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A protective mechanism proposed against beta-amyloid plaques in the cerebellar environment

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Abstract

The cerebellum has long been considered as only being essential for the coordination of movements. However, the idea that the cerebellum is involved in cognition and emotion, has shed light on a whole new branch within the neuroscience research. Nevertheless, the cerebellum is still often neglected in research, as it comes to playing a crucial role in cognitive decline. The current ever-ageing population is accompanied by an increase of people suffering from neurodegenerative diseases, such as dementia. Therefore, this thesis reviews the ageing process in the cerebellum, as well as the unique pattern of Alzheimer's Disease (AD) in the cerebellar environment. It moreover provides new perspectives to change the current train of thought on the cerebellum and gives directions for further research. This analysis puts emphasis on the cerebellar environment and the link between normal healthy ageing and pathological ageing in AD. The characteristic beta-amyloid (Aβ) aggregations and neurofibrillary tangles (NFT) are both less present or even absent in the cerebellum. As the cerebellum is the last brain region to accumulate these markers, it appears that the cerebellar environment provides amongst others greater microglial clearance of Aβ-aggregations in contrast to the rest of the brain *in vitro* and *in vivo* experiments in murine models. Moreover, it is indicated that cerebellar neurons might provide a protection against AD-pathology, as shown in mice experiments. In conclusion, the cerebellar environment might have certain built-in mechanisms to protect against the aggregation of Aβ and is therefore considered as an important key player in cognitive decline. In order to have a better understanding of AD and find a possible cure, the cerebellum should for this reason be taken into account in future research.

Content

Introduction

Understanding the consequences of the current ageing population and its impact on interventions or performance is a rising topic nowadays. Between 1950 and 2000 the European population increased substantially, and by the year 2050 the percentage of people globally aged ≥60 years is likely to increase from approximately 12.0% to 21.5%. This will moreover result in one out of ten being aged 80 years and over by 2050, in nearly all the European countries (Michel & Walston, 2018). Normal ageing is accompanied by performance decline on as well cognitive and motor domains. However, most research on cognitive decline due to ageing, is committed to the cerebrum and in particular to the cerebral cortex (Bernard & Seidler, 2014). The role of the human cerebellum has been neglected for a long time and was thought to be only essential for planning, learning, coordination and execution of movements. However, apart from its involvement in controlling movements, the cerebellum also controls cognition, emotion and the autonomic function (Schmahmann, 2019). It is i.e. activated during reward, fear and activating emotion, but also in cognitive discrimination (Liang & Carlson, 2020). Also, the cerebellum performs according to the context and maintains behaviour around a homeostatic baseline. The cerebellum consists of different parts and is connected to multiple cerebral areas such as the cerebral cortex, the brainstem and the spinal cord. If cerebellar areas are stimulated, activity in other areas can be measured, such as the hippocampus, the amygdala and the anterior cingulate gyrus. Also, the anterior lobe of the cerebellum is mainly involved in sensorimotor functions, whereas the posterior lobe is mainly associated with cognition and emotion (Liang & Carlson, 2020; Schmahmann, 2019).

The ageing cerebellum and the consequences on cognitive decline, have been proven to be more important than was thought initially. Function and volume of the cerebellum are associated with cognitive function, thought organisation and memory. On the other hand, loss of function and volume of the cerebellum appears to play an important role in individuals with Alzheimer's Disease (AD) (Liang & Carlson, 2020). Dementia affected about 47 million people worldwide in 2015 and the numbers will keep rising. The expectation is to have three more times people affected by dementia in the year 2050 and there is still no cure (World Health Organisation, 2015). Difficulties with memory and cognitive abilities are quite common with ageing, whereas neurodegenerative diseases are rather associated with an overall worsened condition and cognitive impairment (Maślińska et al., 2017). AD is one of the most common forms of dementia and is characterised by the presence of beta-amyloid (Aβ) plaques, neurofibrillary tangles (NFT) and neuronal loss in the brain. The main component of plaques is Aβ, which is a toxic fragment of the normal amyloid precursor protein (APP). The protein APP plays a role in the nervous system and is suggested to be involved in the promotion of neurite outgrowth and in the calcium release in long-term potentiation (LTP) (Morley et al., 2019). In ageing, Aβ is suggested to be involved in neuroprotection, as well as in reacting upon hypoxic environments. It has been demonstrated that low (physiological) doses of Aβ strengthen memory, whereas a high (pathological) doses attenuate memory, which is known as hormesis (Morley et al., 2019). Although there is still loads to discover on the role of Aβ in the brain, it seems that the cerebellum might be more important than was thought at first. In fact, the cerebellar cortex only appears to be affected in most advanced stages of AD and is thus maybe characterised by a unique pattern in AD-pathology (Mavroudis et al., 2010).

This thesis aims to make a change in the current train of thought regarding the ageing cerebellum. It provides an overview of the cerebellar environment, in the sporadic form of the neurodegenerative disease AD. Firstly, insights upon cognition in the ageing cerebellum will be provided, after which the cerebellar environment, Aβ-deposits and neurofibrillary tangles (NFT) are described into detail in section two. The second section has moreover been divided into a micro-level and a macro-level, in order to propose an all-embracing conclusion.

Results

1. Cerebellar ageing of the human brain

1.1. Function and anatomy of cerebellum

The role of the cerebellum is well-known in motor coordination of body movements, but also plays a crucial role in cognitive functions such as in language, emotional behaviour, attention, sleep and autonomic functions. Within the central nervous system (CNS), it is also a key player in certain brain connections and circuits (Maślińska et al., 2017). As described by Liang & Carlson, both the cerebellar nuclei and cortex receive input from different cerebro-cerebellar pathways. Additionally, the cerebellum is connected with almost all regions of the neocortex and is activated in at least four intrinsic connectivity networks. These main intrinsic connectivity networks are: the default mode network (DMN), sensorimotor network (SMN), executive control network and the salience network. These networks and the cerebellar circuits appear to be vulnerable in neurodegenerative diseases such as AD, as they show a reduced activity (Liang & Carlson, 2020).

Since the cerebellum is highly involved in the functioning of the rest of the brain, its function has been researched by means of lesions. If lesions in the anterior cerebellum occur, these lead to cerebellar motor syndrome of ataxia, dysmetria, dysarthria and impaired oculomotor control. On the other hand, posterior lobe lesions result in the Cerebellar Cognitive Affective Syndrome (CCAS), which is associated with difficulties in executive function, linguistic skills, visual spatial processing and regulation of affect. (Schmahmann, 2019). The clinical cognitive perspectives of the disease CCAS put therefore again great emphasis on the cognitive role of the cerebellum. People with CCAS show some typical cognitive and personality changes, due to the loss of cerebellar contribution to the cerebro-cerebellar circuits (Jacobs et al., 2017).

The different regions in the human cerebellum, the anterior cerebellum and posterior cerebellum are shown in figure 1**.** The cerebellar cortex consists of three layers. The outer synaptic layer is called the molecular layer, the second intermediate discharge layer is called the Purkinje layer, and third the granular layer, also the inner receptive layer, which is followed by the white matter (The Editors of Encyclopaedia Britannica, 2015).

1.2. Ageing cerebellum and cognition

Ageing of the brain comes together with worsened memory performance on a variety of domains, such as the working memory, the spatial and long-term memory and the processing speed (Bernard & Seider, 2014). To examine the ageing cerebellum in more detail, a study by Andersen et al. measured the volume loss over lifespan with (healthy) post-mortem human cerebella, ranging from 19-84 years. The cerebellar volume remains more or less stable until age 50, but with ageing comes cerebellar shrinkage and functional decline

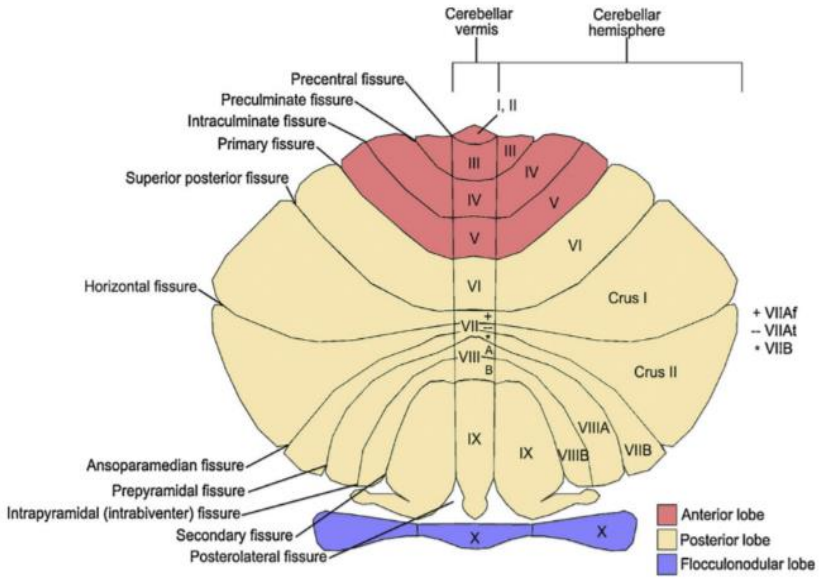

Figure 1: flattened visualisation of the human cerebellum.
The major fissures, lobes and lobules of the cerebellum are shown in this flattened representation. The lobules I to V form the anterior lobe; the lobules VI to IX form the posterior lobe; the lobule X forms the flocculonodular lobe. Crus I and Crus II (hemisphere) are connected to lobule VII (vermis). This figure is adapted from Schmahmann (2019).

(Bernard & Seider, 2014). In more detail however, Andersen et al. demonstrated that while the cerebellar posterior part showed only 10.6% loss of volume and 27% loss of white matter, the anterior part showed about 29% of volume and nearly 36% loss of white matter (Andersen et al., 2003).

Although in healthy ageing the brain is encountering a decline, it still tries to maintain a normal level of performance and compensate for the loss of performance. It has been suggested that additional prefrontal cortical (PFC) recourses are recruited for this compensation in cognitive task performance in older adults, compared to younger adults. Apart from the cognitive decline, there is also a change in the motor domains that influence gait and balance. Namely, it is often more difficult to learn sensorimotor adaptation and motor sequence learning tasks for older individuals. As well as with cognitive compensation, the PFC neuronal recruitment is again important in the motor task compensation (Bernard & Seidler, 2014). In addition, the older individuals appear to recruit additional cortical motor and cerebellar brain resources while performing motor tasks. When looking at the functional activation of the aged brain, deactivation of the DMN was seen on the same levels as younger individuals (Bernard & Seidler, 2014). The DMN is deactivated during most externally-directed cognitive tasks (Jacobs et al., 2017). Therefore, it appears that the elderly are not adapting on activity of the DMN, which might contribute to performance decline. Also, elderly show for instance less activation in lobule VI of the cerebellum in case of symbolic motor learning, compared to younger adults. It was described that posterior lobe of the cerebellum, and especially the lobules Crus I and Crus II, are associated with cognitive functions and are in contact with the PFC.

The compensation of the PFC for loss of performance is an important mechanism within an ageing brain. It could be concluded that the ageing brain is compensating for potential loss of performance in cognitive and motor tasks. The cerebellar posterior lobe is important in cognition and the networks and circuits are considered as the key players. It appears that older individuals show overall altered and lower activation in certain areas of the cerebellum, which decreases the ability to learn. Still, more research is needed on the different areas within an ageing cerebellum and the effect of an ageing cerebellum on cognition. (Bernard & Seidler, 2014). Also, a lot of research on has been devoted to the cerebral cortex, but still little to the cerebellar cortex. The current cerebellar research has been focused on the changing morphology due to ageing. On the contrary, there is also a lot to discover in the field of neuroinflammation together with the impact on memory and cognition (Ardura-Fabregat et al., 2017).

2. Cerebellar pathological ageing and sporadic Alzheimer's Disease

Micro level: ageing and Alzheimer's Disease

2.1. Beta-amyloid deposits and intraneuronal neurofibrillary changes

AD is mainly characterised by extracellular amyloid plaques and intraneuronal neurofibrillary changes in the brain tissue. These lead to the formation of neuritic amyloid plaques (NP), NFT and/or neuropil threads (NT) (Andersen et al., 2012). NFT are intracellular aggregates of the hyperphosphorylated tau protein that form cytoplasmic fibrils and are important markers in AD (Thal et al., 2014). There are different forms of plaques: diffuse amyloid plaques are a pre-amyloid type, whereas the NP are a mature senile type (Tschanz et al., 2011). Although the development from diffuse plaque to NP has been suggested, it is not the case for all diffuse plaques (Thal et al., 2014). Nevertheless, not all characteristics are always present in AD or vice versa. In fact, the mature senile type also occurs in elderly without the diagnosis of AD (Tschanz et al., 2011).

Since neurofibrillary changes are sometimes also visible in nondemented individuals, it is thus possible to have no neurofibrillary changes in the brain tissue of an individual with AD (Andersen et al., 2012). Remarkably, healthy elderly individuals appear to also have amyloidosis-related changes in the cerebro-cerebellar system, but they are not encountering problems with their cognitive performance, yet (Maślińska et al., 2017).

As already identified by Braak et al. a few decades ago, diffuse Aβ-deposits are present in the molecular layer of the cerebellar cortex of individuals with AD, compared to

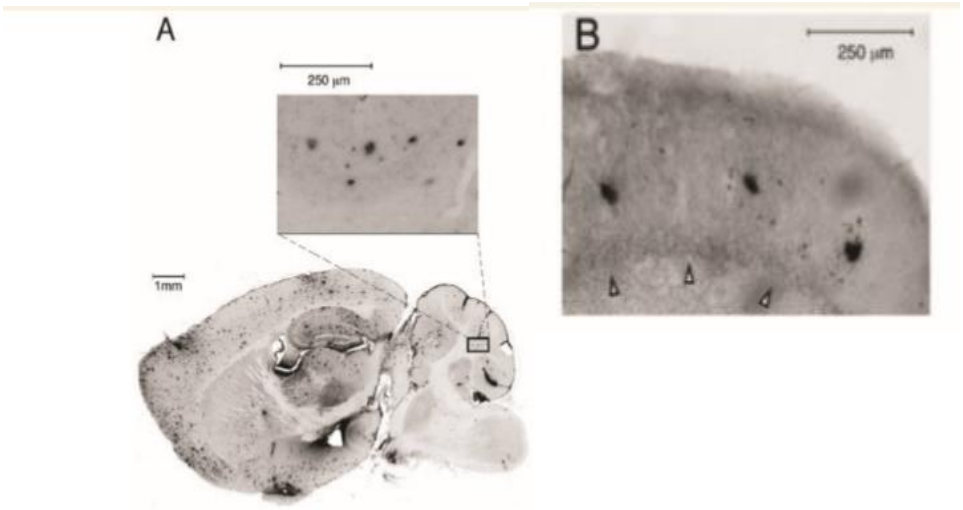

Figure 2: Diffuse plaques in the molecular layer of the cerebellum.
A: The Aβ-pathology is visualised in a post-mortem mouse brain of an AD model, and marked in the molecular layer.
B: This represents the molecular layer of the human cerebellar cortex, the patient is classified in Braak stage 6. The white arrows represent the Purkinje layer, so the Aβ-plaques are seen in the molecular layer. This figure is adapted from Jacobs et al. (2018).

healthy individuals. Most of the diffuse amyloid plaques appear in the molecular layer, while the plaques were less frequent within the granular layer and the white matter, which is demonstrated in figure 2. Moreover, the classic NFT seem absent in the cerebellum (Braak et al., 1989). Therefore, it was hypothesised in a study performed by Andersen et al. that AD is not quantitatively affecting the cerebellum. Although post-mortem AD cerebella show some typical AD-pathology, they confirmed that the major neuropathological changes are indeed absent in the cerebellum of a person with AD. They demonstrated that there was no difference in the number of Purkinje and granule cells in the cerebellum between AD and healthy elderly individuals, but only a reduction of the cerebellar volume in AD. The pathology in the AD cerebella was also more localised than in healthy control cerebella (Andersen et al., 2012). In general, the total volume of the normal ageing cerebellar cortex decreases. As Mavroudis et al. observed, this is due to amongst others loss of Purkinje neurons, loss of dendritic spines and degeneration of dendrites. In AD, the loss also includes a further decline in dendritic branches, spines and density of Purkinje cells. Remarkably, they noted again no typical NP and the presence of few diffuse plaques in the cerebellar cortex (Mavroudis et al., 2010). On the contrary, Zheng et al., 2017 discovered that AD individuals have indeed disrupted patterns of some of the intrinsic connectivity networks, among which the DMN. This disruption was significantly associated with cognitive decline and contributes to the importance of the cerebellum (Zheng et al., 2017). As AD progresses, other brain networks also become functionally disrupted (Jacobs et al., 2017).

The amyloid pathology in the cerebellum disrupts thus various neuronal networks and brain systems. The cerebellum is important in controlling and providing real-time feedback to the cerebral cortex. However, this function appears to be disturbed in neuropsychiatric disorders, among which AD (Liang & Carlson, 2020). This raises the question: what is exactly different in the cerebellar environment in comparison to the rest of the brain, in AD?

2.2. Distinct cerebellar pattern in AD

First of all, the cerebral pathology in AD can be divided into six stages (Braak or NFT stages), ranging from little damage to more damage. As it was already known, the medial temporal lobe (MTL) is hierarchically involved in Aβ-deposits and follows a distinct sequence. However, as Thal et al. have proven, the entire human brain follows a specific sequence. This sequence starts with the Aβ-deposits only being present in the neocortex, after which the allocortical brain regions follow in the second phase. In phase three, the diencephalic nuclei, the putamen, the caudate nucleus, the substantia innominate and the magnocellular cholinergic nuclei of the basal forebrain also display Aβ-

deposits. In the fourth phase several brainstem nuclei are affected and only in the fifth phase, the cerebellum and additional brainstem nuclei show Aβ-deposits (Thal et al., 2002). Secondly, a better memory performance is correlated to a higher cerebellar activity during the encoding process of learning. As it was noted in milder forms of memory impairment (Mild Cognitive Impairment/ MCI), the posterior lobe showed less activation compared to healthy controls. However, people with sporadic AD additionally showed less activation in the anterior lobe. It has been suggested that the progression of sporadic AD-pathology begins posterior and then continuous to the anterior lobe, which is quite overlapping with cerebral atrophy and is consistent with the clinical symptoms on the motor and emotional aspects. The cerebral atrophy starts with the association areas, followed by primary motor and sensory areas (Jacobs et al., 2017). Moreover, as described earlier, AD-pathology is correlated with disrupted patterns of some intrinsic connectivity networks (Zheng et al., 2017), which highlight the vulnerability of the large-scale networks and specific cognitive circuits. As concluded by Jacobs et al., atrophy patterns in AD selectively compromise cerebellar regions that are involved in intrinsic connectivity networks with cerebral DMN regions (Jacobs et al., 2017).

Furthermore, through scoring the Aβ-pathology in the AD cerebellar cortex samples, Catafau et al. showed again that the typical NPs were indeed absent in AD the cerebellar cortex. While other cerebral regions are already highly affected, Aβ-deposits are only present in the cerebellum in the most advanced stages of AD. The pathology of cerebellar Aβ-plaques is quite similar to the cerebral cortex, although it is not thoroughly identical. This is because some specific elements of the pathology of AD differ. These are amongst others the NFT and microglial activation that are either less present or even absent in the cerebellum. This might suggest that cerebellar Aβ-plaques represent an earlier form of plaque evolution or an attenuated stage in the maturation process of plaques. As Catafau et al. also indicated, it might be that the cerebellar pathology in AD should be examined by other techniques than classic neuropathologic staining or classic neuroimaging (Catafau et al., 2016).

On the other hand, Mavroudis et al. investigated the correlation between morphological changes of the human Purkinje-cells and the NP and NFT in the cerebellar cortex of AD individuals. As they also concluded, the cerebellum seems relatively less affected in the AD brain, compared to the hippocampus and the cerebral cortex (Mavroudis et al., 2010).

Looking more in depth, the typical β-pleated sheet conformation of amyloid deposits is not seen in the diffuse Aβ-plaques. As the diffuse plaques and NP appear to have different amyloid core, it would propose a different mechanism in the deposition in the cerebellar environment. As they also noted, the absence or few NFT present in the Purkinje cells in the cerebellum are in contrast with what is seen in the cerebral cortex. In order to unravel the mechanism, other factors, such as vascular pathology, oxidative damage or biological characteristics of the Purkinje cells, should be taken into account (Mavroudis et al., 2010).

2.3. Prediction of AD-pathology

For the relation between the severity of AD clinical symptoms and the reduced volume of the AD cerebella, a study by Bernard & Seidler gave some insights. It could be concluded that smaller volumes of the cerebellar hemispheres, cerebellar vermis and cerebellar posterior lobe were associated with most severe deficits and worsened activity performance. They hypothesised that a smaller volume in the temporal lobe, posterior cerebellum and the cerebellar vermis, in yet healthy individuals, might be a predictor of dementia in a later stage of life (Bernard & Seidler, 2014). Similarly, early stages of AD-related (neurofibrillary and Aβ) pathology, or (diffuse) NP-only/NFT-only situations, appear to be important in the early steps of the process leading to the fully pathological picture of AD. It might thus be possible to identify the non-yet-demented individuals and interfere in the preclinical phase (Thal et al., 2002).

It has been proven that primary pathologies, such as Aβ-plaques and NFT indeed develop many years before the onset of dementia symptoms in AD. The presence of abnormal biomarker levels of Aβ, accompanied with the absence of cognitive impairment, is described as the preclinical phase of AD.

However, it is difficult to exclude the fact that every preclinical phase will eventually lead to the pathology of AD or to AD-related co-pathology. Overdiagnosis of AD through the increased risk by amyloid pathogenesis, becomes therefore more and more problematic (Thal et al., 2014). Furthermore, it is simply not possible to classify individuals based on the absence or presence of Aβ. People differ from person to person and it should be more useful to indicate where individuals are on the pathway of preclinical AD progression by making use of Aβ and biomarkers. These will eventually give a better indication for future neurodegeneration. It is good to note that individuals may respond differently to Aβ-deposits, through their ability to compensate or through other (genetic) factors associated with inflammation and immunity. A visualisation from Jagust (figure 3) shows the potential relation of Aβ-deposits and neurodegeneration, and emphasises the cause and consequence dilemma of AD. The remained question is why Aβ-plaques and NFT and neurodegeneration occur, or if they are the consequence of another event. However, as Jagust also suggests, the relation between Aβ in the brain and atrophy is likely to be subtle, but complex (Jagust, 2015).

It is thus difficult to predict whether someone will develop AD, either by early characteristics or by presence/absence of Aβ. The preclinical phase is however suggested to be an important indicator of further progression. Neuroinflammation and microglia cells have also been proposed to be involved in the potential compensatory mechanism of the cerebellum. The question raises how does the cerebellar mechanism work exactly and what could be potential hypothesises?

2.4. Hypothesis of cerebellar mechanism

To sum up, the cerebellum is the last brain region that accumulates markers of AD and is thus suggested to have a compensatory function that may alleviate early symptoms of the neurodegenerative pathophysiology. While diffuse NP are quite common, NFT are rarely/not present. Consequently, cerebellar pathology is related to worsened cognitive abilities and loss of performance, which puts great emphasis on its role in cognition. It appears that the cerebellum shows less synapse loss than e.g. the PFC cortex and hippocampus. It is therefore hypothesised that the cerebellum may have a protection mechanism or may be resistant in developing AD-pathology to some extent. As also hypothesised by Mavroudis et al., the results would propose that there is a different mechanism in AD-pathology in the cerebellar environment (Liang & Carlson, 2020; Mavroudis et al., 2010). Moreover, it could also be hypothesised that cerebellar Aβ-plaques

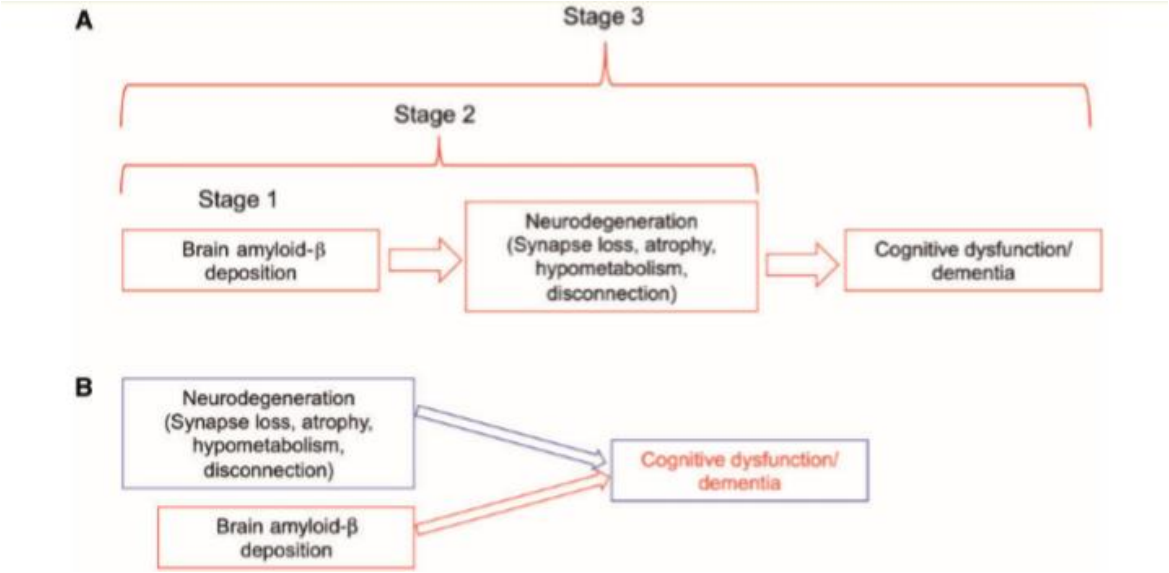

Figure 3: Conceptalisation on the effect of Aβ.
A: In the first, preclinical phase is Aβ the cause, which will eventually result into neurodegeneration. In the third stage, the cognitive decline will be noticeable and indicated as Mild Cognitive Impairment or dementia.
B: Neurodegeneration in combination with Aβ-deposits will result in harmful effects, but only one of them could already potentially lead to cognitive dysfunction or dementia. This figure is adapted from Jagust (2015).

represent an earlier form of plaque evolution or an attenuated stage in the maturation process of plaques (Catafau et al., 2016).

Another point to address is the important shift from normal ageing to pathology. Ample research has been devoted to the cerebellar environment and clearance of the Aβ-deposits. As Catafau et al. also indicated, microglia cells could play a role in the human reaction upon Aβ (Catafau et al., 2016). Microglia cells are found nearby Aβ-deposits and are activated after interaction with the Aβ-deposits. When microglia cells are activated, they change of morphology and start producing chemokines, neurotoxic cytokines and reactive oxygen. They are highly involved in clearance of Aβ-deposits. The clearance is done by either phagocytosis or transforming a plaque towards a soluble form. However, in the case of AD, microglia appear to be unable to efficiently clear the aggregations, as shown *in vitro* and *in vivo* in murine models (Mandrekar & Landreth, 2010) and are therefore considered to play a key role in disease initiation and progression (Hemonnot et al., 2019). The relationship between microglia activation and the Aβ-plaques *in vivo* in mice experiments is supported by mixed arguments. Whereas neuroinflammation plays a significant role in human neurodegenerative diseases, it is questioned whether this role is protective and/or harmful. Microglia cells are detected in the early phases of the disease and could therefore be potential therapeutic targets and interference points (Ardura-Fabregat et al., 2017).

Although the receptor for advanced glycation end products (RAGE) is often associated with microglial activation and clearance of Aβ-plaques, it appears to be reduced in the cerebellum, in contrast to the hippocampus of individuals with AD. Moreover, the microglia cells express amongst others the gene TREM2, which is associated with the clearance of Aβ-plaques. From previous research, it became evident that wild-type mice show increasing levels of microglia in the cerebellum, whereas knock-out mice do not show this. This might suggest that the TREM2-depedent clearance of Aβ, is greater in the cerebellum than in the rest of the brain (Liang & Carlson, 2020). However, more detailed description on common microglial molecular targets and risk genes in AD, can be found in other reviews (Hemonnot et al., 2019; Ardura-Fabregat et al., 2017).

If clearance of the Aβ-deposits would be considered as possible therapeutic targets, how would the cerebellar environment contribute to degradation of (diffuse) NP? Two main enzymes were described by Du et al. that could play a role in the difference between hippocampal and cerebellar AD-pathology. They induced Aβ-degrading enzymes, through *in vivo* experiments in mice. Whereas neuronal metabolites of the cerebellum significantly reduced Aβ-plaques and reversed cognitive impairments, neuronal metabolites of the hippocampus reduced the expression of Aβ-degrading enzymes and induced cerebellar neurodegeneration. This indicates that hippocampal neurons might promote AD-pathology and cerebellar neurons might give protection against the AD-pathology (Du et al., 2009).

However, apart from these possible mechanisms, it is important to realise that there are more factors attributing to the pathology in neurodegenerative diseases, among which oxidative damage, blood brain abnormalities and vascular pathology (Mavroudis et al., 2010).

Macro level: ageing and neuropathology

It is important to see the micro level together with the macro level of neurodegenerative diseases. The society is an ever-ageing population nowadays and the dementia numbers will keep rising. The expectation is to have a three more times people affected by dementia in the year 2050 (World Health Organisation, 2015). Dementia and cognitive decline pose a growing disease burden on society and it has therefore a high priority in life science research (Ardura-Fabregat et al., 2017).

Despite the ample research that is focused on treatment or a possible cure for dementia, there is yet no effective treatment option available. The Aβ-plaques and the NFT are seen as important targets for a possible cure for AD, since they cause the progressive neuronal destruction, resulting into the cognitive deficits. Current medicine is focused on counteracting these factors and the symptoms. However, it still not possilbe to fully cure AD and prevent further progression or

further cognitive decline (Yiannopoulou & Papageorgiou, 2020).

The ever-ageing population in combination with AD is accompanied by some interesting perspectives. The possibility that AD persists existing in the human population due to the extension of the lifespan, has been often hypothesised from an evolutionary perspective. With more wealth, better health-care opportunities and better circumstances in today's society, people have more chance to become older and live longer. It has been proposed that AD is a result of normal brain senescence and not a pathological condition, due to the fact that people become older than in the past. If i.e. everyone became 130 years old, it is suggested by some researches that essentially all people would have AD. Within this hypothesis, it can on the other side be conceived as a set of biochemical and neuropathological changes that are activated by age-related mechanisms. The antagonistic pleiotropy, the combination with other factors such as cardiovascular diseases and the mismatch hypothesises are proposed to be involved in the existence of AD. As this poses more questions, further reading is advised in the article by Fox (Fox, 2018). In my opinion, this indicates again the importance of unravelling the relation between healthy ageing and neuropathology. Although neurodegenerative diseases are almost always perceived as pathologies instead of normal ageing, such hypotheses might help in future research and help to examine the relationship between different internal/external factors.

Conclusion

More and more research is thus indicating that the cerebellum is not only a silent bystander, but is rather highly involved in cognition and the pathophysiology of AD. It is hypothesised that the AD-pathology shows a distinct and unique pattern in the cerebellum, which is in contrast with the rest of the brain.

The cerebellum is highly involved in the functioning of the rest of the brain and plays a crucial role in cognition. With ageing, the brain is able to compensate for potential cognitive or motor performance loss. There is however more decrease in volume of the anterior part than the posterior part in the cerebellum with normal healthy ageing. However, sporadic AD is first represented by further atrophy posterior, followed by anterior atrophy. The effect of posterior atrophy is associated with a worsened cognitive and activity performance. Also, the cerebellum is involved in various neuronal networks and brain systems, among which the DMN. The intrinsic networks are vulnerable in neurodegenerative diseases and show altered activity of various networks, such as the DMN, which might play an important role in cognitive decline. The atrophy pattern is therefore suggested to be involved in the vulnerability of the intrinsic connectivity networks and as a result, compromises the preservation of the level of cognitive function.

As identified by multiple studies, the typical mature NP and NFT of AD are not seen in the cerebellar environment. The NP are rather diffuse and present in small numbers in the molecular layer of the cerebellar cortex and the NFT are even absent in the cerebellum. The relationship between Aβ-plaques/NFT and neurodegeneration is described as rather complex, but might be relevant for prediction in the preclinical phase. However, if the preclinical phase would be an indicator of future progression, it is still not evidential that each case will develop into AD-pathology or into AD-related co-pathology. Together with the sequence of Aβ-pathology showing that the cerebellum is affected relatively late, this might indicate that the cerebellum has another mechanism in AD. Next to the absence of NFT, the microglia cell activation was seen less present or even absent in the cerebellar environment. Whereas the cerebellum seems less affected, the question raises why the other areas, such as the hippocampus or cerebral cortex, are affected and not spared. Thus, what would exactly be the underlying phenomenon that results in the sequence of AD-pathology in the brain? Also, could the preclinical phase play a role in this sequence? And if the cerebellar environment indeed provides favourable circumstances, what would these be?

For instance, the clearance of Aβ-deposits might be one possibility in order to answer these questions. Firstly, microglia cells are highly involved in the clearance of Aβ-deposits, but are unable to efficiently clear the aggregations in AD and might therefore play a role in AD initiation and progression as shown *in vitro* and *in vivo* in murine models. On the other hand, research does not exclude a potential role for active microglia cells in early disease detection. The TREM2-dependent clearance of Aβ-aggregations in mice, shows elevated levels in the cerebellar environment and indicates indeed different microglial activation. Secondly, degradation enzymes of Aβ show different effects in the hippocampal neurons and the cerebellar neurons in mice. It is suggested that the cerebellar neurons might provide protection against AD-pathology, in contrast to the hippocampal neurons that on the other hand, might promote AD-pathology. In short, neuroinflammation and especially microglia cells, act differently in the cerebellar environment. Clearance of Aβ-deposits is a rising topic. However, as is proposed above, the brain seems to already have certain built-in mechanisms, where one appears to be more vulnerable than the other, in neurodegenerative diseases. As hypothesised, the cerebellar environment might provide protection for neurodegeneration and in particular aggregation of Aβ, resulting into typical NP. These findings support the hypothesises that the cerebellar Aβ-plaques might represent an earlier form of plaque evolution or an attenuated stage in the maturation process of plaques, due to the protective effect of the cerebellar environment. However, it is important to realise that there are more factors contributing to the pathology in neurodegenerative diseases and that these mentioned findings are found in mice models. Although these findings provide evidence for

the cerebellar hypothesises, the translation to humans should be further investigated.

The cerebellum has often been neglected in research or seen as less important than the hippocampus or PFC. Nevertheless it seems to deal better with the AD-pathology than other areas, such as the hippocampus. The cerebellum is more than only controlling and has a high impact on cognitive function and the rest of the brain. If the cerebellum has indeed another (protective) mechanism to handle the AD-pathology, it would make it a very interesting starting point for a better understanding of AD and therefore finding a possible cure in the future. In order to achieve this, the link between normal healthy ageing and the transition to pathological ageing must be further investigated. The questions raised by the hypothesises about the existence of neurodegenerative diseases as AD, show the relevance of unravelling the relation between healthy ageing and neuropathology and the underlying causes. These evolutionary hypothesises might provide current research with other perspectives. Moreover, if the brain already has certain (protective) mechanisms against neurodegeneration, why would research neglect this? From my point of view, the cerebellum has to be taken into account in research focussing on the pathology of AD, since evidence points towards a certain protective cerebellar pattern. For future research, the relationship of Aβ and NFT could be further addressed, even as the hormetic effect of Aβ in neuroprotection. Also, the NFT-pathology and clearance has not been appointed in this study, but should be further investigated in the cerebellar environment. Not only does the ageing process in the cerebellum play an important role, but the hippocampal and striatal environment could also provide research with answers on the differences between the environments. Lastly, the relationship between typical NP and diffuse plaques might play an important role in unravelling the mechanisms of the neurodegenerative disease AD.

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