, and Regional Brain Structure. In: Neuropsychology, Vol. 30, No. 8, pp. 988 –997, here p. 988

[223] Woumans, E., Santens, P., Sieben, A., Versijpt, J., Stevens, M., & Duyck, W. (2015). Bilingualism delays clinical manifestation of Alzheimer's disease. *Bilingualism: Language and Cognition, 18*(3), 568–574. URL: https://doi.org/10.1017/S136672891400087X, here p. 568

[224] Cf. Kim Sujin & Jeon Seong Gak et al. (2019) Bilingualism for Dementia: Neurological Mechanisms Associated With Functional and Structural Changes in the Brain. p. 2

[225] Cf. Katrin Bente Karl (2021) Mehrsprachige Pflegebedürftige in deutschen Pflegeheimen und das Projekt UnVergessen. Studierende an der Schnittstelle von Forschung und Gesellschaft, Springer VS, Bochum. p. 15

the difficulties caused by the concomitant neurological diseases are not clear. However, if bilingualism leads to a more strengthened cognitive reserve and can even enable alternative networks to compensate for the decaying ones, it should also counteract against Parkinson's or Creutzfeldt-Jakob, which is neither researched, lacking any indication as base, nor proven to be effective.

An additional and crucial factor that must be recognized, when evaluating bilingualism and its effectiveness is its complex nature. This can be detected upon two aspects. First, the completion of the same task can measure different abilities in monolinguals and bilinguals based on the experimental procedure. In the studies of Bosch & Sebastián-Gallés (2003) bilingual infants failed to discriminate between tokens from the same category according to the 'infant looking time' procedure at 8 months. The results were later corrected as in the study by Albareda-Castellot, Pons & Sebastián-Gallés (2011) bilingual infants were able to discriminate between the same contrast (/e/–/ɛ/), when conducted with the 'anticipatory eye movement' procedure. Second, identical stimuli can cause different responses in monolinguals and bilinguals. This was investigated with minimal pair words, which monolinguals were able to distinguish at 17 months (Stager & Werker, 1997), however bilinguals only 3 months later at 20 months (Fennell, Byers-Heinlein & Werker, 2007). This again was revised by Mattowk, Polka, Rvachew & Krehm (2010) with 17-month-old monolingual and bilingual infants with stimuli produced by bilingual speakers including tokens from different languages. In this case only bilinguals were able to differentiate between the minimal pair.[226]

Lastly, an important factor to consider, when determining the effectiveness of bilingualism is the problematic separation of the impact of bilingualism and immigration. The differences between monolinguals and bilinguals could therefore also be based on other factors such as the individual education, lifestyle, or ethnic background. Bilingualism cannot be treated as a unitary phenomenon or as a single panacea against neurodegeneration, as a combination of several factors are required to achieve an overall protection.[227]

As elaborated above, the beneficial impact of bilingualism, regardless of whether it is regarded as a contributing element to cognitive reserve or in itself, has been proven successfully and universally as a protective strategy against Alzheimer's disease.

[226] Ellen Bialystok (2014) Bilingual advantages, bilingual delays: Sometimes an illusion. In: Applied Psycholinguistics 35(5), pp. 902-905. URL: https://doi.org/10.1017/S0142716414000204, here p. 902-904

[227] Thomas H. Bak & Suvarna Alladi (2014) Can being bilingual affect the onset of dementia? In: Future Neurology 9(2), pp. 101-103. URL: 10.2217/FNL.14.8, here p. 102-103

3.5 Collection and comparison of similarities and restricting differences regarding the effectiveness of bilingualism and its correlation with neurodegeneration

In this chapter, the summary of the research results allows an initial conclusion regarding the efficiency of bilingualism in itself and as a contributor to cognitive reserve delaying the onset symptoms of neurodegeneration.

To establish the pattern of bilingualism, its contribution to cognitive reserve and its impact against neurodegenerative diseases and conclude the tendency of efficiency, the collection and comparison of the similarities as well as restricting differences is necessary.

The composition of studies was constructed in a chronological order, but primarily divided into sections according to each of the four most common neurodegenerative diseases. First, the studies focusing on the correlation between bilingualism and Alzheimer's disease were elaborated. Of the 11 articles included, one was a composed as a summarizing and reviewing article itself.

The confirming studies regarding Alzheimer's disease include Bialystok & Craik et al. (2007) as it reports a delay of onset symptoms of 4 years in bilinguals yet no change in progression.

The summarizing article by Albán-González and Ortega-Campoverde from 2014 elaborated 5 studies from which, varying in their extent, all confirm the presupposed beneficial contribution of bilingualism against neurodegenerative diseases. The Baycrest Research from 2005 reports a delay of onset symptoms by up to 5 years in bilinguals. The Hyderabad research of Dr. Bak between 2006 and 2012, being the largest and longest in its scale reports a similar result with a delay of approximately 4.5 years, even with late L2 acquisition. The study of Tom Schweizer and Michael Weiner from 2007 focused on executive functions and described similar test results in bilinguals and monolinguals but determined twice as much brain damage in bilinguals according to MRI scans, which again confirms the initial hypothesis. The Swedish Experiment from 2012 compared lifelong bilingualism and adult bilingualism in its effectiveness, determining a beneficial contribution of late bilingualism to cognitive control, but not to the same extent as lifelong bilingualism. The studies of Brian Gold in 2013 confirmed that lifelong bilinguals uphold executive abilities longer and at the same time discovered according to MRI scans an increased effort in monolinguals, which point to an earlier onset of symptoms as brain atrophy is detectable earlier than in bilinguals. Manchon & Colombo et al. in 2015 presupposed increased impairment of L2 in contrast to L1, which could not be verified as both languages were similarly affected, indicating a shared language network, resulting in a decreased effectiveness of bilingualism. However, Woumans & Santens et al. (2015) confirmed the effectiveness of bilingualism by determining a 4.6 year delay in manifestation and 4.8 years

diagnosis of AD. Perani & Farsad et al. (2016) analysed the contribution of lifelong bilingualism to cognitive reserve by measuring the cerebral hypometabolism indicating a more severe brain atrophy in the bilingual group, yet an increased connectivity in executive control networks. In this case the beneficial impact was determined based on the 5 years seniority of bilinguals in contrast to the monolinguals. The dissertation of Franzmeier in 2017 determined an increased resting-state functional networks due to cognitive reserve, contributed by bilingualism, also verifying its effectiveness. The results of the review article by Klimova & Valis et al. (2017) were inconclusive, with a slight tendency of an eight to six ratio towards a positive confirmation of the effectiveness of bilingualism, due to the contrast of the confirming retrospective literature to the prospective negative outcome. De Leon & Grasso 2020 confirmed the contribution bilingualism to cognitive reserve, which is a central aspect of its efficiency, however regarding AD no significant differences between monolinguals and bilinguals could be determined, only in lvPPA as patients were 5.4 years older at time of diagnosis. Mendez & Chavez (2020) determined a 4 year delay in bilinguals despite their low MMSE scores and also assess a regression to L1 gradually defining the L1 network as supporting system for compensation. The study of May in 2020, included multilingualism additionally to bilingualism could however not determine any direct evidence as to the beneficial correlation between bilingualism and the delay of AD symptoms. Nevertheless, the benefits in structural contribution to neural reserve and compensatory networks must be considered. Lastly, Liu and Wu (2021) confirmed bilingualism as contributor to cognitive reserve however not as a sufficient factor in itself.

The two included studies regarding Parkinson's disease could not confirm the hypothesised neuroprotective impact of bilingualism. The study by Hindle & Martin-Forbes et al. in 2015 determined no significant difference between monolinguals and bilinguals, except regarding the correlation between the bilingual index and an enhanced performance in nonverbal reasoning and working memory, which is not sufficient in its effectiveness. Similarly, Fishman & Roberts (2021) determined lower scores in attention and working memory measures bilinguals PD patients and therefore cannot verify an association with better cognitive performance.

Of the three relevant studies regarding Huntington's disease and bilingualism, all three confirm the hypothesized positive correlation. Bonner-Jackson & Long et al. in 2013 determined that higher cognitive reserve contributed to a slower rate of progression primarily in the brain areas related to disease onset and therefore bilingualism ensures indirectly the delay of symptoms as well as mitigation of progression through its contribution to cognitive reserve. Calabria &

Martínez-Horta et al. in 2018 evaluated the two mechanisms of bilingual language control and while language inhibition is related to bilingualism as it is part of the HD pathology affected by cognitive reserve, cross-language interference is not. The study by Martínez-Horta and Moreu in 2019 investigated bilingualism regarding its contribution to an increase in GMV. According to the results it enhances the inhibitory control and cognitive flexibility and therefore decreases the clinical expression of symptoms. Lastly, Migliore & D'Aurizio et al. (2022) focused on lifetime intellectual enrichment, including bilingualism, which all contribute to an enhanced cognitive performance, and therefore also delay of onset symptoms of HD.

Of the six studies investigating multiple sclerosis, all confirm the beneficial contribution of bilingualism as a counteracting factor against MS and two of which verify a mitigation of the progression rate of cognitive deterioration, in contrast to the other neurodegenerative diseases. Sumowski and Chiaravalloti in 2009 determined an increased efficiency in complex information processing and verbal learning and memory due to higher cognitive reserve and therefore indirectly due to bilingualism as well. Another study by Sumowski and Chiaravalloti et al. in 2009 determined the contribution of cognitive reserve to a better IP efficiency and therefore the ability to withstand MS neuropathology with lower impairment for a longer period of time. Sumowski and Leavitt (2013) focused primarily heritable factors such as MLBG, but also cognitively challenging leisure activities, including bilingualism, determining not only an initial beneficial impact but also slightly a slower deterioration process. The study of Sumowski (2015) determined the effectiveness of higher cognitive enrichment and cognitive reserve, including bilingualism, to delay the onset symptoms as well as slower the progression of cognitive decline. Martins da Silva and Cavaco et al. in 2015 focused on higher education, including bilingualism, as a strategy to mitigate the amount of cognitive deficit.

The results of the study by Aveledo & Higueras et al. in 2020 however showed no significant differences between monolinguals and bilinguals in their ability to compensate for cognitive decline.

In the section focusing on Alzheimer's disease, the studies can primarily verify the effectiveness of bilingualism through the delay of onset symptoms varying from 4 to 5 years, slightly increasing according to the chronological order. The studies focusing on Parkinson's disease did not determine a significant beneficial contribution of bilingualism as a compensatory mechanism. Huntington's disease and multiple sclerosis however can be effectively mitigated with the contribution of bilingualism, even slowing the progression rate of cognitive decline with MS.

The main requirements to ensure and enhance the effectiveness of bilingualism against neurodegeneration include, among other details, high frequency, referring to frequent switching between the languages, age of acquisition, differentiating between lifelong and late bilingualism, and the proficiency in each language.

To sum it up, lifelong bilingualism is not a prerogative for an impact against neurodegenerative diseases, is however almost directly proportional to its effectiveness. The variation within bilingualism is the strongest factor creating varying results and additional controversy among researchers. Although its extent can vary strongly, as bilingualism contributes to an enhanced neural connectivity, its effectiveness as such can be verified in general, which leaves only its efficiency to be determined.

Although the studies presented and analyzed consider a high number of factors bearing significance, this study, due to its extent, does not explore all relevant aspect in their full spectrum and therefore cannot determine the final scope of area of effect requiring further research.

According to the statements above, the success of bilingualism cannot be generalized, yet its effectiveness can be proven in most cases and research environments, but not without the acknowledgment of restrictions.

The studies included in this thesis contribute to the complementing evaluation of the hypothesis and offer partial verification as, although of varying significance, accuracy and structure, the neural characteristics of bilingualism can be determined as a neuroprotective strategy.

3.6 Concluding arguments and overall results

This final paragraph summarizes and offers a brief overview of the previous research results allowing for an initial conclusion regarding the effectiveness of bilingualism as a neuroprotective strategy. The analysis of the hypothesis described above intends to verify the effectiveness of bilingualism as a protective factor against the majority of neurodegenerative diseases. As the extent of this study does not allow a complete analysis of all research results and different scientific domains involved, the focus lies on the ones which have bilingualism and the neurodegenerative diseases Alzheimer’s, Parkinson’s, Huntington’s, and multiple sclerosis as their interest.

The expected outcome as well as the aim of this study is the verification of a positive correlation between not only bilingualism and Alzheimer’s, which has been effectively proven by previous studies, but also through the demonstration of bilingualism acting as a mitigating factor in the procession of other neurodegenerative diseases, as a general protective factor against

neurodegeneration. Through the construction of cognitive reserve and its strengthening effect of the neuronal connections, the brain becomes more resistant against cognitive deficit and brain damage.

The previous findings highlight the importance and crucial significance of bilingualism as a contributing factor to cognitive and brain reserve and therefore providing initial protection against neurodegenerative diseases.

The coherence of bilingualism and both degenerative neurological illnesses is the strengthened functional connectivity leading to a high cognitive reserve delaying the onset of dementia and Alzheimer's, which has been also investigated and initially proves in the three most frequent neurodegenerative disease, Parkinson's, Huntington's disease, and multiple sclerosis. Although the outcome of a heightened cognitive reserve can be successfully achieved through bilingualism, it is not the only contributing aspect, which must be considered, when determining its effectiveness. As bilingualism cannot be identified as an isolated aspect influencing or improving the idiosyncrasy and further progression of neurodegeneration, the various lifestyle enrichment factors also need to be taken into consideration and examined as the generalization of these individual elements can, under specific circumstances, unconsciously change the results of the related research.

As other individual factors and brain-stimulating activities can also result in a higher cognitive reserve, the question is whether or which strategies achieve the status of the highest and most adequate cognitive reserve to enable the patient to suppress early onset symptoms of neurodegenerative diseases.

As among the other contributing factors to cognitive decline caused by these neurodegenerative diseases, bilingualism being the one common component, its determination as a generalized protective factor when facing neurodegeneration is plausible.

In this study, bilingualism has been determined as the most efficient factor contributing to cognitive reserve as it enhances brain connectivity by forming alternate pathways, which is of crucial significance when facing neurodegeneration, as they can be used to uphold the executive function of the brain.

Although previous research results focused mainly on the preventative strategies to postpone the manifestation of onset symptoms and concluded that bilingualism strengthens the cognitive abilities and therefore aids to delay early onset symptoms, the suspected outcome was intended to include the analogical results for slowing the progression of further deterioration of neurodegenerative diseases. This could be verified for the neurodegenerative diseases included in this study, however they vary strongly in their efficiency and extent.

According to the argumentation and research results presented in this study, although it has yet not been analysed further for all neurodegenerative diseases, the beneficial effect of bilingualism cannot be extended universally for the progression of cognitive decline after the manifestation of onset symptoms, which was implied and presumed from the effectiveness of bilingualism to delay onset symptoms. The presumption is based on the fact that if bilingualism can increase cognitive reserve and therefore ensure a higher resistance of the brain against cognitive decline, analogically, the same conclusion could be drawn for the further progression of the diseases, as a strengthened functional and neurological brain connectivity is more equipped to use alternate pathways and compensate for caused damages delaying or mitigating the surfacing of further symptoms and could consequently slow down the process. The fact that bilingualism contributes to a delay of clinical symptoms by establishing a greater threshold tolerating a higher amount of brain atrophy often results in a more rapid progression after initial symptoms surface. The effort to uphold the resistance enables the patients to withstand the disease for longer, cannot however slow down the further progression as once this threshold is crossed the deterioration disperses at a faster pace.

Although dementia and Alzheimer's represent a large percentage of research interest regarding disease-related cognitive decline, the recognition, which improvement can be achieved through bilingualism can also be generalized to a certain extent aiming to enhance cognitive reserve and therefore function as a preventative intervention or at least coping strategy in combination with other neurological diseases. According to previous research, arguments and contradictory elements discussed above, obtained by a retrospective literature review, the beneficial relation between bilingualism and the delay of onset symptoms of dementia and Alzheimer's as well as the three most common neurodegenerative diseases following, Parkinson's disease, Huntington's disease, and Multiple sclerosis the effectiveness of bilingualism can be confirmed, being proven by several clinical trials. Therefore, also the hypothesis that a higher cognitive reserve increases the resistance of the brain and is effective against neurological decline, is conclusive.

Collecting all the related research results and analyzing the data regarding their similarities and effectiveness allowed to take a step towards being able to determine, whether bilingualism can in fact be declared as a generalized protective factor against neurodegeneration including eventual limitations and restrictions. The indication of regularity or certain conditions, in which bilingualism affects the onset symptoms of neurodegenerative diseases positively, could identify an eventual trigger that signifies whether bilingualism can be viewed as a universal factor. Such restrictions consist primarily of the duration of bilingual language use, including

the frequency of use, frequency of switching and level of proficiency, as described in chapter 3.2.2 focusing on the bilingualism gradient.

Overall, it can be stated that cognitive reserve is an efficient and effective counteracting strategy against neurodegeneration and, although several factors, including cognitively stimulating activities, can contribute to cognitive reserve, bilingualism can be identified as the common denominator according to the majority of studies conducted in this field. It is not only the frequent reoccurrence in studies focusing on bilingualism and cognitive reserve as a preventative strategy against cognitive decline but also its character as an omnipresent element of everyday life that concludes its significance as the most effective single component, as part of cognitive reserve, to delay the onset symptoms of neurodegenerative diseases.

With the establishment of the fundamental aspects and initial framework through the collection of representative studies, the contribution to other neurolinguistic studies with similar interests in the future is provided.

4. Inferences and prognosis

Although the previous detailed analysis included the most relevant aspects regarding the beneficial impact of bilingualism, its contribution and significance regarding cognitive reserve and the correlation between bilingualism and the individual neurodegenerative disease, including the most prevalent forms, it is not possible, based on the scope of this study to draw universal conclusions. However, the foundation for further studies has been hereby successfully established and the conduction of following research regarding the correlation between bilingualism, cognitive reserve and the remaining neurodegenerative diseases will allow for a universal determination of its effectiveness, methodological restrictions, and overall application options.

To achieve a universal outcome, that could also serve as a basis for following academic work in this field, further analysis, and comprehensive research regarding the correlation between bilingualism and all neurodegenerative diseases is necessary allowing a complete comparison of similarities and determination of the full palette of restricting factors.

However, it can prove difficult to conduct research in each neurodegenerative disease as the results can vary strongly based on a differing choice of methodology to measure impairment, the composition of participants and underlying neural and cognitive mechanisms. Nevertheless, to draw a final conclusion and to determine a universal result of the influence of bilingualism to reduce or mitigate the surfacing of symptoms and hence slow down the pace of deterioration,

once onset symptoms are noticeable, further investigation is required. It is necessary to include an established definition bilingualism and measuring technique regarding language use and acquisition, complemented by neural and cognitive reserve methods as a part of a controlled long-term high-quality scientific research with the proper selection of participants.

5. List of abbreviations

ACC	anterior cingulate cortex
AD	Alzheimer's disease
ADL	activities of daily living
AoA	age of acquisition
APOE	apolipoprotein
Aβ	beta-amyloid
Aβ42	beta-amyloid 42
BDNF	brain-derived neurotropic factor
BLC	bilingual language control
CNS	central nervous system
CR	cognitive reserve
CRIq	cognitive reserve index questionnaire
CRIq_LA	cognitive reserve index questionnaire leisure time
CSF	cerebrospinal fluid
CT	computerized tomography
DA	dopamine
D-KEFS	Delis-Kaplan Executive Function System
DMN	default mode network
DWI	diffusion-weighted MRI
EBV	Epstein-Barr virus
ECN	network for executive control
EDSS	Expanded Disability Status Scale
EF	executive function
EOAD	Early-Onset Alzheimer's Disease
FCRP	Framingham cardiovascular risk profile
FDG	fluorodeoxyglucose
GBA	glucocerebrosidase
GDNF	glial-derived neurotrophic factor
GM	grey matter
GMV	grey matter volume
HHV-6	human herpesvirus 6
IFG	inferior frontal gyrus
IMT	intima-media thickness
IP	information processing
L2	second language
LRRK-2	leucine rich repeat kinase
lvPPA	logopenic variant primary progressive aphasia
MCI	Mild Cognitive Impairment
MHC	major histocompatibility complex
MINT	Multilingual Naming Test
MLBG	maximal lifetime brain growth
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Image

MS	multiple sclerosis
N	neurodegeneration
NFT	neurofibrillary tangles
NGF	nerve growth factor
NIA	National Institute of Aging
NIH	National Institutes of Health
NP	neuropsychological
PD	Parkinson's Disease
PET	positron emission tomography
PPA	primary progressive aphasia
rCBF	regional cerebral blood flow
RCPM	Raven's Coloured Progressive Matrices
REE	resting energy expenditure
RRMS	relapsing-remitting multiple sclerosis
rs-FC	resting state functional connectivity
SCD	subjective cognitive decline
SES	socioeconomic status
SPECT	single-photon emission computed tomography
STG	superior temporal gyrus
TEA	Test of Everyday Attention
TFC	total functional capacity
TMT	Trail-Making Test
UHDRS-TMS	Unified Huntington’s Disease Rating Scale’s total motor score
VBM	voxel-based morphometry
VEGF	vascular endothelial growth factor
WM	white matter
WRAT-3	Wide Range Achievement Test-Third Edition

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