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HIPPOCAMPAL PLASTICITY DURING THE PROGRESSION OF ALZHEIMER'S DISEASE

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Abstract—Neuroplasticity involves molecular and structural changes in central nervous system (CNS) throughout life. The concept of neural organization allows for remodeling as a compensatory mechanism to the early pathobiology of Alzheimer's disease (AD) in an attempt to maintain brain function and cognition during the onset of dementia. The hippocampus, a crucial component of the medial temporal lobe memory circuit, is affected early in AD and displays synaptic and intraneuronal molecular remodeling against a pathological background of extracellular amyloid-beta (Aβ) deposition and intracellular neurofibrillary tangle (NFT) formation in the early stages of AD. Here we discuss human clinical pathological findings supporting the concept that the hippocampus is capable of neural plasticity during mild cognitive impairment (MCI), a prodromal stage of AD and early stage AD.

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Abbreviations: AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; APP, amyloid-beta precursor protein; Aβ, amyloid-beta; CBF, cholinergic basal forebrain; ChAT, choline acetyltransferease; DG, dentate gyrus; JNK, c-Jun N-terminal protein kinase; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; MTL, medial temporal lobe; NCI, no cognitive impairment; NFT, neurofibrillary tangle; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; $p75^{NTR}$, p75 neurotrophin receptor; SPs, senile plaques.

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INTRODUCTION

In 1906, Dr. Alois Alzheimer first described a form of progressive presenile dementia in a female patient named Auguste Deter (Fig. 1), who over time developed memory loss as well as other behavioral sequelae and died at the age of 55. Brain autopsy revealed dramatic brain shrinkage and tissue sections stained using the newly developed silver impregnation procedures demonstrated the presence of senile plaques (SPs) and neurofibrillary tangles (NFTs) (Alzheimer, 1906), now considered the defining lesions of the disease bearing Dr. Alzheimer's name (Fig. 1). SPs accumulate in the extracellular matrix and contain insoluble fibrils of amyloid-beta (Aβ) peptide, which is cleaved from the larger transmembrane amyloid precursor protein (APP) by successive β cleavage through the beta-site APP cleaving enzyme 1 (BACE1) and the γ secretase complex (Shoji et al., 1992; Haass and Selkoe, 1993; Thinakaran and Koo, 2008). NFTs are composed of argyrophilic aggregates of hyperphosphorylated forms of the protein tau (Trojanowski, 1993; Yoshiyama et al., 2013). These pathological protein aggregates display a beta-pleated sheet conformation and are thought to interfere with cytoskeletal integrity, which ultimately disrupts synapse and neuronal function. In over 99% of patients, the clinical manifestation of Alzheimer's disease (AD) occurs in late adulthood, usually after the age of 65. In the small portion of cases (< 1%), the disease has an autosomal dominant pattern of inheritance ("familial AD"), is caused by mutations in three different genes that effect amyloid metabolism, and have a significantly earlier onset, with notable mutations in APP, presenilin 1 (PS1), or presenilin 2 (PS2). Interestingly, the original histological slides from Auguste Deter's autopsy were discovered a few years ago in the basement of a German hospital, and genotyping of these samples showed that she likely was suffering from a familial form of AD (Müller et al., 2013; Rupp et al., 2014), which was consistent with her early age of onset. Late onset AD is the leading cause of dementia in the

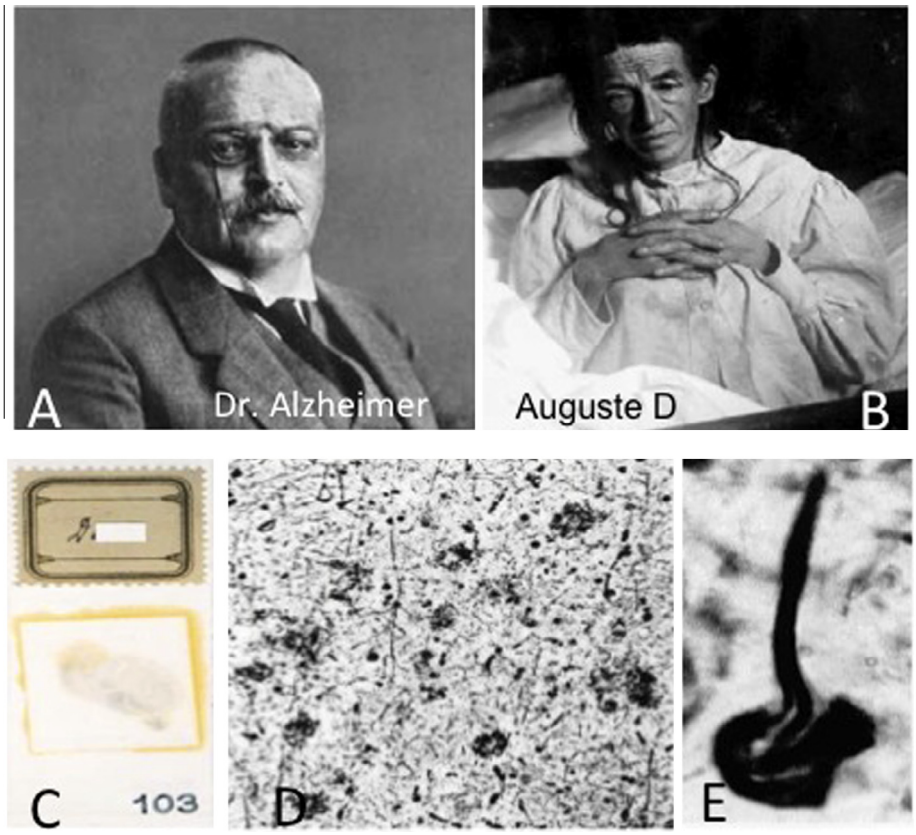

Fig. 1. (A) Photographs of Dr. Alzheimer and (B) his first patient, Auguste Deter. (C) Image of the original postmortem histological slides showing silver impregnated neuritic plaques (D) and a neurofibrillary tangle (E) in the brain of Auguste Deter. Photos A, B and D were obtained from the Internet. Images C and E were reproduced from an internet article posted Friday, November 3, 2006 by Mo Costandi under Alzheimer's Disease, History of Neuroscience, 100 years of Alzheimer;s disease.

USA, affecting an estimated 5.2 million people (Thies and Bleiler, 2013) and is predicted to afflict 13 million people in the USA by 2050.

Recent studies have confirmed that AD has a long preclinical stage and some suggest that the disease process begins between 15 and 20 years prior to emergence of clinical symptoms (Sperling et al., 2014) (Fig. 2). The term mild cognitive impairment (MCI) has been used, synonymous with the term prodromal AD, as describing the intermediate stage between normal brain aging and frank dementia when NFT and Aβ pathology is increased compared to individuals with no cognitive impairment (NCI) (Guillozet et al., 2003; Markesbery et al., 2006; Markesbery, 2010). The clinical concept of MCI was derived from memory clinics, which attracted milder cases of dementia, as well as longitudinal studies of elderly populations in which subjects were evaluated annually for cognitive status. Many of the subjects with earlier, milder cases of cognitive loss did not exhibit impairment in two cognitive domains, a criterion that was required for an NINDS/ADRDA diagnosis of AD established by McKhann and coworkers (1984). In the 1990's, such cases were most frequently, but not always, characterized by an amnestic disorder and the term "Mild Cognitive Impairment" (MCI) was popularized by Petersen et al. (1999). While memory disorder clinics reported that amnestic MCI (aMCI) was the most common form of MCI, it was clear that MCI along with other affected single cognitive domains comprised a small, but significant, component of this clinical presentation. Indeed, people with a clinical diagnosis of MCI comprise a heterogeneous cohort of which those who present solely with memory deficits are classified as single domain aMCI, while those who have a deficit in memory as well as other cognitive domains are categorized as

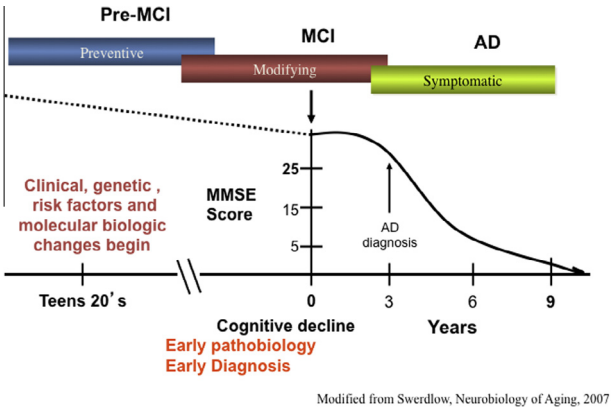

Fig. 2. Graphic representation of the putative prolonged trajectory of Alzheimer's disease cognitive decline throughout adulthood.