A unifying hypothesis for Alzheimer's disease: from plaques to neurodegeneration.

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Abstract

Evidence suggests that amyloidβ is highly toxic to synapses in a phosphoTau-dependent manner. Here I present an hypothesis that links previous evidence from the first rise of amyloidβ through to Tau tangles and neurodegeneration. In the immediate vicinity of plaques, concentrated soluble amyloidβ occurs in equilibrium with deposited forms. Initially, plaques cover only a small percentage of brain volume. Microglia, by efficiently removing damaged synapses, may prevent spread of damage along the axon, restricting damage to the immediate vicinity of plaques. However, as plaque load increases, as seen in Alzheimer's disease, an individual axon may suffer multiple points of damage, leading to dissociation of Tau, formation of a tangle and loss of the axon. As more axons suffer this fate, the network eventually degenerates. According to this hypothesis, the degree of plaque load that an individual can tolerate would depend on the efficiency of his/her microglia in removing amyloidβ-damaged synapses and the distribution of plaques, relative to axon trajectories, would determine the eventual cognitive symptoms.

Connecting the dots

Anyone who has witnessed the effects of Alzheimer's disease will realise the urgency of preventing the clinical onset of this devastating and all too common condition. However, so far, understanding of the cause or the progression of the disease is limited (see Box 1) and, while a few drugs are available that mitigate the symptoms in some people, no treatments are available that prevent the ongoing progression, from the present relatively late stage at which the disease is diagnosed [1].

Rare "familial" forms of Alzheimer's disease are directly due to **mutations** (see Glossary) in the **amyloid** pathway which lead to **plaques** and are sufficient for the development of **Tau tangles** and neurodegeneration. Nevertheless, substantial neurodegeneration and cognitive loss develop only after considerable delay and do not occur in the absence of tangles. Indeed, some *postmortem* brains from people who have died in old age without apparent cognitive dysfunction, show at least as heavy a plaque load as brains from people with advanced symptoms of Alzheimer's disease [2, 3].

Hence, although the high concentration of **amyloidβ,** in and around plaques, clearly causes localised damage to synapses[4] with local **network** disturbances[5], it does not itself cause major network disruption. This is one of the factors that has led to suggestions that amyloidβ is not the essential cause of Alzheimer's disease [6]. However, localised damage does occur. There is considerable evidence that, although low levels of amyloidβ may be entirely normal [7] or even essential to some processes of synaptic transmission and plasticity [8, 9], high concentrations are toxic, affecting many cellular pathways. Recent reviews have covered evidence for many effects and mechanisms of action of amyloidβ on synaptic transmission and plasticity, both in terms of normal function and toxicity [10, 11] and neither this nor the initial triggers for deposition will be reviewed in detail here. Rather, an hypothesis is presented that brings together a wide range of evidence from different laboratories, to address *how* deposition of amyloidβ, once initiated, eventually leads to Tau tangles and neurodegeneration. The hypothesis is consistent with: 1. the long delay as plaques build up, before Tau tangles and neurodegeneration ensue; 2. the closer association of tangles than of plaques with gross synaptic loss; 3. the important role of **microglia** in

influencing disease progression and 4. the substantial variability in plaque load that individuals can carry before neurodegeneration and cognitive deficits occur.

Key observations

Before proceeding to discuss the proposed framework in more detail, a brief overview of its key steps is provided. Two key observations are that (1) initially, synaptic loss is highly localised in the immediate vicinity of plaques, and (2) the actual fraction of brain volume adjacent to plaques is fairly minimal, at least up to the point when the plaque load is very substantial. Thus, while plaque-associated amyloidβ causes damage to nearby synapses, the complexity of the network and its in-built redundancy and potential for **homeostatic** repair imply that these disruptions, by themselves, would initially have only limited effects on network function.

This would only be the case, however, if the damage could be restricted to synapses in the vicinity of the plaque and did not spread along axons. If damaged synapses remained in place, spread of damage along the axon could occur due to ongoing Ca^{2+} influx and consequent dysfunction of highly mobile mitochondria. The hypothesis presented here suggests that this may be prevented by an efficient microglial response, acting to remove damaged synapses. Of course this would only delay but not prevent network damage. Likely not only loss of the synapse but other scars would remain, such as localised amyloidβ-induced phosphorylation of Tau. Gradually, as increasing plaques affected multiple points along an axon, such damage would build up, leading Tau to dissociate, destroying the axon and thereby taking all its synapses out of action. Ultimately, this is a 'one-way' process and, as more axons are lost, network dysfunction will inevitably ensue. In this framework, the plaque load that an individual can tolerate, without cognitive loss, would depend on the genetic make-up of their microglia, determining how efficiently damaged synapses can be **phagocytosed**[12].

Initial effects of rising amyloidβ

All forms of Alzheimer's disease probably begin with a rise in amyloidβ. As outlined above, in the case of **familial Alzheimer's disease**, this is due to mutations in proteins of the

synthesis pathway of amyloidβ, generally leading to a rise in its concentration, or alterations in the relative levels of different lengths of the amyloidβ peptide produced [13, 14]. In contrast, in the **sporadic** disease, the original trigger for rising amyloidβ is less clear. This could be a specific event or series of events such as head trauma or ischaemia, but may often stem from a combination of environmental and genetic factors. For example, type2 diabetes and obesity are associated with increased risk of Alzheimer's disease in old age and the changes that occur due to age itself are also likely important.

Studies in animal models suggest that as soluble amyloidβ starts to rise, it causes increased glutamate release probability. In transgenic mice with amyloid mutations, for instance, electrophysiological recordings of **CA1 pyramidal cells** show substantial increases in release probability, even when the total amyloidβ levels are low and plaques are not yet detectable [15] (Figs. 1A & 2A). In addition, long-term potentiation is increased at these earliest stages in transgenic mice, but becomes impaired as levels continue to rise[16]. These findings are consistent with the proposed physiological functions of amyloidβ [7], and with other previous reports of the positive effects of low picomolar levels of amyloidβ on synaptic transmission as opposed to the toxic effects seen at higher concentrations [11]. Hence, the early changes in soluble amyloidβ concentration may not always be dysfunctional, although, even at low levels, the amyloidβ may cause subtle changes in neural activity.

Initial plaques deposition

As amyloidβ levels rise, plaques begin to be deposited (Fig. 1A). Amyloidβ release is activity dependent [7, 17-19] and therefore plaque seeding may occur where neighbouring synapses release amyloidβ simultaneously, causing a local high concentration; or it may be due to temporal summation, i.e., increased neuronal activity and increased release from specific synapses, resulting in release of amyloidβ at a rate that outweighs its breakdown. Once plaques seed, they tend to increase in size as they attract further amyloidβ deposition, particularly early in disease progression [20]. This may be further exacerbated by plaque-associated damage occurring to neurites in the immediate vicinity, itself resulting in increased glutamate and amyloidβ release from the damaged terminals. Deposition of soluble amyloidβ into plaques may tend to minimise the increase in amyloidβ levels in the

wider tissue area. However, in the immediate vicinity of the plaque, the soluble amyloidβ oligomers are in **equilibrium** with the deposited amyloidβ [21], resulting in a localised highly toxic plaque-associated cloud of concentrated soluble amyloidβ. Hence, the deposition of plaques may initially be advantageous, in one sense, as they restrict the area of toxicity, but they also have negative effects as they not only cause localised damage but also decrease clearance of amyloidβ from the brain, for example across the blood-brain barrier[22]. All of these effects, namely Amyloidβ release, breakdown and clearance, are subject to genetic variability between individuals.

Synaptic damage in and around the plaque

Damage will occur to synapses that are close to a plaque on passing axons (Fig. 2). This is evident from the consistent presence of dystrophic synapses in and around plaques [23, 24], and from the observation that synaptic loss is roughly inversely proportional to the distance from a plaque, with the greatest loss being within 20 μm of the edge of a plaque [4]. This synapse loss starts within a few weeks of a plaque seeding [25]. Moreover clusters of hyperactive neurones have also been reported to occur within 60 μm of plaques in mouse models [26]. Thus the immediate vicinity of the plaque clearly represents a toxic environment for neurones. As outlined above however, it is important to note that even when the plaque load appears to be extensive, particularly across the **hippocampus** and cortex, the percent of brain tissue directly in contact with the plaques and hence affected by this toxic area remains very low. For example in brain sections from a transgenic mouse with hundreds of plaques detectable/mm^2, the plaque coverage of hippocampal area is only ~10% and much lower at earlier stages [16]. Consistent with this, in humans, the total proportion of the neuropil covered by plaques, even in advanced stages of Alzheimer's disease, is generally only around 5-10%, on *postmortem* analysis[27]. Thus, early in the disease, the plaques fill minimal tissue volume. If the only synapses damaged are those in the immediate vicinity of plaques, this would be expected to make little difference to network function. This is especially clear if one considers the effects on the input and output of excitatory neuronal networks where the input is dominated by *en passent* axons, such as in the hippocampus, with each pyramidal neurone receiving tens of thousands of excitatory synapses with considerable functional redundancy [28]. Of course there is a lot of variability in the effects of Alzheimer's disease on different individuals and it could easily be envisaged

that a plaque that happens to occur in a particularly vulnerable network of synapses, could result in specific cognitive effects.

The hypothesis presented here suggests that, if the damage can be restricted to synapses near plaques, without damaging the rest of the **axon** or **dendrites**, then network function will be largely maintained.

Human genome-wide association studies suggest that microglia play a protective role

Recent advances in genome-wide association studies have led to identification of several genes with variants that increase the risk of Alzheimer's disease. Many of these are microglial genes, which has highlighted an important role for these central immune cells in disease progression or its prevention [29-31]. One microglial gene which has attracted particular interest is *TREM2*. Variants of *TREM2* such as R47H increase the risk of Alzheimer's disease by around 3-fold[32, 33]. This mutation and others have been shown to result in a decrement in various functional effects of Trem2, including **phagocytosis**[34-36]. In a mouse model of Alzheimer's disease, increasing the level of TREM2 protein in microglia increased phagocytosis and alleviated various effects of amyloidβ, including the number of dystrophic neurites associated with plaques[37]. Moreover knockdown of *Trem2* expression (together with inclusion of the R47H mutation) in another mouse model had the opposite effect[36]. The effects of altering *Trem2* expression were similar in primary microglia culture [38]. In mice, the proliferation of microglia and strongly increased expression of *Trem2* and other disease relevant microglial genes are tightly correlated with plaque load[12]. Mice with familial Alzheimer's disease mutations do not go through to the full disease, despite the fact that they develop a heavy plaque load comparable to that seen in humans. So, while decrease of Trem2 activity increases risk of Alzheimer's disease in humans, in mice with familial genes for Alzheimer's disease, *Trem2* and other related genes are strongly upregulated as plaque load increases. It seems likely that this very strong microglial response in mice is one of the factors that protects them from progressing to tau tangles and neurodegeneration. It may be that humans who carry a heavy plaque load without developing the full disease, also have a very strong microglial gene set, resulting in a very

strong microglial response. But what precisely are the microglia doing to protect against the disease progressing beyond plaque deposition?

Microglia clustering around plaques may phagocytose damaged synapses.

Microglia clustered around plaques have been suggested to remove amyloidβ, and dysregulation of this process may be a factor in the initial seeding of plaques [39]. However, once plaques are established, despite substantial proliferation of microglia, they continue to grow [16]. There is considerable controversy as to the degree to which microglia can, or do, phagocytose plaques in Alzheimer's disease. An interesting review discusses this question in detail [40] suggesting that while microglia can phagocytose amyloidβ, they are not effective in doing so. Moreover, it has been repeatedly demonstrated that depletion of microglia in mouse models does not change the development of plaque load [41-43]. From a more general perspective, a normal function of microglia is to remove damaged tissue. Regardless of the question of possible effects of microglia on plaques, another tissue element to consider is damaged synapses. A recent study has reported that microglia mediate early synapse loss in mouse models of Alzheimer's disease, in a complement-dependent manner [44] and that the removal of microglia decreases synaptic loss[43]. If, as evidence suggests, microglia are indeed removing synapses, it seems likely that this does not represent inappropriate removal of healthy synapses, but rather that microglia are undertaking their usual function and removing *damaged* synapses, which in the context of Alzheimer's disease, would include ones affected by the high concentration amyloidβ around the plaques. Interestingly, this leads to the possibility of a circular protective effect of microglia, as explained below. This concept comes up, even though somewhat implicitly, when bringing together the two studies by Yuan et al., 2016[19, 45]. One of the studies linked neuronal activity to amyloidβ release and plaque load. Among other findings, the authors show that reducing neuronal activity decreased neuronal dystrophy around the plaques. In a separate study, the group demonstrated that increasing *Trem2* expression in mice with familial mutations increases microglial density around plaques and decreases the presence of dystrophic neurites. The authors also showed an associated decrease in the spread of amyloid fibrils around plaques. Partly because microglial engulfment of synapses wasn't

observed in these conditions, the authors' interpretation was that one of microglia's key protective functions is forming a physical barrier around plaques (rather than removing dystrophic neurites). An alternative interpretation, however, is that *Trem2* overexpression enhanced the efficiency of microglia in engulfing dystrophic neurites. This could decrease the release of amyloidβ from such damaged boutons, and thereby also limit the spread of amyloidβ-induced damage to nearby neurites. Hence, in a circular protective loop, fewer neurites would become dystrophic, and those that did would have been rapidly removed, reducing the likelihood of capturing the engulfment event in fixed tissue. Note that the engulfment of synapses by microglia around plaques has been clearly demonstrated in other studies[44].

This then raises the question of how the microglia are attracted so strongly to the plaques and to the damaged synapses associated with them. One candidate mediator in this process is TREM2 (Fig. 1B). TREM2 has been shown to be a microglial receptor for nanomolar concentrations of amyloidβ, and knockout of *Trem2* prevents the accumulation of microglia around plaques. This suggests that while the low levels of amyloidβ far from plaques are probably not toxic to neurones, amyloidβ may nevertheless attract microglia towards the plaque along an increasing concentration gradient. Further, it is possible that through Trem2-induced activation, the microglia attracted to the plaque would have increased phagocytic activity, allowing them to remove damaged tissue, decreasing the vicious cycle of damage caused by amyloidβ-induced dystrophy (Fig.1B).

Lose the synapse to save the axon.

By removing damaged boutons, microglia may not only break the vicious cycle of amyloidβ – induced synaptic dystrophy outlined above, but their removal might also help to prevent damage spreading along axons (Fig.2). Although there is considerable loss of synapses in the vicinity of a plaque, axons passing near plaques tend to display a striking anatomical pattern: they are often smooth close to the plaque, bending around it, but still show boutons impinging on spines both proximally and distally along the axon, at some distance from the plaque[4]. This suggests that the rest of the axon may remain functional (Fig 2C).

Amyloidβ-induced damage to synapses causes Ca^{2+} influx and mitochondrial damage [46]. Ca^{2+} is an essential element of cellular signalling but its influx needs to be tightly controlled or it can result in cell death [47]. The interactions between amyloidβ, elevated Ca^{2+} concentration in boutons and dendrites, mitochondrial damage and cell death has been extensively reviewed [47]. An interesting recent study clearly shows a loss of mitochondria and presence of dystrophic mitochondria, particularly in presynaptic terminals near plaques in *postmortem* tissue [48], suggesting that such damage would particularly affect the axon. It has also been recently reported that amyloidβ specifically causes mitochondrial damage to neurones[49] and not to microglia or astrocytes [50]. Mitochondria are very mobile in axons and thus ongoing Ca^{2+} influx or further phosphorylation of Tau, causing increasing mitochondrial damage, would not be limited to site of damage but would spread throughout the axon as more mitochondria were damaged over time (Fig. 2B). As transmitter release is a highly energy dependent process, this would be expected to result in wide synaptic damage.

Taken together, these considerations suggest that away from plaques there would be little damage (Fig. 2A). Close to plaques synapses would be lost and if damaged synapses in the immediate vicinity of plaques are allowed to remain, the damage would continue to spread (Fig.2B). Efficient removal of the damaged synapses, by microglia, may prevent further mitochondrial damage thus delaying network disruption (Fig. 2C). Another factors important in the localised effects of amyloidβ on synapses in the vicinity of plaques is that, at least on the postsynaptic side, amyloidβ-induced synaptic damage has been reported to be mediated by phosphorylation of Tau at Alzheimer's disease-relevant sites and this may be the initial trigger of Tau pathology [51-55]. Moreover it has been suggested that immune senescence may be one of the factors that increases the risk of Alzheimer's disease in old age [56, 57] and if senescence of microglia decreases their efficiency in removal of damaged synapses, this could account for increased vulnerability with age. In fact, in neurodegenerative diseases, including Alzheimer's disease, *postmortem* analysis of microglia has suggested regional differences in regulation of microglial gene expression at different disease stages [58] and this could account for some of the selective vulnerability of different brain regions.

It is interesting to note that microglia may also decrease early toxic effects of amyloidβ on presynaptic terminals via release of brain derived neurotrophic factor [59].

As plaque number and size increases, some axons will pass near multiple plaques

As discussed, the loss of a few synapses along the length of an axon is unlikely to substantially affect local network function. However, if a particular axon passed close to multiple plaques along its path, thereby losing groups of its synapses in multiple locations, it seems feasible that the communication via that axon would gradually become compromised (Fig. 3). As the damage to synapses by amyloidβ causes phosphorylation of Tau, damage to large numbers of synapses on the same axon would be expected to result in phosphorylation at multiple sites along its length and this could then cause the dissociation of Tau from the microtubules, resulting in Tau tangles. Phosphorylation of Tau has been clearly shown in dystrophic neurites in both transgenic mice and rats with plaque-causing mutations [60, 61], although Tau tangles do not develop in these animal models.

Interestingly, in mice which have a mutation in Tau, the dendrites and integration properties of neurones that contain Tau tangles can stay intact [62]. However, if the axon were no longer functional, despite a functional dendritic tree and cell body, this would effectively remove the neurone from the circuit, as it would lack output. In another mutant Tau mouse model, phosphorylated Tau is clearly visible in axons before and during initial tangle development but decreases sharply once neurodegeneration begins to occur, presumably reflecting loss of these axons [63]. Thus, there seems to be a progression from phosphorylation of Tau in the axon to appearance of tangles, with the eventual loss of axons coinciding with neurodegeneration. It is, however, important to note that in Alzheimer's disease, the development of tangles is not due to a mutation in Tau but rather is associated with amyloidβ-induced synaptic damage, and so the time course and sequence of tangle development and axon loss could be different. Importantly, the general principle of the loss of the axon preceding loss of the dendrites and soma has previously been shown by staining of phosphorylated Tau in *postmortem* human tissue [64]. Importantly, loss of the full axon would result in a much greater decrease in synapse number than the localised loss around a

plaque, consistent with the observation that synaptic loss is more closely correlated with tangle load than with plaque load.

Lose the axon to delay damage to network dysfunction

Similar to the concept of losing a few synapses being advantageous if their loss saves the rest of the axon, loss of a dysfunctional axon may be preferable to maintaining it, if its dysfunction is disturbing network function. Removing an axon that is communicating inappropriately may initially decrease damage to network function as a whole. Indeed, in the mice mentioned above, in which neurodegeneration coincides with loss of axons that show phosphorylated Tau, only subtle changes in synaptic transmission and plasticity are detected[63].

Clearly, however, the changes outlined above, even if protective early on, represent a one-way process. Although removal of dysfunctional synapses by microglia and removal of dysfunctional axons by Tau phosphorylation might delay the onset of symptoms, this will reach a tipping point and eventually the process of neurodegeneration will lead to damaged network function and impaired cognition (Fig. 3).

Concluding remarks and future perspectives

The hypothesis presented in this article brings together evidence from a wide range of studies across the last two decades. The small percentage of brain volume taken up by plaques early in Alzheimer's disease and the presence of high concentrations of amyloidβ oligomers in and around them, is consistent with the concentrated synaptic loss that occurs in the immediate vicinity of plaques, without this localised damage initially destroying whole axons and with little loss in the rest of the tissue. Amyloidβ-mediated Tau phosphorylation has also been demonstrated. The framework proposed here posits that as plaque load builds up, such localised phosphorylation occurring at multiple sites along an axon during progression of the disease, can lead to dissociation of Tau from microtubules and formation of Tau tangles. It is this multiple-site damage along an axon that is proposed to lead eventually to axon loss, and accordingly, the presence of Tau tangles is expected to be

associated with dysfunction of whole axons, rather than with the localised effects of plaques. Therefore, the proposed hypothesis is also consistent with the repeated observation that synaptic loss and cognitive deficits are more closely correlated with the presence of Tau tangles than amyloidβ load. Moreover, the anatomical position of the cell soma where the tangle occurs may be remote from its projecting axons. The delay between initial plaque deposition and broader network dysfunction would also be explained.

Postmortem tissue analyses reveal that some individuals display a heavy plaque load but no noticeable cognitive impairment. The hypothesis proposed here is consistent with these observations as well: different individuals would tolerate different levels of plaque load before suffering gross neurodegeneration, dependent both on the genetic make-up of their microglia and possibly on the degree of connectivity and redundancy in their neuronal networks (Fig. 3). The latter point would also be consistent with the concept of cognitive reserve, which has been suggested to explain the association of higher education level with resistance to Alzheimer's disease [65].

The question arises as to why mice with amyloid mutations do not develop Tau tangles, even when they have a heavy plaque load. One possible and often discussed explanation is the limited time window for disease progression, resulting from the relatively short lifespan of rodents. Another possible explanation is that the genetic backgrounds of the mouse strains commonly used for modelling Alzheimer's disease result in microglia that are particularly reactive to amyloidβ, strongly upregulating factors shown to be protective in humans such as *Trem2* [12]. Future studies of aged mice that are genetically manipulated to develop plaques, combined with microglial mutations that increase risk in humans, may result in fuller models of the pathophysiology. Moreover, even without addition of further genetic manipulation, recent development of mouse models on different genetic backgrounds may be valuable in this light[66].

The most important test for the current hypothesis will be longitudinal analysis of the prognosis for development of Alzheimer's disease with or without removal of amyloidβ from cognitively normal people who have early plaque development (BOX 2). This population has a considerably higher chance of developing Alzheimer's disease within a few years compared to those without detectable deposit [67] and the hypothesis outlined here predicts that removal of amyloidβ at this early stage would prevent cognitive loss.

Moreover, repeated evidence of cognitively normal individuals with a considerable plaque load but no evidence of dystrophic neurites [3, 68, 69] may support this hypothesis. It would be interesting to analyse the genetic makeup of these individuals to determine whether they have microglial gene variants that result in particularly efficient phagocytosis of localised damage. The more limited the damage remains around a plaque, the greater the plaques density that an individual could sustain before axonal loss and cognitive damage result (Fig. 3).

Over the last two decades there has been considerable progress with information gathered by many labs across the world that sheds light on the individual aspects of Alzheimer's disease. The studies can be loosely divided into two groups. Many are focused on local events (plaques, synapse dysfunction, cellular clearance, Tau phosphorylation etc.). Others, particularly those based on human brain-imaging techniques, look at larger-scale networks, but take a fairly macro-scale/global view (inter-regional connectivity, spread of pathology across brain regions). The present article attempts to bring these two scales of analysis together, connecting the dots and suggesting a framework that pieces together many lines of evidence into a single coherent picture of disease progression.

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Glossary

Amyloidβ: A peptide of varied length (mostly 38, 40 or 42 amino acids) that can be released into the extracellular space and which at high concentrations in some forms is highly toxic to neurones. In Alzheimer's disease, it forms fibrillary deposits – "**plaques**" – in the extracellular space.

Axon: The part of the neurone carrying output messages to up to 10s of thousands of other cells.

CA1 pyramidal cells: A type of primary excitatory neurone in the hippocampus.

Dendrite: The part of the neurone receiving most of the input from other cells. In the case of excitatory input onto most excitatory cells in hippocampus and cortex, 10s of thousands of inputs are received onto dendritic spines.

Equilibrium: Balance; in the context of Alzheimer's disease it means that soluble amyloidβ is deposited into an insoluble form, but like all chemical reactions, this will go in both directions, with soluble molecules depositing and insoluble molecules becoming soluble. Hence, in and around the insoluble plaque, there will be a high concentration of soluble amyloidβ. As the plaque grows, the equilibrium will be more in the direction of soluble to insoluble, but nevertheless it will go both ways.

Familial Alzheimer's disease: A directly inherited form of the disease usually due to mutations in Amyloid Precursor Protein or in the proteins that lead to its cleavage to produce amyloidβ. Familial Alzheimer's disease is a rare condition that is usually severe and occurs at relatively young ages.

Hippocampus: Part of the brain involved in the laying down and retrieval of memory as well as in place orientation which is particular prone to damage in Alzheimer's disease.

Homeostatic mechanism**:** a reaction to a change that returns the system towards its normal level

Microglia: The immune cells of the brain which clear damaged cells and foreign material and mediate inflammation.

Mutation: genetically mediated change in the structure of a protein

Network: The overall connections between neurones that lead to cognitive function. Each excitatory neurone in the hippocampus and cortex can receive messages from up to 10s of thousands of neurones, and send messages via a single axon to up to 10s of thousands of neurones.

Phagocytosed/Phagocytosis: the engulfing of material for removal by microglia

β- and γ-Secretases: Enzymes involved in the production of amyloidβ. Familial Alzheimer's disease is most commonly caused by mutations in one of the presenilins, which are components of γ-secretase.

Sporadic Alzheimer's disease: The common form of Alzheimer's disease caused by unknown factors. The genetic variants that lead to increased risk of sporadic disease are increasingly understood.

Tau (microtubule associated protein tau) is a protein normally associated with microtubules, important in the function of the axon. In Alzheimer's disease, Tau dissociates from the microtubules in the axon and moves into other compartments of the cell folding into **Tau tangles**. Tau tangles are closely correlated with synaptic loss and neurodegeneration.

BOX 1: What is Alzheimer's disease?

Alzheimer's disease is defined as a dementia in which neurodegeneration and cognitive decline are accompanied by brain pathology with: 1. extracellular plaques, mostly composed of amyloidβ and 2. Intracellular tangles of the axonal protein Tau, hyperphosphorylated and displaced into the cell body [70]. Once diagnosed, rapid ongoing atrophy [71] is already far advanced. Even at the stage of mild cognitive impairment, preceding the diagnosis of Alzheimer's disease, there is a heavy plaque and tangle load and around 20% loss of hippocampal volume [72]. Early presymptomatic disease shows that plaques are often present decades before measurable cognitive deficit [73-75]. Tangles build up later than plaques [64] and, together with synaptic loss, are more closely correlated with cognitive decline [76]. Many questions remain about how rising amyloidβ leads to the development of Tau tangles [53] and why the onset of neurodegeneration comes with such a long delay.

Mouse models

There are no complete mouse models in which rising amyloidβ leads to Tau pathology and neurodegeneration and even the introduction of improved knock-in models that avoid problems of overexpression of APP have not altered this[77]. Although *in vivo* brain imaging of plaques and tangles is advancing[78], especially for diagnostic purposes, most of the information about the pathophysiology is gleaned from *postmortem* human tissue or from mice carrying either mutations that lead to rising amyloidβ and plaques or mutations in Tau, leading to tangles. These mutant mice studies provide considerable information about the influence of these two types of pathology [12], but only limited information about how they interact.

BOX 2: Implications of the proposed hypothesis for prevention or delay of disease progression.

The hypothesis outlined in this article suggests that avoiding amyloidβ build up at any stage of the disease will be advantageous; however, unless this is achieved before the advent of substantial plaque load, the effects may be marginal. Even if at early stages some synapses lost around plaques could be recovered [79, 80], once axons are sufficiently damaged to start to develop Tau tangles, it is unlikely that this process could be easily reversed. The sooner amyloidβ is lowered, the fewer the axons that would be terminally damaged.

However, even if full restoration were not possible, at any preclinical stage lowering amyloidβ should decrease the local damage to synapses and the ongoing effects of the disease. In mouse models, relatively small reductions in soluble amyloidβ levels have been shown to cause a dramatic reduction in plaques, but only early in progression [81]. So far this has not translated to the clinic, but regardless of the specific intervention being used, the hypothesis discussed here would suggest that the interventions tested so far in clinical trials have been attempted too late in disease progression.

The recent advances in our knowledge of genetic risk factors for Alzheimer's disease [82], and advances in early detection of it [83-85], raise the hope that it may be possible to identify people who have rising amyloidβ long before cognitive deficits reach a diagnosable level[5]. While many questions remain (see Outstanding Questions), the proposed hypothesis brings together wide ranging research and suggests that applying the already existing amyloid-removing drugs, or drugs preventing amyloidβ production, may be effective, especially when applied much earlier than has previously been tried[86], before the occurrence of substantial axon damage. While in the familial disease this would presumably require nearly life-long treatment, in the sporadic disease, if the triggers that originally caused onset of rising amyloidβ were short-term, it is conceivable that once amyloidβ is cleared, the progression of disease would be halted.

Figure Legends

Fig. 1 Early effects of amyloidβ release: **A**. Amyloidβ is released in an activity-dependent manner with low concentrations causing increased glutamate release. Plaques seed and grow containing deposited amyloidβ surrounded by highly concentrated soluble forms. This causes damage to synapses close to the plaque, and likely further exacerbates amyloidβ release. Microglia (purple) attracted to plaques phagocytose damaged synapses protecting from wider damage. Depending on microglial efficiency, Ca^{2+} influx and mitochondrial dysfunction will spread along the axons or be limited to the immediate vicinity of the plaques as detailed in Fig. 2. **B.** Trem2 senses low concentration amyloidβ far from plaques, resulting in migration up the concentration gradient towards the plaques. As the concentration of amyloidβ increases, Trem2 expression is increased causing morphological change and increased phagocytosis of damaged synapses.

Fig. 2 Protective effect of microglia: **A**. Low concentration amyloidβ in the neuropil far from plaques causes increased glutamate release probability but synapses are not damaged. **B.** Synapses on axons in the immediate vicinity of plaques are damaged by high concentration amyloidβ via phosphorylation of Tau and Ca^{2+} influx causing mitochondrial damage. Ongoing Ca^{2+} influx and spread of damaged mitochondria cause ongoing synaptic damage up and down the axon at a distance along the axon away from the plaque. **C.** If microglia remove damaged synapses promptly damage may be restricted to the immediate vicinity of the plaque.

Fig 3 An equivalent plaque load, with similar trajectory of increase over time, may cause more cognitive damage in some individuals than others. The table represents the effect of the same increasing plaque load in an individual if he/she has (on the left) strong microglia that rapidly remove synapses, or (on the right) ineffective microglia unable to remove damage efficiently. Increasing age, from top to bottom, in the central column indicates a hypothetical example of the years over which the plaque number and size increases, within an axon tract (parallel lines). The indicated ages roughly correspond to the average for

different stages in a typical progression of the disease. Dashed sections on axons represent spreading damage; dotted lines with tangles represent loss of the axon as multiple plaques impinge, causing phosphorylation of Tau at multiple points along the axon. As the table illustrates, if microglia are dysfunctional (such as those with Alzheimer's disease risk mutations), a relatively lower plaque load would be required for cognitive decline to be detected than in individuals with more efficient microglia. Hence the same plaque load results in a more advanced stage of Alzheimer's disease in some individuals than in others.

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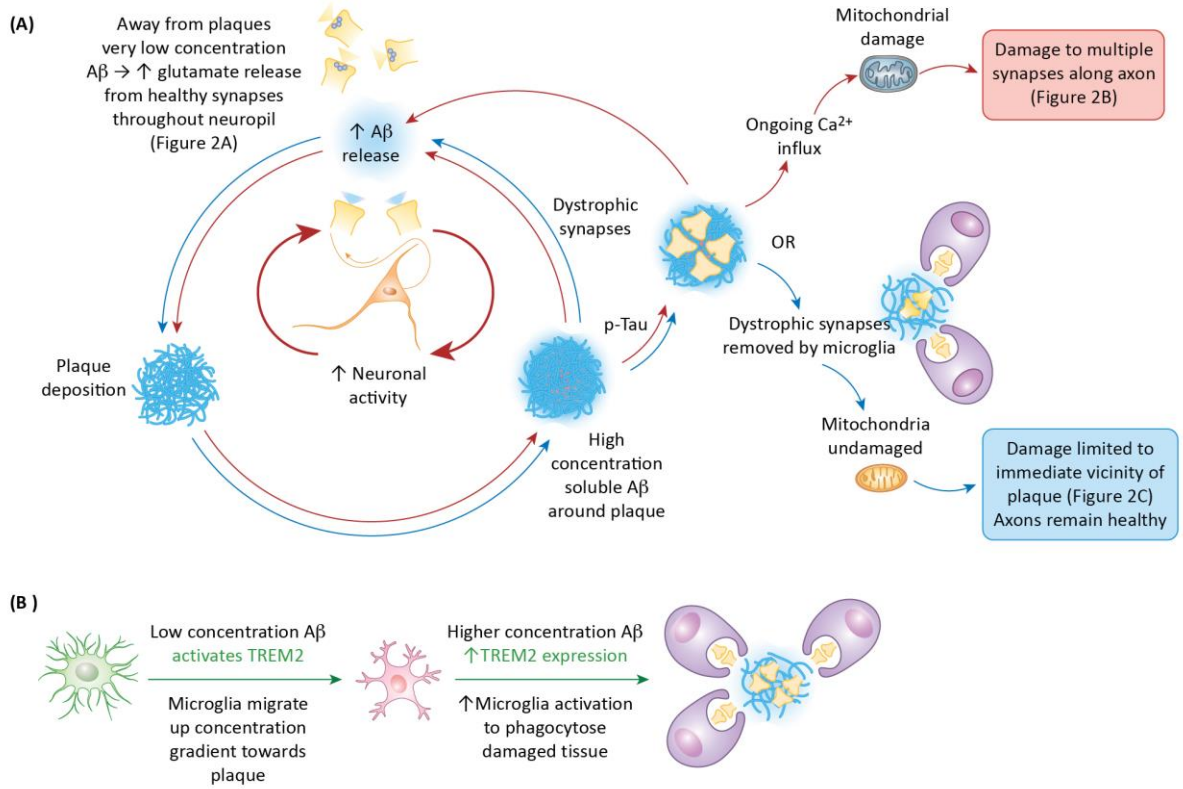
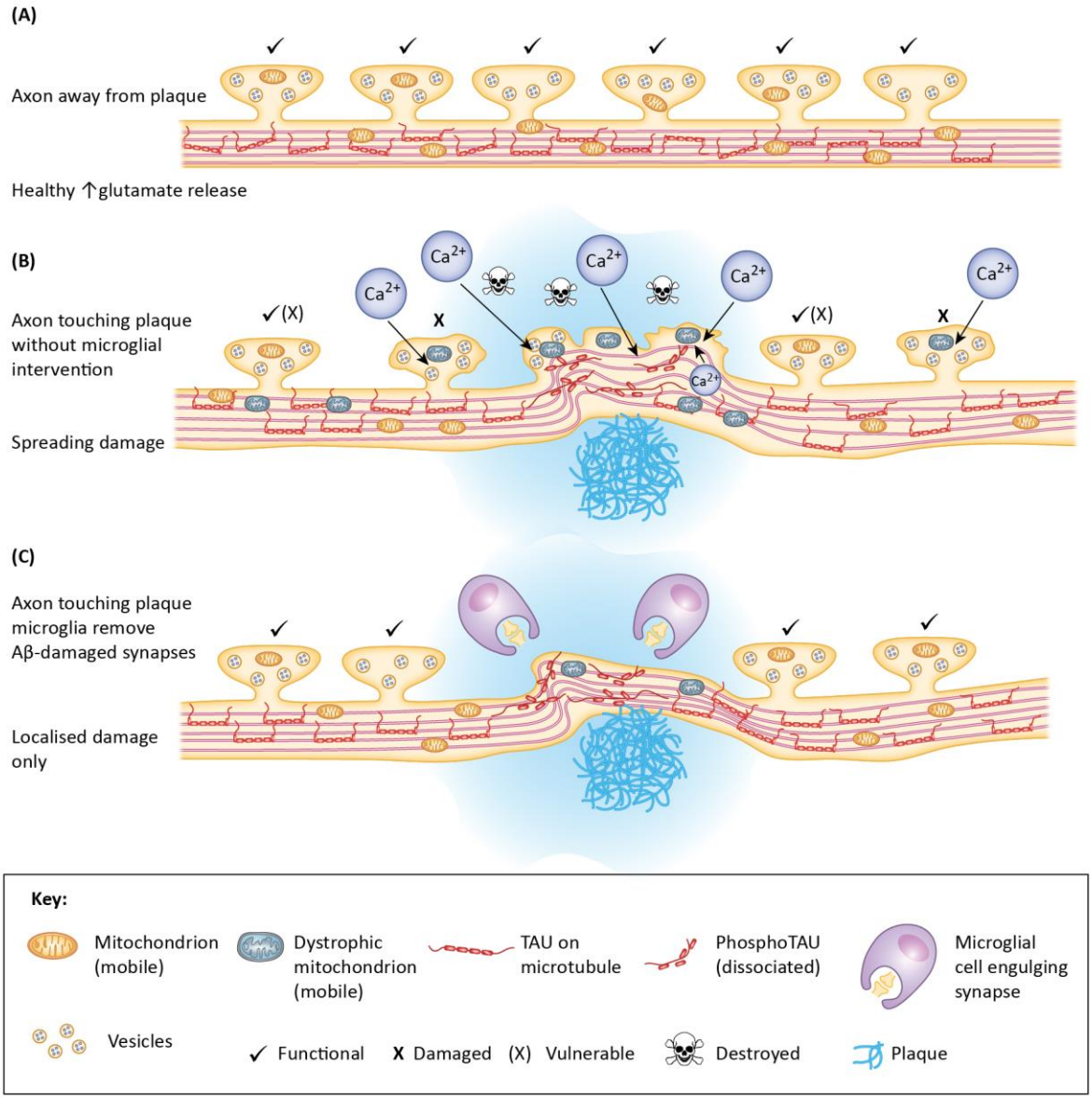
Figure 1


(A)
Away from plaques
very low concentration
Aβ → ↑ glutamate release
from healthy synapses
throughout neuropil
(Figure 2A)
↑ Aβ
release
Plaque
deposition
↑ Neuronal
activity
Dystrophic
synapses
p-Tau
High
concentration
soluble Aβ
around plaque
Mitochondrial
damage
Damage to multiple
synapses along axon
(Figure 2B)
Ongoing Ca2+
influx
OR
Dystrophic synapses
removed by microglia
Mitochondria
undamaged
Damage limited to
immediate vicinity of
plaque (Figure 2C)
Axons remain healthy
(B)
Low concentration Aβ
activates TREM2
Microglia migrate
up concentration
gradient towards
plaque
Higher concentration Aβ
↑TREM2 expression
↑Microglia activation
to phagocytose
damaged tissue

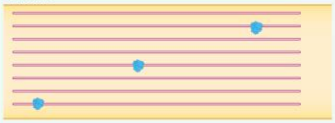
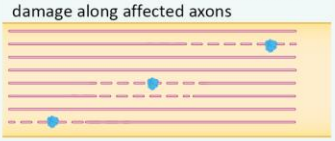
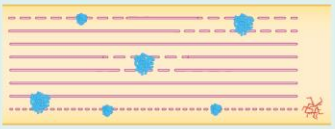
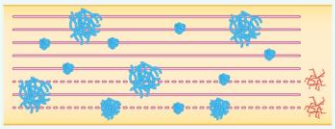
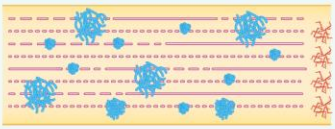
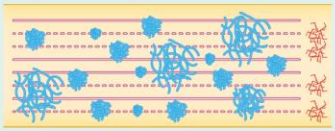
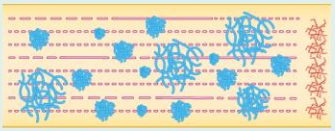
667

Figure 2


(A)
Axon away from plaque
Healthy ↑glutamate release
(B)
Axon touching plaque without microglial intervention
Spreading damage
✓(X)
X
Ca2+
(C)
Axon touching plaque microglia remove Aβ-damaged synapses
Localised damage only
Key:
Mitochondrion (mobile)
Dystrophic mitochondrion (mobile)
TAU on microtubule
PhosphoTAU (dissociated)
Microglial cell engulging synapse
Vesicles
✓ Functional
X Damaged
(X) Vulnerable
Destroyed
Plaque

668

Figure 3

SAME PLAQUE LOAD WITH STRONG MICROGLIAL RESPONSE		OR	WITH WEAK/DYSFUNCTIONAL MICROGLIAL RESPONSE	
Damage to axon function	**Effect on cognition/ diagnosis**	**Age years** (Example)	**Damage to axon function**	**Effect on cognition/ diagnosis**
Isolated synapses lost on occasional axons 	Minimal-undetectable	50s	Only few axons affected but spreading damage along affected axons 	Minor Some self doubt
More axons slightly affected; occasional axons starting to be dysfunctional where many plaque contacts occur 	Minor Some self doubt	60-70	Some axons badly affected both by impinging plaques and spreading damage; starting to lose axons; some tangles 	Detectable MCI
Many axons slightly affected; a few axons lost due to phosphorylation of Tau at many isolated points along axon; some Tangles 	Starting to affect network but often possible to compensate; possible MCI diagnosis	70-80	Starting to lose many axons; clearly measurable neurodegeneration; many tangles 	Badly affected Clear cognitive deficits AD diagnosis
Most axons affected to some degree at several isolated points; many having damage at many point; losing more axons; tangles increasing 	MCI/early AD diagnosis	80-90	Considerable neurodegeneration; many axons lost due to multiple direct contacts plus spreading damage; heavy tangle load 	Late stage AD/death