Recent insights and developments in the pathology of Alzheimer's disease with regards to neuroinflammation

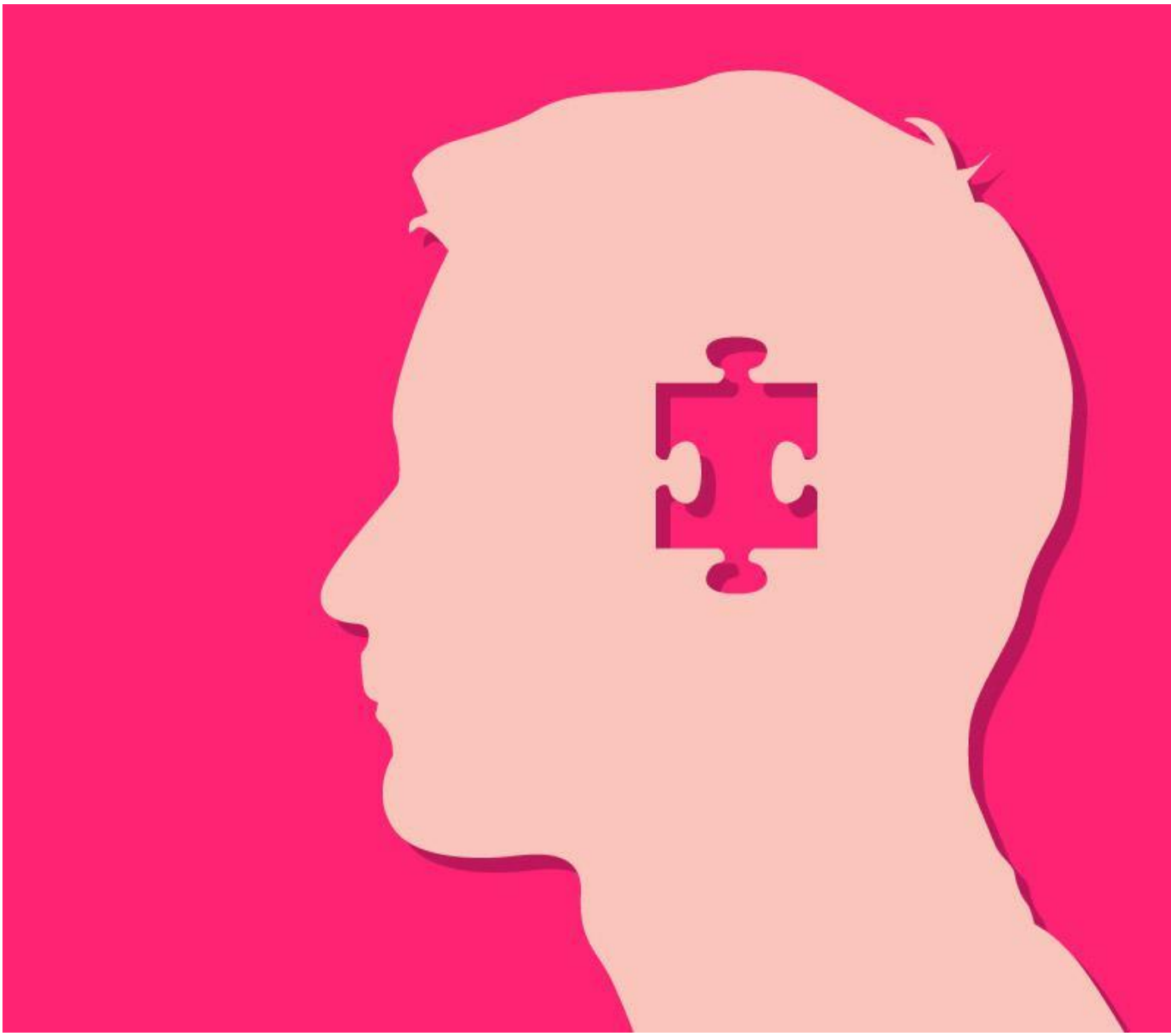

Illustration by Sydney Rae Hass for TIME

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Abstract

Alzheimer's disease is a widespread neurodegenerative disease that is commonly associated with the elderly population. In recent years our understanding of Alzheimer's disease has broadened. Besides Tau-tangles and amyloid- β plaques, neuroinflammation has received increased attention as a possible key factor for the pathogenic progression of the disease. Recent findings have sparked a debate on whether or not neuroinflammation itself might be the cause or rather a consequence of this complex disease. As of today no treatment exist that fully ameliorates the disease up to satisfactory standards. Because of the increasing age of the world population the demands for preventive measures or possibly a cure have never been higher.
This article attempts to shine it's light on several of the new and emerging theories behind the origin of Alzheimer's disease in conjunction to neuroinflammation and possible treatment options that might arise from it.

Key words: Alzheimer's disease, inflammation, microglia, amyloid

Competing interests
The author declares that he has no competing interests.

Contents

I. Introduction

Alzheimer's disease (AD) is the most common form of dementia and is a neurodegenerative disease commonly associated with the elderly population. It is estimated that up to 47 million individuals worldwide suffer from dementia (Prince,. 2015), 60 to 80% of which are diagnosed specifically with AD (Alzheimer's Association., 2016). Due to the rising life expectancy and its associated risks of chronic diseases , the prevalence of AD is almost certainly expected to rise as well (Qiu., 2009). AD patients display a variety of symptoms and most noticeably suffer from memory loss and personality changes (Puzzo., 2015). The disease is notoriously characterised by the formation of tau-tangles and amyloid plaques in the brain and these have long been regarded as the primary contributors for the adverse effects of the disease (Puzzo., 2015). In recent years however the focus has shifted and neuroinflammation is now considered by some to be an integral part of AD as well (Lynch., 2009)(Hong.,2016).
This paper will investigate recent insights on neuroinflammation in AD, regarding pathogenesis and the current scientific consensus, or lack thereof concerning this topic. Firstly the general progression of AD will be discussed, followed by a short introduction on neuroinflammation and the role of microglia. The second part will focus on the origins and possible contributions of neuroinflammation in AD.

Ia. The progression of Alzheimer's disease

Neurodegeneration in AD is not a universally distributed process in the brain. While the rate of progression in AD is considered to be highly individual, the pattern and spread of the disease throughout the brain mostly follows a set course.

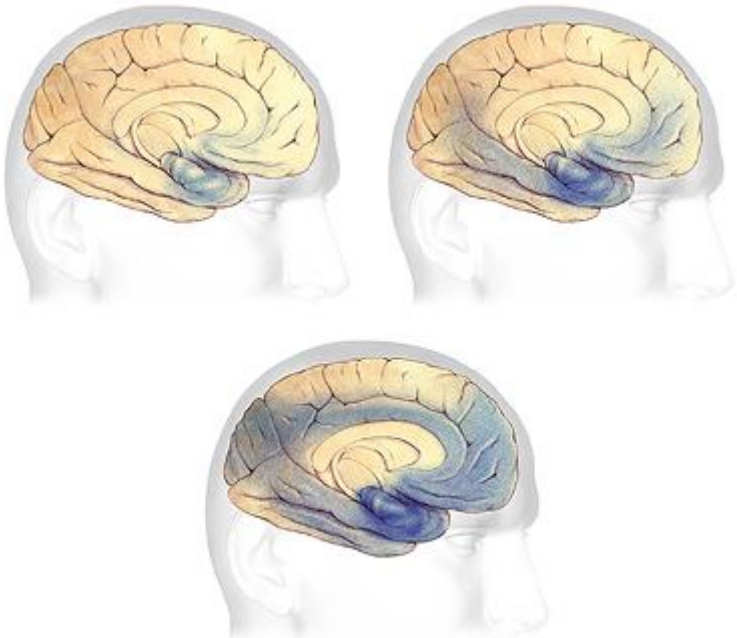

Figure 1. The progression of AD. The upper left corner shows the early stages of AD in which mostly the hippocampus and prefrontal cortex are involved. The Upper right corner shows the mild to moderate phase of AD . Areas of the cerebral cortex that control speech, reasoning and sensory processing are now affected. The lower picture shows the final stage, named severe AD in which neuroinflammation and degeneration are widespread throughout almost the entire brain. (https://www.alz.org/braintour/progression.asp)

As can be seen in figure 1. AD has a recognisable pattern of progression. This pattern can be divided into 3 stages. The 3 stages of AD are here referred to as mild, moderate and severe AD.
Mild AD is preceded however by preclinical/early AD and some scientists believe changes in the brain (neural loss of function) can occur 10 or even 20 years before the first diagnosis of AD (NIA.,2008). Early AD will at some point manifest itself because of brain damage that results in mild cognitive impairment. One of the more prominent and noticeable results of brain damage in the early stage of AD is the loss of memory functions. It is believed that early AD originates deep inside the brain where the entorhinal cortex and hippocampus are located (Engels., 2016). These brain regions are involved in the formation of new memories and spatial recognition, and it is therefore perhaps unsurprising that cognitive problems with regard to these brain functions occur first. In Mild-moderate AD changes in personality become more noticeable and memory loss further continues. Spatial awareness and speech production are likely to be affected at this stage as well. Mild-Moderate AD is typically when most patients are diagnosed and this is largely due to the fact that symptoms can now heavily interfere with daily activities. Following Moderate AD is the final stage called: Severe AD. Patients who have entered this final stage are severely impaired by the effects of the disease. Due to the loss of neurons the brain further decreases its relative volume with regards to the surrounding cerebrospinal fluid. This process is promptly referred to as ''brain shrinkage'' and can be detected on brain scans as well as post mortem autopsy's. A patient suffering from severe AD is as expected, completely reliant on his/her surroundings. Besides the inability to recognise or even communicate properly to their family or caretakers, severe AD is characterised by symptoms that often include but are not limited to: Weight loss, immobility, respiratory failure or even seizures (Pandis .,2012)(NIA., 2008).
*It is important to note that although a 3 part division is made (mild -> moderate -> severe), the boundaries of these stages are arbitrary and simply aid in the understanding of the progression of AD. In reality a disease such as Alzheimer's progresses more like a gradient would.

Ib. Neuroinflammation in the brain

Neuroinflammation can be defined as inflammation of neural tissue, in this case the brain. There are many ''triggers'' that can cause neural inflammation, such as: traumatic brain injury, viral infection or toxic metabolites (Lull., 2010),(Lyman., 2014). Under non-pathological conditions the brain is thought to be immunologically isolated from the rest of the body by a specialised structure called the blood-brain barrier. The central nervous system (CNS) has its own set of immune cells called microglia. They belong to the innate immune system and respond whenever potentially damaging agents such as toxic metabolites are present (Pugazhenthi.,2016). Microglia thus play an important role in maintaining brain homeostasis by getting rid of potentially harmful agitators. When no such agitators are present, microglia have a relatively small cell-body with a high number of long branching extensions called processes. Under such conditions the microglia are often referred to as ''ramified'' or ''resting'' microglia (Torres-Platas., 2014). Resting microglia can however become activated in a process called microglial activation. Microglial activation occurs when the processes of ramified microglia ''detect'' infectious agents. When this happens, microglia alter their gene expression and as a result adapt their appearance. The heavily branched processes begin to retract and perhaps most noticeably the cell-body takes on an amoeba like form. Much like macrophages elsewhere in the body, activated microglia can migrate to the inflamed areas of the brain and excrete cytotoxins and cytokines. Cytotoxins are like their name suggest, toxic towards certain cell types, while cytokines are especially important as they are thought to act in a proinflammatory manner (Reefman.,2010). It is believed by some that these excreted substances can be considered neurotoxic under certain circumstances and negatively impact surrounding neural tissue as well. Besides releasing cytokines, the main role of activated microglia is the removal of dead, damaged or foreign cell material. Microglia achieve this goal through a process called phagocytosis (Sierra., 2013). When an activated microglia approaches damaged cell material, chemical signals are picked up from the debris. These chemoattractants cause the activated microglia to develop special synapses that engulf the debris material. After the target material is fully engulfed a so called phagosome is formed.

As a phagosome matures it fuses with endosomes and lysosomes that are also present in the microglial cells. The newly formed structure is now called a phagolysosome and it contains an acidic PH level as well as special enzymes that can digest the debris material.

Besides an active role in the host's immune system, resting microglia are also thought to be involved in a process called synaptic remodelling (Ji., 2013). Synaptic remodelling is most likely key to the longevity of neurons and their overall function in learning processes. Whenever chronic neuroinflammation occurs and resting microglia change into active microglia, this important function is then compromised and thus contributes to the adverse effects of chronic neuroinflammation.

Ic. Neuroinflammation in relation to Alzheimer's disease

While the precise origins and pathogenesis of AD are at this point mostly unclear, recent studies have investigated the role of neuroinflammation and it's possible contribution to the disease (Calsolaro., 2016). Research suggests that many of the well-known neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and ALS among others, show signs of chronic neuroinflammation. Besides the number of microglia and the change in morphological features of these microglia as opposed to non-pathological conditions. There is also an increase in cytokines and cytotoxins under which also belong the reactive oxygen species or ROS. Prolonged exposure to these substances could lead to neural cell death and they are therefore considered to be neuro-toxic.

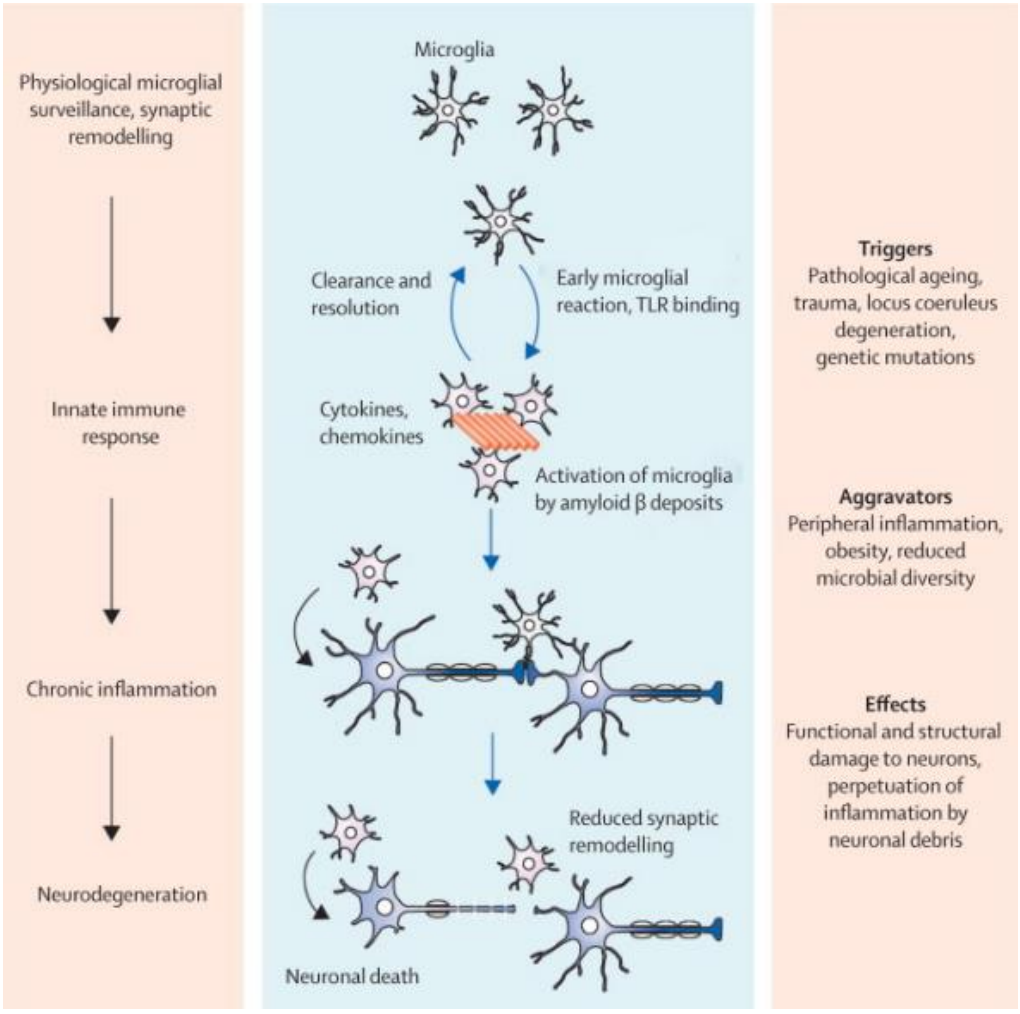

Figure 2. Neurodegeneration as a result of neuroinflammation (Heneka., 2015).

Neuroinflammation in AD is believed to adversely impact the normal functions of neurons in the brain. One way in which inflammation can have a detrimental effect is as an underlying cause of

neurodegeneration (Figure 2.). In the early stages the microglia can be viewed as ''normal'' resting microglia and thus they preform various functions such as scanning for pathogens and cellular debris or providing aid in the synaptic remodelling process. Once these microglia locate molecular structures in the form of cellular debris, they become activated. In AD the debris are called amyloid β deposits and when clustered in plaques these are thought to severely impact neural function in a negative way. Activated microglia are able to bind to these amyloid β deposits and will release cytokines and other potentially toxic substances upon doing so. For reasons not completely understood the activated microglia are not able to fully clear these deposits from the inflamed site (Hickman 2008). The adverse effects of the amyloid β plaques are therefore not resolved and it is possible that the encumbrance of activated microglia now contributes, rather than opposes to the disease known as Alzheimer's. As more and more microglia migrate towards the inflamed parts of the brain, the inflammation enters a chronic state. This state of chronic inflammation is characterised by its persistence and long lasting negative effects on surrounding tissue.

II. Competing views on neuroinflammation.

Although neuroinflammation has established itself as a prominent factor in AD in recent years, questions remain about its precise role in the process. While some may argue that the inflammation itself has potentially detrimental consequences and therefore impacts the progression of AD in a negative way. Others might view this differently. In fact they might look at neuroinflammation as nothing more than a natural response and argue that while prolonged neuroinflammation might not be desirable, it is not the underlying cause of AD.
The goal of this research paper is not to determine who's right or wrong. Rather, it tries to look at these differences and compare both views equally.

IIa. Neuroinflammation as an underlying cause of Alzheimer's disease

So far only several attempts in the form of studies and research articles have been produced to answer the question of whether or not neuroinflammation is an underlying cause or the result of AD (Mcgreer., 2010). The results of these studies sometimes favour or at least support the idea that inflammation might be causal to AD neuropathology.

Before neuroinflammation was even considered to play a major role, the main focus in AD research was on αβ plaques (Heppner., 2015). However recent research suggests that glial cells, which are heavily involved in the brains immune response might show signs of activation even before any noticeable αβ deposition occurs (Kummer., 2014). If this is indeed the case then αβ deposits cannot be solely responsible for all of AD's symptoms. The fact that an inflammatory response seemingly comes up before any plaques have formed is interesting and could open the door for more research. Because neuroinflammation and in particular the idea that it could precede and perhaps cause AD is a relatively new field of study most of the results are yet to come out. Still, early research dating as far back as 2003 (Tarkowski., 2003) has stated that CNS inflammation can be an early hallmark in the pathogenesis of AD. A study done by Tarkowski and colleagues that focussed mainly on both pro- and anti-inflammatory cytokines concluded that an increase in CNS inflammation could well precede the progression of AD. Namely they noticed that TNFα (a pro-inflammatory cytokine) was increased in patients that were at a higher risk of developing AD later on. The same was true for a decrease in the anti-inflammatory cytokine: TGFβ. Not only does this finding cautiously suggest that neuroinflammation might be an underlying cause of AD, it also suggests that cytokines could be used as early markers for the detection of AD.

Perhaps equally important to the claim is the incidence of post-operative cognitive decline (POCD) and AD after surgery. As far as the theory goes, any surgical procedure is accompanied by the release of pro-inflammatory cytokines, prostaglandins and other trauma associated molecules (Fung.,

2012)(Kapila., 2014). Perhaps indirectly, increased levels of these substances can pass the BBB and influence glial activation. It has been proposed that the BBB functions differently in the elderly population than in their younger counterparts and therefore pro-inflammatory signals can more easily get trough (Pugazhenthi., 2016).When this happens a state of neuroinflammation can thus be triggered. The fact that AD symptoms often seem to quickly arise after surgery could indicate that neuroinflammation is an important factor, even in the onset of AD. A surgical procedure is of course a rather acute occurrence but there are also signs that a predisposition for AD like symptoms can arise much earlier (Krstic., 2012). Recently researchers from the university of Zurich conducted a study and concluded that when the immune system is challenged even before birth, this can eventually lead to a predisposition for AD-like neuropathology. When wildtype mice went through an early stage of systemic inflammation they were more likely to develop a more ''exaggerated'' immune response after infection in their adult phase. The symptoms that where accompanied by this second immune response also mimicked many of the tell-tale signs of AD in human patients. These signs included elevation of inflammatory cytokines, increased levels of amyloid precursor protein (APP) and even significant impairments in working memory. These findings suggest that perhaps early changes in the brain's natural immune response are a preceding factor in the development of AD. Furthermore, but perhaps making a leap, these findings could also partially explain why it is that so many elderly develop AD-like symptoms at a relatively rapid pace after surgery. Namely if early infections can cause a patient to develop a predisposition towards developing AD later on then the AD can be ''triggered'' as it were by acute trauma such as a surgical procedure. Perhaps pre-emptive treatment (with NSAID''s ?) for those who are at risk of developing AD is an opportunity well worth considering.

One of the major aspects of AD is the eventual loss of neurons. Current evidence however suggests that so called: loss of function often precedes the eventual neuro-apoptosis (Lyman., 2014).
The debate is still ongoing about whether or not failure to clear αβ plaques is the cause of neural impairment or perhaps it is the inflammatory cytokines that initiate most of the damage themselves. Increased levels of inflammatory cytokines can be associated with an increase in APP synthesis and tau phosphorylation (Krstic., 2012). Perhaps one of the ways chronic-neuroinflammation can be causal to AD is its role in the generation of αβ plaques induced by inflammatory cytokines. β-site APP cleaving enzyme 1 (BACE-1) transcription is an important factor for the rate at which αβ deposition occurs (Kummer., 2012), (Chen., 2011). BACE-1 levels are elevated in sporadic AD patients through an unknown mechanism but the expression of BACE-1 is now known to be influenced by inflammatory cytokines (Kummer., 2012), (Chen., 2011). A study performed by Chen et al. showed that certain pro-inflammatory cytokines such as Nuclear factor-kappa B (NF-κB) are capable of upregulation BACE-1 when significantly increased. Another independent study noted that when inflammation is reduced a decrease in BACE-1 transcription can be the result (Kummer., 2012).
These results indicate that perhaps inflammation in the brain can contribute more to the origins AD, or at least some of its major component than previously thought.

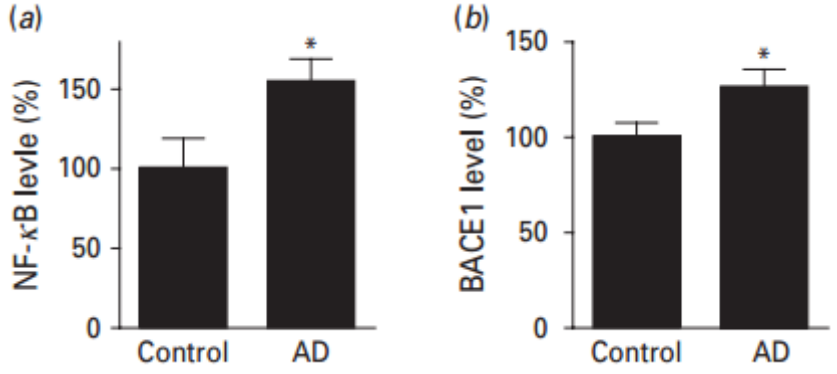

Figure 3. Levels of both NF-κB (a) as well as BACE-1 (b) where elevated in sporadic AD patients. (Chen., 2011)

IIb. Neuroinflammation as a consequence of Alzheimer's disease

The idea that neuroinflammation might be causal instead of consequential can be viewed as problematic by some. First of all, inflammation of any sort is almost always caused by an initial event such as bacterial infection or any sort of trauma. Why then would it seemingly come about on its own in AD?, why would it do so at a later age?

It remains tough to judge whether or not neuroinflammation is the underlying cause or a direct consequence of most AD symptoms. One of the more compelling arguments that could imply the latter comes from studies in which αβ plaques where injected into the central nervous system (Wirz., 2013) (McLarnon., 2008). These studies show that an inflammatory response can be induced after plaques make their way into the brain, thus making it theoretically possible that neuroinflammation is the result of plaque formation. One of the ways in which these studies conclude that there is in fact an inflammatory response is by looking at the activation and migration of microglia. Furthermore the upregulation of certain specific genes such as Cd68 can act as a clear indicator for activated microglia and do support the claim independently (Wirz., 2013).

Perhaps the most well-known and long standing theory on AD is the so called amyloid cascade hypothesis. It states that αβ deposits in the brain are actually causal to AD pathology (Luo., 2016). With that being said, neuroinflammation has a place in it, albeit as a consequence of plaque formation. Most likely it seems that plaque formation causes inflammatory processes and when unresolved they turn into chronically inflamed sites. This can ultimately result in neurodegeneration because of cytotoxic substances that are generated by the glial cells that are present at these sites of inflammation. The amyloid cascade hypothesis has by far been the most researched branch with regards to AD and many of current therapeutic research find their origins within this hypothesis (Karran., 2011). Then there is also the fact that many of the genes that are thought to regulate amyloidogenic or tau related pathways are expressed at a different rate in AD than under non pathological conditions. The rate of expression might also vary along with the onset and progression of the disease itself (Martiskainen., 2014). As mentioned earlier there are also genes (APP, PSEN1, and PSEN2) that are known to contribute and lead to heritable early-onset AD (An., 2016)
However this is just a small number of cases. What they have in common though is that these genes for the most part don't seem to be directly involved in any inflammatory response but rather fit within the amyloid cascade hypothesis. In short this is exactly what you would expect if neuroinflammation was a consequence of AD and not the cause. With so much focus on plaques it's easy to overlook the fact that there could in theory be other causes to neuroinflammation in AD. However some new insights have arisen despite this fact. One theory states that the endoplasmic reticulum (ER) might be more closely involved in misregulated AD processes than previously thought. According to the theory the ER is involved in the recognition of misfolded proteins and cellular $CA2^{+}$ balance (Salminen., 2009). Prolonged cellular stress can cause the ER to respond unfavourably to unfolded proteins. The way by which the ER acts on misfolded proteins is called the unfolded protein response (UPR). It is thought to be activated in neural cells but not glial cells and prolonged ER stress has been demonstrated to induce an inflammatory response trough UPR pathways (Salminen., 2009).

But even if the amyloid cascade hypothesis is essentially correct and αβ plaques are largely the cause of AD, to what extend does neuroinflammation contribute to the progression of the disease?
One theory states that it could well be the final result of inflammation itself that leads to the neuronal damage that we associate with AD (figure 4). According to Frank Heppner and colleagues undetectable levels of inflammatory cytokines (interleukin-12 (IL-12) or IL-23) are present in the brain under non-pathological conditions. When microglia are exposed to αβ however, expression of these cytokines goes up as a result. What's interesting is that astrocytes who are normally unresponsive to these cytokines suddenly begin to express the necessary receptors for these two cytokines. The exact cause or mechanism of this rise in cytokine levels and their complementary receptors remains unknown. It is however accompanied by an increase in the severity of the disease (Heppner., 2015). Inhibition of the IL-12- IL-23 signalling pathway on the other hand is thought to

mitigate several of the pathological aspects of AD. The big questions that remain is whether or not IL-12-IL-13 is the predominant factor in AD progression and what the respective roles of microglia and astrocytes are with respect to AD pathology.

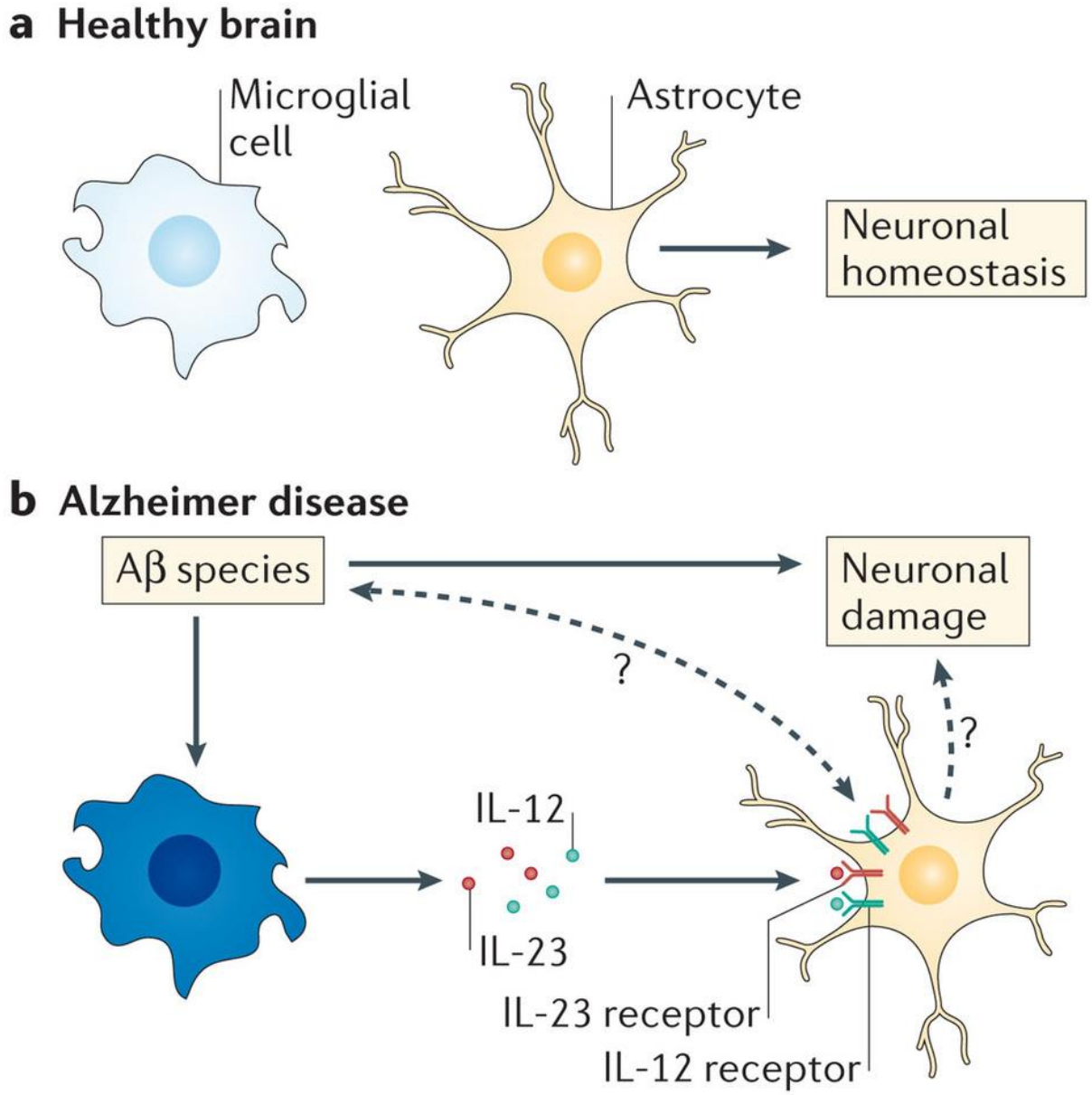

Figure 4. A) Non detectable levels of IL-12-IL-23 are present in the healthy human brain. B) αβ acts on microglia causing the release of cytokines. Astrocytes express the necessary receptors, both processes are accompanied by the progression of AD pathology (Heppner., 2015).

IIc. Treatment options based on neuroinflammation

With so much yet to be discovered and questions still remaining about the impact of neuroinflammation on AD it is hard to pick sides on what compelling theories have so far arisen. However, it is important to note that whether or not neuroinflammation is actually causal or not, it is still regarded by most to be a contributing factor in the pathology of AD (Wirz., 2013). Therefore treatment options that are focussed on relieving inflammation could potentially be viable.
Currently there are no treatment options that result in a cure for the disease. In fact the progression of AD can at this point merely be slowed down (Yiannopoulou., 2013). Much of the focus in today's treatment goes out to relieving symptoms, rather than the disease itself. With that being said, there are possible newly emerging treatments that focus on neuroinflammation. One way to potentially combat any detrimental effects neuroinflammation might have on the brain is by the use of so called non-steroidal anti-inflammatory drugs (NSAID's). Widely accessible, they are mostly known for their pain relieving properties and can go by common household names such as ibuprofen, aspirin or diclofenac among others. The exact mechanism by which NSAID's could influence the progression of AD is not known. Although intervention programmes that rely on NSAID's have mostly come up negative (Imbimbo., 2010). There are indications that prolonged use of NSAID's before the actual onset of AD symptoms might be beneficial (Lehrer., 2014). Exactly how the use of NSAID's could accomplish these effects is at this point not well understood but they could indicate that the origins of AD with regards to neuroinflammation arise before the actual disease process gets underway.
Another treatment option that could potentially be suited in the battle against AD is the use of glucocorticoids. A 2012 post-mortem study (Beeri., 2012) noticed a 50% decrease in the number of senile plaques and neurofibrillary tangles in patients that had received corticosteroids. One of the drawbacks of this study is that the precise duration and dosage varied by an unknown amount among patients. In fact the precise duration of these treatments could often not be determined individually. This makes it very difficult to pinpoint exactly to what extent corticosteroids abetted patients that suffered from AD.
Nevertheless, the fact that large differences were observed between treated and untreated groups indicates that glucocorticoids are perhaps a potential new source of options.

III. Author's opinion (discussion)

So far many different ideas and theories about the origins and the precise role of neuroinflammation have passed. One of the first things that comes to mind in a cause/consequence discussion is that it doesn't have to be a dichotomy. It could in fact be that neuroinflammation is both a cause and a consequence. The fact that the use of NSAID's could potentially influence the onset of the disease does not directly indicate that it is also the cause. It could be the case that neuroinflammation is merely worsening the symptoms but in the early stages a certain threshold has to be reached and now amyloid plaques simply can't get a foothold.
It is also important to note that the use of NSAID's or corticosteroids was often the result of non-AD related symptoms and potentially other medication was also involved. Making it even harder to pinpoint the exact effects these drugs might solely have. Stress itself might also have negative effects and therefore these substances could be beneficial regardless of neuroinflammation.
Also important is that AD is a progressional disease and many treatments so far have trouble pinpointing at what stage patients were. For instance, if no resolution was the result of those treatments many may jump to the wrong conclusion in that the treatment did not work properly. While in reality it could very well be the case that the disease had simply developed too far and irreversible damage had already been done.

In answering the question of whether or not neuroinflammation is a cause or consequence of AD we have to realize that the research done so far has mostly focused on amyloid plaques. Therefore we

could be subject to information bias, simply because most of the research has been done with this thought in mind. Also, as most cases in biology it isn't just a black or white question.
Often multiple cascades are involved in cellular processes that often feedback towards one another, making it harder to directly state the exact origins of most neurological diseases, let alone AD. Noticeable in this debate is the fact that both sides recognize the importance of neuroinflammation in AD progression. At the same time it does appear that αβ deposits play a crucial role in the development of AD. Strong evidence exists for both theories, namely that αβ leads to inflammation and perhaps also that inflammation contributes to αβ plaque formation. The fact that inflammatory cytokines are heavily intertwined with αβ plaque formation makes it even harder to accurately assess and ponder upon the origins of AD neuropathology. While this principle is true and information is still lacking it is at this moment impossible to answer the question of whether or not neuroinflammation is the underlying cause of AD.

In conclusion it is important that more research needs to be conducted regarding the origins of AD. New treatment options based on neuroinflammation are necessary because previous treatments often don't reach therapeutic success or fail to address all of its symptoms. That being said, there is hope as more and more research is directed towards finding the origins of AD, be it inflammatory or other.

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