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Review

Risk and resilience: A new perspective on Alzheimer's disease

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ABSTRACT

Demographic and epidemiological studies predict an increasing number of people with Alzheimer's disease and dementia worldwide. Early diagnosis and intervention will help to attenuate the course of disease and lower its burden on patients, care-givers and the health care systems. Going even beyond early clinical diagnosis, new diagnostic research criteria define preclinical and predementia stages of Alzheimer's disease based on imaging and neurochemical biomarkers. Studying Alzheimer's disease in its preclinical stages gives researchers the chance to explore how brain function and structure mediates the effect of amyloid and other molecular lesions on cognitive performance and how this interaction is modulated by genetic and environmental risk and protective factors. This will have three major implications: (i) to design novel intervention studies that aim to strengthen protective factors and cognitive reserve, (ii) to provide an *in vivo* test system for the mode of action of potentially protective interventions, and (iii) to serve as a secondary endpoint for the effectiveness of interventions. This review summarizes key findings of the best established imaging markers of Alzheimer's disease, including markers of amyloid, metabolic and synaptic function, structural connectivity and brain atrophy. It outlines the present and future role of multimodal imaging in defining a preclinical stage of Alzheimer's disease and in the identification and evaluation of factors of risk and resilience of Alzheimer's disease.

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1. Introduction

1.1. The relevance of Alzheimer's disease and early clinical diagnosis

Alzheimer's disease is the most frequent cause of dementia in people 60 years and older. Epidemiological data as well as secondary data from German health insurances suggest an

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exponential increase of the prevalence of Alzheimer's disease and dementia after age 60. Prevalence are below 2% in age cohorts below 65 years, reach 5% at age 75 years and about 35% at age 90 years and older (Ferri et al., 2005; Ziegler and Doblhammer, 2009). The increasing proportion of elderly in Germany and the predicted increase of life expectancy will lead to an increase of the number of demented people in Germany from 1.4 Million in 2010 to almost 3 Million in 2050 (Ziegler and Doblhammer, 2009).

Although these numbers illustrate the need for early diagnosis and treatment of dementia, it has been estimated that at most 50% of people with dementia receive a diagnosis in the primary care system (Stoppe et al., 1994; Belmin et al., 2012). However, early clinical diagnosis is required to provide early medical treatment, including symptomatic anti-dementive medication (Birks, 2006), and systematic medication review (Jahns et al., 2012) to reduce the load of anticholinergic drugs. Medical treatment has been shown to be most efficient and cost effective if applied in early stages of dementia (Neumann et al., 1999; Teipel et al., 2007a, 2007b, 2007c). In addition, early diagnosis provides the chance for the patient and the family to make informed decisions and provides the opportunity to support and train the caregivers. Early care-giver based interventions are key elements for successful patient management to amend the course of disease, prevent behavioral symptoms and delay institutionalization (Olazaran et al., 2010). Already to date an early clinical diagnosis can be reached by using established standard procedures as proposed by national and international guidelines (NICE, 2006; DGPPN and DGN, 2010; Hort et al., 2010). These procedures include a detailed clinical history and history by proxy, neuropsychological testing, a basic neurological examination and laboratory testing as well as structural imaging using CT or MRI to exclude other causes of dementia. Diagnosis in atypical cases and very early stages can further be supported by the use of neurodestruction markers in the CSF and cortical metabolic changes in FDG-PET.

1.2. The neurobiological basis of prodromal diagnosis

In the past 5 years, researchers have pushed the diagnosis of Alzheimer's disease towards predementia and asymptomatic stages (Dubois et al., 2007; Albert et al., 2011; Sperling et al., 2011). The rationale for this approach is provided by the seminal work of Braak and Braak who suggested based on large autopsy series that neuropathological changes precede the onset of clinically manifest dementia by many years and even decades (Braak and Braak, 1991). The two hallmarks of Alzheimer's disease at post-mortem diagnosis, amyloid plaques and neurofibrillary bundles, are believed to spread in a systematic fashion through the brain over many years, until increasing synaptic dysfunction and neuronal loss lead to the manifestation of first clinical symptoms. Therefore, biomarkers that detect these early pathological features can be employed to reach a diagnosis of Alzheimer's disease before the clinical manifestation of dementia and cognitive impairment. A dynamic model of biomarker changes in Alzheimer's disease has been proposed based on the assumption of a specific pathogenetic cascade in Alzheimer's disease (Jack et al., 2010). The amyloid cascade hypothesis suggests that atypical processing of amyloid precursor protein leads to the accumulation of unsoluble Abeta oligomers with neurotoxic properties (Hardy and Higgins, 1992). Synaptic dysfunction, axonal degeneration and finally neuronal loss occur downstream from this primary event together with the accumulation of neurofibrillary bundles. The amyloid cascade hypothesis reflects findings in autosomal dominantly inherited cases of Alzheimer's disease (Bateman et al., 2011). These rare conditions lead to very early onset Alzheimer's disease (typically in the fourth to fifth decade), where 5% of cases have a known mutation in the amyloid precursor protein (APP), the presenilin 1 (PS1) or PS2 genes. Additionally, APP-, PS1- and PS2-transgene mouse strains provide a model for the development of key pathological features of Alzheimer's disease (Teipel et al., 2011a, 2011b). However, sporadic Alzheimer's disease is the by far most prevalent form and cannot be linked to a single genetic cause. Still, based on the amyloid cascade hypothesis, biomarkers focussing on the *in vivo* detection of amyloid changes, including CSF A42 and amyloid PET, are expected to be among the most sensitive markers to detect early signs of Alzheimer's disease in the brain. Biomarkers for the downstream events (including neurofibrillary pathology as detected by the Tau protein and the Phospho-Tau protein in the CSF, axonal degeneration as detected by diffusion tensor imaging, synaptic dysfunction as detected by FDG-PET and fMRI, and neuronal loss as detected by atrophy in the structural MRI) would only come later in the disease course, but still years before the onset of clinically manifest dementia. A simplified model of disease pathogenesis and associated *in vivo* surrogate markers is provided in Fig. 1.

1.3. The relevance of preclinical diagnosis

Preclinical diagnosis of Alzheimer's disease is relevant for three reasons: (i) the enrichment of at risk samples in preclinical stages of Alzheimer's disease to test primary preventive interventions, (ii) the use of *in vivo* biomarkers to test the validity of the pathogenetic cascade model that has been derived from basic research data, and (iii) the identification of mechanisms of resilience. Findings from autopsy studies suggest only a stochastic association between the degree of amyloid and tau accumulation in the brain and the manifestation of a cognitive phenotype (Xuereb et al., 2000; Negash et al., 2011) so that even in advanced stages of cerebral amyloidosis and tau pathology a small proportion of subjects remain devoid of clinically observable signs of dementia. This is illustrated by single case studies in subjects 90 years and older who showed no clinical signs of dementia despite extended cortical amyloid plaques and neurofibrillary tangles (Berlau et al., 2007). For the first time, we now have access to biomarkers that allow determining the longitudinal course of cerebral amyloidosis in asymptomatic subjects. This will help us to identify mechanisms of cerebral resilience which may become a future target of treatment. Such a treatment would focus on strengthening mechanisms of cognitive and cerebral reserve in order to maintain cerebral resilience against Alzheimer's disease pathology.

The following sections will summarize the use of imaging biomarkers to determine the association of brain function and structure with modifiable risk and resilience factors of dementia and demonstrate how these imaging markers can serve as a heuristic principle to test assumptions on the pathogenesis of Alzheimer's disease *in vivo*. Future treatment will include interventions to strengthen cognitive reserve in presymptomatic and predementia stages of Alzheimer's disease. There is an urgent need for a preventive treatment of Alzheimer's disease in order to reduce the burden imposed by the disease on the individual patient and his/her family and the resources of the healthcare systems.

As a note of caution, we have to keep in mind that the model of preclinical and predementia Alzheimer's disease is an obvious simplification of a much more complex reality. As a rule, there is no typical preclinical Alzheimer's disease subject. Rather, the manifestation of the disease will be modified by a range of comorbidities and the level of overall medical care. As the model of preclinical Alzheimer's disease has been developed in the context of university-based expert centers, it is not easily transferable to the situation in a primary care situation. Still, from a scientific perspective this model is the first step in the identification of mechanisms of brain resilience as future treatment targets