Diplomarbeit

Resting-state functional brain connectivity in patients with Alzheimer's Disease in relation to healthy controls and disease severity

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Graz, am ……

Orkan Attila Akguen

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List of abbreviations

ACC	Anterior cingulated cortex
aAD	Entire cohort of AD patients
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ApoE	Apolipoprotein E
BA	Brodmann area
BOLD signal	Blood oxygen level dependent signal
CNS	Central nervous system
CSF	Cerebrospinal fluid
DLPFC	Dorsolateral prefrontal cortex
DMN	Default-mode network
FC	Functional connectivity
fcMap	Functional connectivity map
fcMRI	Functional connectivity magnetic resonance imaging
FDG-PET	Fluorodeoxyglucose- positron emission tomography
fMRI	Functional magnetic resonance imaging
HC	Healthy controls
ICA	Independent component analysis
IPL	Infraparietal lobule
ITC	Inferior temporal cortex
LTC	Lateral temporal cortex
mAD	mild Alzheimer's disease
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
mPFC	medial prefrontal cortex
NIA-AA	National Institute on Aging – Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
OFC	Orbitofrontal cortex
PCC	Posterior cingulated cortex
PSEN 1, PSEN 2	Presenilin 1 gene, Presenilin 2 gene
p-tau	Phospho-tau
ROI	Region of interest
sAD	Severe Alzheimer's Disease
SD	Standard Deviation
t-tau	Total-tau

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Abstract

Objectives: Alterations in default mode network (DMN) activity of the brain have been observed in several neuropsychiatric CNS disorders, in particular in patients with Alzheimer's Disease (AD) and even in patients with mild cognitive impairment (MCI). The DMN is usually considered to consist of the posterior and anterior cingulate cortex (PCC and ACC), and structures in parietal and temporal lobes.
We here performed functional connectivity (FC) analyses from PCC and ACC (as main constituents of the DMN) to other brain regions using resting-state-fMRI (RS-fMRI) data to test for a correlation between RS-pattern and disease severity.

Methods: 12 patients with more severe AD (sAD; MMSE: 15,7 ± 1 SD), 11 patients with milder AD (mAD; MMSE: 24,2 ± 3) and 23 age matched healthy controls (HC) underwent neuropsychological screening with MMSE and RS-fMRI at 3.0T.
fMRI-data were preprocessed using SPM5. BOLD-signal fluctuations at
0.009-0.08 Hz within the seed-regions were correlated with whole-brain voxels using REST1.3 to identify regions with significantly correlating signal change. T-tests served to determine FC differences between groups. Multiple regression analyses were used for examining correlations between MMSE-score and connectivity patterns.

Results: Both the sAD- and mAD-group showed FC patterns different from HC.
Patients with sAD showed more profound alterations and differed from the mAD group. sAD-patients had decreased FC, including but not limited to, between PCC and the medial prefrontal cortex (mPFC). Increased FC was observed in sAD patients deriving from ACC to prefrontal regions. No such results were observed in patients with mAD. Alterations in FC correlated with increasing disease severity (assessed by MMSE) in the patients.

Conclusion: Using a relatively novel seed-based voxel-wise FC-analysis, we here confirm previously suggested alterations of FC in AD. Deviations of FC also increased with increasing clinical severity of the disease. Longitudinal studies should test whether these network changes at rest bear predictive value on the disease course.

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1 Background

This chapter is divided into three main parts:
It begins with a synopsis about Alzheimer's dementia in general, giving an overview over the clinical syndrome, the pathogenesis, diagnosis and therapy of the disease.
The second part focuses on the default-mode network, which has aroused considerable attention in neurosciences in the past few years. This network is affected in several disorders of the central nervous system (CNS) as well as in Alzheimer's dementia.
The third chapter summarizes the observations of the default-mode network in patients with Alzheimer's disease.
Objectives of this study are described at the end of this chapter.

1.1 Alzheimer's disease

Nosology and clinical symptoms

Alzheimer's disease (Alzheimer's dementia, AD) is defined as a neurodegenerative disorder, described first by the Bavarian psychiatrist Alois Alzheimer in 1906 (1). The disease manifests by cognitive and memory deterioration, progressive impairments in daily living and a variety of other neuropsychiatric symptoms (2).
The pathologic changes of AD presumably begin many years or even decades before the development of the clinical signs, going through a prodromal stage with early memory loss but without limitation to domains implicated in daily living of the patients. This state is referred to as *mild cognitive impairment* (MCI) (3), which may or may not progress to AD. A big field of research regarding AD is to define a threshold, which can give one the possibility to identify individuals with an increased likelihood of progression to dementia or AD (s. Fig.1).
The disease is characterized by cognitive dysfunction, evident as short- term memory loss in the early stages. This manifests as a difficulty of recalling new information, for example when the patient has problems remembering arrangements or details of a recent conversation (4).

Related to the memory loss is disorientation in time and place.

The remote memory is initially well preserved, but is diminishing with progression of neurodegeneration. Later on, these long-term informations are corrupted, resulting in forgetting names of friends and relatives (4).

Language malfunctions are also distinct features of the disease, which include reduced conversational output, word-finding difficulties or reduced vocabulary.

With the disease progression, the patient becomes more and more non-fluent, culminating in global aphasia (4).

Areas involved in the pathologic processes, such as the parietal lobes, are responsible for diverse deficits in cognition: visuospatial dysfunction contributes to getting lost or to problems with drawing figures, apraxia leads to problems to produce meaningful movements even with normal strength (3, 4). Later on, the involvement of the frontal lobes leads to deficits in problem solving, abstraction, reasoning, decision-making and judgment (4).

Neuropsychiatric symptoms of AD include depression in up to 50% of patients.

Agitation, anxiety, psychosis and insomnia are commonly observed as symptoms of the disease (4). Fig. 2 illustrates the manifestations of the disease throughout the disease.

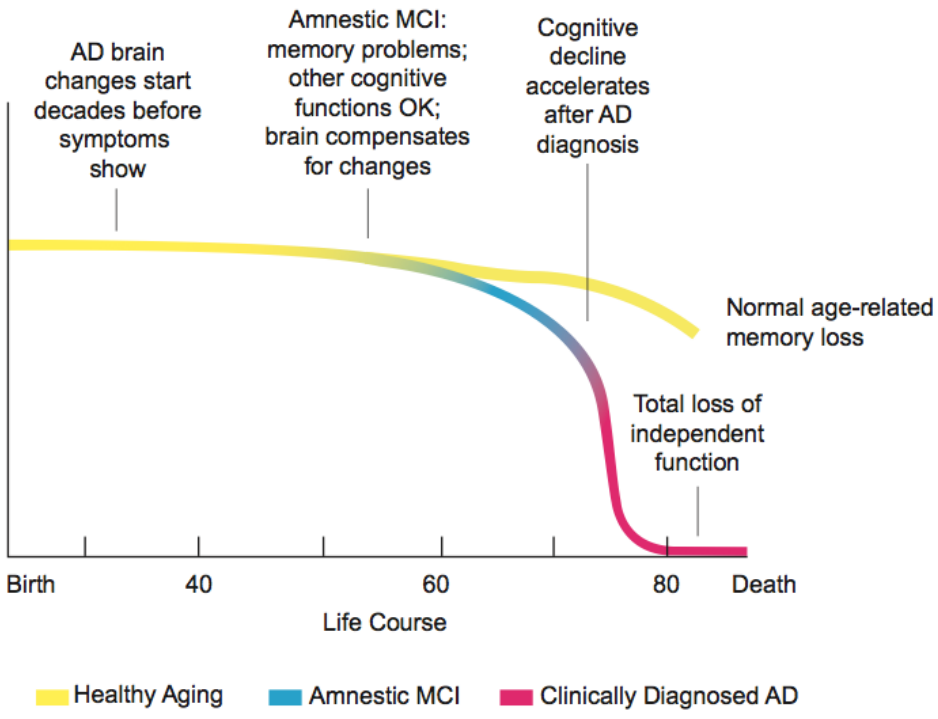

Fig. 1: Presumed evolution of cognitive deficits in relation to time, modified according to Whitbourne, 2013 (5)

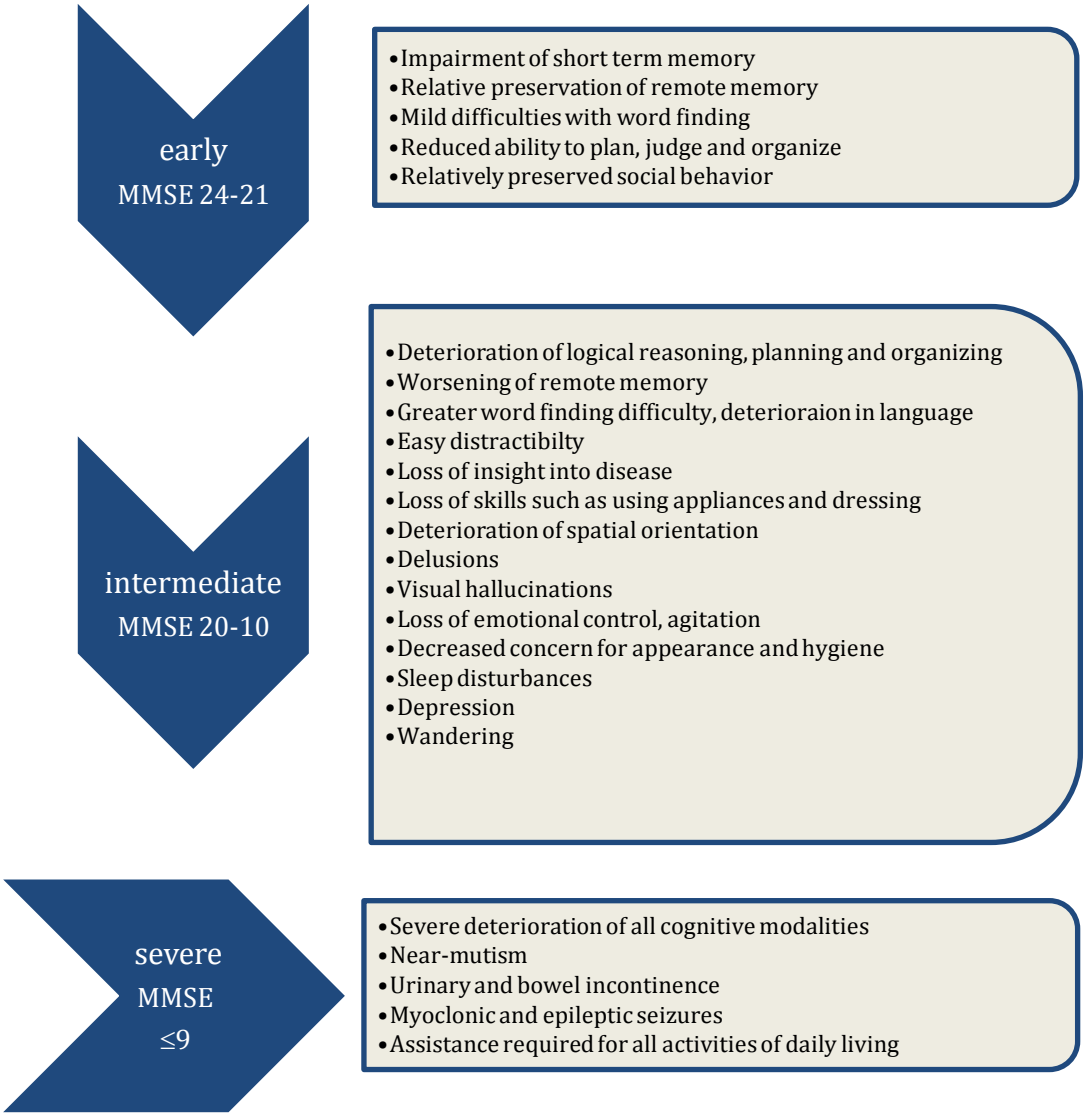

Fig. 2: Clinical symptoms of AD, modified according to Yaari and Corey-Bloom, 2007 (4)

Epidemiology

The Delphi study (6) estimated that by 2005 24 million people worldwide will suffer from dementia and the number of people suffering from dementia will double every 20 years with approximately 4,5 million new cases occurring every year: 48 million in 2020 and 81 million in 2040.

The highest prevalence of dementia, among regional populations of individuals aged over 60 years, can be found in North America with 6,4% and Western Europe with 5,4%, followed by Latin America with 4,9%, China with 4% and Eastern Europe with 3,8% (6).

In Austria, approximately 100.000 people suffer from dementia and this amount is expected to increase to 230.000 by 2050 (7).

60% of all demented people live in developing countries, and the incidence is assumed to be four to five times higher in developing countries than in developed countries (6).

AD is the most common cause for dementia affecting individuals over 65 years, accounting for about 60 - 80% of all cases of dementia, followed by vascular dementia with 15-20% and Lewy-Body-Dementia (7-20%). Other types of dementia are rare (<10%) (7) (s. Fig. 3).

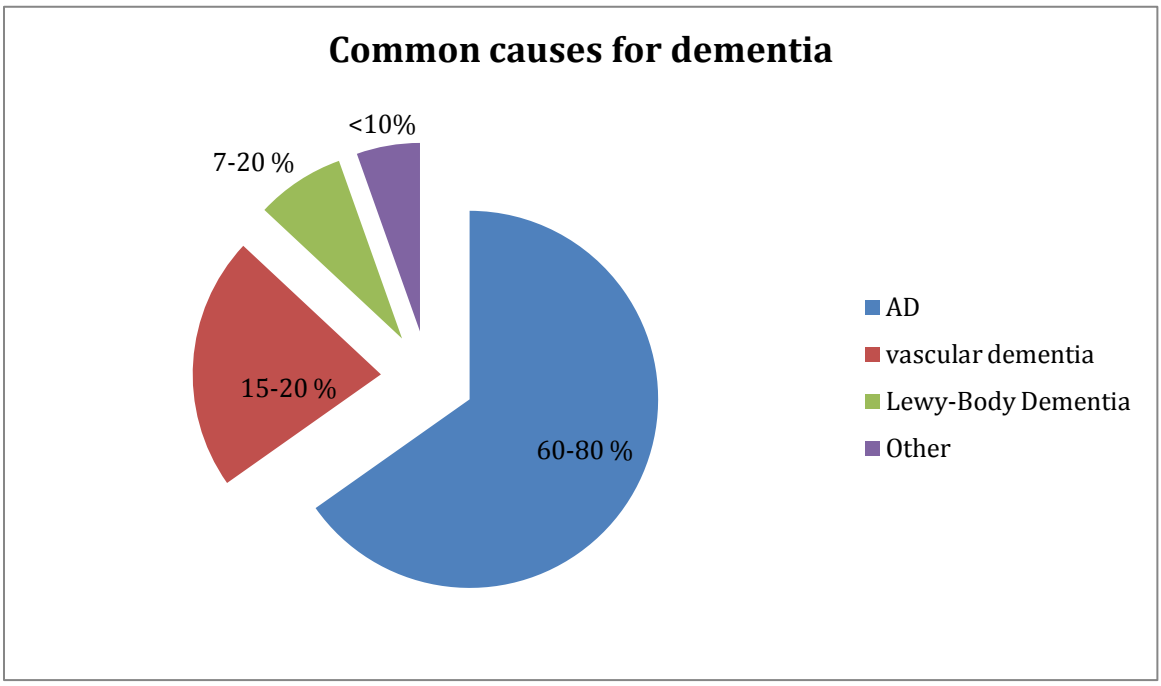

Fig. 3: Most common causes for dementia, adapted from www.alzheimer-gesellschaft.at (7)

The prevalence of AD rises from 2,8 per 1000 person-years in the age group from 65-69 years to 56,1 per 1000 person-years in the age group older than 90 years, showing an exponential increase of AD prevalence and incidence rates with age (8).
After diagnosis, the median survival time for persons diagnosed with AD at the age of 65 years is approximately 8,3 years, with a median life span reduction of 65%. Individuals diagnosed with AD at the age of 90 years show a median survival time of 3,4 years, with a median life span reduction by 39% (9).

Pathogenesis

The following section gives a short overview of the underlying pathology of AD and takes a closer look at the characteristic pathological hallmarks of the disease first. Extracellular amyloid plaques from amyloid beta (Aβ) accumulation, intracellular neurofibrillary tangles made of hyperphosphorylated tau τ, loss of synapses and shrinkage of neurons (4, 10) may lead to brain inflammation, shrinkage of the hippocampus and degeneration of specific cholinergic neurons (1, 11), which may be responsible for the cognitive symptoms of AD ultimately.
Microscopically the earliest aberrations of the AD-brain are loss of synapses in the frontal- and temporoparietal-, entorhinal cortices and the hippocampus (12). The loss of basal forebrain cholinergic neurons innervating the hippocampus and the neocortex, neuritic degeneration and gliosis are accountable for the cognitive deficits in AD (10).
Earlier metabolic changes of the brain, as a pattern of bilateral temporoparietal hypometabolism, can be visualized by Positron Emission Tomography (PET), that are mirroring the forfeit of cognitive performance (12) (s. Fig.4).
Atrophy of the cortex, especially of the frontal-, temporal- and parietal cortices are macroscopically detectable and also seen on neuroimaging, with widened sulci and shrunken gyri, the atrophy tends to spare the primary motor, sensory and visual areas (13).
Functional alterations of brain networks have been also observed in AD (14-17), since functional magnetic resonance imaging (fMRI) gives a great opportunity for studying neurological and psychiatric diseases examining functional activations / deactivations. With functional connectivity MRI (fcMRI), correlated blood oxygen level dependent (BOLD) signals of remote brain regions during resting conditions are

identified, indicating functional relationships of the distant brain regions. These correlations are referred to as functional connectivity (FC) (18).

Especially one resting-state network has been associated with AD: the default-mode network (14-17), later chapters will cover such observations.

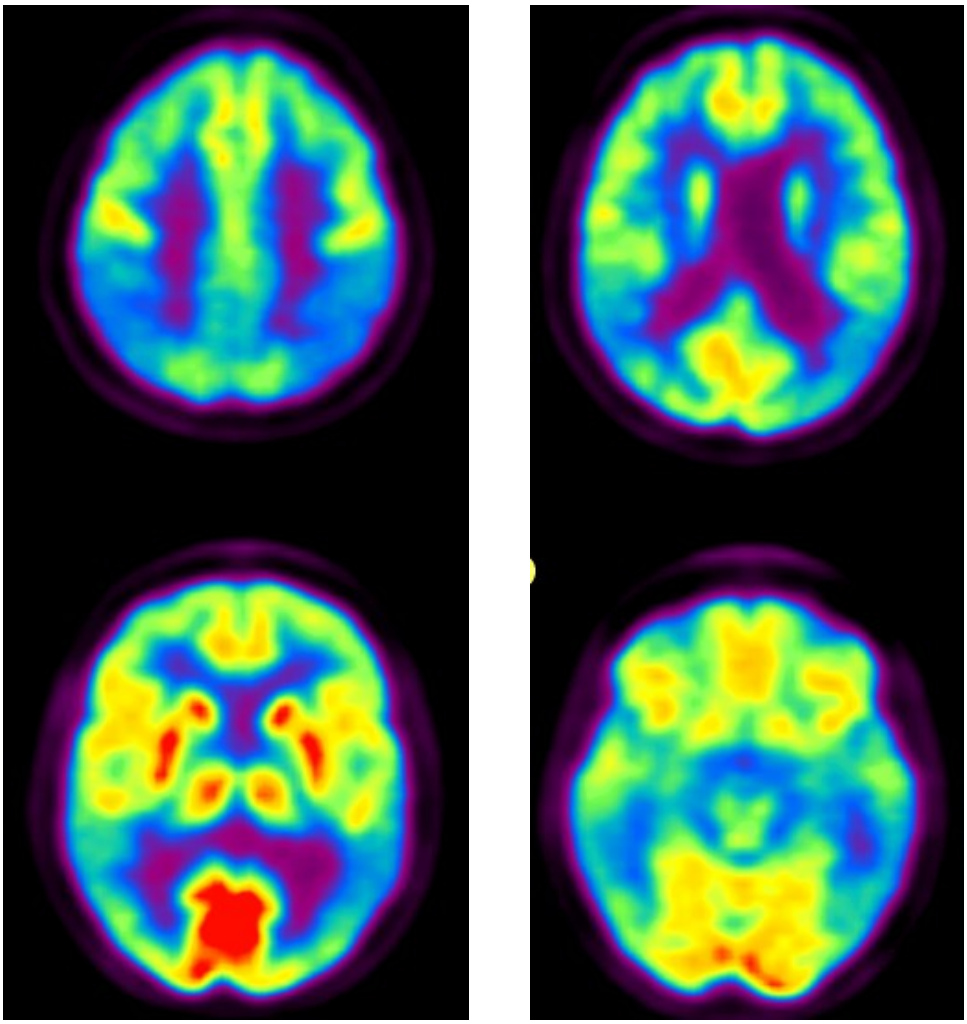

Fig.4: axial ^{18}fluordesoxyglucose (FDG) FDG-PET showing decreased FDG-uptake in temporoparietal regions of a patient with AD (courtesy of Medical University of Graz, Neurological Clinic)

Neuritic / senile plaques

The amyloid cascade hypothesis (s. Fig 7, p.12) suggests that the accumulation of Aβ triggers neuronal dysfunction and consequently cell death (4, 19).

Aβ is a natural protein present in the brain and cerebrospinal fluid (CSF) of healthy humans and is produced at cholesterol-rich regions of membranes and is secreted into extracellular space (20).

The cleavage of amyloid precursor protein (APP) into $A\beta_{40}$ and $A\beta_{42}$-peptides is carried out by α-, β- and γ- secretases, and the site of cleavage of APP influences the ratio of these two isoforms (19, 21). Mutations of the APP gene or genes encoding for the secretase-complexes, can promote the amyloidogenic pathway by raising the $A\beta_{42}/A\beta_{40}$ ratio (22). $A\beta_{40}$ represents the most abundant Aβ species in healthy people and brains affected by AD, followed by the $A\beta_{42}$ (11, 22). $A\beta_{40}$ tends to accumulate in leptomeningeal, cerebral cortical and cerebellar blood vessels (13), $A\beta_{42}$ has hydrophobic attributes and aggregates more readily than $A\beta_{40}$ (13, 22).

When the molecules aggregate into insoluble fibrils of 6-10 nm in diameter, the molecules become pathogenic (23), forming a central core of aggregated Aβ surrounded by dystrophic neurites, activated microglia and reactive astrocytes (20).

According to the amyloid cascade hypothesis, the formation and accumulation of insoluble $A\beta_{42}$ forming plaques triggers a neurotoxic cascade, that includes the formation of intracellular neurofibrillary tangles and ultimately leads to synaptic and neuronal loss in areas critical for cognitive functions like memory (22).

However, despite the association of deposition of Aβ and predisposition of AD, the plaque burden is poorly associated to disease severity (24).

Rare genetic mutations may also be associated with the production of Aβ, which are associated with the early-onset of the disease in younger individuals (25).

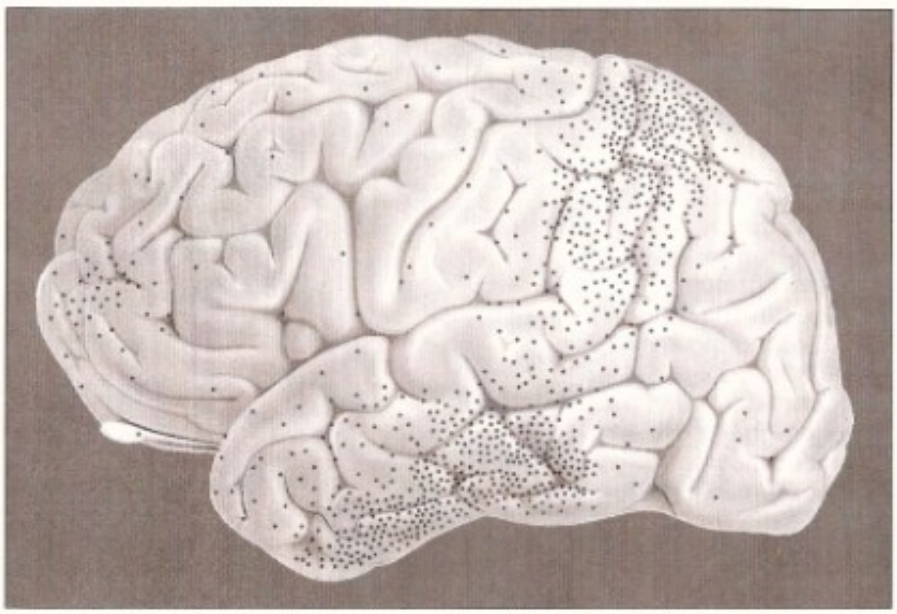

Fig. 5: Distribution of amyloid-plaques according to Brun et al. (26)

Neurofibrillary tangles

The second characteristic hallmarks of AD are intracellular polymers of hyperphosphorylated protein tau τ, which form *neurofibrillary tangles.*

Tau τ is a microtubule associated protein, the main constituent of neurofibrillary tangles. According to the amyloid cascade hypothesis, changes in tau and the formation of neurofibrillary tangles are triggered by toxic concentrations of Aβ (19).

In healthy neurons, tau binds and stabilizes microtubules, constituting the cytoskeleton of the cell by reversible enzymatically mediated phosphorylation and dephosphorylation processes. When dephosphorylation of this protein does not happen, it is unable to bind other microtubules, resulting in polymerization of the phosphorylated tau into straight filaments consequently assembling paired helical filaments (27), leading to disruption of the neuronal transport and consequently to neuronal cell death (27).

Neurofibrillary tangles in the AD-brain are plentiful in the entorhinal cortex, hippocampi (HiCa), amygdala, association cortices of the frontal, temporal and parietal lobes and certain subcortical nuclei that project to those regions (27).

In contrast to Aβ, the neurofibrillary pathology relates to disease severity (31). The loss of perfusion in specific brain regions corresponds with the specific distribution of neurofibrillary changes in the brain (28).
Small amounts of neurofibrillary tangles and amyloid plaques can be found in healthy elderly as well (4), therefore new diagnosis criteria have been proposed (29) (see below), describing the continuum of pathogenesis, to evaluate the point of accumulated pathology, which ultimately causes the neuropsychiatric symptoms.
Until now, the identification of these two hallmarks in the brain of the patient by autopsy leads to the definite diagnosis of Alzheimer's disease (13).

Genetics

Inheritance of AD in an autosomal dominant pattern is possible. 5-10% of cases are inherited forms of AD (1).
Dominant mutations of genes encoding for APP and the Presenilin 1 gene (PSEN 1) on chromosome 14 and Presenilin 2 (PSEN 2) on chromosome 1 are being held responsible for the early-onset (<60-65 years) form of AD in midlife (19-23).
PSEN1 and PSEN2 are encoding for proteins being components of γ- secretases, which cleave APP producing Aβ. Familial mutations of these genes alter the production of $A\beta_{42}$ by shifting the cleavage site of APP, forming plaques more readily than $A\beta_{40}$ (11, 19).

Mutations within the Apolipoprotein E (ApoE) gene are a risk factor for developing the late-onset (>65 years) form of AD. Three isoforms of this gene are known: ApoE2, ApoE3 and ApoE4.
The inheritance of ApoE4 is raising the risk for developing AD, while ApoE2 seems to be protective (11); Individuals with two ApoE4 alleles have a more than seven times increased risk for developing AD compared with carriers of ApoE3 alleles (19).
The ApoE protein is a cholesterol transport protein and may bind Aβ, with the ApoE4 isoform binding most strongly to it (30). This could explain the low amount of Aβ in the CSF and the stronger deposition of it in the brain of ApoE4-carriers (28).
A genome-wide association study by the *Alzheimer's Disease Neuroimaging Initiative* (ADNI) (31), found out that only the tau measures were associated with dementia, whereas the Aβ levels in the CSF were associated with the ApoE genotype. Thereby the ApoE-genotype seems to play a vital role in developing AD.

Synaptic loss

Additionally to Aβ-plaques and the neurofibrillary tangles, synaptic loss is a pathologic feature of AD, corresponding well with the severity of cognitive dysfunction in AD patients (32).

There are two major cholinergic pathways in the basal forebrain (11):

i) One pathway derives from Ncl. basalis magnocellularis (Meynert) which projects primarily to the cerebral cortex

ii) The other pathway derives from the medial septum and projects primarily to the hippocampus

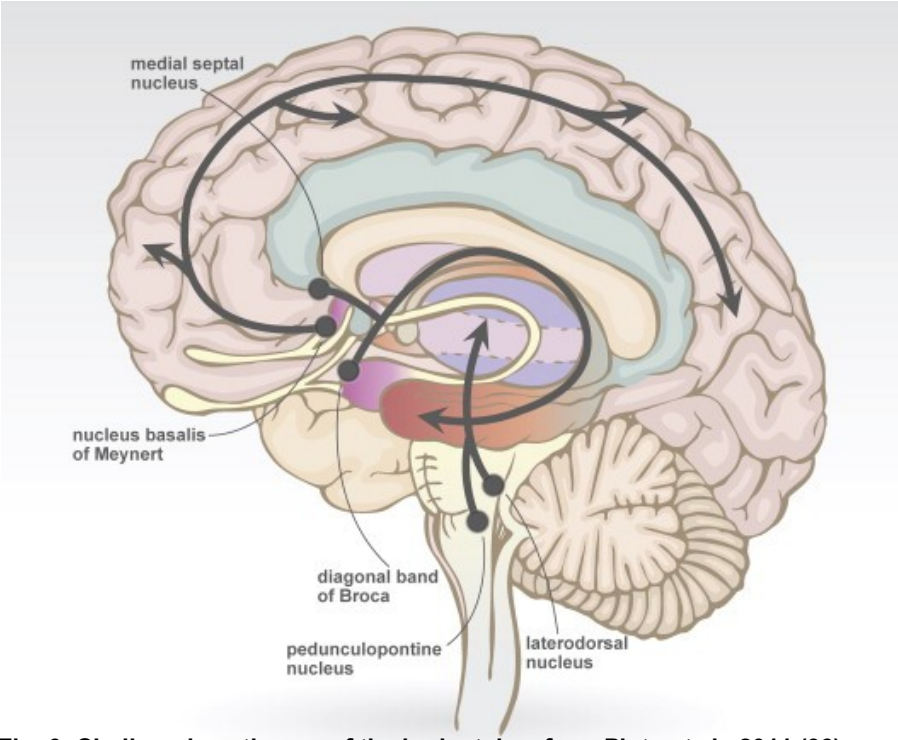

Fig. 6: Cholinergic pathways of the brain, taken from Pinto et al., 2011 (33)

Lesions within the basal forebrain cholinergic pathway result in significant learning and memory impairment, thus indicating that these cholinergic pathways play an important role in memory processing (11).

In biopsied brain tissue of AD-patients, a loss of cholinergic neurons has been found (20), with a synaptic loss of 36% in MCI-patients (32) and 45% in AD-patients (13).

The neuronal or rather synaptic loss occurs in conjunction with the tauopathy, which lead Braak and Braak (34) to propose six stages of neurodegeneration on behalf of the tauopathy:

Stages I-II show the clinically silent but selective involvement of neurofibrillary tangles in the transenthorhinal cortex.

Stages III-IV are characterized by the increasing defects in entorhinal regions and the involvement of the limbic system, corresponding to the mild cognitive decline.

Stages V-VI represent widespread neocortical destruction and the clinical evident dementia (13, 34). In further consequence the synaptic loss leads to decreased metabolism and blood flow, atrophy and alteration in the chemical composition in various brain regions (28).

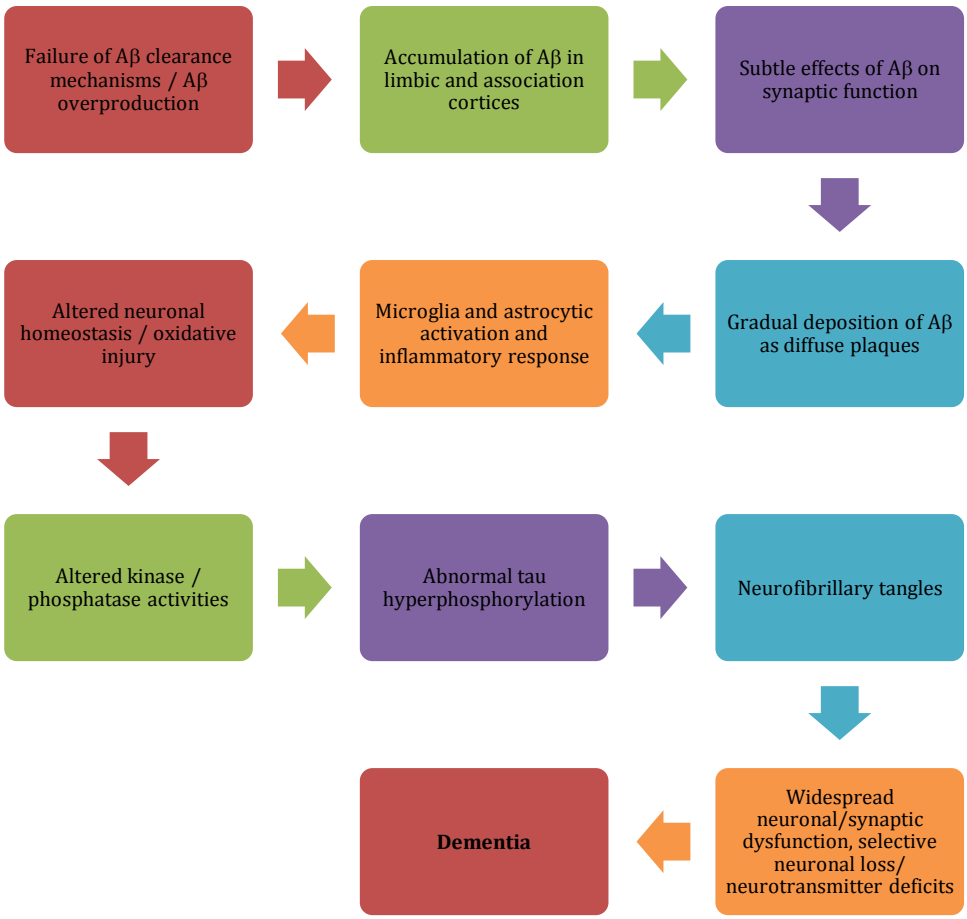

Fig. 7: The amyloid cascade hypothesis, modified according to Klafki et al. 2006 (20)

Risk factors

Two main risk factors, beside the genetic predispostion (see above), are known for developing AD:

Age: Age is the greatest risk factor for development of sporadic AD. Incidence rates between the ages 65 to 85 years show an exponential growth, independently from gender differences, with doubling every 5 years (35).

Vascular and metabolic factors: Arterial hypertension (36) and high levels of serum cholesterol (37) may contribute to the emergence of dementia through arteriosclerotic and other vascular changes leading to cerebral hypoperfusion, which together may initiate or accelerate neurodegenerative processes (36).

The most common coexisting condition with AD is stroke and more specifically ischemic infarction. In brains of AD-patients one or more ischemic lesions are frequently found, but to determine the relative contribution of the vascular co-morbidities in cognitive impairment or the underlying AD remains difficult (13).

Hypercholesterolemia may contribute to the development of AD by increasing the synthesis of $A\beta_{42}$ through modulation of the APP cleavage pattern or by influencing the transport of this peptide (38), in addition to vascular defects within the context of elevated blood fats.

Stenosis of the carotid artery is another strong risk factor supporting the notion that chronic cerebral hypoperfusion may lead to neurodegeneration in susceptible brain areas (39).

Diagnosis

The diagnosis of AD is primarily based upon the clinical symptoms the patient presents, by means of the DSM-IV-TR and ICD-10 classification (40).
Language, praxis and recognition skills are affected early in the course of AD, while motor or sensory skills are spared until later (40).
The basic diagnostic criteria for AD have been laid by the *NINCDS-ADRDA* (National institute of Neurologic and Communicative Disorders and Stroke - Alzheimer's disease and Related Disorders Association) (41). According to these criteria from 1984 the AD diagnosis is:
definite: when the clinical diagnosis is confirmed by the typical histology

probable: when the typical clinical picture is present, but not confirmed histologically

or *possible*: when the patient shows atypical clinical features, but no alternative diagnosis is apparent and when no histological confirmation is available (41).

Because neurohistological examinations by brain biopsy are usually not done in living individuals, except for limited cases by brain biopsy, the clinical diagnosis is dominated by the expression of 'probable AD'. The *definite* diagnosis of AD requires post-mortem histopathological confirmation, although earlier diagnosis might be possible with improvements in diagnostic techniques or refined criteria.
Subsequently, with the achievement of modern diagnostics, e.g. PET or CSF-markers, the NINCDS-ADRDA criteria have been revised by Dubois and colleagues in 2007 (42), proposing that a diagnosis of AD can be made when there is both a typical clinical appearance of the disease and evidence of Alzheimer's pathology in-vivo.
The biomarkers at present are thought to represent in-vivo evidence for the presence of AD pathology (s. section 'biomarkers', p.20) which led to a change of the diagnosis of AD. The integration of these in-vivo biological manifestations of the AD pathology and the typical clinical appearance of the disease into the diagnostic criteria could lead to a finer differentiation of the different stages of the continuum developing AD (29).
Based on the work of Dubois et al. (29), the National Institute on Aging-Alzheimer's Association (NIA-AA) published in 2010 recommendations concerning the diagnosis

of MCI due to AD (43) and the diagnosis of dementia due to AD (44). The next section will cover this topic.

Diagnosis of MCI

Certain cognitive functions, such as mental flexibility or processing-speed, decline in normal aging (45). This makes it important to differentiate between normal age-related changes of cognition and the transition to MCI or AD.
The distinction is rather difficult, because the cognitive complaints of normal elderly overlap with the symptoms of early AD (45).

As mentioned before, MCI represents a state, which is supposed to be a preclinical phase of AD including individuals who are at risk getting affected by the full spectrum of AD dementia. The MCI stage is a contentious topic, because it represents a transitional stage between normal aging and dementia rather than a pathologic entity. The central point of defining MCI due to AD is to identify individuals who are symptomatic but not demented, with an AD specific pathophysiological basis of the cognitive decline (43).

According to the NIA-AA recommendations, a person should considered as mildly cognitive impaired, when
a) there is evidence of concern about a change in cognition, in comparison with the person's previous level and
b) the cognitive performance decline of the person is greater than it would be expected for the person's age and educational background and
c) the person can generally keep his independence in daily living, with minimal aids or assistance, even he or she has mild problems performing complex tasks, which were performed previously without problems (43).
To evaluate the cognitive impairment of an individual, cognitive tests are useful to objectify the degree of impairment. Scores on cognitive tests for individuals with MCI are typically 1 to 1,5 standard deviations below the mean of their age and educational level matched peers in culturally appropriate normative data (43).
A point of distinction between age-related cognitive changes and disease related cognitive decline is that people with age-related changes can learn new information and recall previously learned information, although they may do so less rapidly and less effective (46). Moreover, the age-related changes are *not* progressive like AD-related decline and do *not* impair daily living (46).

Diagnosis of AD

The NIA-AA proposes the following terminology:

1) probable AD dementia
2) possible AD dementia
3) probable or possible AD dementia with evidence of the AD pathophysiological process.

The first two concepts are meant for use in all clinical settings, whereas the third should be used for research purposes (44).
Clinically, only a diagnosis of probable AD is possible at present, the definite diagnosis is still made histologically.

Probable AD is diagnosed, when the patient meets the general criteria for dementia (s. Tab. 1) and, in addition, shows an insidious onset of symptoms over months to years, an unequivocal history of worsening of cognition by report or observation, and shows the initial and most prominent cognitive deficits in one of the following categories (44):

- *Memory*: the most common presentation of AD, including impairment in learning and recalling of recently learned information (*amnestic presentation*)
- *Language*: prominent deficits in word-finding
- *Visuospatial*: prominent deficits in spatial cognition
- *Executive dysfunction*: prominent deficits in impaired reasoning, judgment and problem solving (44).

Interference with the ability to function at work or at daily living; *and*
Decline from previous levels of functioning and performing; *and*
Symptoms are not explained by delirium or major psychiatric disorders;
Cognitive impairment is diagnosed through a) history taking of the patient b) objective cognitive assessment
Cognitive and behavioural impairment should consist of minimum two of the following: • Impaired ability to acquire and remember new information • Impaired reasoning and handling complex tasks, poor judgment • Impaired visuospatial abilities (recognizing faces or objects) • Impaired language functions • Changes in personality, behaviour or comportment

Tab.1: Core clinical criteria for dementia in general according to McKhann et al. (44)

The authors of this study underscore, that the use of biomarker-evidence (see p. 21 table 3) which are currently in clinical use, "[…]may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process […]", but do "[…]not recommend the use of AD biomarker tests for routine diagnostic purposes at the present time, because (1) the clinical criteria provide very good diagnostic accuracy in most patients, (2) more research has to be done to ensure that criteria that include the use biomarkers have been appropriately designed, (3) there is limited standardization from one locale to another and (4) access to biomarkers is limited to varying degrees in community settings" (44).

Summarizing, the NIA-AA claims that the diagnosis of AD is first and foremost a clinical diagnosis and part of a continuum of clinical and biological phenomena; the core clinical criteria of AD must be first met, to support the diagnosis by biomarkers (44).

Tab. 2: Criteria proposed by Dubois et al. in 2010 (29); AD should be differentiated into different stages depending on the clinical appearance and the detection of specific biomarkers.

Prodromal AD ('predementia state of AD')

Early symptomatic phase of AD with

(a) clinical symptoms including episodic memory loss of the hippocampal type (free recall deficit), but not severe enough to affect activities of daily living

(b) biomarker evidence from cerebrospinal fluid or neuroimaging for support of pathological changes

AD dementia

Phase during which cognitive symptoms are severe enough to interfere with social functioning and activities of daily life. Changes in episodic memory and in at least one other cognitive domain.

Typical AD

Most common clinical phenotype of AD with early significant and progressive episodic memory deficiency that remains dominant in the later stages of the disease, and is associated with deficits in other cognitive domains (executive dysfunction, language, praxis, etc.) and neuropsychiatric symptoms (s. Fig. 2). Support of one or more in-vivo positive biomarkers.

Atypical AD

Less common clinical phenotype of AD. Syndromes include primary progressive non-fluent aphasia, logopenic aphasia, frontal variant of AD, posterior cortical atrophy. Support by in-vivo evidence of amyloidosis in the brain or in the CSF.

Preclinical states of AD (including 'asymptomatic at-risk state of AD' and 'presymptomatic AD')

Referring to the long asymptomatic stage between the earliest pathogenic events and the first appearance of specific cognitive changes. Two preclinical states can be isolated in-vivo:

- *Asymptomatic at-risk state for AD*: requires in-vivo evidence of amyloidosis in the brain or in the CSF.
- *Presymptomatic AD*: refers to individuals who will develop AD. Can be confirmed only in families affected by autosomal dominant monogenic AD mutations

Mild cognitive impairment (MCI)

individuals with measurable MCI with absence of significant effect on daily life.

This label is applied, if no disease is identified to which MCI is attributable.

Term of exclusion for patients who are suspected to have but do not meet proposed criteria diagnosing AD; memory symptoms not characteristic for AD or absence of positive biomarkers.

Neuropsychological testing

The personal level of education, premorbid intellectual and occupational functions and parallel medical and psychiatric conditions, eventual medications or possible substance abuse should be considered, when a cognitive disorder is being evaluated (3). Most common complaints of elderly people regarding their cognition concern their working memory, the speed of processing, executive functions, attention and concentration (46).

A point of distinction between age-related cognitive changes and disease related cognitive decline, is that people with age-related changes can learn new information and recall previously learned information, although they may do so less rapidly and less effective (46). Moreover, the age-related changes are not progressive like AD-related decline and do not impair daily living (46).

The Alzheimer's Association (47) lists *10 key warning signs* of AD, which also highlight the key differences between normal aging and more serious symptoms of possible AD:

- Memory loss
- Challenges in planning or solving problems
- Difficulty completing familiar tasks
- Confusion with time or place
- Trouble understanding visual images or spatial relations
- New problems with words in speaking or writing
- Misplacing things and losing the ability to retrace steps
- Decreased judgement
- Withdrawal from work or social activities
- Changes in mood and personality

Assessment of cognitive functioning is essential for making the clinical diagnosis for AD. For this purpose, measuring scales are used, to assess the cognitive functioning, psychopathology and psychosocial functioning in patients with dementia.

The '*Mini Mental State Examination'* (MMSE) (48), as used in this study, is a well-known cognitive measure and the most commonly used instrument to assess the cognitive status of the individual. It takes to 5-10 minutes to complete the MMSE and the maximum result is 30 points.

Patients with AD show progressive disability and a predictable rate of decline of approximately 2,8 points in the MMSE per year, with slower decline in milder stages and faster decline in the moderate and severe stages of the illness (3).

Biomarkers

CSF Analysis

The typical CSF pattern of AD consists of decreased levels of $A\beta_{42}$ and increased values of total-tau (t-tau) or phospho-tau (p-tau). Usually the $A\beta_{42}$ levels are altered before t-tau values (49), and the combination of measuring p-tau and $A\beta_{42}/A\beta_{38}$ results in a sensitivity of 94% for AD-detection and 85% specificity for excluding other forms of dementia (50).

Imaging Methods

Positron Emission Tomography

Using ^{18}fluorodesoxyglucose (FDG) it is possible to evaluate the cerebral glucose metabolism. The pattern of decreased glucose utilization of the brain is measurable with FDG-PET, showing impaired metabolic activities in the PCC and temporo-parietal regions, constituting the characteristic metabolic phenotype of AD (51).

In the recent years researchers have focused on developing new more specific ligands, which directly bind to Aβ and may visualize the pathologic burden of this peptide in individuals in vivo.

Of special interest is the PET ligand 'N-methyl-[^{11}C]2-4-methylaminophenyl-6-hydroxybenzothiazole or simply 'Pittsburgh Compound B' (PiB). In vitro PiB has been shown to bind specifically to extracellular and intravascular fibrillar Aβ deposits in post mortem AD brains (52), while it does not bind to other protein aggregates such as neurofibrillary tangles or Lewy-bodies. It thus provides a suitable tracer for discriminating AD from other forms of dementia without Aβ deposits (52).

Magnetic Resonance Imaging

Atrophy of the medial temporal cortex (MTC) is a well-noted feature in AD, although it has a low specificity (22). MTC-atrophy is also noted in fronto-temporal dementia (53), dementia with Lewy-bodies and vascular dementia (54) and Parkinson's disease with dementia (55).

New quantitative methods for evaluating AD are being investigated with promising prospects: diffusion tensor imaging (DTI), MR spectroscopy and fMRI, which will be discussed thoroughly in later chapters.

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid (CSF)		
$A\beta_{42}$	⇓	
Total-tau, phospho-tau	⇑	
PET		
Amyloid - tracer uptake	⇑	
FDG – uptake		⇓
Structural MRI		
Medial temporal atrophy		⇑

Tab.3: Currently best validated AD-biomarkers (modified according to Dubois, 2010 (29)

The pathophysiological markers concur with the presence of the two main hallmarks of this degenerative disease: the amyloid path resulting in extracellular neuritic plaques and the tauopathy path resulting in intracellular neurofibrillary tangles.

The topographical markers refer to the less specific brain changes that correspond with the regional distribution of AD pathology in the brain, namely medial temporal atrophy and reduced glucose metabolism in temporo-parietal regions measured by PET (29).

Therapy

Because AD is a pathological continuum, the symptoms the patient develops in the disease course may change and may even be different between patients. This may explain, at least partially, why the treatment effects differ intra- and interindividually (22).

For that reason, ideally a therapeutic strategy must act directly on the mechanisms of the pathogenesis of AD and should be administered early in the disease, before significant neurodegeneration has occurred.

However, the currently approved treatments are still symptomatic. These therapeutics are able, at least temporarily, to ameliorate the cognitive and functional deficits of the affected individual and to lessen the neuropsychiatric symptoms. These treatments are nonetheless not intervening in the disease progression (22). The intervention with these drugs aims at two objectives: to revert, albeit transiently, some cognitive deficits and improve functional capacity and to revert disturbing neuropsychiatric symptoms or behaviors (22).

Currently five drugs are approved for the treatment of AD:

Five cholinesterase inhibitors and one N-methyl D-aspartate antagonist:

Cholinesterase inhibitors *(ChEI)* (donepezil, rivastigmine, galantamine)

Cholinesterase inhibitors are the first choice for the treatment of mild to moderate forms of AD (MMSE 10-26) (56).

These drugs have slightly different pharmacological properties, but all work by inhibition of the disassembly of acetylcholin by blocking the enzyme cholinesterase.

Donepezil and galantamine are both selective for acetylcholinesterase, whereas rivastigmine is an inhibitor of both acetylcholinesterase and butyrylcholinesterase (57).

ChEI tend to stabilize memory during the first year of treatment, and the subsequent memory decline may be slowed under ChEI-therapy (3).

NMDA antagonist

Memantine, an uncompetitive N-methyl D-aspartate antagonist, is recommended for treatment of moderate to severe AD. A study reported that patients with advanced

AD, who were treated with a memantine monotherapy, showed reduced decline in cognition and function than those treated with placebo (58).

Oxidative stress and excitotoxicity through glutamate are believed to play a crucial role in the neurodegenerative process of AD (59).
With advancing age, neurons have to cope with increased oxidative stress and face impaired energy metabolism, which undermine membrane-protein functions relevant for membrane excitability and intracellular Ca^{2+}-dynamics.
Toxic forms of Aβ can induce the Ca^{2+}-influx into neurons by causing membrane-oxidative stress making neurons vulnerable to excitotoxicity and apoptosis (60).
Therefore memantine has a moderating effect in protecting the brain from the glutamatergic excitotoxicity and toxic levels of calcium by blocking the receptor, and allows normal signalling among brain regions (61).
Starting the treatment with a ChEI soon after the diagnosis of AD is recommended and the dose should be titrated, as tolerated, to the high end of the therapeutic range (62). When the clinical state of AD advances to moderate stages (MMSE 10-20), memantine should be added to the ChEI (3, 62).
The advantage of ChEI is the attenuation of the decline of the disease rather than the improvement in cognitive symptoms (3).

Non-pharmacological treatment

Non-pharmacological approaches for treatment of AD, including cognitive training, cognitive rehabilitation and cognitive stimulation therapy, offer modest, but significant advantages concerning cognitive symptoms in patients, as current evidence suggests, and there may be additive benefits in combination with ChEI. The results are mainly limited to the cognitive domains on which the intervention is focused, further the assessment of the cost-effectiveness of these therapeutic strategies is essential (63).

There are many ongoing drug investigations on AD, with the majority aiming to show a disease modifying effect, instead on targeting only on symptomatic treatment, e.g. drugs preventing the aggregation of Aβ, promoting the clearance of Aβ or targeting protein tau (20, 64).

1. 2 The Default-Mode Network

The default-mode network (DMN) is a specific set of brain regions or rather a neuronal network, which received much attention in the past few years. This network has been shown to increase in activity, whenever a person is not focused on a specific task and decreases in activity when the person is responding to external stimuli.

The following section gives a brief historical outline of the DMN, the measurement of such resting state networks with functional connectivity MRI will be explained and the brain regions investigated in this study (PCC and ACC) are introduced.

Finally, already observed changes of the DMN via fcMRI in regard to AD will be summarized.

Early Observations

Studying the human brain as an integrative network of functionally related brain regions can give a deeper insight of the extensive neuronal communications in the brain, making it possible to comprehend how information is being processed, to figure the relationship to human behavior and to describe how this organization is changing during neurodegenerative diseases (65).

The introduction of PET methods brought a deeper understanding of the metabolism of the brain. The typical PET-studies included many task and control conditions for comparisons and provided a large amount of knowledge about the role and function of each brain region, so several dozen imaging studies were completed that investigated perception, language, attention and memory (66, 67).

For comparing the task condition (e.g. word-reading) to a control condition, images of the resting brain (test person lies quietly in the scanner) were acquired. The images consistently showed brain regions that were more active in the control condition, the ‘resting-state’-condition, than during the active target tasks. This observation was originally referred to as ‘deactivations’. Regions relatively more active during specific tasks compared to the control conditions were tagged ‘activations’ (66).

These task-induced activations of the cortex have been shown to be task specific and vary depending on the demanded task, whereas the deactivations are varying little in their location and appear to be task independent (68, 69).

Two PET studies were conducted to reveal the anatomy of this network during the rest- or control periods, which has been observed consistently activated during the resting-state of an individual.

Shulman et al. (68) were able to show in a meta-analysis of 9 task-driven PET-studies the existence of brain regions, which showed a decrease of activity when a given language task (word reading, verb-generation, etc.) was to perform.

Consistent decreases of activation during these tasks were seen in the *posterior cingulated cortex* (PCC), the left and right *inferior parietal lobules* (IPL), *left dorsolateral frontal cortex*, *left lateral inferior frontal cortex*, *left inferior temporal cortex* (ITC), areas of *medial frontal regions*, and the right *amygdala*.

In analogy to the study of Shulman and colleagues, the meta-analysis of 9 task driven PET-studies by Mazoyer et al. (70) revealed that there exists a 'task'-negative network, which is attenuated at externally oriented tasks (visually and auditory cued tasks) and shows increased activity during the resting control condition.

This Network consisted of especially midline structures including the

medial prefrontal cortex (mPFC),

the posterior cingulate cortex (PCC),

the *angular gyri* in the parietal lobes,

the left medial frontal and

anterior cingulate cortex (ACC),

the left superior and *medial frontal gyrus* and

the left inferior frontal cortex.

Both meta-analyses showed the consistent overlap of activation of these areas, when the individuals were 'left undirected to think to themselves'. Later on, Raichle and colleagues (69) firstly labelled this network the '*default- mode network*', considering about the difficulty defining a baseline state for neuroimaging studies.

They postulated that "[…] Areas decreasing their activity in this manner (<A/N> during active task-states), may be tonically active in the baseline state, as distinguished from areas that are transiently activated in support of varying goal-directed activities" (69). Raichle and colleagues discriminated between different forms of task-induced deactivation and distinguished deactivations defining the DMN from other forms of deactivations, e.g. the attenuation of activity of sensory areas not activated at the moment.

They also found out that the mPFC and the PCC are consistently activated during the rest-episodes between the different task-blocks and identified them as parts of the DMN (69).

Functional connectivity MRI (fcMRI)

Beside the analysis of task-related activations and deactivations via PET to assess the functional anatomy of the brain, the measurement of the brain's intrinsic activity by fMRI is a probable way to do so. The patterns of spontaneous activity are believed to reflect directly and indirectly anatomic connectivity (66, 71). The characterization of synchronized spontaneous fluctuations in the *blood oxygen level dependent* (BOLD) signal of different brain regions seen on fMRI has become a more modern tool for investigating the spontaneous neuronal activity of the brain; a method called *functional connectivity MRI* (fcMRI) (72-74) or resting-state fMRI.

Unlike task-related fMRI, fcMRI does not require a comparison between an experimental and a control condition; it detects interregional temporal correlations of the BOLD-signal fluctuations, which implicate a compact connected neural network (16).

Greicius et al. (16, 74) used fcMRI to map the DMN. In their initial study (74), they assessed the spontaneous activity of the PCC and correlated the BOLD time series with all other voxels in the brain to identify functionally correlated regions with the PCC during rest. With this method, choosing the PCC (beside ventral ACC) as the reference to other brain regions, they obtained a functional connectivity map of the DMN, which overlapped significantly with the regions Shulman and Mazoyer (68, 70) acquired in their study observing task-induced deactivations. Figures 8 a-c show the functional maps Greicius et al. (74) acquired using the PCC and vACC as references.

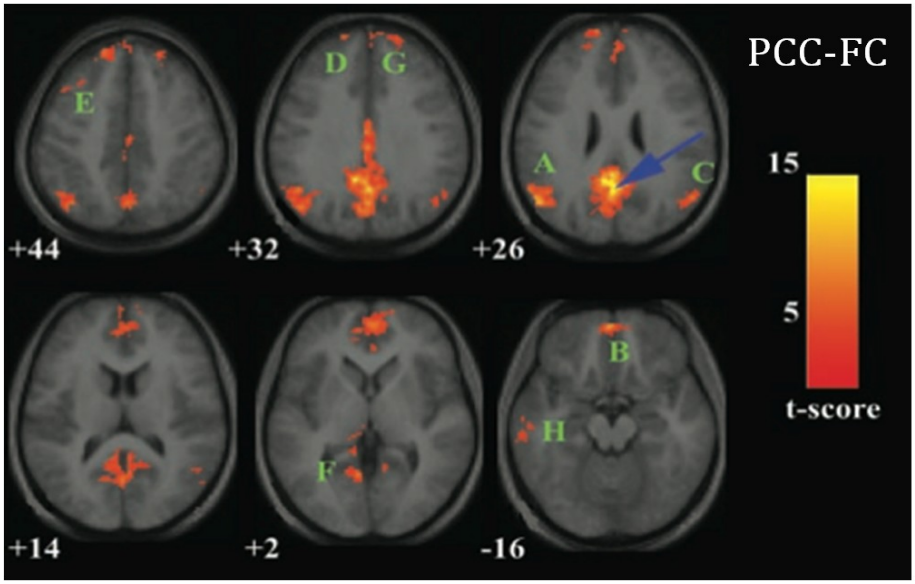

Fig. 8a: Map of resting-state neural connectivity with the PCC as seed-region Blue arrow indicates PCC, taken from Greicius et al., 2003 (74)

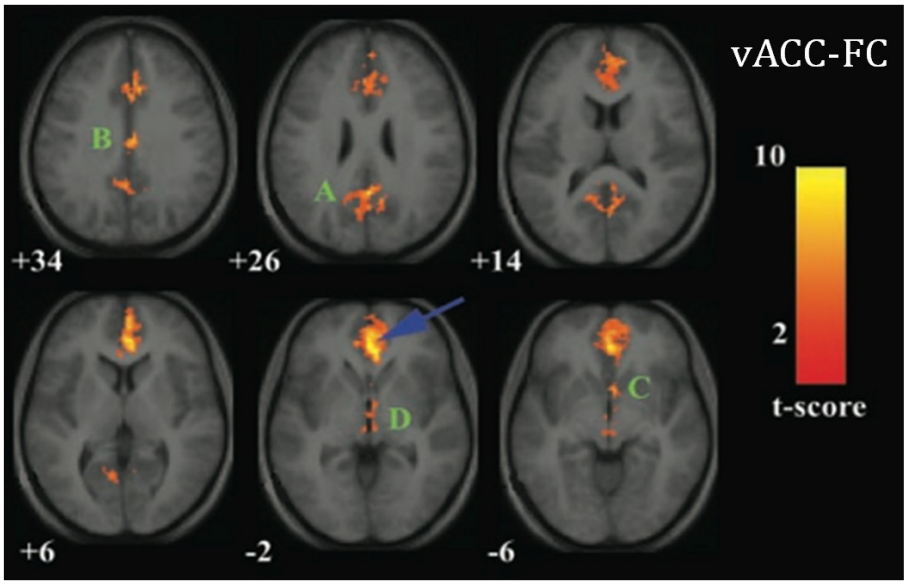

Fig. 8b: Map of resting-state neural connectivity with the vACC as seed-region. Blue arrow indicates vACC (74)

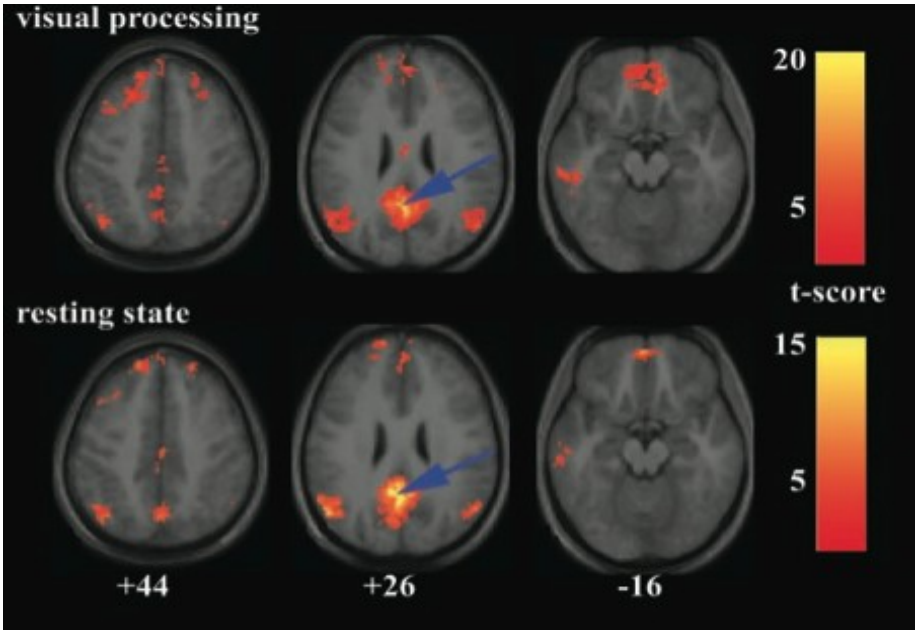

Fig. 8c: Comparison of PCC connectivity patterns during a low-demanding (passive) visual processing task (upper) and the resting-state (lower) (74)

The physiological basis of fcMRI is the linkage between neuronal activity and regional blood flow. The activation of neurons in a given area demands an increase of regional blood oxygenation for the neurons to maintain their function. The ratio of oxygenated diamagnetic to deoxygenated paramagnetic haemoglobin is shifting for the benefit of the oxygenated haemoglobin changing the regional magnetic susceptibility. These focal BOLD signal changes are induced through stimulation and reflect neural changes mediated by the hemodynamic response indirectly (75).
In functionally related brain regions, these BOLD signal fluctuations are synchronous, even in anatomically separated regions, implying the existence of neuronal activity that facilitates coordinated activity between distinct brain regions. The changes in the BOLD signal induce correlated fluctuations of the signal intensity, which is measurable with fMRI. (76).
In classical fMRI studies, these temporally changing blood flow signals are correlated with the applied task or stimulus to localize the region of hemodynamic change to deduce on the brain region involved in execution of a specific task (76). This traditional approach for imaging is to compare a low level condition (e.g. resting with eyes closed, base-line) with a higher-level cognitive task, such as picture naming or memorizing-tasks.

To examine *functional connectivity* (FC), originally described as the "temporal dependency between spatially remote neurophysiological events" (77), the same technique is used by studying synchronous BOLD signal fluctuations of different brain regions to examine the strength of neural connections between these regions, while they are *not* activated by a given task and remain in the resting state (76).

That condition, in which the participant remains idle and is not performing any externally oriented task during the fMRI scan is referred to as the *'resting-state*' or '*default-mode-condition'.*
The traditional way for investigating the default-mode activity of the brain was to contrast a low level condition (resting with eyes closed) with a cognitive task of higher level, analogous to the PET-studies of Shulman and colleagues (68).

A relatively novel approach for examining functionally related brain regions is to isolate networks of brain activity that occur during the resting-state alone.

Generally, two methods are used to accomplish this:

1) Using *independent component analyses* (ICA), coherent spatiotemporal patterns occurring during the resting state are identified and the component related to the interesting network is defined by the characteristic regional pattern of activity (78).
   With ICA it is possible to simultaneously separate several coherent and functionally related networks and to regress out head motion-effects or physiological disassembling like cardiac pulsation and the respiratory cycle (78-80).

2) Using *region-of-interest* (ROI) analyses, as used in this study, a region (*seed-region*) is usually chosen a priori and regions with similar temporal time courses of activation are then determined (80). To correlate the resting-state time series of an outlined brain region against the time series of all other brain regions is the most straightforward way to investigate the functional connectivity of a particular brain area, resulting in a *functional connectivity map* (fcMap) defining the functional connections of the predefined region (67, 73, 76).

Of special interest are the synchronous oscillations of BOLD signals of spatially distinct brain regions at low frequencies ≈ 0,01 – 0,1 Hz in resting-state fcMRI time series (73, 81).
The true neuronal basis of these oscillations remains unclear, and in the past years it has been argued whether these fluctuations may merely result from respiratory and cardiac oscillations or from co-activations in spontaneous neuronal activation patterns, measured through the hemodynamic response function (65).
Typical fMRI protocols have a low temporal resolution with a common acquisition rate of 2-3 s per scan; that causes highly frequent respiratory and cardiac oscillations which are aliased back into the lower resting-state frequencies at 0,01-0,1 Hz (67). Consequently, these higher frequent respiratory and cardiac oscillations could warp the BOLD-time series of anatomically separated brain regions, producing false positive results of functional relation to the investigated brain regions. Cordes et al. (76) observed that the spontaneous BOLD-signals during fMRI are dominated by

lower frequencies (<0,1 Hz) with only a minimal contribution of the higher frequent cardiac and respiratory oscillations.

Information supporting the hypothesis, that fcMRI scans indeed mirror coordinated neuronal activity between brain regions, comes from studies investigating the overlap of function and neuroanatomy (65, 73, 78, 81).
As such, activity patterns occur between brain regions that overlap both in function and neuroanatomy like in the motor cortex and visual and auditory networks, indicating that these brain regions form a functional network during rest, with a high level of spontaneous neuronal activity that is strongly correlated between these anatomically separated brain regions (67, 78).
To date 8 resting-state networks are known, including the DMN (78, 82) as shown in Fig. 9.

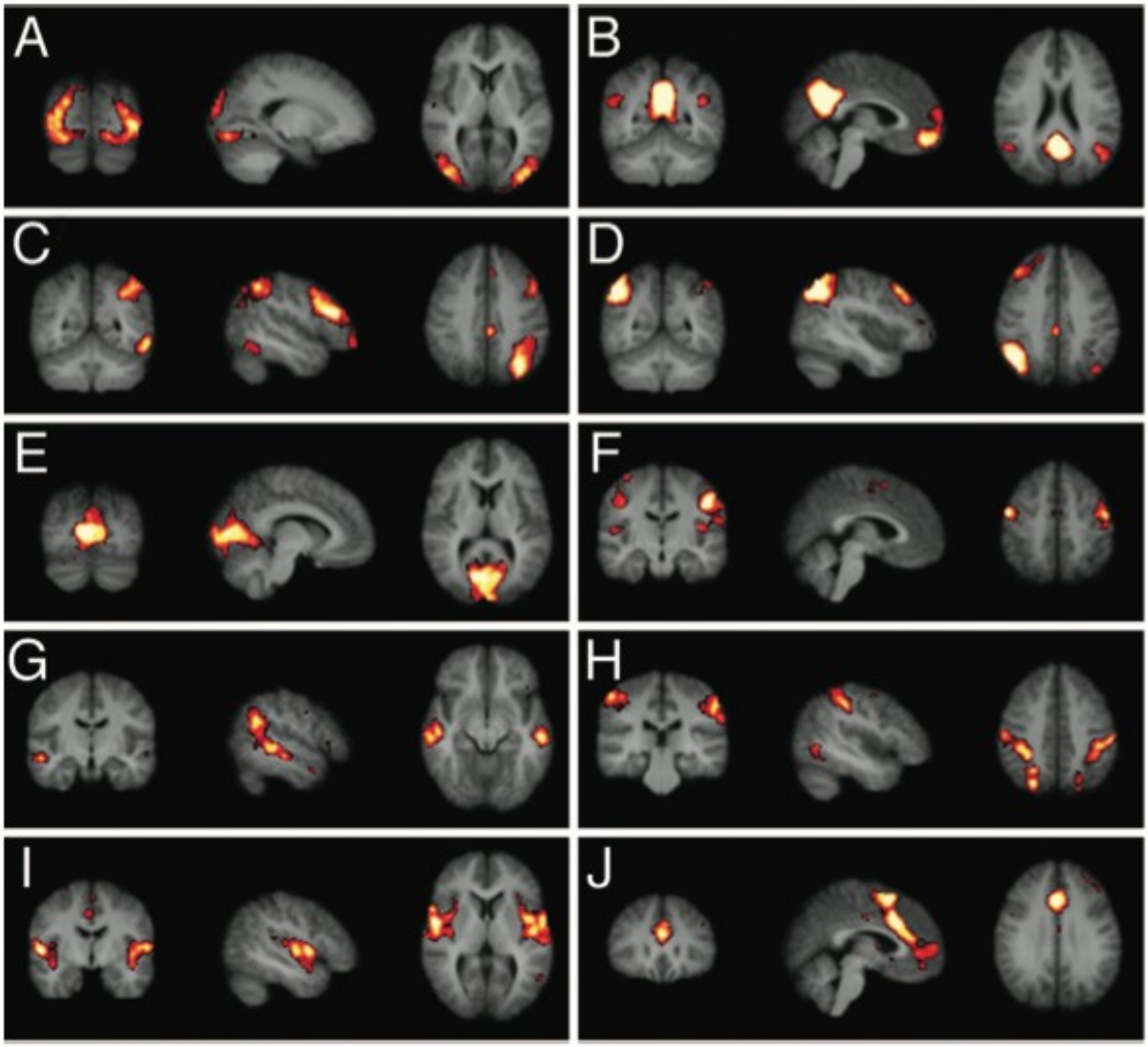

Fig. 9: Seperate resting-state networks as identified by an ICA approach by Damoiseux et al. 2006 (78) characterized by the synchronous activation of their components. These networks are partially anti-correlated. The networks are in standby condition in the resting-state and are activated when a fitting stimulus is applied.

A: Network consisting of peristriate area, lateral and occipital gyrus – parts of the visual cortex
B: Network consisting of prefrontal region, ACC, PCC, inferior temporal gyrus, superior parietal region – the DMN
C and D: components predominantly in left and right hemisphere: middle frontal gyrus, orbital gyrus, superior parietal gyrus, middle temporal gyrus, and PCC – these areas show strong lateralization and are involved in memory function.
E: striate and parastriate regions - the second component of the visual network (cf. A)
F: pre- and postcentral gyri – motor and sensory network, as described by Biswal et al.1995
G: superior temporal as main element, with involvement of cingulate and superior frontal regions
H: superior parietal cortex with involvement of occipitotemporal and precentral areas
I: superior temporal and insular and postcentral cortex – the auditory cortex
J: frontopolar area, prefrontal cortex, dorsal ACC, and superior parietal cortex – this frontal network is proposed to play a vital role in executive control and memory function (83)

The convergence of data obtained by the task-induced deactivation PET-studies and functional connectivity analyses revealed, that the core of the DMN is composed of three regions, building hubs (66):

- the precuneus / posterior cingulate cortex (PCC, BA 23,31)
- the medial prefrontal cortex (mPFC, BA 10,32) (incl. anterior cingulate cortex (ACC, BA 24,32,33)
- the inferior lateral parietal lobes (IPL, BA 39,40) bilaterally

The hippocampus (HiCa), lateral temporal cortex (LTC) and the parahippocampal formation (incl. entorhinal and surrounding cortex) are observed to integrated as well in the DMN, as they show activation independently of the approach used (task-induced deactivation by PET or fcMRI). However, because of the inconsistent overlap of these regions throughout the studies, the HiCa, LTC and the parahippocampal formation may represent functional subsystems connected mono- or polysynaptically with the above mentioned hubs of the DMN (66).
Using a spring-embedding algorithm, Buckner et al. (66) calculated correlational strengths of the different brain regions to each other, suggested to involved in the DMN of healthy young adults (Fig. 8). Regions with strong correlations to each other are congregated near each other, regions weakly correlated are positioned away form each other.
Fig. 10 displays the separation of the medial temporal lobe subsystem (represented as the hippocampal formation HF and the parahippocampal cortex PHC). Additionally, the graphic also illustrates, that the medial temporal subsystem is less strongly associated with the core hubs of the DMN (66).

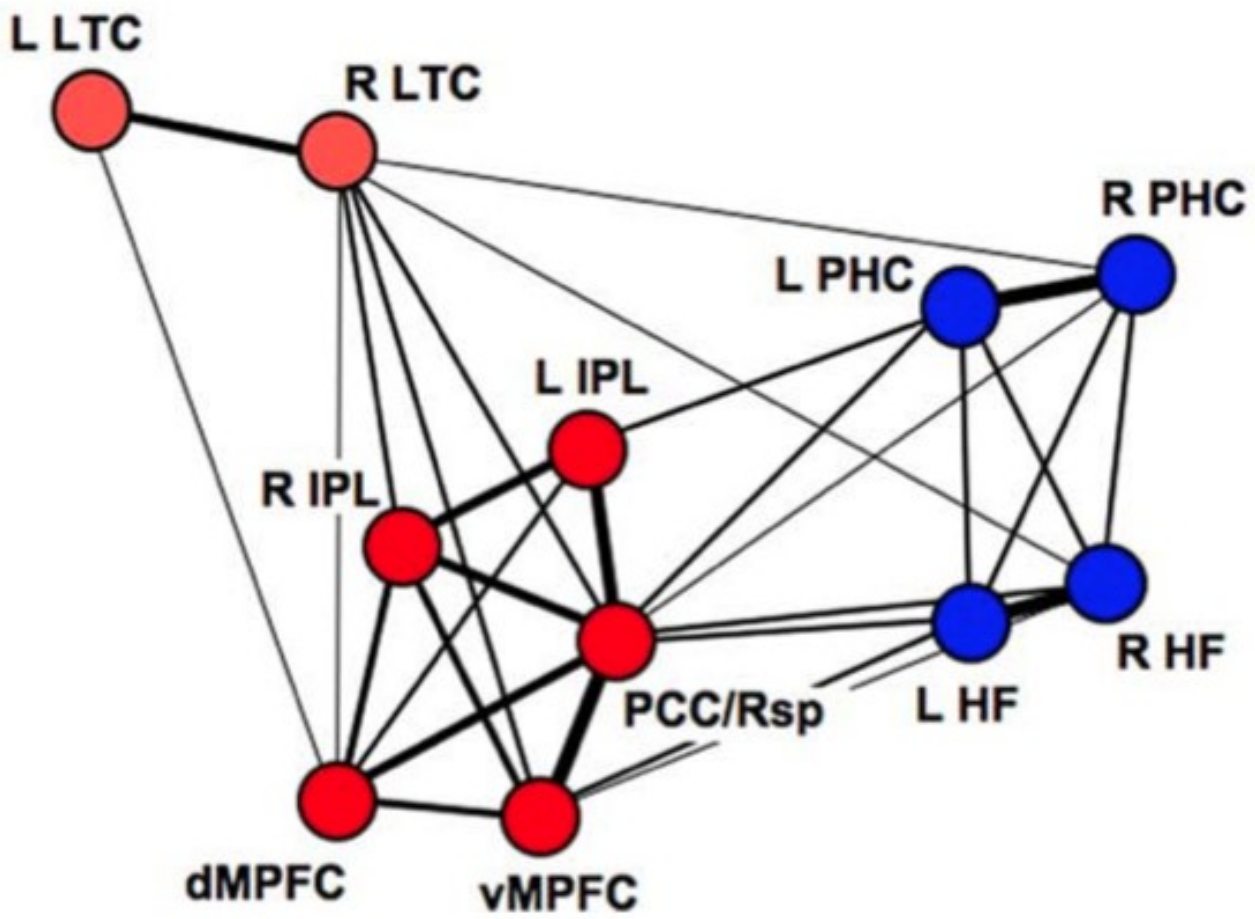

Fig. 10: Correlational strengths (lines) between core regions of the DMN and the subsystem medial temporal cortex (MTC) (blue) structures according to Buckner et al (66). Gauge of the lines represents the degree of correlation strength.
MTC includes the hippocampal formation (HF) and the parahippocampal cortex (PHC). MTC is correlated with core hubs of the DMN.
PCC/Rsp=posterior cingulate cortex / retrosplenial cortex
IPL=inferior parietal lobule
vMPFC / dMPFC=dorsal/ventral medial prefrontal cortex (vACC/dACC)
LTC=lateral temporal cortex
LTC is distant because of the weaker correlation with the other structures

Posterior cingulated cortex

The PCC seems to be particularly important for the DMN, since it belongs to the most intensively interconnected (84) and metabolically active (69) regions in the whole brain.

Additionally, the PCC is directly connected with the other nodes of the DMN (84, 85), implying that it mediates intrinsic connectivity across these regions. A combined diffusion tensor imaging (DTI) and fcMRI study showed that the PCC is directly connected with the MTC and the mPFC, and that the mPFC and MTC have no direct connections to each other, suggesting that functional connections between those two regions are mediated by the PCC (65). Furthermore, ROI-based analyses with the PCC show a significant overlap with the findings of ICA based explorations concerning the DMN (Fig. 9) (78).

In an event-related fMRI study, Cabeza and colleagues (86) posited that the PCC might own a critical role for episodic memory retrieval, supported by studies demonstrating that the PCC is among the regions metabolically affected early in AD (16, 87, 88).

Some studies showed that when the individual was to memorize new information, increased activation in the hippocampus was observed; reciprocally the IPL was deactivated during the acquisition of new information. But when it came to memory retrieval, reactivation of the DMN was ongoing (89), which supports the theory about the contributions of the DMN to memory retrieval (74). All components integrated in the DMN are accountable for diverse cognitive functions, e.g. the *dorso-lateral prefrontal cortex* (DLPFC) is commonly implicated in working memory (90) and retrieval of episodic memories (91). The IPL bilaterally show consistent activations during working-memory tasks (92).

In a complex task-driven PET study, Maguire and Mummery (93) were able to show that all components of this network are integrated in memory processing. In a complex combination of four memory retrieval tasks (personal and non-personal memories, personal and non-personal facts) consistent activations were observable. Specifically the PCC, IPC bilaterally, the mPFC, the left parahippocampal gyrus and the left ITC showed increases of activity.

The Hippocampus (HiCa) bears an integral role in memory consolidation by “binding novel asscociations into cohesive episodic memory traces” (94) and forming new

associations between previously unrelated information (95). The tight junction of HiCa with the PCC and the DMN offers a further explanation of memory function of this network, besides the selective vulnerability of associative memory processes in preclinical AD (94).
Although the MTC respectively the hippocampus, seems to possess rich interactions with the DMN and is enlisted in memory consolidation (91), it is per se not described as a core hub in the DMN in literature; in contrary, it is regarded as a subsystem communicating directly or indirectly with the core hubs, especially with the PCC (66).

The consistent overlap of components of the DMN deactivated during external stimuli driven tasks in PET-studies and the consistent increases during the resting, but conscious state via fcMRI, led to the *'theory of mind'*-hypothesis.
According to this theory, the DMN is to monitor internal and external stimuli and by means of its prompt attenuation of activity, when a stimulus of the external environment stimulates the individual, direct and focused behaviour represented by activation of other networks of the brain can be made possible.
Furthermore stimulus independent, introversive, self-reflective thoughts as well as daydreaming, autobiographical memory, empathy and envisioning the intentions of others has been commonly attributed to this network, and recent theories propose that more fundamental intrinsic processes such as information consolidation and stabilization may be related to activity in the DMN (66, 69, 74, 88, 96-99).

Anterior cingulated cortex

The second seed-region we chose for determining functional connectivity was the anterior cingulate cortex (ACC).
The mPFC including ACC, commonly accepted as a hub of the DMN, is just rostral of the genu of the corpus callosum (100), and is functionally divided into two sections: a ventral part (vACC), which is associated with affection, and a dorsal portion (dACC), which is presumed to be involved in cognitive processes (101, 102).

The cognitive dorsal subdivision of ACC is a constituent of an attentional network, maintaining reciprocal connections with *lateral prefrontal regions*, *parietal cortices*, *premotor and supplementary motor areas* (101). Functions accredited to the dACC are modulation of attention or executive functions by influencing sensory or response selection, complex motor control, motivation, error detection and working memory, and the anticipation of cognitively demanding tasks (101). Gusnard et al. (96) proposed that the dorsal portion of the mPFC is increasing in activity when attention is directed specifically toward self-referential or introspectively oriented activity.

The vACC on the other hand has been primarily linked to paralimbic and subcortical structures associated with affective and autonomic processing: the *amygdala*, the *orbitofrontal cortex* (OFC), nucleus accumbens and hypothalamus (74, 101).
These anatomical relationships suggest that the mPFC, respectively ACC, hold the function of integrating information collected from internal and external environments with visceromotor aspects of emotional processing (96).
Moreover it was observed, that these two divisions of ACC are reciprocally inhibiting each other (103). Therefore the affective vACC is inhibited, when the cognitive domain dACC is being activated during working memory tasks, and the dACC was suppressed in activity during intense emotional states (101).
This lead to the hypothesis, that connections between PCC and ACC may form an important coupling in the DMN between functions processing higher cognitive (conscious) and more basic (subconscious) functions for calibrating affective and autonomic states (74). They may thus provide an instance for emotion and cognition-control mechanisms (104), by serving an attentional network showing connections to limbic structures, the PCC, parietal and frontal cortices (105).

Diverse behavioural symptoms of AD could be understood as a malfunction of ACC or reductions of its connectivity to other brain regions important for integrating information to make behaviour possible.

For example, a neurologic syndrome called akinetic mutism, characterized by a significant reduction of spontaneous speech and movement despite preserved motor ability is associated with lesions in the ACC (102). In the terminal phase of AD, mutism-like states are occurring in the individual, consistent with defects in this area or connections to it.

Accordingly, apathy in AD has been correlated with cortical atrophy chiefly in prefrontal regions, especially in ACC and OFC (106) and respective hypoperfusion and hypometabolism in ACC (107). This notion gets support by Kim and colleagues (108), who demonstrated the failed communications between ACC and other structures in the brain are aggravating the symptoms of apathy in AD – independently of concomitant depression or psychotropic medications.

Appetite loss in AD is associated as well with hypoperfusion measured by single positron emission computer tomography (SPECT) in mPFC areas, namely the ACC and OFC (109).

1.3 Default-Mode Network and Alzheimer's Disease

Changes in the DMN have been observed in several neuropsychiatric diseases, such as autism or schizophrenia (110), but recent researches focused on AD (16, 17, 111, 112) .

DMN-activity changes may also occur in healthy older individuals, although not to an extent as in AD-patients. Deactivation of the DMN during task performance is also decreased in older adults compared to younger and middle-aged individuals in medial frontal cortices and in the ACC and PCC (111, 113). AD patients do not deactivate the DMN when confronted with specific tasks compared to healthy subjects (16, 111).

Studying the DMN activity is especially insightful regarding AD patients, since the structures serving the DMN demonstrate a significant overlap with the presumed depositions of Aβ (s. Fig.5), regional brain atrophy and reduced metabolism in the temporal and parietal lobes in early AD (114, 115).

Greicius et al. (16) applied an ICA to compare brain activity between healthy subjects and AD patients with regard to determination of the DMN and found the MTC to be functionally connected to PCC, suggesting the hypometabolism of PCC in early AD might result because of a) the early affections of AD pathology in the MTC and consequently b) the detachment of PCC from hippocampal structures.

Further they noted, that the hippocampal activation during resting-state in AD patients was deviant from healthy subjects, i.e. reduced.

Most studies examining FC with task-induced deactivations of the DMN in AD and MCI patients observed reduced connectivity within this network, especially between PCC and HiCa (16, 111, 112, 116). Disconnections between LTC, mPFC and IPC (87, 117) and the decrease of interconnectivity of bilateral HiCa have also been observed (118). These studies continuously show degraded efficiency of deactivations of the DMN with the progression of AD, with MCI patients showing more deviant behaviour in deactivations than healthy subjects, and patients with AD showing the most abnormal deactivation, suggesting an incremental affection of the DMN along the AD course.

Using fcMRI, functional connectivity between parietal and temporal regions has been shown to be decreased in AD patients, and an increase of activation in prefrontal regions was observed (15, 119, 120).
During cognitively demanding tasks a dynamic attenuation of the DMN is required to achieve an accurate behavioural performance in healthy subjects (121), which is impaired in patients with AD.
An expanding disconnection of DMN-nodes in the course of AD has been characterized (17) with midline regions mostly affected by disconnection, i.e. the ventral mPFC and PCC.
In addition, to a minor extent, decreases of activation were observed in bilateral ITC, the left HiCa and right IPC.

Sorg et al. (122) found the DMN and the executive attentional system to be specifically affected by connectivity failures in AD using ICA comparing eight resting-state networks of healthy subjects and MCI patients. Again, the FC of PCC, mPFC, both superior parietal lobes and bilateral inferior frontal gyri of the executive attention network were altered in MCI patients. By subsequently applying a seed based analysis, reduced connectivity of both HiCa to PCC was revealed, suggesting an early corruption of the HiCa – parietal memory systems in MCI-patients (122).

Contrary to those findings, increases of FC in AD patients have been reported as well.
Regions with significantly increased connectivity were found in the left mPFC and DLPFC in mild AD, extending to the supplementary motor area (SMA) and primary motor and sensory cortices in moderate and severe AD (14), between left HiCa and right lateral PFC (120), between parietal and occipital lobes (119) and most consistently between PCC and mPFC (17, 87).
These observations of activity elevations led to the *compensatory hypothesis* (123), which claims, that increased frontal lobe activities compensate reduced temporal and parietal functions.
This may explain the heterogeneity of MCI patients concerning their cognitive abilities and support the concept of cognitive reserve (124) that some MCI or AD patients are performing better despite comparable pathological burden (124).

Further studies that sought to investigate the FC of the DMN in AD patients regarding their actual disease status have been performed. These demonstrated pathological changes in FC occur already in MCI, concluding that the disconnection of FC in functional networks is advancing through the course of AD and is associated with the progression and severity of this disease (14, 17, 117).

1.4 Objectives of this study

With increasing life expectancy, it is realistic to expect a dramatic rise of incidence of AD in the future, reinforcing the importance of early recognition of AD and to filter individuals of risk of AD to test new therapies to delay the progression of the disease.

Beside the established biomarkers CSF and PET, fcMRI bears the potential to discriminate healthy people from patients with MCI on a network-level without the necessity to apply radioactive agents or invasive procedures.
Most importantly fcMRI also promises to provide a deeper insight into the functional consequences of AD and its related pathology, helping to understand the disease and its evolution.

This study aims at 3 targets:

a) Can fcMRI distinguish healthy elderly from AD patients by measurement of the DMN activity, consistently reported in literature?
b) Does DMN activity allow distinguishing between healthy controls and patients with mild and severe AD?
c) Do the FC patterns scale with the severity of the disease (as assessed with MMSE)?

2 Methods

Patients and healthy controls

23 patients with a clinical diagnosis of probable AD from the Department of Neurology of the Medical University of Graz were recruited for this study.
The patient cohort was stratified into mildly and severely diseased patients according to their MMSE-score [mild AD: MMSE 24,1 (±3,3 SD); severe AD: MMSE 15,7 (±1 SD)] to scrutinize FC-differences between different AD states. In contrast to existing literature, we here did not use an MMSE cut-off score for classification of the impairment level, rather we used age- and education adjusted norms (125), resulting in 12 patients with more severe AD (sAD) and 11 with mild AD (mAD) (s.Fig. 11 and Tab. 4). Performance measured with MMSE of mAD patients was 1,5 SD and of sAD patients 2 SD below the age- and educational-matched, healthy control peers.
Please note that the nomenclature of the AD subgroups is not in accordance with the MMSE scores associated with the clinical picture shown in Fig. 2.

23 age-matched healthy control subjects were obtained from the Austrian Stroke Prevention Study (ASPS).
For evaluating FC changes in the AD subgroups, the control group was age-matched and had the same size; for mAD n=11 HC and for sAD n=12 HC.

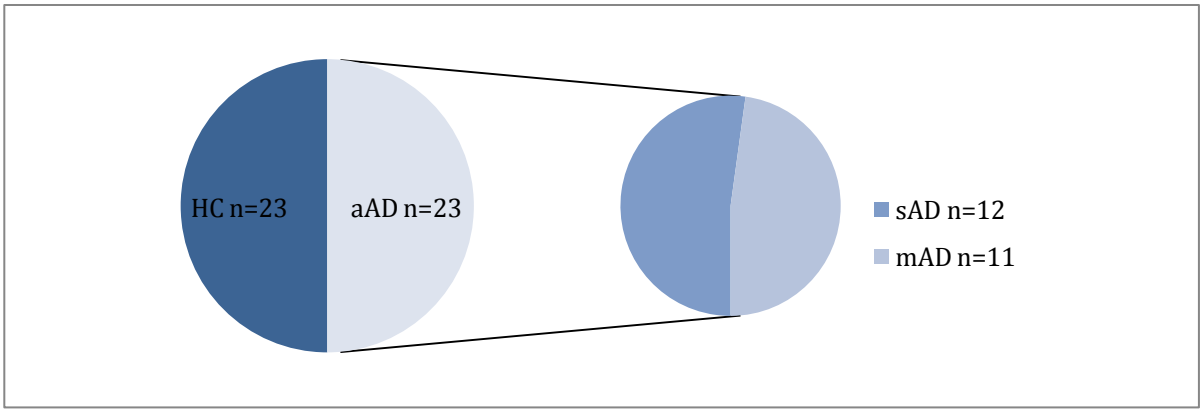

Fig. 11: Stratification of AD patients was done according to their MMSE-score, educational years and age. HC = healthy controls, aAD = all Alzheimer-patients, sAD = severe Alzheimer's, mAD = mild Alzheimer's

	HC n=23	aAD n=23	Significance p<0,05	mAD n=11	sAD n=12	Significance p<0,05
age (in years)	70,3 (±7,3)	72,8 (±8,2)	0,286	76,3 (±6,4)	69,9 (±8,5)	*0,045*
education (in years)	10,9 (±2,6)	9,6 (±2,2)	0,07	10,1 (±2,6)	9 (±1,7)	0,265
MMSE	27,6 (±1,8)	19,7 (±5,5)	*0,000*	24,1 (±3,3)	15,7 (±1)	*0,000*
sex (m/f)	9 / 14	8 / 15	0,763	4 / 7	4 / 8	0,928

Tab.4: Data are arithmetical mean values (±SD). Significant differences were found in the age group between mAD and sAD, and in the achieved MMSE score between all groups. HC=healthy controls; aAD=all AD-patients; mAD=mild AD, sAD=severe AD

Demography and neuropsychological testing

The demographic characteristics and results of neuropsychological screening are shown in Tab. 4.

No significant differences in age, educational years and gender-ratio were observed between the patient and control group.

Comparison of mAD and sAD showed significant differences in age and scored MMSE.

Standard protocol approvals, registration and patient consents

The ethics committee on human experimentation of the Medical University of Graz approved the study. All participants gave informed consent.

MRI data acquisition and analyses

Imaging was performed at a 3.0 T scanner (Tim Trio, Siemens, Erlangen, Germany) using a 12-element head coil.

A single shot gradient-echo EPI-sequence (repetition time = 3000 msec, echo time = 30 msec, flip angle = 90°, matrix size = 64 x 64, pixel size = 3.0 x 3.0 mm^2) was used for fMRI, discarding the first 2 volumes to account for T1 saturation.

To assess FC between related brain regions, correlation analyses were performed between a seed region (region-of-interest) and all remaining voxels of the brain (ROI-analysis).

The fMRI time series were processed as follows:

1) Preprocessing of data using statistical parametric mapping SPM5 software (Wellcome Department of Cognitive Neurology). This included realignment and normalization to an EPI-template.
2) Using REST 1.3 (Song Xiaowei, http://resting-fmri.sourceforge.net) the additional preprocessing was done to reduce spurious variance.
   Band-pass filtering at 0.009 Hz < f < 0.08 Hz, spatial smoothing using SPM 5 with a full width half maximum (FWHM) Gaussian filter at 6x6x6 mm, regression of 6 parameters obtained by rigid body head motion correction, regression of the whole brain signal averaged over the whole brain, regression of the ventricular signal averaged from a ventricular ROI, and regression of white matter signal averaged from a white matter ROI.

FC Maps were calculated based on an a priori defined cluster mask of the PCC and ACC, created with WFU-Pickatlas-toolbox. FC was calculated assessing the correlation coefficient between the average time series of each seed-region to any other voxel of the brain.
A Fisher's z- transformation was applied to improve the Gaussianity of the obtained correlation coefficients, allowing an individual creation of a resting-state-FC map with the seed-regions (Fig. 12).

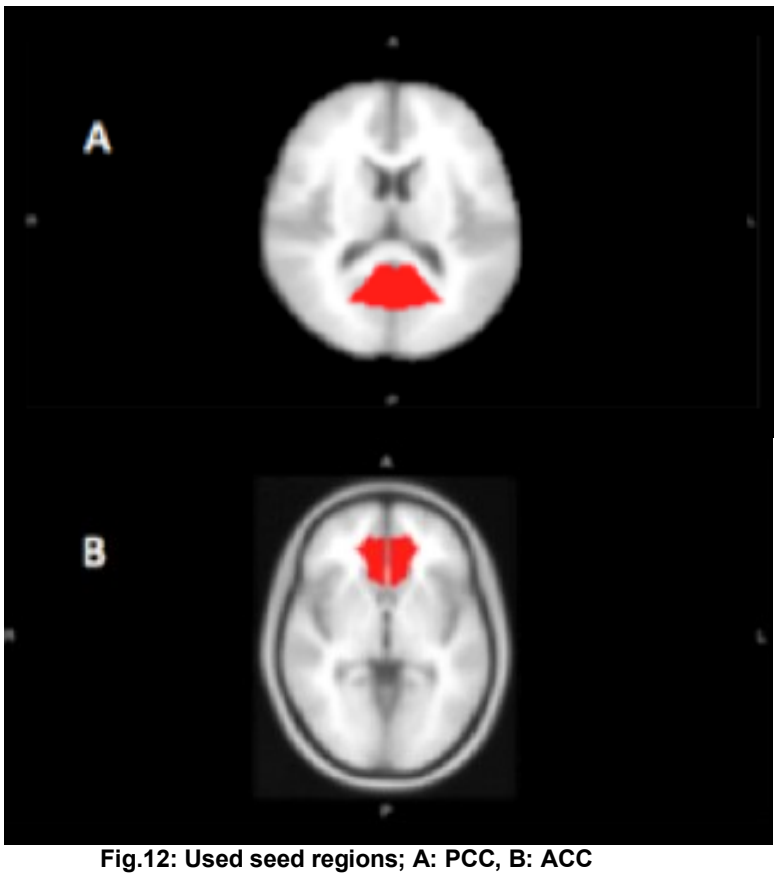

Fig.12: Used seed regions; A: PCC, B: ACC

Statistical analyses

To assess the fcMaps with PCC and ACC of controls, sAD and mAD patients separately, the obtained individual FC-spatial maps of z-scores were entered in a SPM 5 random-effect analysis (one-sample t-test, $p<0,05$, uncorrected).

For examining differences in activation in resting-state between groups, a two-sample t-test was used.

For obtaining correlations between the achieved MMSE scores by controls and patients and the FC, multiple regression models were used ($p<0,001$, uncorrected).

For all analyses, only clusters exceeding a size of $k=30$ voxels are reported.

3 RESULTS

3.1 PCC

PCC within group-analyses

The following section illustrates regions functionally correlated with the PCC in healthy controls (HC), all AD patients (aAD), patients with milder AD (mAD) and patients with more severe AD (sAD).
A one-sample t-test was used to achieve the within-group results of resting- state functional connectivity analyses of PCC.
We computed maps within each group using the PCC as seed-region, and obtained functional connectivity maps (fcMaps), indicating areas functionally connected with the PCC.
For illustration purposes the maps are shown in a transparent brain mask.
Fig. 13 shows the DMN after choosing the PCC as seed-region in 23 healthy controls.
Tables 5-8 show the mean FC values (expressed as Z-scores) and the Talairach coordinates, Figures 14-17 show the corresponding maps.

HC show widespread functional connections originating from PCC throughout the cortex, including the bilateral IPL, namely the angular gyri, the bilateral inferior temporal cortex (ITC), superior medial frontal cortex incl. ACC, both parahippocampal gyri, the left fusiform gyrus and left and right superior frontal gyrus (Fig.13, Fig. 14)

The entire cohort of all AD patients showed correlations to left IPL, the superior medial frontal cortex including ACC, the middle temporal gyrus bilaterally and the left parahippocampal gyrus (Fig. 15).
On visual inspection, the mean FC of PCC in HC shows more widespread correlations over the brain than in all AD patients.

Mean fcMaps of mAD-patients show PCC-FC to the angular gyri bilaterally, the left parahippocampal gyrus, the thalamus bilaterally, left putamen and left orbitofrontalcortex (OFC) (Fig. 16).

Patients with sAD showed on the mean map connections to bilateral IPL, superior medial frontal cortex incl. ACC, and right OFC (Fig.17).

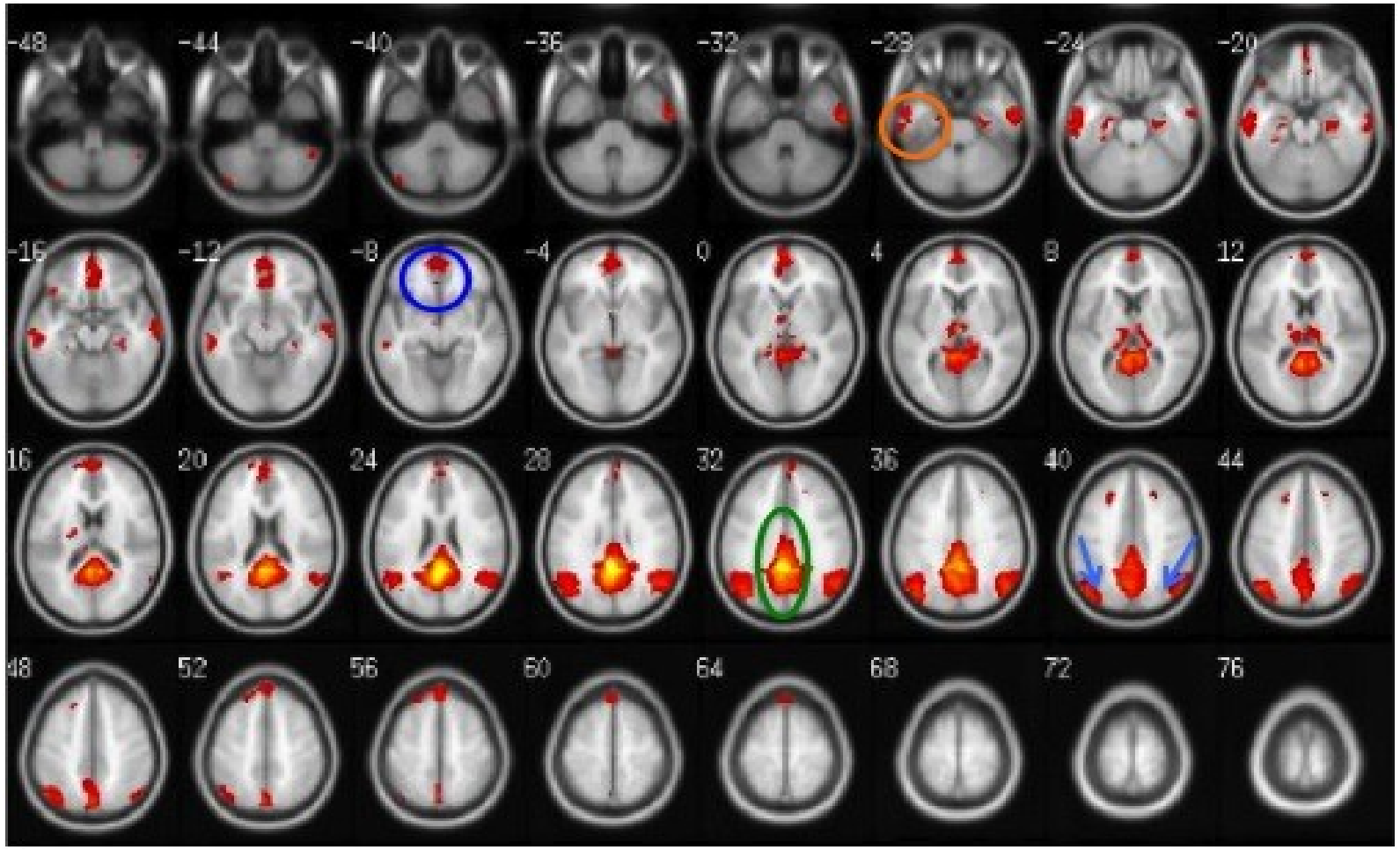

Fig.13: DMN in 23 healthy subjects during fcMRI after ROI analysis with the PCC as the seed-region; this map includes the lateral temporal cortices (red circle, slice -29) as well as subcortical regions (e.g. thalamus), the mPFC ventrally (blue circle, slice -8), the PCC (green circle, slice 32) and the inferior parietal lobules IPL (arrows, slice 40).

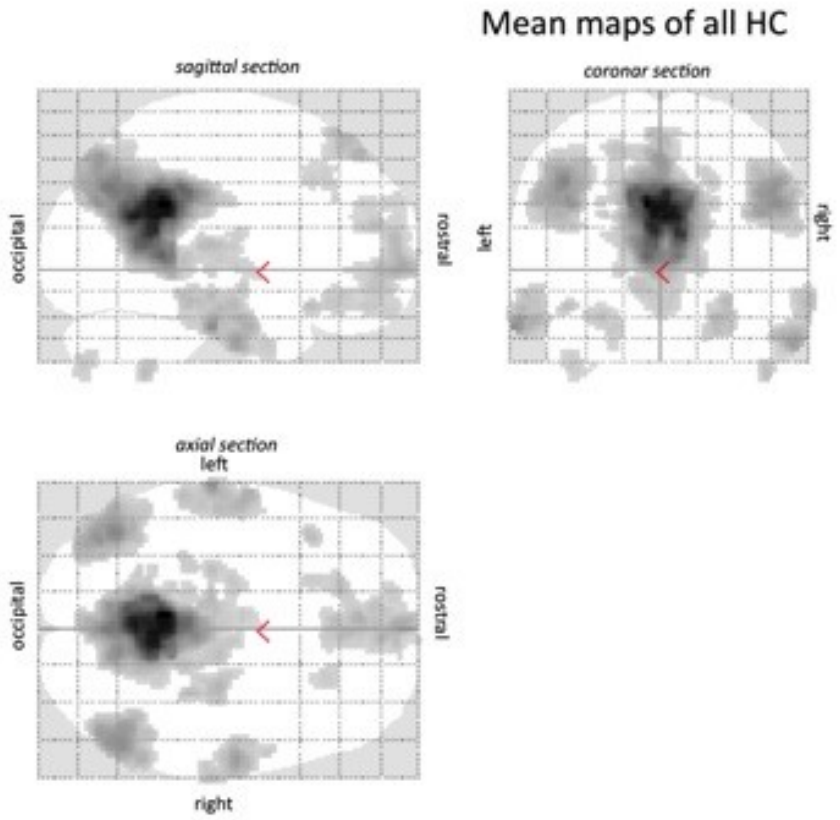

Fig. 14: Mean fcMap of PCC obtained from HC

Healthy controls show widespread functional connections deriving from PCC throughout the cortex: bilateral IPL, bilateral ITC, superior medial frontal cortex incl. ACC, bilateral parahippocampal gyri.

Tab. 5: Talairach coordinates of PCC connectivity in HC

Region L/R	Z max	x	y	z	clustersize	p corr.
PCC L	25,9	-6	-42	30	7351	<0,001
PCC R	23,21	2	-46	24		
vermis 4 5	22,05	-2	-56	24		
Angular gyrus L	10,47	-44	-66	40	1637	<0,001
occipital middle gyrus	9,27	-42	-74	32		
angular gyrus L	6,62	-46	-58	26		
angular gyrus R	9,64	52	-64	30	1323	<0,001
parietal inferior gyrus R	8,6	54	-62	40		
angular gyrus R	6,64	60	-54	34		
Temporal inferior gyrus	9,58	-66	-22	-26	649	<0,001
Temporal middle gyrus	6,78	-62	-4	-26		
	6,47	-62	-18	-18		
Temporal inferior gyrus	8,42	60	-10	-34	541	<0,001
Temporal inferior gyrus	6	68	-12	-16		
	5,96	68	-22	-12		
frontal superior medial gyrus L	7,31	-2	64	0	1576	<0,001
	6,23	4	56	0		
	6,08	0	62	12		
	6,73	-4	46	54	377	<0,001
frontal superior medial L (ACC)	6,21	2	38	58		
	5,82	-4	34	64		
parahippocampal gyrus R	6,27	26	-18	-22	229	<0,001
	5,85	30	-32	-14		
	4,44	22	-28	-18		
frontal inferior orbital gyrus R	5,67	-42	24	-16	35	0,599
Parahippocampal gyrus L	5,66	-26	-22	-22	121	0,007
	4,94	-20	-12	-26		
	4,02	-22	-10	-34		
cerebellum crus 2 R	5,57	48	-58	-48	37	0,547
cerebellum crus 2 L	4,67	-40	-80	-44	90	0,033
fusiform gyrus L	4,62	-32	-34	-22	43	0,409
frontal middle gyrus R	4,58	24	32	40	57	0,194
Frontal superior gyrus R	4,03	20	34	32		
frontal superior gyrus L	4,52	-22	24	40	72	0,086

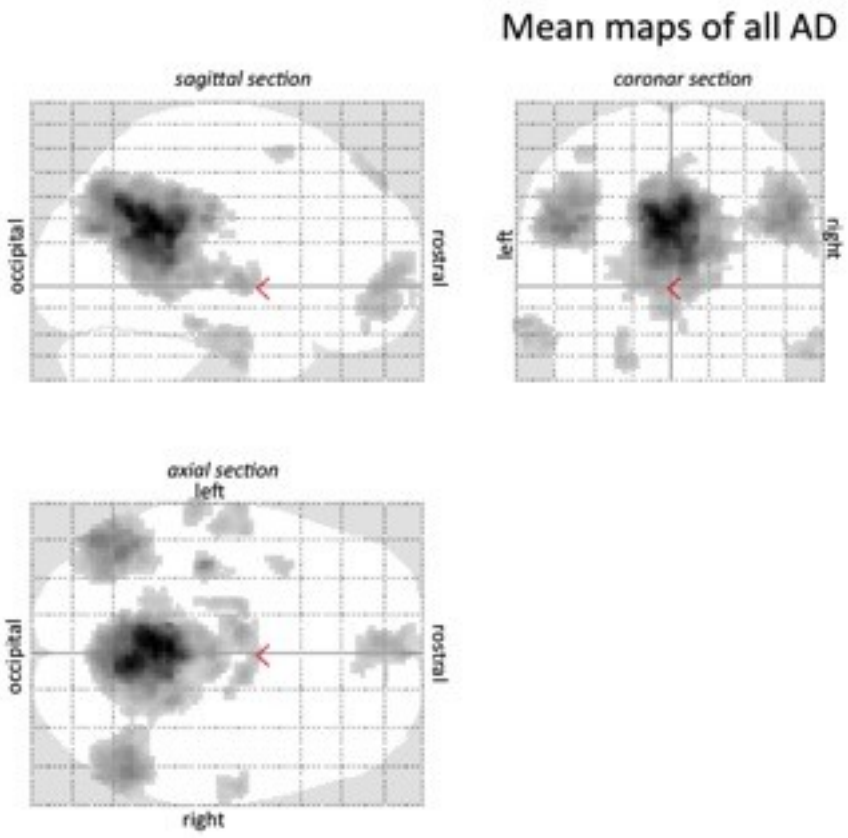

Fig. 15: Mean fcMap of PCC from all AD patients

The mean fcMap of the entire cohort of AD patients shows FC of PCC to bilateral IPL, the superior medial frontal cortex incl. ACC.

On visual inspection the overall functional connectivity is not as widespread as in the cohort of healthy controls (cf. Fig.13)

Tab. 6: Talairach-coordinates of PCC connectivity in aAD

region	Z max	x	y	z	clustersize	p corr.
PCC L	20,76	-2	-46	28	9125	<0,001
Precuneus R	19,39	6	-56	32		
PCC R	14,87	2	-34	30		
angular gyrus L	9,75	-44	-60	26	1750	<0,001
	9,45	-50	-72	26		
	8,92	-50	-64	32		
Inferior parietal cortex L	8,88	-40	-24	30	135	0,004
insula L	3,74	-36	-14	24		
ACC L	6,35	-4	52	-2	544	<0,001
frontal superior medial gyrus L	6,12	-4	60	6		
frontal medial orbital gyrus L	5,52	-2	52	-10		
temporal middle gyrus L	5,75	-64	-28	-16	60	0,177
temporal inferior gyrus R	5,53	60	-8	-30	86	0,046
temporal middle gyrus R	4,16	64	-16	-24		
Parahippocampal cortex L	5,49	-20	-8	-34	103	0,02
	4,84	-22	-20	-24		
temporal middle gyrus L	5,28	-54	-6	-26	158	0,002
	5,2	-64	-8	-22		
	5,19	-56	-18	-24		
frontal superior medial gyrus	5,19	0	54	46	68	0,116
front superior medial gyrus R	4,16	8	44	58		
	3,86	10	56	46		
frontal middle gyrus L	4,87	-38	12	60	44	0,406

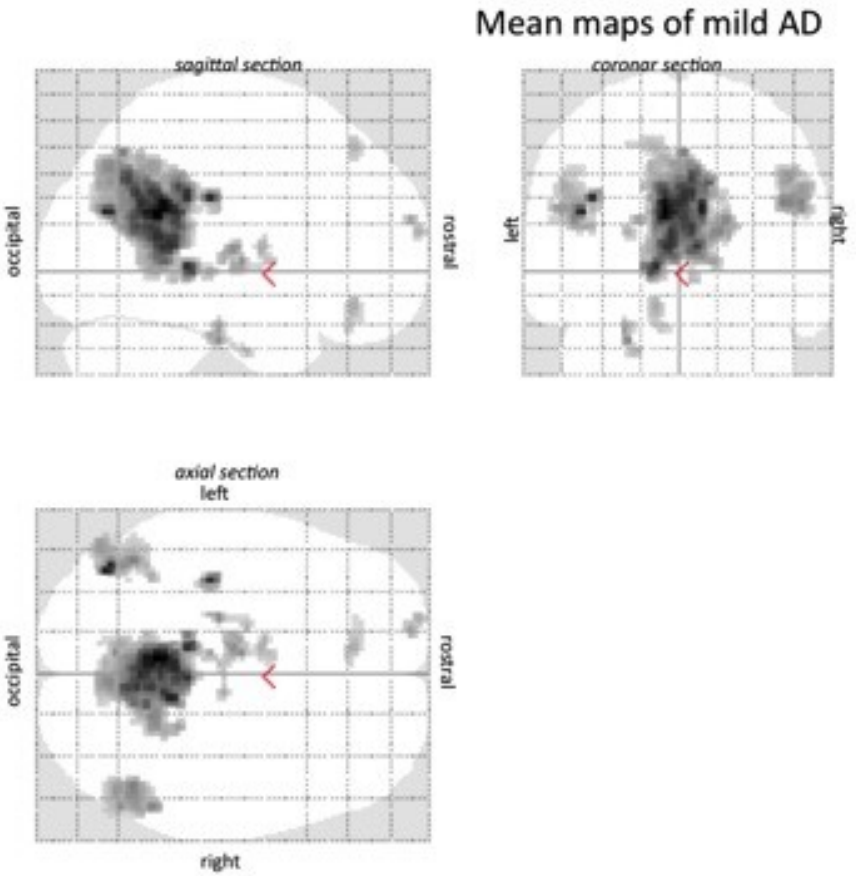

Fig. 16: Mean fcMap of PCC from mAD-patients

The mean fcMaps of 11 patients with mAD are shown. FC to IPL bilaterally, the left parahippocampal gyrus, left putamen and left orbitofrontal cortex (OFC) is illustrated.

Tab. 7: Talairach-coordinates of PCC connectivity in mAD-patients

region	Z max	x	y	z	clustersize	p corr.
PCC L	15,44	-6	-48	24	3722	<0,001
PCC R	12,86	10	-42	26		
PCC L	12,56	-4	-40	24		
occipital middle gyrus L	12,85	-42	-70	24	456	<0,001
temporal middle gyrus L	7,84	-46	-58	22		
angular gyrus L	6,77	-50	-72	26		
Inferior parietal cortex L	12,06	-38	-24	30	48	0,038
angular gyrus R	7,82	46	-58	28	301	<0,001
	7,55	54	-50	28		
	7,23	54	-64	26		
Parahippocampal cortex L	7,47	-22	-20	-28	36	0,137
	5,76	-18	-8	-32		
thalamus L	7,28	-8	-10	4	129	<0,001
thalamus R	5,99	8	-18	6		
Putamen L	5,9	-14	0	10		
frontal superior gyrus L	6,36	-18	64	22	31	0,235
	5,78	-22	68	16		
frontal medial orbital gyrus L	6,04	-10	38	-14	38	0,11
	4,77	-8	36	-24		
frontal superior medial gyrus L	5,61	-10	40	50	42	0,072

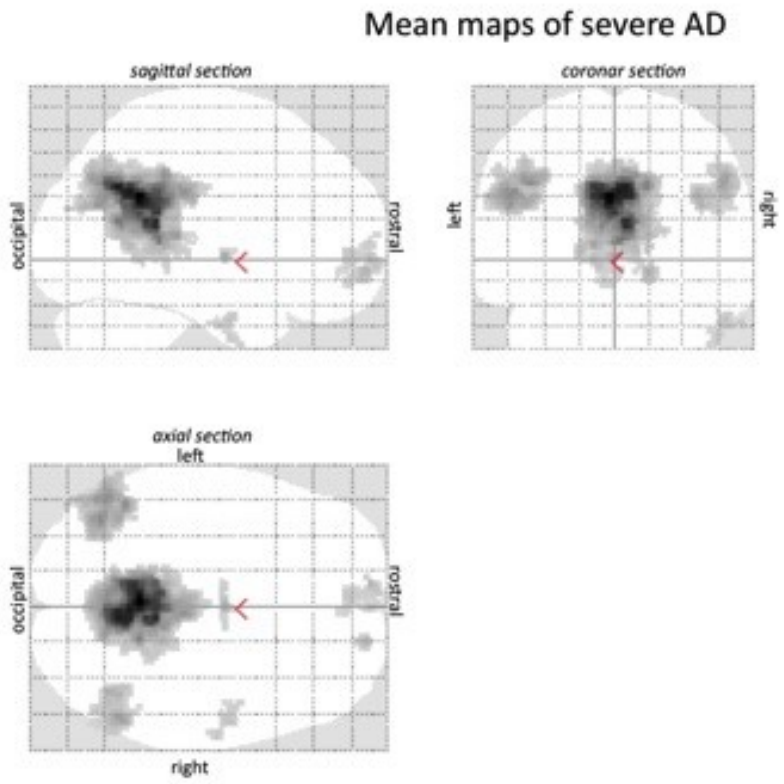

Fig. 17: Mean fcMap of PCC from sAD-patients

The mean fcMaps of 12 patients with sAD are shown. FC of PCC to bilateral IPL, superior medial frontal cortex incl. ACC and right OFC are illustrated.

Tab.8: Talairach-coordinates of PCC connectivity in sAD-patients

region	Z max	x	y	z	clustersize	p corr.
PCC L	22,41	-2	-48	30	4553	<0,001
precuneus R	18,76	6	-58	34		
PCC R	17,21	6	-40	34		
angular gyrus L	9,34	-40	-66	36	829	<0,001
	9,06	-50	-64	30		
	9,06	-48	-54	32		
angular gyrus R	7,96	52	-58	36	465	<0,001
	6,84	42	-58	26		
	4,97	50	-68	44		
CSF (thalamus?)*	6,92	0	-6	2	32	0,442
frontal superior orbital gyrus R	6,53	16	62	-6	37	0,307
frontal superior medial gyrus L	6,34	-10	64	0	145	<0,001
ACC L	5,27	-6	52	2		
frontal superior medial gyrus R	5,24	2	64	8		
temporal middle gyrus R	5,31	54	-4	-28	51	
	5,1	62	-10	-30		
	4,74	50	-4	-36		

*activation was seen in regions nearby the thalamus and in the lateral ventricles. This result could be due to misregistration.

PCC between-groups analyses

To evaluate FC-changes between HC, aAD, mAD and sAD two-sample t-tests were calculated.
Relative increases of FC of the interesting group with the compared one were indentified this way.

HC showed increased FC relative to all AD patients in the right superior temporal pole (Fig. 18), this was also observable when compared with mAD, although with a smaller clustersize.
Increased FC to mPFC, precisely the gyrus rectus, was observed in HC when compared to sAD (Fig. 19).

The reverse contrasts showed small clusters of FC in the right SMA in mAD compared with HC, and also to the gyrus rectus when compared with sAD (Fig. 20).

In reverse, both the entire group of all AD patients as well sAD patients showed increased BOLD signals in the CSF compared to HC and in ITC compared to mAD. Such clusters were disregarded as most likely related to brain atrophy in AD patients, for the brainmaps were not coregistered for the individual subjects.

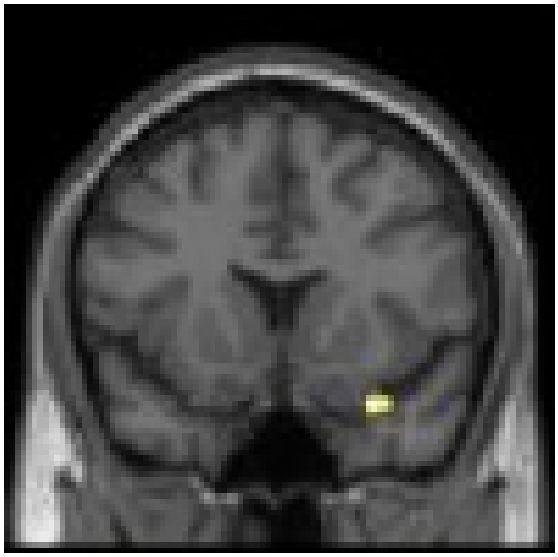

Fig. 18: increased PCC-FC to superior temporal pole in healthy controls compared to all AD patients

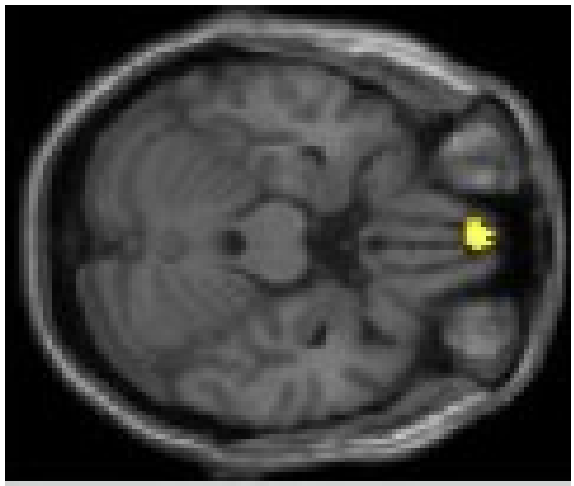

Fig. 19: increased PCC-FC to gyrus rectus in healthy controls compared with sAD patients

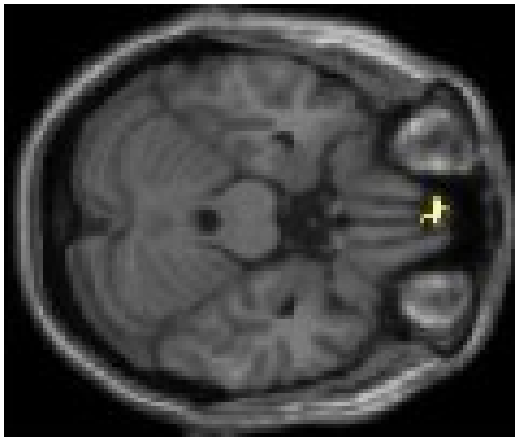

Fig. 20: increased PCC-FC to G. rectus in mAD-patients compared to sAD-patients

Despite the consistent results of PCC-FC to gyrus rectus, it is to note that the signals are artefact prone regions as the brain atrophy was not included into calculation of the brain maps and could represent misregistration.

Tab. 9: Differences in PCC-FC between groups

region	Z max	x	y	z	clustersize	p corr.
HC > aAD						
Temporal superior pole R	5,53	32	14	-24	53	0,382
	3,28	36	8	-20		
aAD > HC						
CSF (precuneus R?)*	5,65	22	-40	14	90	0,08
postcentral gyrus L	5,09	-38	-22	28	48	0,465
SMA R	4,57	6	4	62	54	0,366
PCC R	4,53	4	-38	12	50	0,43
corpus callosum	3,67	0	-30	18		
Calcarina L	4,46	-24	-50	10	39	0,644
HC > mAD						
Temporal superior pole R	5,65	32	18	-26	20	0,945
mAD > HC						
SMA R	4,97	6	4	64	26	0,829
	4,51	0	-38	14	21	0,931
HC > sAD						
Gyrus rectus	6,16	0	56	-20	117	0,01
sAD > HC						
CSF (precuneus/calcarina?)*	4,62	22	-40	14	55	0,227
	4,43	18	-32	24		
mAD > sAD						
Gyrus rectus	4,55	0	54	-20	61	0,163
sAD > mAD						
Temporal inferior gyrus R	5,33	48	-2	-38	40	0,485
	4,57	46	-8	-32		

*activation was seen in regions nearby the thalamus and in the lateral ventricles. This result could represent misregistration.

PCC functional connectivity correlations with MMSE

To relate the disease severity of AD patients with their PCC-fcMap, the achieved MMSE score of each group was correlated with the corresponding fcMaps, applying multiple regression-analyses.

In the following, positive correlations imply that the better the AD patients performed in MMSE, the more functional connectivity they showed deriving from PCC. Negative correlations imply, the worse AD-patients scored at MMSE, the more functional connectivity to a specific area was observed in the fcMaps.

Positive correlations were found in all AD patients in the left precentral gyrus and frontal lobe. In sAD patients positive correlations were observed in the right fusiform gyrus.
Negative Correlations were observed in all AD patients from PCC to the right OFC (Fig. 21). mAD-patients showed negative correlations from PCC to IPL (Fig. 22), with a cluster-size of k=30.
Additionally, sAD-patients showed increased FC negatively correlated with MMSE to left OFC, nevertheless, this result did not survive the voxel threshold of 30.

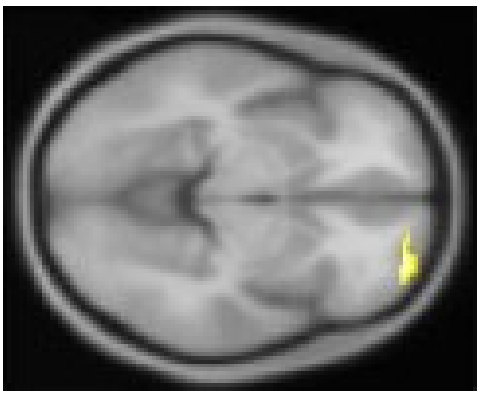

Fig. 21: MMSE correlations: all AD patients showed increased FC to the right orbitofrontal cortex with worse MMSE score

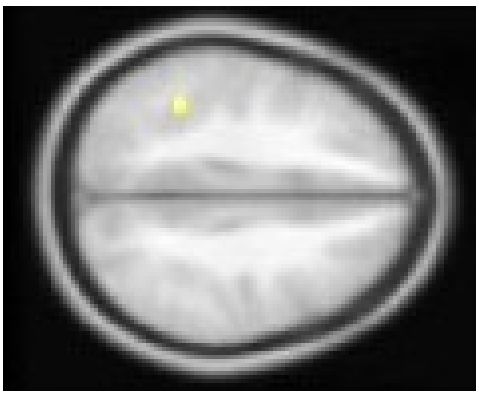

Fig 22: MMSE correlations: the worse mAD patients were at MMSE, the more FC was observable to the IPL

Tab. 10: MMSE-correlations with PCC-FC in AD patients

region	Z max	x	y	z	clustersize	p corr.
aAD pos						
precentral gyrus L	4,19	-34	6	40	40	0,484
frontal lobe WM	3,87	-26	8	40		
aAD neg						
frontal superior orbital gyrus R	5,37	32	60	-6	141	0,003
	4,43	22	60	-2		
	3,81	18	62	-10		
mAD pos						
precuneus L	7,36	-10	-52	44	18	0,681
mAD neg						
Inferior parietal cortex L	6,99	-42	-44	38	43	0,035
sAD pos						
fusiform gyrus R	8,38	30	-4	-42	30	0,431
sAD neg						
Frontal middle orbitalgyrus L	6,22	-20	64	-12	16	0,941
	4,69	-26	66	-4		

3.2 ACC

ACC within-group analysis

Analogous to the PCC analyses, examinations of the functional connectivity of ACC in healthy controls, aAD, mAD and sAD-patients were performed, to spot the functionally related regions in the brain with ACC.
Therefore a one-sample t-test for each group was performed, to achieve mean maps showing BOLD- signal correlated brain regions with ACC. Tab. 11-13 show the Talairach-coordinates, and Fig. 23-26 show the corresponding mean maps.
Due to technical problems during post-processing (data deleted), the cluster table of Fig. 24 is not available.

HC showed FC to the left and right superior frontal cortex incl. SMA bilaterally, superior medial frontal cortex, the middle cingulum, the left inferior temporal gyrus, and the right OFC (Fig. 23)

Mean maps of mAD-patients exhibited ACC-FC to the left and right basal ganglia (putamen and caput caudatus), and the left OFC (Fig. 25).
sAD-patients showed FC dominantly to medial frontal cortex (Fig. 26).

On visual inspection, the FC of ACC seems to decrease in an anterior-posterior pattern in the brain throughout the course of AD.

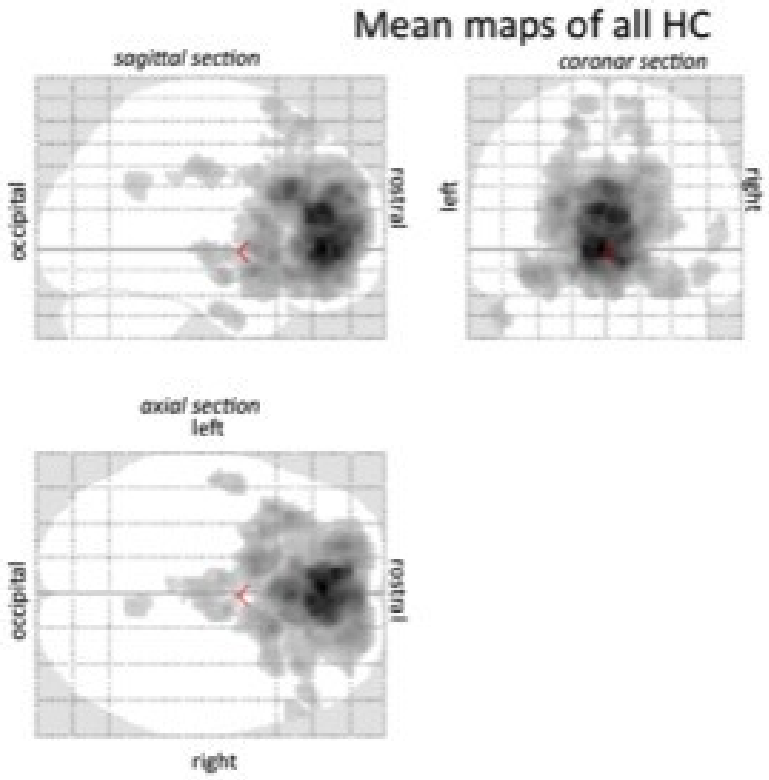

Fig. 23: mean maps of ACC in healthy controls

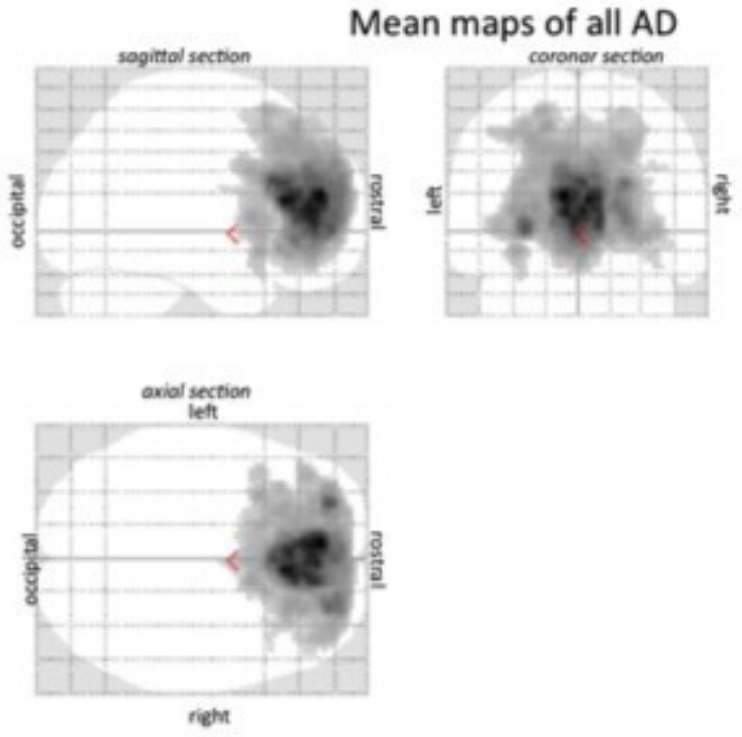

Fig. 24: mean maps of ACC in all AD patients

Tab.11: Talairach-coordinates of ACC-FC in HC

region	Z max	x	y	z	clustersize	p corr.
region	**Z max**	**x**	**y**	**z**	**clustersize**	**p corr.**
ACC L	20,48	-2	42	0	15652	0
	17,83	-10	48	0		
	17,39	-4	42	18		
frontal superior gyrus L	5,92	-16	30	60	90	0,044
frontal superior medial gyrus R	3,97	-12	34	48		
frontal superior gyrus L	3,71	-18	38	54		
middle cingulum	5,83	0	-18	38	241	0
	5,22	-2	-8	36		
	3,75	-4	-34	36		
frontal superior gyrus R	5,2	18	26	56	275	0
SMA R	4,8	10	20	70		
frontal superior gyrus R	4,32	18	18	62		
temporal inferior gyrus L	5,17	-54	-10	-28	114	0,014
precentral gyrus L	5,05	-50	0	34		
SMA L	4,95	-12	20	70	78	0,08
frontal inferior orbital gyrus R	4,75	46	34	-12	68	0,132
frontal inferior triangular gyrus R	4,68	58	32	12	57	0,231
	4,27	54	26	2		
middle cingulum	4,38	6	-52	32	102	0,025

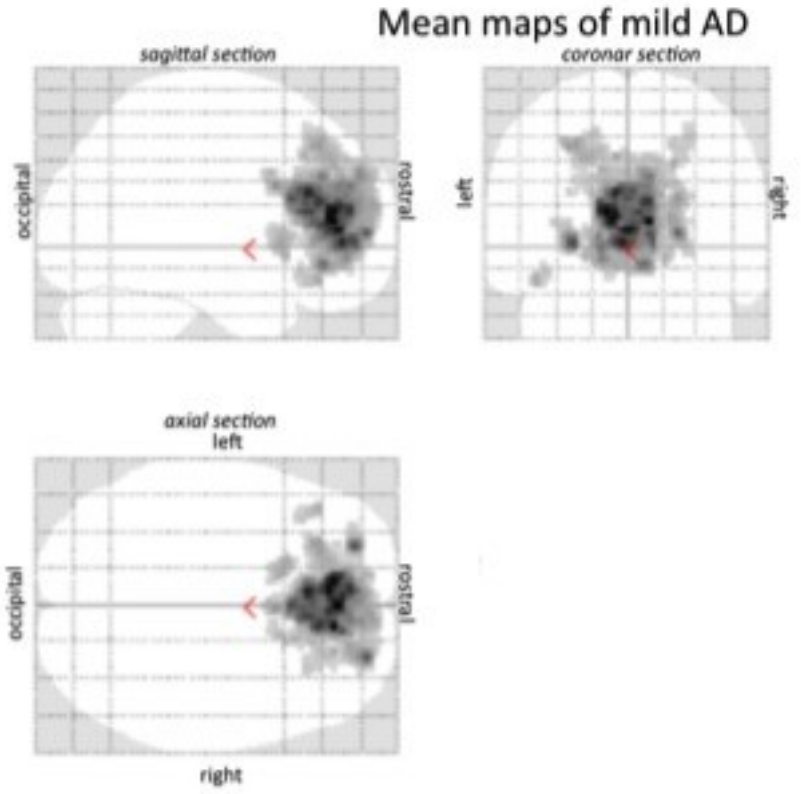

Fig. 25: mean fcMaps of mAD-patients

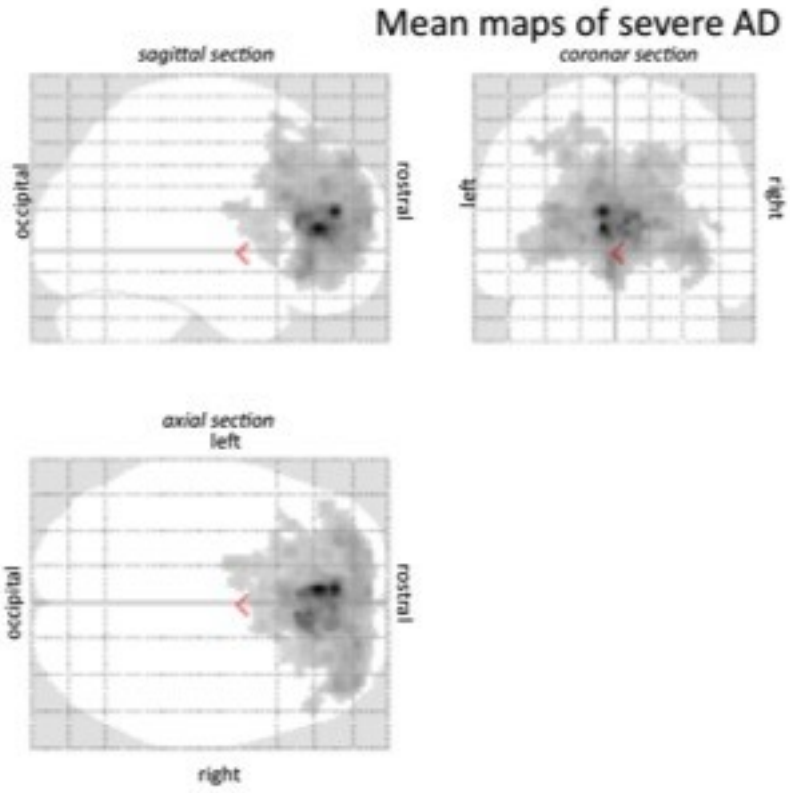

Fig. 26: mean fcMaps of sAD-patients

Tab. 12: Talairach-coordinates of ACC-FC in mAD-patients

region	Z max	x	y	z	clustersize	p corr.
ACC L	19,02	0	44	8	6044	0
	18,29	10	42	16		
	18,11	-10	42	16		
Frontal middle gyrus L	12,69	-26	52	2	125	0
putamen L	6,95	-20	20	2	104	0
Caput caudatus L	6,75	-14	16	2		
frontal inferior orbital L	6,72	-44	34	-14	54	0,016
	5,3	-38	26	-12		
Caput caudatus R	6,24	14	16	4	41	0,066
Corpus caudatus R	4,66	8	14	10		
Caudatus R	4,56	20	26	2		
ACC L	19,02	0	44	8	6044	0
	18,29	10	42	16		
	18,11	-10	42	16		
Frontal middle gyrus L	12,69	-26	52	2	125	0
putamen L	6,95	-20	20	2	104	0
Caput caudatus L	6,75	-14	16	2		
frontal inferior orbital L	6,72	-44	34	-14	54	0,016
	5,3	-38	26	-12		
Caput caudatus R	6,24	14	16	4	41	0,066
Corpus caudatus R	4,66	8	14	10		
Caudatus R	4,56	20	26	2		

Tab. 13: Talairach-coordinates of ACC-FC in sAD-patients

region	Z max	x	y	z	clustersize	p corr.
region	**Z max**	**x**	**y**	**z**	**clustersize**	**p corr.**
ACC L	33,41	-6	38	10	11957	0
frontal superior medial L	30,58	-6	46	18		
ACC R	18,44	6	28	14		
frontal inferior triangular gyrus R	5,63	48	34	12	30	0,591
frontal middle gyrus R	4,4	42	38	18		

ACC between-group analyses

Using two-sample t-tests, differences in correlation patterns between groups were examined.

HC showed more ACC-FC (Fig. 27) to left putamen, left thalamus, left hippocampus, left pulvinar and left OFC than all AD patients. The reverse contrast showed increased FC in all AD patients superior medial frontal cortex (Fig. 29)
Compared to patients with mild AD, HC showed increased FC to left caudatus and putamen (Fig. 28).
In comparisons with severe AD-patients, HC showed increased connectivity to the left hippocampus, the left thalamus, the left parahippocampal gyrus, the precuneus and PCC and left fusiform gyrus, and left supramarginal gyrus.

mAD-patients showed increased ACC-FC to left cerebellum than HC (Fig. 30), and increased ACC-FC to the left supramarginal gyrus, the cerebellum and lingual gyrus (BA 18) than patients with sAD.

When sAD patients were compared with HC, they showed increased ACC-FC to medial frontal cortex and reciprocally to ACC and to left OFC (Fig. 31).
Comparisons with mAD-patients, sAD-patients showed increased connectivity in the ACC (Fig. 32).

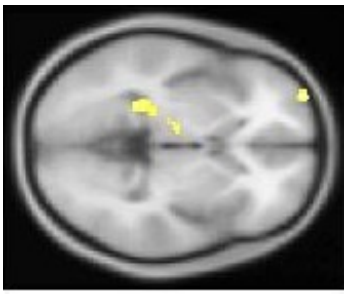

Fig. 27: increased ACC-FC in HC compared to aAD in the basal ganglia and left OFC

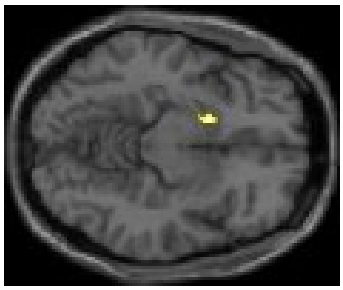

Fig. 28: increased ACC-FC in HC compared to mAD to left putamen and caudatus

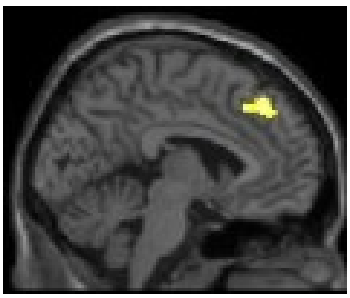

Fig. 29: increased ACC-FC in aAD compared to HC in superior medial frontal cortex

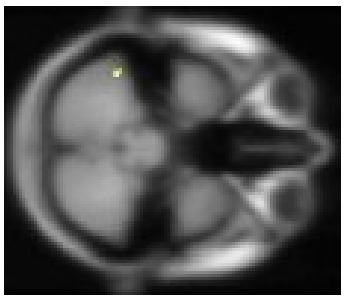

Fig. 30: increased ACC-FC in mAD compared to HC to left cerebellar cortex

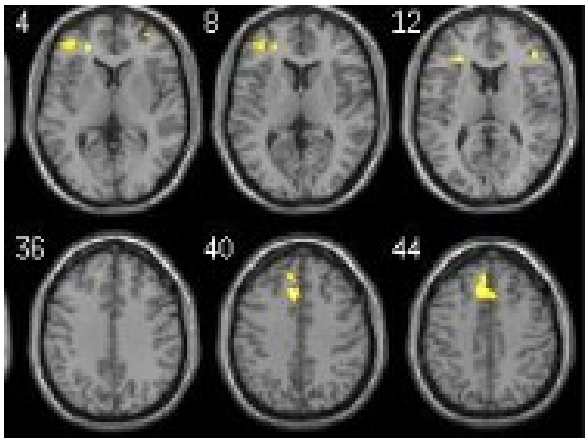

Fig. 31: increased ACC-FC in sAD compared to HC to the left OFC and medial frontal cortex

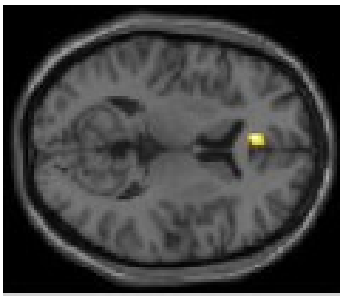

Fig. 32: increased ACC-FC in sAD compared to mAD in ACC

Tab.14: Differences in functional connectivity between groups

region	Z max	x	y	z	clustersize	p corr.
HC vs aAD						
Putamen L	4,87	-14	8	-12	61	0,312
frontal middle orbital gyrus L	4,63	-30	66	0	43	0,601
Thalamus L	4,11	-10	-14	-2	32	0,816
Hippocampus L	4,11	-26	-36	-2	57	0,364
Pulvinar L	3,9	-14	-28	16	30	0,851
aAD vs HC						
frontal superior medial L	4,96	0	38	42	241	0,001
	4,48	-8	40	40		
	4,17	-2	28	44		
HC vs mAD						
Caudatus L	5,64	-14	10	-12	57	0,179
Putamen L	3,87	-22	10	-8		
	3,83	-18	2	-8		
mAD vs HC						
Cerebellum crus1 L	5,36	-36	-56	-36	50	0,265
Cerebellum crus2 L	4,23	-46	-48	-44		
HC vs sAD						
Temporal superior gyrus L	4,99	-48	-14	0	35	0,645
Hippocampus L	4,88	-22	-40	2	89	0,048
Thalamus L	4,03	-22	-30	-2		
parahippocampal cortex L	3,74	-22	-38	-8		
precuneus R	4,62	10	-46	8	34	0,67
cerebellum 4 5 L	4,58	-14	-48	-14	35	0,645
PCC L	4,52	-6	-44	14	33	0,695
	3,94	-6	-42	6		
Fusiform gyrus L	4,34	-36	-26	-20	50	0,33
	4,34	-32	-20	-24		
supramarginal gyrus L	4,29	-54	-24	18	41	0,503
Temporal superior gyrus L	4,08	-68	-30	14		
supramarginal gyrus L	3,96	-62	-26	18		
sAD vs HC						
frontal superior medial gyrus L	6,12	-6	24	42	252	0
	4,26	-10	40	40		
SMA R	4,11	8	22	46		
insula L	5,85	-28	30	14	47	0,381
frontal medial gyrus L	5,74	-22	42	4	34	0,67
frontal middle orbital gyrus L	5,25	42	52	-6	131	0,007
frontal middle gyrus R	4,11	32	54	2		
frontal middle gyrus L	4,87	-30	16	54	59	0,211

	4,84	-36	46	4	86	0,055
ACC R	4,69	14	34	20	42	0,481
	3,93	6	28	16	46	36
frontal inferior triangular gyrus R	4,66	46	36	12	101	0,027
frontal middle gyrus R	4,46	46	36	22		
mAD vs sAD						
supramarginal gyrus L	5,74	-60	-26	18	67	0,129
cerebrellum 6 L	4,92	-8	-80	-14	48	0,343
lingual cortex BA 18 L	3,58	-14	-80	-8		
sAD vs mAD						
ACC L	7,44	-6	38	10	40	0,504
Postcentral gyrus	5,51	66	-14	26	41	0,482

ACC functional connectivity correlations with MMSE

Multiple regression analyses with the achieved MMSE of patients and their fcMaps resulted in correlations between the clinical picture and the FC of ACC in the patients.

Positive correlations in all AD-patients were found in the left and right calcarina, the left lingual gyrus, the right cerebellum and the left inferior occipizal gyrus (Fig. 35). A negative correlation in aAD was found in the right middle frontal gyrus (Fig. 36).

For mAD-patients no such results were observed.

sAD-patients showed a positive correlation to the right postcentral gyrus and a negative correlation to the left inferior temporal gyrus (Fig. 37).

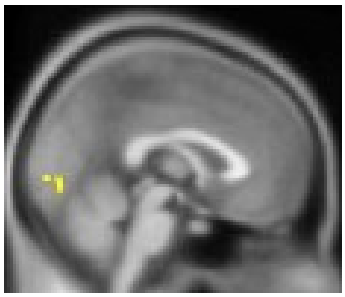

Fig. 33: positive correlations of MMSE in aAD

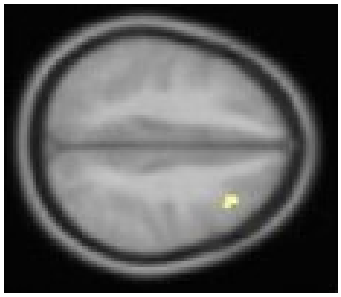

Fig.34: negative correlations of MMSE in aAD

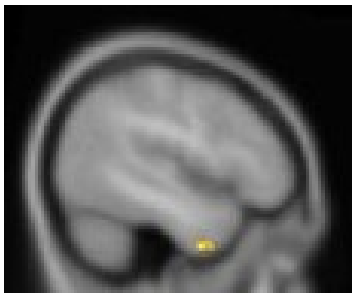

Fig. 35: negative correlations of MMSE in sAD

Tab.15: MMSE-correlations with ACC-FC

region	Z max	x	y	z	clustersize	p corr.
aAD pos						
calcarina R	5,84	24	-48	4	40	0,519
lingual cortex L	5,21	-8	-80	-12	103	0,023
calcarina L	4,94	-2	-92	-2		
	4,22	2	-84	-4		
cerebellum 8 R	5,13	20	-64	-40	43	0,453
lingual cortex L	4,55	-26	-84	-14	43	0,453
occipital inferior cortex L	4,24	-18	-94	-12		
calcarina L	3,74	-18	-52	4	50	0,324
aAD neg						
frontal middle gyrus R	4,94	34	26	42	54	0,265
	4,1	38	20	38		
mAD pos						
	N.A	N.A	N.A.	N.A	N.A	N.A.
mAD neg						
	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
sAD pos						
postcentral gyrus R	9,18	24	-44	72	49	0,127
sAD neg						
temporal inferior gyrus L	8,26	-50	0	-40	31	0,484

4 Discussion

This crossectional ROI-based fMRI study investigates the baseline activity of the brain of individuals with milder Alzheimer's disease and more severe Alzheimer's disease compared to healthy, age-matched controls. The severity of AD was measured with MMSE.

The literature reports the DMN consisting of the infraparietal lobules (IPL) bilaterally, the posterior cingulated cortex (PCC), the anterior cingulated cortex (ACC) and medial prefrontal cortex (mPFC) (126). We were able to identify the described network in healthy controls, as well as in AD-patients even though not the extent like in healthy elderly (s. p. 47, Fig 12) by choosing the PCC as seed region. Under visual inspection, the analyses of PCC-FC show the mean maps portraying the complete extent of the DMN in HC commonly reported in literature. Greicius et al. (74) were able to demonstrate in an early study the DMN by choosing the PCC as well. Their results imply FC of PCC to IPL bilaterally, to the left parahippocampal gyrus, the mPFC and to the left inferior temporal cortex. Our results also show PCC connectivity to bilateral IPL (specifically to both angular gyri), to bilateral ITC, to mPFC and ACC and both parahippocampal gyri.

Fig. 38 represents a simplified scheme of the DMN as Raichle (69) and Greicius et al. (74) described it already and as Buckner et al. visualized it with correlational strengths (p. 33, Fig. 9).

To address the functional connectivity differences between the AD groups and healthy controls, comparisons of PCC-FC were made.

Patients with sAD had decreased FC to gyrus rectus compared with mAD patients, and patients with mAD had decreased FC to gyrus rectus compared with healthy controls. This observation of gradually decreasing FC of PCC to mPFC (from HC to sAD) suggests that the corruption of FC from PCC to mPFC proceeds with the progression of the disease.

We also found a negative correlation of the MMSE score with the PCC-fcMaps in the entire AD cohort. Increased functional connectivity to the right orbitofrontal cortex (OFC) in the entire AD group was observed, the worse their MMSE performance was. Such increases of FC in frontal regions of MCI and AD patients have been reported in literature (17, 87, 123), and it is still a matter

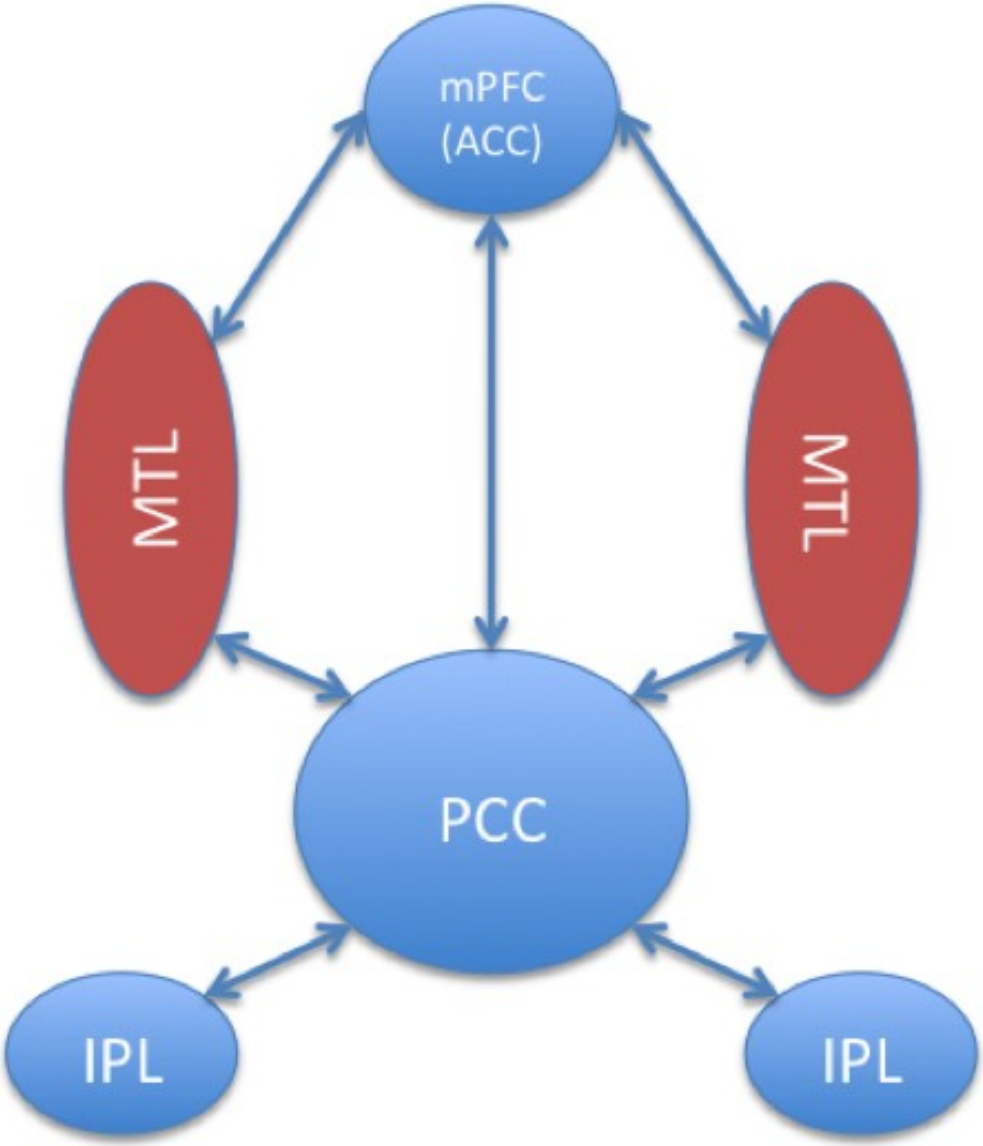

Fig. 36: Simplified scheme of the DMN; mPFC (ACC) = medial prefrontal cortex (anterior cingulated cortex), MTL = medial temporal lobe, PCC = posterior cingulated cortex, IPL = inferior parietal lobule

of debate, if these increases of functional connectivity in prefrontal regions mirror compensation mechanisms. Zhang et al. (17) speculated that the regions later involved in the AD pathology would be recruited for compensation and plasticity and suggested that frontoparietal regions might be involved in an antinetwork of the DMN, which are increasing in activity when the DMN activity was reduced.
Similar to those findings, Damoiseux et al. (127) showed disrupted local connectivity in AD with decreased FC between the temporal lobes and other cortical and subcortical areas, and increased FC within the frontal lobe (127).

Our findings suggest a possible speculation, that the increased FC from PCC to right OFC may reflect the loss of inhibitory influences of PCC on mPFC, which is on its part initializing synchronized activity with structures adjacent to the right OFC as shown in Fig. 39 p. 74.
Also it is conceivable, that an interposed region is mediating the synchronous activity between the PCC and the right OFC, which was not detected in the FC analyses.
Thus the blue path in Fig. 39 portrays our findings, which postulate that the functional disconnection of PCC from specific prefrontal regions leads to increased FC of OFC with the PCC and ACC through omission of inhibition of PCC on ACC.
This could be an endeavour for compensation of disrupted connections between these regions or it can be understood as a maladaption, as the network-breakdown is a result of failed information processing due to increased FC to OFC.

The red path delineates the possibility of the existence of an unknown interposed region, to which a neuronal path is being established during the disease, mediating the synchronicity of the right OFC with ACC and PCC.

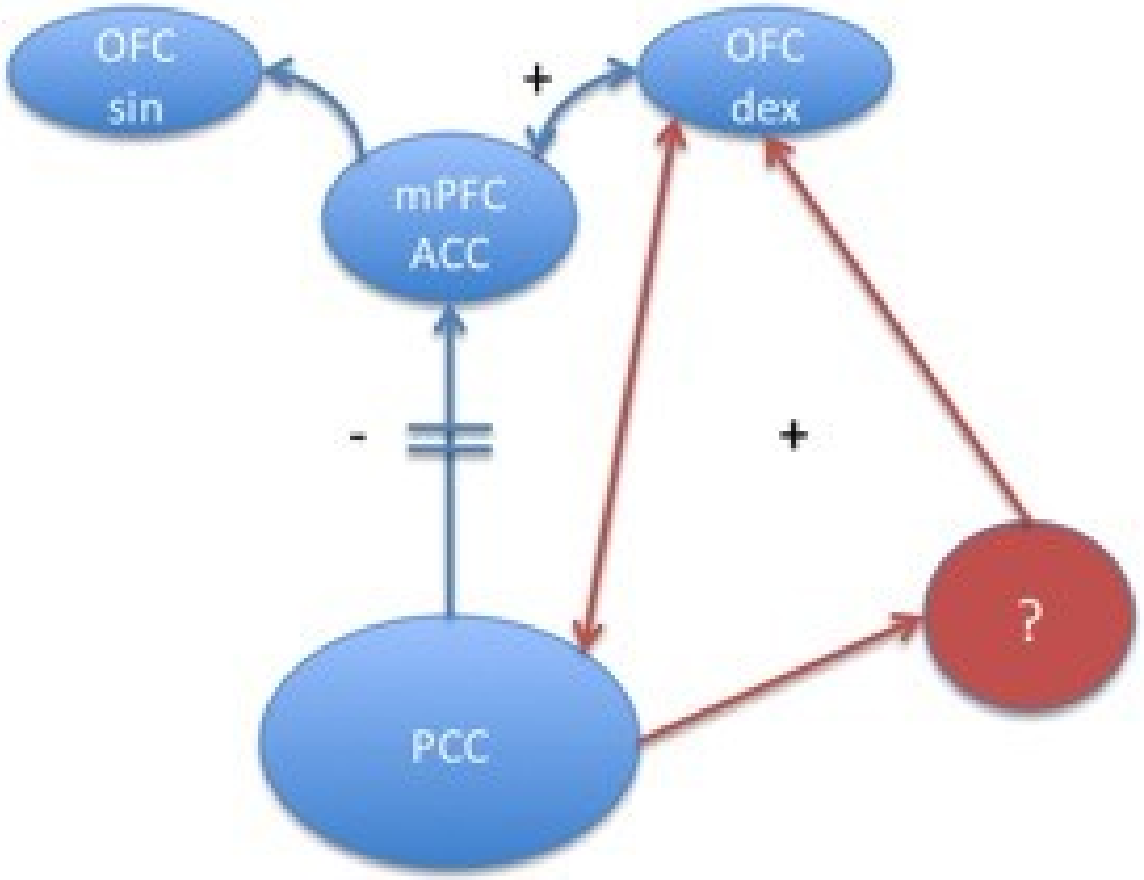

Fig. 37: Two possibilities of synchronized activity of the right OFC with PCC and ACC. OFC = orbitofrontal cortex, PCC = posterior cingulated cortex, mPFC/ACC = medial prefrontal cortex(anterior cingulated cortex

Support for this hypothesis comes from the results of ACC-FC analyses. The mean maps of ACC-FC hint that the functional connections of this area to more posterior parts of the brain decline in the course of the disease. This result, however, is only seen on visual inspection of the mean maps, and has no statistical relevance. Our between-group analyses showed that HC show increased FC to subcortical regions e.g. the putamen and pulvinar compared to mAD and sAD deriving from ACC.
Interestingly, patients with sAD showed increased synchronized ACC activity with regions in immediate proximaty to ACC. Such observations of increased FC in prefrontal regions were also reported in literature (17, 83, 123) interpreting these as compensatory mechanisms of the brain for the forfeit of functional connections in the AD-brain.
Jones et al. observed 3 characteristic, age-related changes of the DMN: 1) the anterior DMN disconnects from posterior DMN with advancing age, 2) the posterior DMN declines in within-network connectivity and 3) the anterior DMN has both decreases and increases in within-network connectivity (128). Further they noted, that the age-related connectivity declines of the posterior DMN are greater in AD patients, and the changes of the anterior DMN in AD patients lose specificity showing diffuse connectivity in the frontal lobe, but no decreases (128).

A question, which still remains unresolved is what effects FC changes evoke, as adaptive as well as maladaptive are conceivable. To explore this question in a clinical setting, a possible approach would be an extensive neuropsychological testing to conclude that increased FC in this manner warrants maintaining the function of the system.

It has been suggested, that different components of the DMN have different cognitive functions; as such explicit self-reference was preferentially engaged the dorsal mPFC, rest alone engaged the precuneus, and self-referential thoughts and rest together engaged the ventral mPFC and PCC (129).
The amyloid plaque distribution (c.f. Fig. 5, p. 8) is similar to that of the DMN (112) and the cardinal symptom of AD is episodic memory loss (16), so it is reasonable to expect the DMN to have an integral role in memory.

The human brain is sub classified into many subtypes of memory systems, depending on its persistence, contents of stored information and the presence of consciousness during learning (130).

Based on the operating characteristics and the type of information, which is processed, all memory systems can be divided into 2 major systems: declarative and non-declarative memory systems.

The declarative memory system refers to memory contents, which are retrieved consciously and is being differentiated into an episodic memory and a semantic memory. The episodic memory stores personally experienced, autobiographical events, the semantic memory system is storing gerenal knowledge of facts and concepts.

The non-declarative memory on the other hand, does not need awareness like the declarative memory system for memory contents, but does need consciousness and it contains other systems like the procedural memory, which forms the basis for automatic functioning skills and is responsible for phenomena like conditioning, simple associative learning and cognitive, perceptual and motoric skills (130, 131).

Another distinguishing feature of memory systems is the temporal aspect, so one may differentiate between long-term memory and short-term memory.

The concept of the working memory by Baddeley & Hitch (131) has prevailed: The working memory system is capable of maintaining and manipulation of present sensory data and retrieved information from long-term-memory. The core of the working memory is the *central executive*, which has access to data of different sensory storages or *slave systems*, like the phonologic loop or the visual-spatial memory (131).

Anatomically the working memory is associated with fronto-temporal regions of the cortex, the declarative memory systems particularly with limbic structures, the medial temporal cortex and the association cortices; procedural memory performances are associated with the basal ganglia and the cerebellum (131, 132).

Despite the anatomical similarities of these memory systems with the topological distribution of the DMN, the exact function of the DMN and its role in memory consolidation is still unclear.

Changes of the DMN have been observed in various other CNS disorders as well, e.g. schizophrenia, the autism spectrum disorder or depression and anxiety (133),

and future work will provide us with a comprehensive view of the function of the DMN.

Donald Hebb suggested that information is sustained in the short term memory by neuronal activity, before it is transferred into the long-term-memory and proposed that memory consolidation is achieved through a growth process, where the reciprocal connections between the neurons are getting stronger (what fires together, wires together) (132, 134).
In our case with the DMN, this hypothesis could be pertained to distinct regions in the brain (e.g. mPFC, PCC, IPL), where the sufficient performance of cognition is dependent on the synchronous activity of these brain regions.

The PCC, as the most metabolically active site (69) as well as obtaining the most efferent and afferent nerve fibres in the brain (84), could play a vital role as a relay station between the different memory systems. As mentioned earlier, the hippocampus is an important structure for cognition and long-term memory, but is not counted directly as a part of the DMN per se in literature (66). Frontal and parietal regions are components of working memory as well of the DMN.
The early desynchronization or functionally disrupted connections of the PCC with the different memory systems could explain partially, besides the corruption of important neuronal networks in vital regions for memory, such as the hippocampus, why AD-patients encounter increasing difficulties retrieving / making information conscious and memorizing new information successfully.

Our results suggest, that the PFC is playing a prominent role in the pathophysiology of AD, as it was observed that AD patients show increased PCC-FC to the right OFC, increased ACC-FC to PFC regions and decreased PCC-FC to mPFC.
Such increases of FC in AD patients are believed to be some kind of compensation in current literature (17, 87, 123).
Further the results suggest, that the functional disconnection is proceeding along the course of the disease, yet it is not possible to what extent the functional deviations occur. The assignment of observing the course of disease with resting-state fMRI over a longer period is of high importance to get to know the dynamics of such a process. Finding the critical point of conversion of MCI to AD and ultimately

recognizing elderly with high risk for developing AD, these network analyses hold great potential in the upcoming fields of research in the future.

Strengths and limitations

The advantages of resting-state studies, such as this one, is the simplicity of the experimental design, there are no complex paradigms necessary to evaluate resting-state-networks. Specifically regarding cognitively impaired individuals for whom it might be more difficult to adhere to a task it is beneficial to follow such an approach.
This study used a seed-based analysis approach, investigating the functional connectivity between the a priori chosen seed-regions (PCC and ACC) and all other brain voxels. The basis of choosing these seed regions lies on previous study findings demonstrating these regions to be affected in individuals with AD compared with control subjects (17, 74, 87, 119). Other studies using model free methods do not require a prior hypothesis and search for all functional connections in the brain (123, 125).
Weaknesses are that seed-based approaches are biased by the selection of the seed-region and functional connections that might be of interest are missed if they do not show connectivity with the chosen seed (136). Model-free methods such as ICA on the other hand do not require a predefined region, but their lack of specificity the results can be hard to interpret (136), as it would be an arbitrary decision what is deemed relevant.
Also the number of subjects in each group was relatively small. The possibility of observing more significant differences between the groups would have been raised, when the group sizes were larger. However, other resting-state studies have had fewer subject group sizes (16, 87, 118, 135).

This study ascertained MMSE scores only. This screening test may not be sufficient enough to fully capture the range of cognitive deficits and to associate the clinical status of the patients with the alterations of their functional connectivity.
Further limitations include possible effects of medications on resting-state networks, for that study waived the taken medications by the Alzheimer-group. For example, a previous study by Lorenzi et al. (137) demonstrated that patients with AD taking memantine showed increased resting-state activity in the precuneus region over 6 months compared with AD-patient not taking memantine.

The brain atrophy, which also characterizes AD was not assessed in this study, which can also confound results due to misregistration, therefore the results should be interpreted with caution, as on Fig. 18 (p.58) activation in the sulcus lateralis was observed.

In a recent study, Damoiseux et al. (127) investigated FC differences between AD patients and healthy controls and found the same areas showing significant changes with and without a voxel-wise grey matter correction, only the clustersize of the areas differed. However, the authors propose that grey matter correction should be included in all fMRI studies including aging population, because grey matter volume differences can also hide functional changes (127).

Conclusion

We here found differences in functional connectivity in healthy controls, with mild AD and patients with more severe AD. The results suggest decreasing functional connectivity between PCC and mPFC, and increased functional connectivity in the frontal lobe. The results should be interpreted with caution and should be checked on their reproducibility.

However, we cannot tell how functional connectivity changes over time in AD, as this study is a cross-sectional one. Longitudinal studies could gain further insights into network changes over time and its association with the disease progression.

With improvements in methodology, functional connectivity MRI promises to be a useful tool for monitoring AD progression.

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