Cutting Edge of Alzheimer’s Disease Research: Literature Review for the Changes in Brain Function in the Prodromal Stages of Alzheimer’s Disease

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Abstract
Alzheimer’s disease (AD) is a complex neurodegenerative disorder that is estimated to affect 44 million people worldwide, and the global incidence of AD is expected to triple by 2050, thus making it a major current topic with the ageing global population. Whilst symptoms generally present late in life, many details of AD pathogenesis remain unclear. Current thinking suggests cognitive tasks are performed not by individual brain regions working in isolation, but by functionally connected networks. Hence AD research is turning to the study of large-scale networks such as the Default Mode Network (DMN), primarily involved in processing memories, which is observed as the first locus of the disease. Consequently, there is a paradigm shift towards focused research on earlier stages. Mild cognitive impairment (MCI) is a prodromal stage of AD, displaying cognitive deficit but neither marked functional impairment nor satisfying established clinical criteria for dementia or probable AD. MCI subjects are at risk of AD but otherwise are unimpaired in daily living. It is noted that if MCI is a portal into potential AD, the field must work towards a better understanding of the MCI stage and emerging therapies for MCI. Thus, there is a clear need to make use of the data freely available from the ongoing Alzheimer’s Disease Neuroimaging Initiative (ADNI) to investigate changes in network function in the prodromal stages of AD with the ambition of gaining a better understanding of the MCI stage of AD.

Introduction
AD is a complex neurodegenerative disorder characterized by an accumulation of β-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) comprising tau amyloid fibrils leading to memory impairment and other cognitive problems (Weiner et al., 2015; Petersen, 2003; Huang et al., 2018). One of the most common dementia diseases, AD has swiftly become a serious health problem for ageing populations around the world (Jiang et al., 2015). According to the 2014 World Alzheimer report, the cost of dementia was more than US$600 billion in 2010 (Weiner et al., 2015). Many details of AD pathogenesis remain uncertain with symptoms usually starting around the age of 65 years, except in 5.5% of patients with early onset (33–60 years) autosomal-dominant AD (Badhwar et al., 2017; Zhu et al., 2015).

The brain is organized into large-scale networks, collections of widespread brain regions showing functional connectivity (Riedl et al., 2016). Networks can be determined based on similarity in grey matter structure between brain areas as measured with structural magnetic resonance imaging (sMRI) (Dicks et al., 2018). Current thinking suggests that cognitive tasks are performed not by individual brain regions working in isolation, but by functionally connected networks (Riedl et al., 2016). One such network is the DMN – which is activated during internally-oriented tasks such as daydreaming, envisioning the future, and retrieving memories (Riedl et al., 2016). The DMN is usually affected in the earliest stages of AD before networks involved in visual-spatial, sensorimotor,
language, behavioural, and executive faculties decline as a function of targeted AD pathophysiology (Jones et al., 2017). Put simply, AD targets the interconnectivity element between networks. Network analysis can provide insight into key organizational principles of brain structure and help identify structural changes associated with brain disease (Raj and Powell, 2018).

There is currently no known long-term treatment that slows the progression of AD (Weiner et al., 2015). Drugs available for AD provide limited short-term treatment of symptoms such as reducing rate of memory loss and confusion. Trials of disease-modifying therapies for AD dementia patients have been unsuccessful, likely because intervention at this stage is too late to affect the neurodegenerative process (Badhwar et al., 2017). Focus now is on therapeutic intervention at the MCI and/or preclinical disease stages, with delay of dementia onset constituting a major clinical endpoint for clinical trials (Badhwar et al., 2017). MCI is a prodromal stage of AD, displaying cognitive deficit but neither marked functional impairment nor satisfying established clinical criteria for dementia or probable AD (Huang et al., 2018; Dicks et al., 2018).

Alzheimer’s Disease

*Ich habe mich sozusagen selbst verloren.*

This phrase, translating as “I have lost myself, so to speak”, was uttered by Auguste Deter to Alois Alzheimer in a Frankfurt asylum in 1901 in recognition of her strange behavioural symptoms and short-term memory loss (Maurer et al., 1997). Upon Deter’s death on 8 April 1906 at the age of 55, Alzheimer brought her medical records and brain to his Munich laboratory where he identified amyloid plaques and NFTs, the same characteristics used to diagnose AD today (Maurer et al., 1997).

The initiating event in AD is related to abnormal processing of the Aβ peptide, ultimately leading to formation of Aβ plaques in the brain (Jack et al., 2010) (Figure 1). This process occurs while individuals are still cognitively normal. After a lag period, which varies from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes (Jack et al., 2010). This neurodegeneration is accompanied by synaptic dysfunction (Jack et al., 2010). The neuropathology typically begins in the entorhinal cortex – located in the medial temporal lobe – and hippocampal formation; consequently, and as the hippocampus is responsible for memory retention, the corresponding clinical symptoms include early signs of memory dysfunction (Petersen, 2003).

![Figure 1. Generation of soluble Aβ fragments from APP. According to the Aβ hypothesis, AD begins with the abnormal processing of the transmembrane Aβ precursor protein (APP). Proteolysis of extracellular domains by sequential β and γ secretases results in a family of peptides that form predominantly β-sheets, Aβ. The more insoluble of these peptides, mostly Aβ42 (a more fibrillogenic form of Aβ), have a propensity for self-aggregation into fibrils that form the senile plaques characteristic of AD pathology (Weiner et al., 2015).](image)

Historically AD has been viewed as a disease of abnormally aggregated proteins by pathologists and molecular biologists and a disease of clinical symptoms by neurologists and psychologists (Jones et al., 2016). A complementary way to view the disease is through a pathological interaction between the microscale proteinopathy and macroscale brain networks leading to characteristic cascading failures that impair clinical symptomatology (Jones et al., 2016). Bridging the divide between these scales has been elusive, but the study of brain networks appears to be a pivotal inroad to accomplish this task (Jones et al., 2016).

NFTs follow a stereotypic topographic progression pattern, first appearing in the brainstem and transentorhinal area, then progressing to the hippocampus (Jack and Holtzman, 2013).

Risk Factors

Risk factors for AD, include age, family history, and head injury, as well as midlife hypertension, stroke, diabetes, midlife hypercholesterolaemia, and a low level of education, and most notably late-onset AD.
Genetics

The ε4 allele of Apolipoprotein E (APOE) is the largest known genetic risk factor for AD (Baik et al., 2016). Further genes implicated in AD are familial mutations of APP and Presenilin (PSEN) which result in Aβ plaques being generated and deposited in neural cells (Jiang et al., 2015). Other genes implicated in AD have been comprehensively reviewed elsewhere (Ballard et al., 2011).

Early-Onset versus Late-Onset AD

AD is commonly categorized clinically as either early-onset (pre-age 65) or late-onset. Early-onset AD is uncommon (Jack and Holtzman, 2013). A proportion of such cases occurs in individuals with autosomal-dominant mutations in one of three genes: the APP gene on chromosome 21, PSEN1 gene on chromosome 14, or PSEN2 gene on chromosome 1 (Jack and Holtzman, 2013).

LOAD accounts for the overwhelming majority of cases (Jack and Holtzman, 2013). While most autosomal-dominant AD is usually believed to be caused by overproduction and subsequent aggregation of Aβ42 from the beginning of life, LOAD may most often be a disease of inadequate Aβ clearance, again leading to increased aggregation and accumulation (Jiang et al., 2015; Jack and Holtzman, 2013). As mentioned earlier, genetics plays a very important role in AD risk: the ε4 allele of the APOE gene is the major known genetic risk factor (Jiang et al., 2015; Jack and Holtzman, 2013). The ε4 allele of APOE increases the risk of developing AD by greater than 20% and also lowers the mean age at onset of the disease in a dose-dependent fashion (Jack and Holtzman, 2013; Baik et al., 2016). The major mechanism by which APOE ε4 contributes to AD pathogenesis appears to be by modulating the aggregation and clearance of the Aβ peptide, leading to increased deposition, which implicates this pathway in causation of late-onset AD (Jack and Holtzman, 2013; Ballard et al., 2011). Thus, from a genetics standpoint, sporadic AD is complex.

By the late 70s, approximately 97% of the population has some tauopathy, while only 17% have Aβ deposits (Jack and Holtzman, 2013). Definitively identifying the initiating event in the molecular cascade that eventually leads to clinical and pathological AD has been controversial for decades (Jack and Holtzman, 2013). The amyloid cascade hypothesis, first proposed by Glenner and Wong in 1984, assumes serial causal events initiated by abnormal Aβ production/aggregation (Glenner and Wong, 1984). A sequence of pathological events proposed by Price and Morris in 1999 for LOAD seems best to explain the fact that while small amounts of medial temporal tauopathy often precede amyloid plaque formation, Aβ seems to drive the progression of the disease (Jack and Holtzman, 2013; Baik et al., 2016).

Mild Cognitive Impairment

The most noticeable deficit in pre-dementia subjects is short-term memory loss, but these first prodromal first symptoms are often mistakenly attributed to ageing or stress (Waldemar et al., 2007). This preclinical, or prodromal, stage of the disease is also termed MCI (Weiner et al., 2015; Arnaiz and Almkvist, 2003) (Figure 2).

MCI represents a transitional state between the cognitive changes of normal ageing and very early dementia (Grundman et al., 2004). Originally defined in 1999, MCI is a condition in which subjects are usually only
mildly impaired in memory with relative preservation of other cognitive domains and functional activities and, therefore, do not meet the criteria for dementia (Weiner et al., 2015). Risk factors of both dementia and MCI are considered to be the same, although individuals with MCI have increased oxidative damage in their nuclear and mitochondrial brain DNA (Wang et al., 2006).

Epidemiological studies of participants aged 70 to 89 years who were nondemented found the prevalence of MCI in this population to be approximately 15%, with an approximate 2:1 ratio of two identified phenotypes: amnestic and non-amnestic (Weiner et al., 2015). MCI patients progress to AD at a yearly rate of 10% to 15%, and predictors of this conversion include whether the patient is a carrier of the ε4 allele of the APOE gene, brain atrophy, and Aβ deposition (Weiner et al., 2015).

In America, the National Institute on Aging-Alzheimer’s Association has developed criteria for MCI due to AD that use biomarkers to determine the likelihood of AD pathology and classify patients accordingly (Weiner et al., 2015). MCI patients are not characterized by a significant decrease in structural connectivity, unlike AD patients, suggesting integrated structural/functional connectomics could provide a useful tool for assessing disease progression from MCI to AD (Palesi et al., 2016).

## Criteria for MCI

Typically, the earliest presentation of MCI involves forgetfulness (Petersen, 2003). The individual will have memory complaints, preferably corroborated by an informant (Petersen, 2003). Other criteria for MCI include normal general cognition, not demented, objective memory impairment in line with the individuals age and education, whilst also maintaining activities of daily living. Currently, there are three documented types of MCI (Petersen, 2003) (Table 1).

## Current Therapies

There is no proven therapy for MCI (Petersen et al., 2018). Grundman et al. speculates that as MCI may represent a prodromal state to clinical AD, treatments proposed for AD, such as antioxidants and cholinesterase inhibitors,
may be useful in MCI (Grundman et al., 2004) (Table 2). The lack of an available therapy for MCI, combined with an urgent requirement to understand fully the concept and mechanisms of this stage of AD, urgently warrants further studies. If MCI is a portal into potential AD, the field must work towards a better understanding of the MCI stage and emerging therapies for MCI.

**Large-scale Brain Networks**

Mapping the network structure of the brain is often done via a method called tract tracing (Sporns, 2013). It has an important role to play for the study of anatomical connections in animal models, particularly in non-human primates, and is of vital importance for validating anatomical data derived from noninvasive imaging technology (Sporns, 2013).

**Default Mode Network**

First described by Greicius et al. in 2004 as the first resting-state network (RSN) implicated in AD pathophysiology (Brier et al., 2014b), the DMN has distinct subsystems with unique functional-anatomic connectivity, cognitive associations, and responses to Alzheimer’s pathophysiology (Jones et al., 2016) (Table 3). These distinctions provide a window into the systems-level pathophysiology of AD (Jones et al., 2016).

The PCC is activated in all tasks involving the DMN, including those related to the self, to others, memory, thinking about the future, and spatial navigation. The mPFC processes personal and emotional information, whilst the angular gyrus connects perception, attention, and spatial cognition (Andrews-Hanna et al., 2014) (Table 3).

The dorsal medial subsystem is involved in social directed thought such as determining or inferring the purpose of others’ actions, the theory of mind, and retrieval of social semantic and conceptual knowledge (Andrews-Hanna et al., 2014) (Table 3).

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<thead>
<tr>
<th>Functional Hubs: (information regarding the self)</th>
<th>Dorsal Medial Subsystem: (thinking about other)</th>
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<tr>
<td>Posterior cingulate cortex (PCC) and precuneus</td>
<td>Functional hubs</td>
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<tr>
<td>Medial prefrontal cortex (mPFC)</td>
<td>Dorsal medial prefrontal cortex</td>
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<td>Angular gyrus</td>
<td>Temporoparietal junction</td>
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<td>Lateral temporal cortex</td>
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Table 3. DMN: Functional hubs (Andrews-Hanna et al., 2014) and Dorsal medial subsystem (Andrews-Hanna et al., 2014).

Figure 3. A schematic of the hypothetical model relating large-scale brain networks, beta-amyloid, and tau across the AD spectrum (Jones et al., 2017).
Reduced DMN connectivity as measured by functional MRI (fMRI) has arguably become the hallmark fMRI biomarker of AD (Kehoe et al., 2014). Using ADNI data, it has been found that the posterior DMN fails before measurable amyloid plaques and appears to initiate a connectivity cascade that continues throughout the disease spectrum (Jones et al., 2016; Sperling et al., 2010). High connectivity between the posterior DMN and hubs of high connectivity is associated with amyloid accumulation (Jones et al., 2016; Sperling et al., 2010) (Figure 3). This supports a system model best characterized by a cascading network failure, with the failure beginning in the posterior DMN, which then shifts processing burden to other systems containing prominent connectivity hubs (Jones et al., 2016; Sperling et al., 2010).

Pathophysiological Changes in the Brain
The initial changes seen in the brain are alterations in CSF-based Aβ42, followed by an increase in amyloid as measured by PET with alteration in CSF-based tau. This leads to changes in neuronal function occasioning cognitive impairment and the appearance of the symptoms of AD (Kehoe et al., 2014). The most consistent sMRI finding is reduced volume of the hippocampus and entorhinal cortex in individuals at an increased genetic risk of AD without any overt symptoms; reduced hippocampal volume in individuals with amnestic MCI is predictive of conversion to AD (Kehoe et al., 2014; Appel et al., 2009; Weiner et al., 2015). The location of these grey matter changes mirrors the appearance of NFTs in these regions early in AD and supports the observance of severe memory impairment as the quintessential neuropsychological symptom of the disease (Kehoe et al., 2014; Appel et al., 2009). Thus, hippocampal volume is currently being considered for inclusion in trials to detect prodromal AD (Kehoe et al., 2014).

Conclusion & Value of Research Area
The translational end result of this research is that only five medications are currently used to treat the cognitive problems of AD: four acetylcholinesterase inhibitors and an NMDA receptor antagonist, although the benefit from their use is small (Prescrire Int., 2012). No medication has been clearly shown to delay or halt the progression of the disease (Prescrire Int., 2012). Each new hope – such as the recent case of Solanezumab (Lilly, 2016) – has focused on patients who are beyond the prodromal stages of AD. Each drug has disappointed in clinical trials.

The logical conclusion for this is that research has focused on too late a stage of the disease for effective therapies to make meaningful impact. There has been a recent paradigm shift towards focusing on MCI, the prodromal stage of AD. Catching the disease before the onset of pathological proteinopathies and functional connectivity breakdown appears to make much more sense.

Thus, research is starting to focus on subjects with MCI, who are at risk of AD but otherwise are unimpaired in daily living. In conclusion, we are left with the pressing requirement to gain a greater understanding of network analysis and interconnectivity, with a further aim to investigate if the changes in network function are predictive of the longitudinal clinical development of MCI subjects and their cognitive impairments.

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