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Review article

Neurophysiological assessment of neural network plasticity and connectivity: Progress towards early functional biomarkers for disease interception therapies in Alzheimer's disease

C. Walsh, W.H.I.M. Drinkenburg, A. Ahnaou *

Dept. of Neuroscience Discovery, Janssen Research & Development, A Division of Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

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ABSTRACT

Despite a great deal of research into Alzheimer's disease (AD) over the last 20 years, an effective treatment to halt or slow its progression has yet to be developed. With many aspects of the disease progression still to be elucidated, focus has shifted from reducing levels of amyloid β (Aβ) in the brains of AD patients towards tau, another pathology, which initiates much earlier in deeper brainstem networks and is thought to propagate via cell-to-cell processes prior to the onset of amyloid pathology and cognitive impairments. In-vitro, ex-vivo molecular biology/biochemistry read-outs, and various transgenic animal models have been developed, yet clinical failures have highlighted a clear disconnect and inadequate use of such animal models in translational research across species. AD pathology is now estimated to begin at least 10–20 years before clinical symptoms, and imaging and cerebrospinal fluid biomarkers are leading the way in assessing the disease progression at a stage where neuronal damage has already occurred. Here, we emphasize the relevance of assessing early disruptions in network connectivity and plasticity that occur before neuropathological damage and progressive memory dysfunction, which can have high translational value for discovery of pre-symptomatic AD biomarkers and early mechanism-based disease interception therapeutics.

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Abbreviations: Aβ, amyloid Beta; ACh, acetylcholine; AChEI, acetylcholinesterase inhibitor; ACH, amyloid cascade hypothesis; AD, Alzheimer's disease; APP, amyloid precursor protein; ARIA-E, amyloid related imaging abnormalities related to edema; CSF, cerebrospinal fluid; EEG, electroencephalogram/electroencephalography; EROS, event-related oscillations; ERP, event-related potentials; fAD, familial Alzheimer's disease; fMRI, functional MRI; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; LC, locus coeruleus; LTP, long-term potentiation; MAOI, monoamine oxidase inhibitor; MCI, mild cognitive impairment; MEG, magnetoencephalography; NA, noradrenaline; PDGFB, platelet derived growth factor B; PET, positron emission tomography; PP2A, protein phosphatase 2A; PS, presenilin; pTau, phosphorylated tau; sAD, spontaneous Alzheimer's disease.

* Corresponding author.
E-mail address: aahnaou@its.jnj.com (A. Ahnaou).

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is the cause of approximately 60–80% of dementia cases (Alzheimer's Association, 2015). Symptoms include impairments in cognitive function and loss of memory, which increase in severity over the progression of the disease. In the late stages of the disease, loss of motor skills such as swallowing and walking result in a complete loss of independent living. Two hallmark lesions are found in the brains of AD patients: extensive extracellular plaques of amyloid beta (Aβ) and intracellular neurofibrillary tangles made up of hyperphosphorylated tau protein. Additionally, AD brains also present with severe neurodegeneration and widespread neuroinflammation. This multifactorial nature of AD has made determining the direct impact of each individual factor to the overall disease state very difficult.

AD is primarily a disease of the elderly; most people who are diagnosed are aged 65 or older (Alzheimer's Association, 2015). Increases in life expectancy coupled with decreases in fertility have resulted in an ageing global population (United Nations Department of Economic and Social Affairs, 2015). It has been predicted that in the next ten years, for the first time in history, over 65's will outnumber children under 5 (US Census Bureau, 2009). There are currently an estimated 46.8 million people living with dementia worldwide, a number which has been predicted to double every 20 years (Prince et al., 2015). Currently there are no drugs available which stop or slow the progression of Alzheimer's disease, and only 4 compounds have been licensed to alleviate cognitive impairments. AD is a rapidly growing public health problem that, without any available treatment to slow its progression, will continue to grow unchecked.

A review of completed clinical trials for 244 AD compounds between 2002 and 2012 found an overall success rate for approval was 0.4%, among the lowest for any therapeutic area (Cummings et al., 2014), including some high profile, costly late stage failures (Table 1). The aim of this review is to address the recent stagnation in AD drug discovery, explore some recent developments in Alzheimer's research and their implications for possible therapeutics. Finally, the review will cover some of the important considerations in translating preclinical breakthroughs into clinical success.

2. AD and Aβ

2.1. Amyloid cascade hypothesis

In 1907, in a post mortem analysis of the brain of a severely demented 51 year old woman, Alois Alzheimer described "peculiar bundles of fibrils", and "miliar foci of a peculiar matter", distributed throughout the cortex (Alzheimer, 1907; Strassnig and Ganguli, 1987). This was the first clinical recognition of the senile plaques and neurofibrillary tangles of what would later be described as Alzheimer's disease. It was not until the mid-1980's when the main components of these lesions, amyloid beta and tau protein, respectively, were identified (Glenner and Wong, 1984; Kosik et al., 1986). Soon after, it was discovered that a mutation in the gene for amyloid precursor protein (APP) on Chromosome 21 could cause familial Alzheimer's disease (fAD) (St George-Hyslop et al., 1987). APP is cleaved by γ-secretase to produce Aβ (Kopan and Ilagan, 2004). This also explained the common occurrence of AD in Downs Syndrome, a genetic disorder caused by an extra copy of chromosome 21 (Jacobs et al., 1959; Lejeune et al., 1959). This led to formulation of the Amyloid Cascade Hypothesis (ACH) by (Hardy and Higgins, 1992), a hypothesis which would go on to shape AD research and drug discovery.

The ACH posits that an accumulation of Aβ, as a result of increased production or reduced clearance, causes a cascade of neurodegenerative processes including synapse loss, inflammation and neurodegeneration (Hardy and Higgins, 1992). Importantly, this hypothesis places tau pathology as a downstream effect of amyloid pathology, and suggests that Aβ accelerates the formation of neurofibrillary tangles. This attractive hypothesis considered both genetic and biochemical factors, and provided the pharmaceuticals industry with an appealing target; by reducing levels of amyloid beta in the brain, the progression of AD could be slowed or halted. In the following years, both research and industry turned their focus to this target; between 2002 and 2012, 65% of the clinical trials for AD modifying agents targeted Aβ, yet all have failed so far (Cummings et al., 2014). Although these failures are not the main focus of this review, we will briefly cover some notable examples, some possible reasons for their lack of success, and the consequences of these failures.

2.2. Aβ – example therapeutic strategies

There have been a number of different approaches to reducing levels of Aβ in the brain. One compound, Semagacestat, was shown to inhibit γ-secretase, theoretically reducing production of Aβ (Kopan and Ilagan, 2004). Preclinical data demonstrated reductions in cerebrospinal fluid (CSF) Aβ (Hyslop et al., 2004), but no reductions in levels of plaques. Phase 2 clinical trials showed that while Aβ production could be effectively inhibited, cognitive function, as measured by ADAS-cog, was worsened (Fleisher et al., 2008). Additionally, it was shown that the dosage was limited by side effects, such as rashes and changes in hair colour. These side effects were suggested to result from alterations in Notch

Table 1
Notable Alzheimer's disease interventional agents that completed Phase III of Clinical trials and did not meet their endpoints.

Drug	Institution	Mechanism
Bapineuzumab	Janssen Research & Development/Pfizer	Aβ Antibody
Solanezumab	Eli Lilly and Co.	Aβ Antibody
Tramiprosate	Neurochem Inc.	Aβ Antibody
Semagacetat	Eli Lilly and Co.	γ-Secretase Inhibitor
Phenserine	Axonyx Inc.	Inhibits APP expression
Atorvastatin	Pfizer	Reduces Cholesterol production
Docosahexaenoic Acid	Martek Biosciences Corp./NeuroBioPharm Inc.	Omega-3 Fatty Acid
Naproxen	Procter & Gamble/Roche	Non-steroidal Anti-Inflammatory
Tarenflurbil	Myriad Genetics & Laboratories	Non-steroidal Anti-Inflammatory
Prednisone	National Institute on Aging	Steroidal Anti-inflammatory
Valproate	Abbott Laboratories	GABAergic anti-convulsant
Rosiglitazone	GlaxoSmithKline	PPAR-γ receptor agonist

signalling, which is important in cell differentiation, as Notch is another substrate of γ-secretase. Phase 3 clinical trials were terminated due to severe side effects, including increased incidence of skin cancer, likely resulting from Notch signalling (Doody et al., 2013). Patients showed no improvements in cognitive function, levels of CSF Aβ or Aβ deposition. A similar story can be seen in the development of Bapineuzumab, an antibody targeted at increasing clearance of amyloid plaques. While preclinical and phase 2 data supported that Bapineuzumab could reduce amyloid deposition when used in a preventative manner (Rinne et al., 2010; Schenk et al., 1999), it failed to show any improvement in cognitive function in phase 3. Dosing was also limited by a high incidence of vasogenic oedema, a serious side effect involving disruption of the blood brain barrier, that is now referred to as Amyloid related imaging abnormalities related to edema (ARIA-E) (Salloway et al., 2014). Another antibody, Solanezumab, targeted the soluble form of Aβ as opposed to the insoluble form found in plaques. Preclinical data, although inconsistent, suggested that Solanezumab could capture soluble Aβ in the blood and act as a sink to increase efflux of Aβ from the CSF, and therefore reduce Aβ deposition (DeMattos et al., 2002, 2001). Early clinical data supported this, as increases in levels of Aβ in the both plasma and CSF were demonstrated, suggesting plaque clearance (Siemers et al., 2010). In Phase 3 trials, Solanezumab failed to show a consistent improvement in cognitive performance, and while significant increases in CSF and plasma Aβ were seen, there was no change in deposits of Aβ (Doody et al., 2014).

While these are merely a few examples, these three compounds exemplify the main shortcomings of a number of the amyloid AD modifying agents: firstly, that preclinical efficacy in reducing levels of Aβ in animal models is rarely translated to efficacy in humans, and secondly, that clearance of Aβ in humans has as of yet shown no clinical benefit. The first point calls into question the predictive validity of the amyloid AD models: how well pre-clinical efficacy in these models can predict clinical efficacy. The majority of amyloid transgenic models utilize mutations in the APP and PS1 genes that commonly cause familial AD, and do not present with significant neurodegeneration or tau pathology, disputing their usefulness for modelling sporadic AD (Philipson et al., 2010). This second point has been divisive in the field, and has led to calls for a reassessment of the ACH. Proponents of the ACH have suggested the need for a better understanding of the direct role of Aβ in AD, as well as the possibility for increased efficacy through earlier intervention, or prophylactic treatment. A recent review has critically analysed the merits and shortcomings of the ACH, and has anticipated, along with others in the field, that current amyloidocentric therapies in phase 3 of clinical trials are unlikely to demonstrate a significant clinical benefit (Karran and De Strooper, 2016). With this in mind, many in the field have shifted their focus towards tau protein, and its role in AD.

This increasing interest in the role of tau is not unwarranted. The extent of tau pathology in the brain correlates well with the severity of AD (Braak and Braak, 1995). Furthermore, tau pathology alone has been shown to cause neurodegeneration and cognitive impairment in both animal models (Santacruz et al., 2005; Yoshiyama et al., 2007), and in humans, in a range of diseases known as tauopathies (Williams, 2006). The following section will cover a number of recent developments in tau research, and the implications they have for AD drug discovery.

3. Tau pathology in AD

In 1986, it was discovered that the NFTs found in the brains of AD patients were composed of hyperphosphorylated tau protein (Kosik et al., 1986). Tau is a microtubule associated protein important in the formation and stabilization of microtubules, and as such, is of great physiological importance (Weingarten et al., 1975). The binding ability of tau to microtubules is regulated by its phosphorylation state (Lindwall and Cole, 1984), yet when hyperphosphorylated, tau becomes pathological, and is able to sequester other tau proteins and aggregate to form the NFTs seen in AD (Alonso et al., 2004). Although its relevance in AD was discovered a mere 2 years after that of amyloid beta, the relevance of tau in AD has often been overlooked. However, a number of key aspects of tau pathology in AD make tau a valuable and worthwhile research target in AD drug discovery.

3.1. Braak staging of neurofibrillary changes

Firstly, tau pathology progresses in a relatively stereotypical manner, with little variability between individuals. This discovery allowed the definition of neuropathological stages of tau pathology in Alzheimer's disease, beginning in the transentorhinal region of the temporal neocortex, then spreading to the limbic system, and finally ending up widespread throughout the neocortex (Braak and Braak, 1991). Following this it was discovered that the spatial distribution of neurofibrillary tau pathology of AD correlates well with neurodegeneration and the clinical symptoms experienced (Braak and Braak, 1995): the early episodic memory impairments can be explained by primarily limbic pathology; the involvement of association areas heralds the onset of further cognitive impairments; and finally, the late involvement of the sensory and motor cortex explains the late development of sensory and motor dysfunction (Braak and Braak, 1995). Further investigation indicated that cognitive symptoms seem to first appear following the destruction of the entorhinal cortex, a region that acts as an interface between the limbic system and neocortex (Braak and Braak, 1997). By the time patients are classified as having mild cognitive impairment (MCI) (due to Alzheimer's disease), approximately 30% of the neurons in the entorhinal cortex have already been lost (Gómez-Isla et al., 1996). There can be a number of causes of mild cognitive impairment so it is important to note that MCI, when mentioned

in the context of this review, is referring to MCI due to Alzheimer's disease.

This stereotypical progression has stimulated discussion as to its cause. One theory explains this through a "hierarchal vulnerability" of neuronal cell types: that AD pathology develops within certain neurons of certain areas due to increased type-specific vulnerability (Van Hoesen et al., 1995). However, this theory does not explain differences in vulnerability of neurons of the same type to NFT formation. An example given by (Braak and Tredici, 2014) is the cortical pyramidal neurons in layer Va, which are often heavily lesioned, while those in the adjacent layer IV are widely spared. A controversial theory suggests that misfolded pathological tau molecules spread like prions along the axons of affected neurons and template, or "seed", pathology in anatomically connected areas (Brundin et al., 2010). This effectively explains the pattern of progression of AD as well as the long prodromal period, and has been supported by a number of "seeding" experiments; in which administration of pathological tau *in vitro* and *in vivo* can template pathology which spreads to areas anatomically connected to the site of administration (Clavaguera et al., 2009; Iba et al., 2015; Peeraer et al., 2015). This hypothesis is still controversial and requires further experimental validation, but may open up a possible target for therapeutic intervention. By preventing transmission of misfolded tau between neurons, the spread of tau pathology could effectively be halted before extensive involvement of the limbic system and cortex.

3.2. Identifying the toxic species of tau

Secondly, as mentioned earlier, the amount of neurofibrillary tangles in the brain also correlates well with the severity of AD symptoms (Braak and Braak, 1995). These two factors in combination suggested that it was in fact these insoluble neurofibrillary tangles that are the toxic form of tau, and that tau pathology results from a gain of toxicity, and not a loss of normal function. Young tau knockout mice show no overt phenotype, but when aged demonstrate some motor impairments but not behavioural or cognitive abnormalities, supporting the gain of tau toxicity as the primary pathological mechanism (Ke et al., 2012). The specific form and mechanism of tau toxicity is of great importance for research into therapeutic intervention, as compounds will most likely target either soluble or insoluble forms of tau. The development of intraneuronal neurofibrillary pathology undoubtedly affects the function of neurons, through impaired axonal transport for example, but affected neurons have been shown to be able to survive for many years (Morsch et al., 1999). While neurodegeneration can often be found in the presence of NFTs, neurodegeneration can also be found in the absence of NFTs (Spires et al., 2006). The development of a mouse model in which expression of human tau could be switched off through administration of doxycycline has allowed investigation of this relationship (Santacruz et al., 2005). The authors found that turning off expression of human tau in aged 4 month old mice resulted in protection from further neuron loss and an improvement in cognitive function, while numbers of NFTs increased. These new NFTs were likely acting as a sink for excess tau, suggesting that the soluble forms of tau are toxic. These studies have uncovered another possibility for the role of NFTs in AD; that they are the result of a defence mechanism by the cell to prevent further damage. This is supported by the discovery that the aggregation of tau into NFTs diminishes its capacity to sequester further tau, thus reducing the loss of normal tau function in the cell (Alonso et al., 2006). It is of note that, unlike tau pathology, neither the extent nor distribution of amyloid pathology correlates with the severity of dementia in Alzheimer's disease, or the specific symptoms experienced (Arriagada et al., 1992). This supports the relevance of tau pathology in Alzheimer's disease.

In a recent post-mortem study of brain of individuals under the age of thirty, it was discovered that the pathological process of AD may begin much earlier than previously expected, with a number of these brains showing tau pre-tangles in the brainstem locus coeruleus (LC) (Braak and Del Tredici, 2011). While it had been established that the LC undergoes significant neurodegeneration in AD (Mann et al., 1982), this study has indicated that tau pathology may originate there, leading to a reassessment of the early Braak stages. Another study discovered that a subgroup of senile dementia patients with the extremely severe degeneration of the LC presented with equally severe dementia and a relatively early death (Bondareff et al., 1982). As the field turns towards earlier interventions and the role of tau, understanding where and when tau pathology first begins would provide a window of opportunity, in which disease modifying agents may be able to slow, halt, or even partially reverse pathological progression before lasting damage is done.

3.3. Pathological tau – example therapeutic strategies

While the shift in focus towards tau may seem unwise, due to extensive research into amyloid beta, this venture may soon prove worthwhile. LMTX is a second generation tau aggregation inhibitor, currently nearing the end of its Phase 3 clinical trials for treatment of AD and behavioural variant Frontotemporal dementia. LMTX is a stabilized version of its predecessor, Methylthionium chloride (MTC), which suffered from problems with bioavailability and tolerability (Wischik et al., 2015). The rationale behind both compounds is an inhibition of aggregation of tau, and a breakdown of pre-existing aggregates. Both MTC and LMTX were shown to restore spatial learning and memory in a novel mouse model of AD, and motor learning in a novel mouse model of Frontotemporal lobar dementia, another tauopathy (Melis et al., 2015, 2014). Histopathological analysis demonstrated that MTC and LMTX reduced tau pathology load in the brains of both mouse models. The company behind MTC and LMTX, TauRx Pharmaceuticals, has stated a 90% reduction in AD progression over 2 years in their MTC Phase 2 trial (TauRx Pharmaceuticals, 2016). These results seem promising, and the results from the LMTX Phase 3 trials are expected to be released this year (Table 1). If these clinical trials are successful, and the regulatory licensing process runs without significant delay, the first AD modifying agent may be available in the near future. The clinical benefit of clearing tau pathology without altering amyloid pathology may appear counterintuitive, considering the aforementioned problems with targeting amyloid pathology in isolation. However, in a study by (Roberson et al., 2007) the authors found that reducing levels of tau in tau knockout mice with mutant APP, reduced excitotoxity and prevented behavioural impairments, without affecting levels of APP or Aβ. A further study found that reduction of tau in APP mice also rescued deficits in synaptic plasticity, increased inhibitory currents, and reduced spontaneous seizure activity (Roberson et al., 2011).

While LMTX is currently the only tau targeted therapy in the late stages of clinical testing, there are numerous other tau targeted compounds currently in Phase 1 or preclinical stages, and while LMTX attempts to treat tau pathology in AD by preventing aggregation of tau, as with Aβ, there are various other strategies being tested (Khanna et al., 2016). There are currently strategies focused of both of the main suggested mechanisms of tau toxicity: gain of toxicity and loss of function. As previously mentioned, inhibition of tau aggregation has shown promising results in the case of LMTX (Melis et al., 2015), while TPI-287 is a microtubule stabilising compound which attempts to restore effective axonal transport, and is currently in Phase 1 of clinical trials for AD (NLM Identifier: NCT01966666). Notably, TPI-287 is also currently in early stages of clinical trials for the treatment of brain tumours, due

to its high blood brain barrier penetration as compared to other microtubule stabilisers (Fitzgerald et al., 2012). Recently, there have been suggestion that a combination of a tau aggregation inhibitor and a microtubule stabiliser may be an effective treatment at targeting both aspects of tau pathology (Perry et al., 2015). Finally, strategies that attempt to modulate enzymes that break down or post-translationally modify tau may have problems with specificity, as many of these enzymes have multiple substrates (Khanna et al., 2016), and as exemplified by Semagacestat, serious health problems can arise from non-specific enzymatic effects (Doody et al., 2013).

The aforementioned Aβ and tau based example therapeutic strategies are merely a few of the current interventional agents that have been developed. While an in depth description of all of the currently ongoing AD clinical trials is outside the scope of this review, (Table 2) briefly outlines some notable compounds in Phase 3 of clinical trials at the time of writing this review.

As indicated earlier, recent clinical trial failures have deemed it necessary to critically analyse the AD drug discovery process and the way these compounds were evaluated at the preclinical stages. Three of the most prevalent reasons for clinical failure of these compounds are thus: that compounds did not reduce levels of amyloid beta or amyloid plaques in humans as they did in animals, that clearance of pathology provided no clinical improvement in these patients, and that the compounds were administered too

late in the disease progression. The failure to translate a preclinical effect in animals into a clinical effect in humans has brought into question how well the amyloid beta animal models used in these trials reflect the human condition. The following section will discuss and critically analyse the currently available animal models of Alzheimer's disease, as well as introducing some more novel models and notable developments in this field.

4. Animal models in preclinical drug discovery

Effectively being able to model a disease in animals allows us a means to better understand the disease, as well as providing a platform for testing the efficacy of experimental therapeutic compounds. However, efficacy in preclinical animal models does not always translate to efficacy in humans. This "translational gap" has been a continuing problem in AD drug discovery, and can be attributed to a number of causes, some of which will be discussed later in this review.

Due to their widespread use and availability, as well as their physiological advantages for translation to humans, this review will focus on mouse models. It is important to note however, that there are a number of available non-rodent species that have been used in AD research as well. There are many transgenic AD mouse models available, so for the purpose of this review, a selection of the most commonly used models will be described and critically analysed. There are a number of excellent reviews which characterise in detail these animal models (Chin, 2011; Puzzo et al., 2015).

4.1. Aβ transgenic mouse models

4.1.1. Mutant APP mouse models

One of the first mouse models of AD, PDAPP, was developed by (Games et al., 1995), and overexpresses human APP with the fAD Indiana mutation, which favours pro-aggregate Aβ42, under a platelet derived growth factor B (PDGFB) promoter. These mice express approximately ten times as much APP as their wild type background animals, and develop amyloid plaques at around 6–8 months of age, starting in the hippocampus and later in the cortex. These animals suffer from loss of synapses, as well as impairments in spatial memory, as tested by the Morris Water Maze. However, the brains of these animals show very limited neurodegeneration and are absent of neurofibrillary tangles. Since the development of this model, there have been numerous APP models developed, with a variety of fAD APP mutations and promoter combinations. Some notable examples are the Tg2576 mouse, and the APP23 mouse. Tg2576 mice overexpress human APP with the fAD double Swedish mutations, which increase production of Aβ42 and 40, under Hamster Prion Promoter (Hsiao et al., 1996). These mice express approximately five times as much APP as their wild type background animals, and subsequently develop plaques later than PDAPP mice, with hippocampal plaques appearing at around 9 months of age. Subtle memory impairments have been demonstrated to start at around 8 months of age, before amyloid deposition, yet these animals show no neurodegeneration or tau pathology. APP23 mice also overexpress human APP with the Swedish mutation, but under a non-neuron specific Thy1.2 promoter (Sturchler-Pierrat et al., 1997). As such, alongside plaque development at 6 months of age, the brains of these mice present with cerebral amyloid angiopathy: the deposition of Aβ within the walls of cerebral blood vessels. While these animals do not present with tau pathology, a modest loss of neurons was demonstrated in the CA1 region of the hippocampus, but not in the cortex.

4.1.2. Mutant presenilin mouse models

Mutations in the APP gene are not the only amyloid mutations seen in familial Alzheimer's disease; presenilin (PS) mutations have been demonstrated to shift processing of APP to longer, pro-

Table 2
Interventional Agents that are currently being tested in Phase III Clinical Trials .

Drug	Institution	Mechanism
Crenezumab	Hoffmann-La Roche	Aβ Antibody
Gantenerumab	Hoffmann-La Roche	Aβ Antibody
Immune Globulin	Instituto Grifols, S.A.	Aβ Antibody
Sodium Oligo-mannurarate	Shanghai Green Valley Pharmaceutical Co.	Inhibits Aβ aggregation
AZD3293	Eli Lilly and Co./AstraZeneca	BACE inhibitor
CNP520	Novartis Pharmaceuticals	BACE inhibitor
JNJ-54861911	Janssen Pharmaceutica/Shionogi	BACE inhibitor
Verubecestat	Merck Sharp & Dohme Corp	BACE inhibitor
CAD106	Novartis Pharmaceuticals	Vaccine against Aβ
LMTM/LMTX/TRx0237	TauRx Therapeutics Ltd.	Inhibits Tau aggregation
Lisinopril	Emory University	ACE inhibitor
Candesartan	Emory University	Angiotensin receptor blocker
Idalopirdine/Lu AE58054	H. Lundbeck A/S	5-HT6 receptor antagonist
Intepirdine/RVT-101	Axovant Sciences Ltd.	5-HT6 receptor antagonist
Insulin	University of Southern California	Blood glucose regulating hormone
Masitinib	AB SCIENCE	Tyrosine Kinase Inhibitor
Nilvadipine	University of Dublin, Trinity College	Calcium channel blocker
Pioglitazone	Takeda	PPAR-γ receptor agonist

aggregate Aβ42/40 species (Scheuner et al., 1996). Presenilins are transmembrane proteins that make up the γ-secretase complex. While singly transgenic mutant PS mice have been developed that have elevated levels of Aβ in their brains, they do not develop plaques (Duff et al., 1996; Wen et al., 2004). This demonstrates the importance of pro-aggregate APP mutations in the aggregation of amyloid beta into insoluble plaques. In order to circumvent this, PS mice have been crossed with APP mice to produce doubly transgenic mice. One example is the PSAPP mouse, created from crossing the Tg2576 mice described earlier, with PS1M146L mice (Holcomb et al., 1998). These mice have elevated levels of Aβ42/40, and accelerated amyloid deposition (6 months), as compared to its Tg2576 progenitor (9 months). Additionally, these animals suffer from accelerated memory impairments, yet no substantial neurodegeneration. Lastly, the 5XFAD mouse was developed utilizing 5 fAD mutations: the Swedish, Florida and London APP mutations, and the M146L and L286V presenilin 1 mutations (Oakley et al., 2006). These mice rapidly develop amyloid pathology, with high levels of Aβ42, and plaque formation at 2 months of age, while synapse loss, memory impairment and neurodegeneration take place at around 4 months of age.

As demonstrated, there are a number of well characterized amyloid models of Alzheimer's disease. These amyloid models have proven to be extremely effective at modelling the amyloid pathology of Alzheimer's disease, and have been commonly used as the preclinical model for several the aforementioned amyloid directed clinical trials. However, many of these models fail to replicate two major pathologies of Alzheimer's disease, tau pathology and substantial neurodegeneration. Moreover, these models utilize familial AD (fAD) mutations to attempt to model spontaneous AD (sAD). fAD is far less common than sAD, and thus this approach does not address the currently unknown aetiology of the spontaneous disease, as the widespread expression of such high levels of amyloid beta does not replicate the human condition. There are also a number of tau transgenic mouse models available, which are becoming more widely used following the increasing interest in tau. Unlike with amyloid beta, there are no mutations related to tau that cause Alzheimer's disease, however a number of mutations have been discovered that cause Frontotemporal dementia, another tauopathy, and these mutations have been used to develop mouse models (Goedert and Spillantini, 2000).

4.2. Tau transgenic mouse models

While not technically the first tau transgenic model developed, the JNPL3 model was the first tau transgenic mouse model that presented with neurofibrillary tangles and neurodegeneration (Lewis et al., 2000). These mice express the P301L mutation found in Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), under a mouse prion promoter, and develop extensive NFT formation throughout the hindbrain, including the brainstem and spinal cord, resulting in neuron loss and severe motor impairments. The value of this model is limited by these motor impairments, and the hindbrain pathology does not reflect the predominantly forebrain pathology seen in AD (Braak et al., 2011). A later model, rTg4510, also utilizes the P301L mutation, but under a CaMK-II promoter, for a predominantly forebrain expression, effectively overcoming the limitations of the JNPL3 model, the hind limb paralysis (Santacruz et al., 2005). NFTs develop first in the cortex at 4 months of age, and later in the hippocampus, while cognitive and electrophysiological impairments occur prior to tau accumulation. Severe and extensive neurodegeneration in the rTg4510 brains, eventually results in gross forebrain atrophy (Santacruz et al., 2005). The P301S mutation found in FTDP-17 has also been used in transgenic mouse models. The hTau.P301S model expresses P301S mutant tau under a Thy1 promoter (Allen et al., 2002), while the PS19 model utilizes a mouse prion protein promoter (Yoshiyama et al., 2007). As with the JNPL3 model, both develop severe motor impairments. Tau pathology in the PS19 line develops primarily in the hippocampus and then spreads to the entorhinal cortex and neocortex, while tau pathology in the hTau.P301S line is predominantly found in the hindbrain.

4.3. Seeding models

The first step in the organization of soluble amyloid beta and tau into insoluble aggregates, nucleation, is the rate limiting step in the formation of senile plaques and NFTs (Friedrich et al., 2010; Vasconcelos et al., 2016). (Baker et al., 1994) suggested that if insoluble amyloid beta could act as a nucleating or "seeding" agent, by enhancing further nucleation, the increase in pathology could be exponential. This hypothesis was tested by injecting amyloid containing AD brain homogenates into the brains of marmosets. It was found that this was sufficient to induce amyloid pathology in the brains of these animals, effectively "seeding" pathology (Baker et al., 1994). However, it important to note that in a meta-analysis of neurological disorder transmission studies using non-human primates, AD brain homogenates were injected into hundreds of primates, with no conclusive evidence of transmission (Brown et al., 1994). Following this, amyloid seeding was also demonstrated in Tg2576 mice, and resulted in premature and augmented pathology in these animals as compared to age matched Tg2576 controls (Kane et al., 2000). As discussed earlier, while tau pathology seems to originate from a single focal area in the brain and progress in a relatively stereotypical manner to anatomically connected areas (Braak and Del Tredici, 2011), amyloid pathology first develops diffusely in the basal temporal neocortex and spreads throughout the adjacent cortical areas (Thal et al., 2002). While directed seeding of amyloid pathology in a certain area is possible, it can be argued that the more focal nature of tau pathology in AD is better suited to these experiments. The in vivo seeding potential of tau was confirmed by (Clavaguera et al., 2009), through injection of tau-containing brain homogenates from P301S mice into the brains of another tau transgenic mouse, ALZ17 (Probst et al., 2000). ALZ17 mice do not naturally develop NFTs, yet injection of tau-containing brain homogenates initiated robust tangle formation in the brains of these animals (Clavaguera et al., 2009). A more recent tau seeding model experimentally tested the updated Braak stages by injection of K18 aggregates into the locus coeruleus of PS19 mice (Iba et al., 2015). This initiated tau pathology at the injection site that spread to anatomically connected areas in a strikingly similar manner to that seen in Alzheimer's, giving support to the locus coeruleus hypothesis and the use of tau seeding models in research. A surprising limitation of this seeding model, however, is the absence of pathology in the hippocampus and frontal cortex. A locus coeruleus seeding model that more completely reflects the spatial progression of tau pathology in AD would be invaluable in understanding the mechanisms of this spreading, and for preclinical testing of compounds that could halt or slow this progression. Detractors of seeding models may argue that introducing toxic exogenous materials into the brains of transgenic animals does not reflect the natural disease pathology. However, an elegant study has recently been published which describes a pseudo-seeding model in wild type mice, through the stereotaxic injection of okadaic acid, a protein phosphatase 2A (PP2A) inhibitor (Baker and Gotz, 2016). PP2A dephosphorylates tau, and on injection into the amygdala, okadaic acid caused increased tau phosphorylation and aggregation in the amygdala and anatomically connected areas. The fact that such robust pathology could be induced both at the site of injection and in anatomically connected areas suggests that the initial cause of tau pathology in the brain could be a focal shift in the phosphorylation state of tau due to reduced phosphatase activity. Future

studies involving targeted enhancement of tau phosphorylation may provide unique insight into the earliest stages of Alzheimer's disease.

4.4. Aβ-Tau transgenic mouse models

Both amyloid and tau transgenic models of AD are extremely valuable for investigating the relevance of either pathology in isolation. However, while there are a range of these models available, this approach is limited in that it may neglect any interactions between these pathologies when found in combination in AD. There have been attempts to develop transgenic mouse models with both amyloid and tau pathology, however the field has much to learn about the interplay between these two pathologies, so the current value of these models seems to be limited. One such combined transgenic model, 3XTg, was developed by microinjection of human cDNA with the Swedish APP mutations and P301L tau mutation into an embryo with the Presenilin 1 M146V mutation (Oddo et al., 2003). This model develops both amyloid plaques and neurofibrillary tangles, and synaptic dysfunction in the form of impaired LTP is apparent prior to the presence of both plaques and tangles. This model may prove to be a useful model for investigating the effects of clearance of amyloid pathology on tau pathology and vice versa. However, care should be taken when extrapolating results from this model to the human condition. The authors of this study posit that the appearance of amyloid pathology prior to tau pathology in this model supports the amyloid cascade hypothesis, assuming that amyloid pathology is the cause of the tau pathology. This does not take into account that none of these mutations are not found in spontaneous Alzheimer's disease, or that both Swedish and M146V amyloid mutations result in early onset amyloid pathology (Clark et al., 1995; Mullan et al., 1992). It is more accurate to say that the overexpression of APP found in the 3xTg mouse and therefore the accumulation of Aβ, resulted in increased tau pathology as compared to the 2xTg (PS1x P301L) model (Oddo et al., 2003). This demonstrates that the presence of intraneuronal amyloid beta augments tau pathology, but does not make assumptions about interdependencies. The hypothesis that the presence of amyloid beta has a positive influence on the development of NFTs is gaining support, and has been supported by studies in which tau pathology in mouse models is accelerated by the presence of amyloid beta, whether it is injected (Götz et al., 2001), or transgenically overexpressed (Lewis et al., 2001). A recent study in which Aβ heterotypically aggregated tau proved to be an effective seed *in vitro* and *in vivo* has suggested that the presence of amyloid beta may influence tau aggregation through "cross seeding" to overcome the rate limiting nucleation step (Vasconcelos et al., 2016).

5. Validity of animal models

Animal models are often discussed with regard to three criteria first elaborated by (Willner, 1986). The better an animal model fulfils these three sets of criteria, the more successful the translation of preclinical data to clinical applications likely to be: *Face validity*: the animal model resembles the human disease condition on a superficial level, for example, biochemistry or symptomatology; *Predictive validity*: the animal model can successfully discriminate between successful and unsuccessful treatments for the human disease condition; *Construct validity*: the animal model is based on a sound theoretical rationale, requiring a good understanding of the human disease condition. Notably, construct validity examines whether a variable tested is addressed by the experiment and does not require superficial similarity. There is also another form of validity, *Translational validity,* which attempts to assess the degree to which constructs of the animal model are accurately captured by a psychometric instrument, translated into the operationalization, using subjective judgment – face validity – and examining content domain – construct validity. It is a subjective process, in which theoretical knowledge of the concept is used to judge the degree to which the instrument reflects our understanding of the concept. Recently, a very important and promising project seeking to develop new ways to classify mental disorders proposes a new research Domain Criteria approach (RDoC) that may facilitate translational research based on behavioural and neurobiological measures. Understanding the neural circuitry underlying a mental disorder holds promise for understanding the neurobiology of fundamental processes and abnormal behaviour arising from early neurodevelopmental alterations, and may provide a closer link between animal models and the disorders they model (Cope et al., 2016; Elmer et al., 2016).

Present preclinical animal models AD have advantages and shortcomings in relation to their capacity to address critical questions capturing cardinal features of the disease, and, as there is still much of AD that has yet to be explained, construct validity will always be limited. As demonstrated, there are numerous available animal models for Alzheimer's disease, but the choice of animal model is extremely important. Some of the notable AD mouse models mentioned throughout this review are summarized in Table 3, along with some of the strengths and limitations of these models. While no currently available animal model fully recapitulates the pathology of Alzheimer's seen in humans, recent developments are coming closer and closer to this goal. The use of tau seeding models is allowing further investigation into the spread of tau pathology, while the emergence of combined tau-amyloid models has already produced promising insight into the interactions between tau and amyloid beta. This last point is of great interest, as a firm understanding of the relationship between tau and amyloid beta could also unite the currently divided field towards a common goal. As there is growing interest in the earliest stages of Alzheimer's, tau seeding models that focus on the early stages in the new Braak staging, in which tau pathology spreads from the locus coeruleus to the entorhinal cortex, such as that of (Iba et al., 2015), would be invaluable for testing the efficacy of disease modifying treatments. While the addition of these early Braak stages may seem insignificant, a great deal of recent research has demonstrated that the loss of locus coeruleus neurons and the subsequent reduction in noradrenergic signalling in the brain during AD may have a significant impact on the developing pathology.

6. The locus coeruleus and the relevance of Noradrenaline in AD

The locus coeruleus is the major noradrenergic nucleus in the brain (Foote et al., 1983), and alongside its well-known functions in stress and alertness, noradrenaline has a number of other physiological functions in the brain that relate to Alzheimer's disease. The relevance of noradrenaline in both normal physiological function and in AD has been extensively tested through the use of lesion and pharmacological models. Neurotoxins such as *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (dsp-4) and 6-hydroxydopamine (6-OHDA) have been used to selectively destroy noradrenergic neurons (Harik, 1984; Jonsson et al., 1981), while noradrenergic antagonists such as Prazosin have been used to investigate the effects of noradrenaline in vivo (Kleinlogel, 1989). There is a growing body of research on the relevance of the locus coeruleus and noradrenaline in AD. The effects of the loss of locus coeruleus neurons in AD and the subsequent reduction in noradrenaline in the brain have been described as a "triple threat", that potentiates the developing pathology and cognitive impairments (Chalermpalanupap et al., 2013).

Table 3
Table summarizing some of the available mouse models of AD mentioned in this review, and some of their main strengths and weaknesses. As currently available seeding models do not have names as such, more detailed information on previous seeding models can be found in-text.

Type of Model	Name	Rationale	Strengths	Weaknesses	Conclusion
Amyloid Transgenic Mice	PDAPP, Tg2576, APP23, PSAPP, 5xFAD	Overexpression of pro-aggregate species of Aβ using fAD mutations results in high levels of both soluble and insoluble Aβ as seen in spontaneous AD.	Animals present with amyloid plaques and cognitive impairment, pathology is progressive, effectively models AD amyloid pathology	Utilises fAD mutations to model sAD, no models develop tau pathology, few models present with severe neurodegeneration, many rely on high levels of Aβ.	Valuable for investigating the effects of amyloid pathology in isolation but in the absence of heavy neurodegeneration or tau, these models ignore two main pathologies of AD
Tau Transgenic Mice	JNPL3, rTg4510, hTau. P301S,P301L, PS19	Pro-aggregation FTDP-17 tau mutations result in the formation of neurofibrillary tangles and extensive neurodegeneration, similarly to as seen in AD.	Animals present with neurofibrillary tangles and cognitive impairments, pathology is progressive, effectively models AD tau pathology	Utilises FTDP-17 mutations to model AD, no models develop amyloid pathology, spatial progression of pathology does reflect that in humans, hindbrain expression results in motor impairments.	Valuable for investigating the effects of tau pathology in isolation, but models are based on mutations that are not found in AD
Seeding Models		Injection of Aβ or tau in a region of the brain simulates the initiation of these pathologies in AD and their subsequent spread throughout the brain.	Both Aβ and tau can be seeded, allows for relatively rapid induction of progressive AD pathology, allows investigation into the spread of amyloid and tau pathology	Current seeding models still require transgenic AD mice for sufficient pathology, injection of toxic aggregates into the brain may have non-specific effects.	Valuable for investigating the spread of pathology in AD, but better suited to tau seeding due to the more focal nature of early tau pathology in AD
Neuro-transmitter Models	LC/Basal Forebrain Lesion, ACh/NA blockade	Neurodegeneration of the locus coeruleus and basal forebrain occurs in AD, and results in reduced levels of NA and ACh, which cause cognitive impairment and EEG slowing.	Relatively simple protocols, can be performed in wild type animals, allows testing of related compounds with possible cognitive enhancing potential	Does not model the progressive aspect of AD, or the hallmark pathologies, unsuitable for testing of disease modifying agents	Useful for investigating the relevance of reduced cholinergic and noradrenergic signalling in AD, but limited by the lack of AD pathology

6.1. Alertness, sleep and clearance of Aβ

An intricate relationship exists between sleep, circadian rhythms and the physiopathology of AD (Musiek et al., 2015; Urrestarazu and Iriarte, 2016). While AD pathology causes disruptions in both circadian rhythms and sleep, which have a major impact on the quality of life of patients and their caregivers, recent accumulating evidence indicate that sleep and circadian rhythms influence AD pathology. Dysfunction of the suprachiasmatic nucleus due to lack of light input impairs its function and its link to the pineal gland and melatonin production, diminishing circadian input to the sleep/wake networks (Skene and Swaab, 2003; Wu and Swaab, 2007).

The involvement of noradrenaline in sleep and alertness is well established (Renton and Weil-Malherbe, 1956), and while noradrenaline itself is a wakefulness promoting agent, in vivo its effects are more complex than that. While dopamine beta-hydroxylase knockout mice, which cannot synthesize noradrenaline, have been shown to have more sleep than controls, they have half the amount of REM sleep and increased sleep fragmentation (Ouyang et al., 2004). Similarly, the administration of Prazosin, an alpha 1 adrenergic receptor antagonist, to rats was found to reduce REM sleep, while increasing active waking and slow wave sleep (Kleinlogel, 1989). Similarly, sleep disturbances are seen in Alzheimer's disease, with common complaints being the insomnia at night, and excessive drowsiness in the daytime. Moreover, it was found that 70% of caregivers stated sleep disturbances as their decision to institutionalize an elderly relative (Pollak and Perlick, 1991). A recent study has shown that approximately 65% of amyloid beta clearance is undertaken by the glymphatic system, a para-arterial system in which solutes are exchanged between the CSF and interstitial fluid (Iliff et al., 2012; Tarasoff-Conway et al., 2015). Glymphatic clearance was found to increase during sleep, attributable to a ~60% increase in interstitial space (Iliff et al., 2012). Interestingly, recent evidence suggests a specific role for slow wave sleep in this clearance of waste products from the interstitial space in the brain including Tau and Aβ (Gao et al., 2008; Klein et al., 2015; Xie et al., 2013). This demonstrates the importance of sleep in removal of amyloid beta and tau from the brain, and suggests potential treatment for a number of other neurological disorders known to be associated with accumulation of these species such as traumatic brain injury and stroke (Cam et al., 2013; Martinez-Vargas et al., 2012; Mendelsohn and Larrick, 2013; Morawska et al., 2016; Xie et al., 2013). This indicates that the impairments in sleep associated with locus coeruleus degeneration may also lead to a reduction in clearance of metabolites including amyloid beta, resulting in their accumulation, and further damage to the brain.

Sleep also plays a key role in the balance of synaptic strength in the brain. Slow wave sleep has been shown to downscale the accumulated load of synaptic potentiation elicited during wakefulness (Vyazovskiy et al., 2008). An association has been established between neuronal activity and release of Aβ and tau, and studies have begun to explore how modulation of sleep networks affects those AD factors. Orexin contributes to sleep wake regulation by increasing arousal levels and maintaining wakefulness (Sutcliffe and De Lecea, 2000). Sleep fragmentation associated with high number and duration of nightly awakenings has been linked to impairments in orexinergic signalling (Friedman et al., 2007;

Liguori et al., 2014; Roh et al., 2014). A dual orexin receptor antagonist has been shown to decrease Aβ plaque formation in amyloid precursor protein in human APP transgenic Tg2576 mice, likely through facilitation of sleep (Kang et al., 2009). Due to its roles in the mechanisms of wakefulness and alertness, LC noradrenergic signalling facilitates modulation of vigilance states, and is likely to greatly impact tau and Aβ pathogenesis in the brain (Carter et al., 2010; Femminella et al., 2016; Ross et al., 2015).

6.2. Inflammation

Secondly, aside from its relevance in arousal and wakefulness, noradrenaline also has a role in the inflammatory response in the brain, and acts on beta adrenergic receptors on astrocytes and microglia to promote anti-inflammatory effects, by promoting and suppressing the expression of anti and pro inflammatory genes respectively (Sutin and Shao, 1992; Tanaka et al., 2002). Therefore, it can be suggested that the loss of noradrenaline in AD and health promotes inflammation. A number of animal models support this; dsp-4 lesions have been shown to increase microglial and astroglial activation and increase their production of pro-inflammatory cytokines in two transgenic amyloid mouse models of AD (Heneka et al., 2010). As chronic neuroinflammation can lead to further neurodegeneration and neuronal dysfunction, the loss of noradrenaline may potentiate the pathology of AD. A recent study has found that activation of the complement cascade in AD may lead to excessive synaptic pruning by microglia (Hong et al., 2016). Increased levels of complement protein C1q were found associated with synapses, and in the presence of soluble Aβ, lead to early microglial mediated synapse loss. Microglia have also been shown to mediate clearance of Aβ in the brain through phagocytosis and degradation (Heneka et al., 2010). In this study, depletion of NA in dsp-4 treated APP transgenic mice resulted in reduced recruitment of microglia to amyloid plaques and reduced phagocytosis of Aβ by microglia. Moreover, administration of L-*threo*-DOPS, a precursor of noradrenaline, partially restored the clearance of Aβ (Heneka et al., 2010). This demonstrates that the loss of noradrenaline in the brain may potentiate the neuropathology of AD by increasing neuroinflammation, thus further decreasing clearance of amyloid beta and increasing synapse loss.

6.3. Cognition

Finally, the role of noradrenaline in cognition has recently been investigated. The severity of cognitive impairment in AD has been correlated with the extent of EEG (electroencephalogram) slowing (Kowalski et al., 2001), a shift from high frequency oscillations to low frequency oscillations, making EEG slowing a possible functional indicator of cognitive impairment. This slowing may be attributed to reductions in cholinergic signalling, resulting in cognitive impairment (Bartus et al., 1982; Ray and Jackson, 1991). It has also been demonstrated that reductions in levels of neurotransmitters such as serotonin and noradrenaline also result in cognitive impairments in humans and animal models (Dringenberg, 2000). It is of note that both postsynaptic noradrenergic and cholinergic receptors are largely spared in Alzheimer's disease, indicating that reductions in their tone may be attributed to reduced innervation (Dringenberg, 2000). A recent study has found that this monoaminergic deficit, in combination with cholinergic deficits, produce much more severe impairments, as well as a more severe slowing of the EEG. These findings suggest that drugs that increase levels of noradrenaline (NA) in the brain, as well as acetylcholine (ACh), may in fact provide a more effective form of symptomatic relief in Alzheimer's disease. In this study cognitive impairment and EEG slowing were induced in rats, using a combination of scopolamine and either a monoamine release inhibitor or a serotonin synthesis inhibitor. Following this, animals were administered an AChEI or monoamine oxidase inhibitor (MOAI), in order to restore levels of acetylcholine or monoamines respectively (Dringenberg, 2000). It was shown that a combination of an AChEI, Tacrine, and a MOAI, Pargyline, more effectively reversed both the cognitive impairments and EEG slowing than Tacrine alone. There are currently a number of clinical trials recruiting subjects for the investigation of the efficacy of increasing noradrenergic signalling for the symptomatic treatment of MCI (NLM Identifiers: NCT02590874, NCT01522404, NCT02326038, NCT02180529).

Recently, it has been speculated that to treat the combination of disease factors that make up Alzheimer's disease, the most effective therapy would take the form of a cocktail of drugs which attempt to clear both amyloid and tau pathology. We have previously discussed the relevance of noradrenaline in both the disease progression and symptomatology of Alzheimer's disease, and while the value of therapeutics which solely increase noradrenaline signalling in the brain could be expected to be poor, these compounds may prove to be an effective part of this therapeutic cocktail.

As mentioned earlier, while numerous experimental AD drugs were effective at clearing amyloid pathology in clinical trials, they failed to demonstrate clinically beneficial effects. There are a wide range of cognitive behavioural tasks available for use with mice that can be used to investigate AD related cognitive changes, and while it is not possible to fully predict whether clearance of pathology will be clinically beneficial in humans using mice, cognitive behavioural tasks allow screening of compounds with possible cognitive enhancing potential.

7. Cognitive behavioural tasks

Currently available cognitive and behavioural tasks used in AD drug discovery are generally focused on memory, such as: the Morris water maze and radial arm maze for spatial "hippocampal dependent" learning and memory; the spontaneous alternation T and Y mazes for working memory; and passive inhibitory avoidance for contextual memory (Webster et al., 2014). These tasks are well suited to the investigation of AD related changes, as memory impairments are among the first clinical manifestations of the disease, yet these tasks may not be sensitive enough to detect the earliest MCI stage. As changes in brain function have been demonstrated to precede the onset of Alzheimer's symptoms (Stomrud et al., 2010) and predict the onset of AD in MCI patients (Davatzikos et al., 2014; Poil et al., 2013; Serra et al., 2016), functional biomarkers have become a topic of great interest in humans. AD functional biomarkers also show great promise for application to animal models, and may help to overcome the translational gap in AD drug discovery. The final section of this paper will address this interest in functional biomarkers, outline a number of current techniques and suggest valuable translational future directions.

8. Biomarkers in AD

Biomarkers are measurable characteristics of a biological function or response that can be used to investigate processes in health or disease. While the gold standard of AD diagnosis is still post-mortem histological analysis of the brain, a wide range of ante mortem biomarkers are used, including CSF concentrations of tau and amyloid beta, and measures of brain atrophy through structural MRI (McKhann et al., 2011). Table 4 lists the currently used diagnostic biomarkers for Alzheimer's disease, and some possible future functional biomarkers. Additionally, until very recently, as previously mentioned, plasma levels of Aβ were also considered to be a possible risk biomarker of AD. However, a very recent study has shown that plasma concentrations of Aβ did not differ between pre-

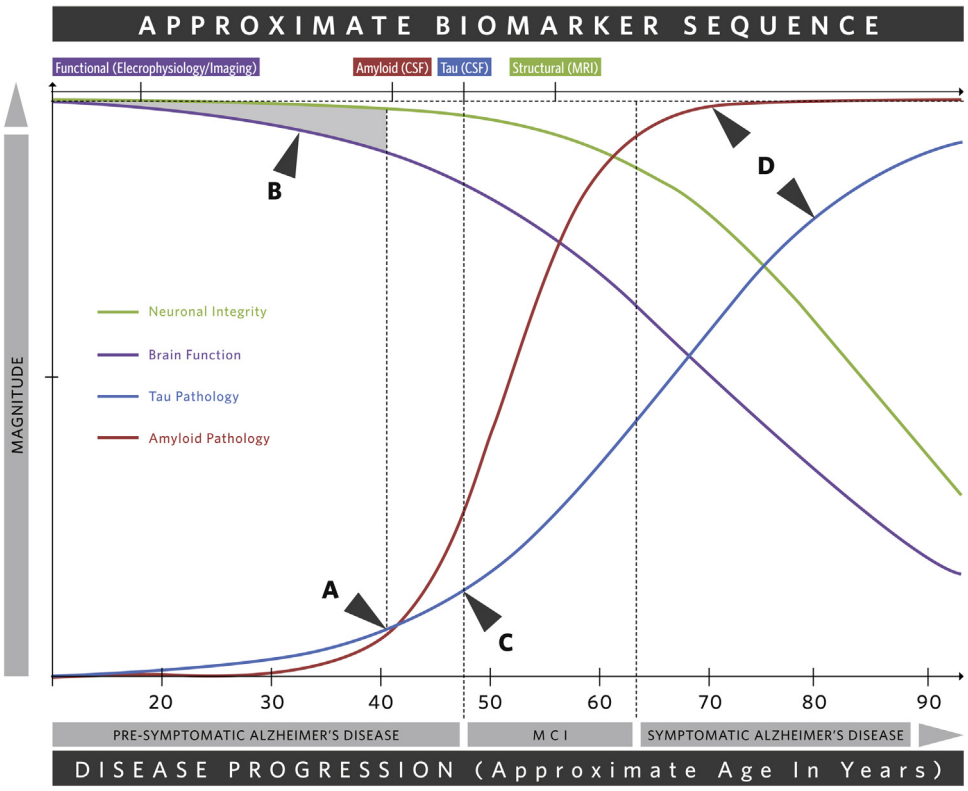

Fig. 1. Scheme depicting the main changes across the whole progression of Alzheimer's Disease and the sequence of associated biomarkers. A) Tau pathology appears many years prior to amyloid pathology, but is limited to a few regions. Amyloid pathology begins diffusely in the basal temporal neocortex later and continues to develop in adjacent regions. Tau biomarkers are absent, while amyloid biomarkers begin to appear. B) The hatched area indicates a window within which tau pathology and early amyloid pathology cause functional impairments prior to extensive neurodegeneration. Functional impairments at this stage are not great enough to result in clinical symptoms, and CSF changes in Aβ and tau are absent. Detection of functional biomarkers at this stage would provide a window of opportunity for pharmacological intervention, prior to extensive amyloid or tau pathology, and while there is little to no neurodegeneration. C) Clinical symptoms of early cognitive impairment become apparent. Amyloid biomarkers are present, while tau biomarkers are appearing. As CSF tau is an indicator of neuronal injury, tau biomarkers only appear now due to degeneration of tangle bearing neurons. At this stage, amyloid and tau pathology develop fairly rapidly, and both neuronal integrity and brain function decrease. While pharmacological intervention at this stage could be effective, amyloid and tau pathology are already high, and neurodegeneration is quite severe. D) Clinical symptoms are progressive and severe at this stage, and reflect rapidly declining brain function. While amyloid pathology begins to plateau, tau pathology continues to develop, and various regions demonstrate atrophy as measured by volumetric MRI. At this stage, the effectiveness of pharmacological intervention is likely to be poor, and worsens as the disease progresses. This scheme illustrates that the most effective treatments will be initiated during the early pre-symptomatic stage of the disease, as demonstrated by the hatched area, when any damage may be reversed. At this stage electrophysiological techniques such as EEG and magnetoencephalography (MEG) may be able to pick up biomarkers of impaired brain function.

Table 4
Notable AD Biomarkers.

Currently used AD Diagnostic Biomarkers
CSF Biomarkers
Decreased AB42 in the CSF
Increased total tau in the CSF
Increased phosphor-tau in the CSF
Imaging Biomarkers
Amyloid deposition as measured by Pittsburgh B PET scans.
Cerebral atrophy, as measured by structural MRI
Changes in glucose metabolism, as measured by FDG-PET
Possible Functional Biomarkers
Spectral "slowing", as measured by EEG
Altered functional connectivity, as measured by fMRI or EEG
Impaired synaptic plasticity, as indicated by EEG
Altered event-related potentials (ERPs) and oscillatory responses (EROs)
Altered sleep-wake architecture, as measured by polysomnography

clinical AD patients and healthy controls, suggesting that plasma Aβ may not be a suitable biomarker for AD (Lövheim et al., 2016; Wood, 2016). The importance of accurate and reproducible biomarkers is especially high in AD, as its clinical profile significantly overlaps with a range of other types of dementias, often resulting in misdiagnosis. In clinical research settings, some of the most commonly used biomarkers of AD include: CSF biomarkers of Aβ and tau; PET amyloid plaque density and volumetric MRI patterns of brain atrophy. In general, the appearance and progression of these biomarkers follows a temporal sequence, allowing staging of the disease (Fig. 1). It is important to note that the sequence and progression of these biomarkers is not an exact reflection of the underlying pathology. For example, It has been hypothesized that tau pathology precedes amyloid pathology in AD, yet it has been shown that changes in CSF amyloid precede changes in CSF tau (Braak et al., 2013). A recent study into the use of MRI patterns of brain atrophy to predict conversion of MCI to AD found that these patterns of atrophy were even able to predict progression in MCI subjects with normal CSF levels of Aβ (Davatzikos et al., 2014). Excluding the possibility of false negatives, this can indicate two things: that the biomarker changes in pre-symptomatic AD do not follow a homogenous temporal sequence, or that a number of these MCI subjects were in fact developing a different neurodegenerative disorder. The possibility for variability in the sequence of preclinical AD biomarkers has been addressed in a recent review (Edmonds et al., 2015).

Moreover, in the clinical trials for Solanezumab and Bapineuzumab, PET imaging showed that the brains of approximately 25% of people in the mild AD group did not contain any amyloid deposits, and therefore did not have AD (Karran and Hardy, 2014). This meant that these patients were unsuitable for these amyloid targeted clinical trials and possibly had what has recently been classified as SNAP: suspected non Alzheimer's pathology. This highlights the importance in testing for amyloid pathology for inclusion

in amyloid clinical trials, but also brings up a possibly even more important point; that a significant number of Alzheimer's diagnoses may in fact be wrong. These cases may have one of many tauopathies, and while these people should theoretically respond well to therapies which target tau pathology, the administration of amyloid based therapies would be ineffective. CSF or positron emission tomography (PET) biomarkers tests for Aβ would have quickly and easily detected these amyloid negative cases, and identified these people as unsuitable for clinical trials, and subsequently, these tests are becoming more common for use in clinical trial enrolment. Finally, to add further

Biomarkers are also of great importance when investigating the efficacy of an experimental disease modifying agent in clinical and preclinical stages of drug development. As mentioned earlier, in a number of clinical trials for AD treatments, clearance of Aβ did not result in functional improvements. Preclinical data for Semagacestat demonstrated a reduction in the levels of Aβ in the CSF and plasma (Hyslop et al., 2004). According to the amyloid cascade hypothesis, this would stop progression of the disease, and halt or rescue cognitive dysfunction, yet no attempts were made to investigate any cognitive benefit in animal models. In Phase 2 clinical trials, cognitive performance was actually worsened (Fleisher et al., 2008). Finally, in Phase 3, the program was terminated following safety issues, and notably, a worsening of a range of measures of cognition (Doody et al., 2013). Similarly, in the preclinical testing of Bapineuzumab, there were no attempts to investigate cognition in animal models (DeMattos et al., 2002, 2001; Schenk et al., 1999). While Bapineuzumab was demonstrated to reduce amyloid deposition in Phase 2, and showed a slight improvement in cognition (Rinne et al., 2010), it failed to demonstrate this in Phase 3 and thus failed to meet its primary endpoints (Salloway et al., 2014). Solanezumab demonstrated circumstantial evidence of clearing plaques and peripheral capture of Aβ in the blood, but failed to demonstrate a reproducible cognitive benefit, even when the primary outcome measures were changed (Doody et al., 2014). If these compounds were tested for cognitive enhancing potential in animals, this lack of clinical benefit may have been indicated earlier, and although clinical benefit can only be definitively determined in humans, these models are still mechanistically relevant in terms of face validity. Additionally, while it is not possible to fully predict clinical improvement in humans based on cognitive rescue in mouse models of AD, an understanding of the biological correlates of cognitive decline in AD, such as synapse loss, reduced cholinergic signalling and electrophysiological changes could provide more translatable predictors of cognitive enhancement in preclinical drug discovery. Through investigation of various electrophysiological changes in the brain it could be possible to use these as correlates of cognitive performance. A possible reason for the lack of clinical improvement following clearance of amyloid pathology by these compounds could lie in the fact that these compounds did nothing to target tau pathology. It has been shown that in a mouse model which develop both plaques and tangles, reduction of both soluble amyloid and tau is necessary to rescue cognitive decline (Oddo et al., 2006). As tau pathology is ubiquitous in human Alzheimer's disease, this must be addressed and as mentioned earlier, it is possible that an effective treatment would take the form of a cocktail of drugs which address the pathology of AD in all its forms.

As previously mentioned, functional changes take place in the AD brain during the pre-symptomatic stage (Stomrud et al., 2010). To understand how amyloid beta and tau affect the function of the entire brain, first one must understand the functional effects amyloid beta and tau have on individual groups of neurons.

8.1. Functional effects of Aβ and tau

Tau and Aβ have been shown to induce neurodegeneration through processes such as oxidative stress, mitochondrial dysfunction and excitotoxity. However, as previously demonstrated, tau-affected neurons may survive for decades, during which time, tau pathology has been shown to cause a number of alterations in the normal function of the cell. In fact, cognitive deficits are often seen prior to severe neurodegeneration, at a time when few neurons are affected (Menkes-Caspi et al., 2015; Santacruz et al., 2005). Several other studies have found that both tau and amyloid beta cause functional alterations in the electrophysiology of neurons, and reveal a promising aspect of the disease pathology: that these functional alterations may provide useful biomarkers at the earliest stage of the disease, before symptoms even appear. The reason for the absence of clinical manifestation of these alterations has been suggested to be due to compensatory mechanisms by currently unaffected regions. Functional synaptic alterations are common in the brain of AD patients and synaptic plasticity is decreased in several mouse models of AD (Ahnaou et al., 2016; Marchetti and Marie, 2011; Menkes-Caspi et al., 2015; Shankar et al., 2008; Trinchese et al., 2004; Warmus et al., 2014). Dendritic excitability has a key role in synaptic plasticity, and aberrant dendritic morphology and ion channel activity contribute to hyper-excitability signalling and disintegration of neuronal networks (Ahmed et al., 2016; Cochran et al., 2014; Nestor and Hoffman, 2012). In the last decade, several reports have demonstrated that exposure to Aβ generally induces morphological alterations; impairs functional activity of synapses and conversely increases electrical activity of excitatory neuronal networks, leading to epileptogenesis and convulsive seizures (Almeida et al., 2005; Coleman and Yao, 2003; Minkeviciene et al., 2009; Palop and Mucke, 2010; Selkoe, 2002). Similarly, Tau oligomers have been shown to impair synaptic function through alteration of dendritic morphology and induction of spine loss, leading to abnormal dendritic signalling through dendritic receptors and downstream effectors (Cochran et al., 2014).

As demonstrated, tau and Aβ pathology have various effects on the electrophysiology of neurons, which are often detectable before symptoms arise. By reversing these electrophysiological alterations prior to lasting changes, it could be possible to prevent neuronal injury and the onset of cognitive impairments (Busche and Konnerth, 2016). Further investigation into these early and often subtle changes requires technological means with high resolution, and may elucidate possible early functional biomarkers of Alzheimer's disease. The two modalities that hold the greatest potential for investigation into these subtle changes are functional MRI (fMRI) and EEG/ERPs.

8.2. fMRI and AD

fMRI is a relatively novel imaging modality that indirectly measures local changes in neuronal activity in the brain through changes in local blood flow (Gore, 2003). fMRI is extremely safe and non-invasive, allowing for repeated use during the monitoring of patients. This is well suited to the monitoring of AD as it allows longitudinal investigation of brain function, to determine the rate of disease progression and to form an accurate prognosis. While structural MRI is most useful for detecting patterns of brain atrophy due to neurodegeneration fMRI studies generally involve either investigating coherent activity between different brain regions during rest (spontaneous) or investigating changes in activation of different brain regions in response to a certain stimulus (event-related). The combination of fMRI and cognitive tasks have demonstrated reduced activation of the hippocampus and parahippocampal gyrus during memory encoding, as compared to healthy elderly volunteers (Rombouts et al., 2000), while conversely, in another study,

increased activity was demonstrated in the prefrontal cortex, suggesting possible compensatory mechanisms (Grady et al., 2003). Interestingly, another study found that patients in the early stages of MCI demonstrated hippocampal hyperactivity, which became hypo-activation by the later stages of MCI, seemingly mirroring the divergent effects of amyloid beta and tau on the electrophysiological activity of neurones (Celone et al., 2006). Interestingly this hyperactivity has been correlated with increases in cholinergic signalling in the early MCI stages (Dekosky et al., 2002), a stark contrast with the hippocampal hypo-activation and impaired cholinergic signalling seen in the late stages of AD (Bartus et al., 1982; Rombouts et al., 2000). Patterns of spontaneous resting activity, also known as the default mode network, have demonstrated reduced functional connectivity between the hippocampus and posterior cingulate cortex in AD, and that reductions in default mode network connectivity have been shown to correlate with disease severity (Petrella et al., 2011), elucidating some possible functional biomarkers (Greicius et al., 2004). The ability of fMRI to probe subtle changes in the activity of deep brain structures gives it an advantage over EEG, which is limited to signals that can be picked up from the scalp, however, fMRI technology is far less widely available than EEG, and is still in relative infancy compared to EEG.

8.3. EEG and ERP in AD

Electroencephalography, or EEG, involves the measurement of neural oscillations in the brain, and has long been established as a robust and valuable tool for investigating changes in neural function, and to characterise the effects of compounds in pharmaco-EEG. However, following the development and increasing use of functional imaging techniques such as fMRI and PET, EEG has lost favour. This can be attributed to the fact that while EEG has superior temporal resolution, modern imaging techniques have far superior spatial resolution. Yet while there are now *in vivo* imaging techniques available for rodents, as with human imaging, they are expensive and not widely available. As with fMRI, EEG studies generally focus on investigating spontaneous neural activity or "event-related potentials". Several multimodal approaches are readily available for measuring plastic changes in neuronal network activities under both resting states and cognitive tasks, including event-related potentials (ERP) and oscillations (EROS) (Babiloni et al., 2015, 2011; Drinkenburg et al., 2015; Teipel et al., 2016; Yener and Başar, 2013). Due to the un-intrusive nature of EEG, it is a widely used tool for investigating these changes in humans. Moreover, a number of hallmark alterations have been noted in the EEG of AD patients (Jeong, 2004). As previously mentioned, one of the most notable alterations in AD is a "slowing" of the EEG, in which there is a relative increase in low frequency oscillations (Coben et al., 1985, 1983). A possible explanation for this is a loss of cholinergic tone, due to reduced levels of acetylcholine in the brain (Bartus, 2000). Moreover, until recently, the cognitive impairment of AD has also been attributed to neurodegeneration of the basal forebrain, a major cholinergic nucleus in the brain (Bartus et al., 1982; Ray and Jackson, 1991). Scopolamine, an antagonist at muscarinic acetylcholine receptors, can reproduce this impairment, and the slowing of the EEG (Ahnaou et al., 2014). Similarly acetylcholinesterase inhibitors (AChEI) have been shown to rescue cognitive function and reverse the EEG slowing by reducing breakdown of acetylcholine (Ahnaou et al., 2014). In a study by (Menkes-Caspi et al., 2015), *in vivo* electrophysiological recordings in tau transgenic mice revealed that pathological tau in a small number of neurons is able to reduce the activity of neocortical networks as a whole. This was suggested to be due to reduced connectivity and synaptic insufficiency, and could also explain the slowing of the EEG in Alzheimer's disease. Reduced connectivity, as measured by coherence, has also been demonstrated in human Alzheimer's disease, both within and between hemispheres (Sankari et al., 2011). Coherence is a measure of temporal synchronization of two oscillations and is indicative of communication between regions of the brain. Phase synchronization through coherence is key in facilitating coincident synaptic inputs to arrive at postsynaptic neurons. This allows optimal information transmission from one brain region to another and supports neuronal communication and plasticity (Azouz and Gray, 2000; Fell and Axmacher, 2011; Fries, 2005). Accordingly, impairments in coherence suggest impaired neural communication and reduced connectivity. Moreover, a study into functional connectivity in resting state EEG of AD patients with varying disease severity, found that decreases in functional connectivity and changes in functional hub locations in posterior regions of the brain correlate with disease severity (Engels et al., 2015), seemingly mirroring previously discussed changes in the fMRI DMN (Petrella et al., 2011). Synaptic dysfunction and synapse loss are seen in a number of tauopathies, and less severely in normal ageing (Morrison and Baxter, 2012), and the extent of synapse loss is currently the best biological correlate with the severity of cognitive impairment in AD (DeKosky et al., 1996). Both tau and amyloid transgenic mouse models have demonstrated dysfunction and loss of synapses (Kopeikina et al., 2013; Spires, 2005). Synaptic plasticity is a process by which the strength of synaptic connections can be strengthened or weakened, and has gained great interest in recent years due to its relevance in learning and memory (Takeuchi et al., 2014). Impairments in the long term strengthening of these synapses, known as long term potentiation (LTP), have been demonstrated in AD (Koch et al., 2012). Theta-gamma coupling is a mechanism of communication between distant brain regions, and involves the phase of theta frequency oscillations from one area modulating the amplitude of gamma frequency oscillations in another area, and has been suggested to have a role in LTP (Canolty and Knight, 2010). Impairments in theta-gamma coupling have also been demonstrated in mouse models of AD, indicative of impaired synaptic plasticity, and thus, learning and memory processes (Ahnaou et al., 2016; Booth et al., 2016; Goutagny et al., 2013).

Alterations in the oscillatory neural responses to sensory and cognitive challenge stimuli have also been noted in Alzheimer's disease (Yener and Başar, 2013). In terms of sensory elicited oscillations, hyper-excitability has been demonstrated in the sensory and motor cortices (Yener and Başar, 2013), two areas affected very late in the progression of AD (Braak et al., 2011). More relevant to the earlier stages of Alzheimer's disease perhaps, are the alterations seen in the oscillations elicited from a stimulus with a cognitive load, including decreased frontal theta phase-locking in AD, that is improved following the administration of a cognitive enhancing cholinesterase inhibitor (Yener et al., 2007). Similarly, during a visual event related cognitive stimulus, AD patients showed decreased coherence between numerous connections with the frontal regions, in lower frequency bands (Başar et al., 2010). In general, these findings echo a recurring aspect of Alzheimer's disease: impaired connectivity. Finally, it has been demonstrated that repeated sensory stimulation can be utilised to induce long term potentiation within the sensory cortex, depending on the type of sensory stimulation (auditory or visual) (Clapp et al., 2012, 2005; Kirk et al., 2010). The combination of this approach with non-invasive measuring techniques such as EEG provides a means for testing for changes in synaptic plasticity in humans, which could provide a novel functional diagnostic test for use in neurological diseases associated with reductions in synaptic plasticity, such as AD (Clapp et al., 2012).

8.3.1. Functional EEG biomarkers as efficacy indices

As previously mentioned, the EEG of AD patients shows hallmark alterations that correlate well with severity of the disease

symptoms (Muller et al., 1997), and rescue of cognitive impairment through the use of cognitive enhancing drugs is reflected in normalization of the EEG in rats (Ahnaou et al., 2014). This suggests that functional biomarkers of cognitive impairment can be used to test the clinical benefit of possible AD therapies. Moreover, a current clinical trial will soon begin recruiting to investigate the use of a functional EEG index of cholinergic activity; called the EEG-cholinergic index, as a predictor of if an AD patient will respond to AChEI therapy (NLM Identifier: NCT02623764). As mentioned earlier, animal pharmaco-EEG has also suggested efficacy of therapies which restore monoamine signalling as well as cholinergic signalling in AD, for more effective symptomatic treatment (Dringenberg, 2000). The use of animal EEG in sleep-wake research is also well established, and as sleep alterations in humans may be an early indication of noradrenergic AD pathology (Pollak and Perlick, 1991), functional EEG biomarkers of changes in sleep wake architecture may also prove to be valuable. Functional EEG biomarkers in AD may deserve further investigation, as early indications of efficacy in preclinical drug development could greatly benefit the pharmaceuticals industry and eventually, patients.

8.3.2. Functional biomarkers in AD diagnosis and prognosis

Finally, functional biomarkers are becoming more relevant in predicting whether MCI will progress to Alzheimer's disease. MCI has proven to be extremely heterogeneous, as sufferers may convert to Alzheimer's disease, revert to a cognitively healthy state, or languish in a state of MCI for a variable duration. MCI can have a number of underlying causes, so diagnosing "MCI due to AD" is important to allow the patient and their family to prepare, and also to determine whether they are suited to recruitment into clinical trials (Albert et al., 2011). As the pharmaceuticals industry begins to focus more on early intervention, this is becoming particularly salient. The National Institute of Aging – Alzheimer's Association (NIA-AA) has developed a number of diagnostic criteria for various stages of AD, including two for mild cognitive impairment due to AD: one for use in clinical research settings; and one for "healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis" (Albert et al., 2011). This second set of criteria brings to light an extremely important, yet underappreciated point. In 2015, 58% of all people with dementia lived in low and middle income countries (Prince et al., 2015). In the instance that an effective AD modifying agent is licensed in the near future, it will likely be targeted at early intervention, possibly at or before the onset of MCI. For this therapy to be useful there must be in place robust criteria for screening people with MCI that will convert to AD, for whom this therapy would be effective. In many low and middle income countries, advanced imaging techniques or CSF analysis are not available, so these criteria must make use of inexpensive and accessible methods. As highlighted earlier, EEG is both inexpensive and accessible, and a recent study has addressed this, and introduced integrative EEG biomarkers for prediction of conversion to AD, that are more effective predictors than the Mini-Mental State Examination (Poil et al., 2013). EEG has also been shown to effectively differentiate between AD and other dementias, notably vascular dementia (Neto et al., 2015).

In summary, in order to accurately diagnose preclinical AD and MCI due to AD, biomarkers must be robust and specific. Special emphasis must be placed on biomarkers that are widely accessible, to maximize early diagnosis, to identify those at a stage where interventional disease modifying agents may be most effective.

9. Conclusions

As demonstrated in this review, the pathological progression and cognitive decline of AD is driven by several intertwined pathologies (Fig. 2). A number of these pathological changes occur early in the disease progression, and may form the basis of future AD biomarkers. AD drug discovery has had one of the lowest success rates of any therapeutic area (Cummings et al., 2014), and the current absence of disease modifying agents that halt or slow disease progression will soon result in an almost unmanageable global socioeconomic burden. The reasons for the lack of clinical success are varied, and while we have the advantage of hindsight, it could be said that some of these problems could have been avoided. Numerous clinical trials were initiated without any indication of clinically beneficial effects, due to the absence of any preclinical cognitive behavioural testing in animals (DeMattos et al., 2002, 2001; Hyslop et al., 2004; Schenk et al., 1999). While this would not necessarily be a good predictor of clinical efficacy in humans on its own, previously mentioned biological substrates of cognition could provide valuable additional translational indicators. It has long been known that amyloid pathology load does not correlate well with clinical severity of AD (Arriagada et al., 1992). The expectation that clearance of amyloid pathology would improve cognition could be attributed to an over reliance on the amyloid cascade hypothesis; by assuming that downstream pathology was dependent on amyloid pathology, it could be hypothesized that clearance of amyloid pathology would also result in amelioration of all downstream effects (Hardy and Higgins, 1992). However, some compounds did show a clinical benefit in animals (Dodart et al., 2002; Kukar et al., 2007), which did not translate to humans, which brings us on to the next point; in order to predict clinical efficacy to a reasonable extent, animal models of AD should attempt to recapitulate the pathology of the disease as closely as possible. An excellent in-depth analysis of the translational gap in neuroscience drug discovery has been performed by (Geerts, 2009). A possible explanation for the translational gap faced by amyloid therapies is that they were tested in animal models with solely amyloid pathology. It has been shown in transgenic mice that in the presence of amyloid and tau pathologies, clearance of amyloid alone is not sufficient to reduce cognitive decline (Oddo et al., 2006). This suggests that solely amyloid targeted therapies may be doomed to fail, and highlights the possible value of combined tau-amyloid therapies. The discovery that the earliest signs of tau pathology can be found in the locus coeruleus of young adults has made the role of the locus coeruleus and noradrenaline in AD a novel target of research (Braak and Del Tredici, 2011). Animal studies into the use of NRIs in treating the symptoms of AD in combination with current cognitive enhancing drugs have suggested increased efficacy (Dringenberg, 2000). Moreover, due to the roles of noradrenaline in the regulation of inflammation and the sleep wake cycle (Ouyang et al., 2004), the benefits of increasing noradrenaline signalling in AD may be multifaceted. This could be achieved through pharmacological rescue of noradrenergic signalling, or through the prevention of substantial LC neuron loss. Future research into repurposing currently available compounds that increase noradrenergic signalling to treat AD alongside current symptomatic therapies may prove to be very successful, and may prove to be a valuable temporary solution until approval of an effective disease modifying agent (Dringenberg, 2000). Finally, increasing emphasis on early disease intervention has made the discovery of robust and sensitive biomarkers necessary to determine therapeutic efficacy in animal models prior to overt cognitive impairment, and to identify people who are likely to develop Alzheimer's disease, for early diagnosis and enrolment in clinical trials. While the thought of an effective AD treatment gaining regulatory approval in the near future is enticing, efforts must be made to avoid rushing compounds into clinical stages and causing more costly late stage failures. In the last decade, many of the largest pharmaceutical companies have heavily downsized their neuroscience discovery programs in order to manage the high cost of failure (Choi et al., 2014), and to facilitate and finance exter-

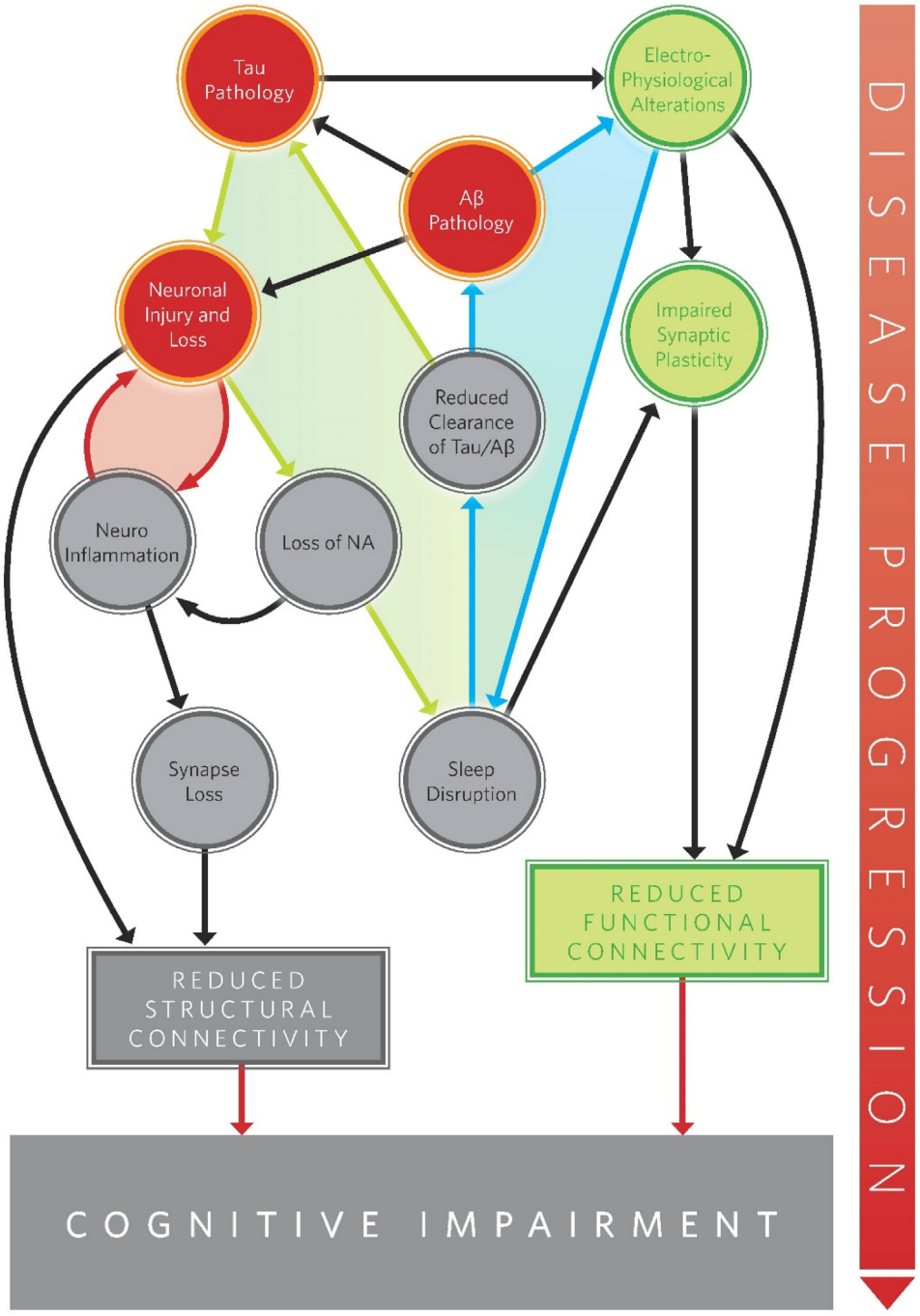

Fig. 2. Scheme demonstrating the complex interplay between some of the factors and alterations involved in the progression of Alzheimer's Disease that have been described in this review. The first pathology to develop in Alzheimer's disease is Tau pathology, which according to the new Braak stages, begins in the brainstem Locus Coeruleus. Damage to these neurons results in loss of noradrenergic signalling, resulting in increased inflammation and disruptions to sleep. This chronic inflammation causes further neuronal injury, resulting in a pathological cycle, as shown by the red shaded cycle. Inflammation increases synaptic pruning, and along with neurodegeneration, results in reduced structural connectivity in the brain. Disruption of sleep reduces glymphatic clearance of Tau and Aβ, further increasing Tau pathology (green shaded cycle) and causing a build-up of Aβ. Both Tau and Aβ cause electrophysiological alterations in affected neurons, prior to neurodegeneration. In the case of Aβ this can result in further sleep disruptions, resulting in further impairments of Aβ clearance, and increased Aβ build up (blue shaded cycle). The electrophysiological alterations caused by Tau and Aβ include impaired synaptic plasticity, reduced coherence, and changes in neuronal activity, and a number of these alterations cause a reduction in functional connectivity between brain regions. Combined, the reduced structural and functional connectivity in the AD brain causes a loss of effective neural communication which in part explains the cognitive impairments seen in AD.

nal innovation and clinical development. In order to avert the fast approaching dementia epidemic, critical analysis of current AD animal models and hypotheses, as well as continued research into exciting recent developments may hopefully provide a solution to what could be the greatest challenge to public health ever.

Disclosure statement

None of the authors has any conflict of interest to disclose with respect to the work presented herein. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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