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Early diagnostic of mnestic disorders in neurodegenerative diseases

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Dedicated to my parents

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LIST OF ABBREVIATIONS

AACD – Age-Associated Cognitive Decline

AAMI – Age-Associated Memory Impairment

AD – Alzheimer's Disease

ADCS – Alzheimer Disease Cooperative Study

ADL – Activities of Daily Living

ANCOVA – Analysis of Covariance

ANOVA – Analysis of Variance

ApoE – Apolipoprotein E

APOE – Apolipoprotein E gene

APP – Amyloid Precursor Protein

- **α-sAPP** – Alfa-Secretase-Cleaved Soluble APP
- **β-sAPP** – Beta-Secretase-Cleaved Soluble APP

AVLT – Auditory Verbal Learning Test

Aβ – β-amyloid

Aβ42 – 42 amino acid form of β-amyloid

BDI – Beck Depression Inventory

BNT – Boston Naming Test

BPSD – Behavioural and Psychological Symptoms of Dementia

BSF – Benign Senescence Forgetfulness

BVA – Blue Velvet Arena

BVRT – Benton Visual Retention Test

CDR – Clinical Dementia Rating

CDT – Clock Drawing Test

ChEI – Cholinesterase inhibitor

CFT – Category Fluency Task

CIND – Cognitive Impairment No Dementia

CJD – Creutzfeldt-Jakob Disease

CT – Computerized Tomography

CTF – C-Terminal Fragment

CSF – Cerebro Spinal Fluid

CVLT – California Verbal Learning Test

DAD – Disability Assessment for Dementia

DLB – Dementia with Lewy Bodies

DSM – Diagnostic and Statistical Manual of Mental Disorders

EDR – Elderly Dependency Ratio

EEG – Electroencephalography

FAQ – Functional Activities Questionnaire

FTD – Frontotemporal Dementia

FTLD – Frontotemporal lobar degeneration

fvFTLD – behavioural-dysexecutive (frontal) variant of FTLD

GB's – Grober Buschke's (test)

GDS – Geriatric Depression Scale

HGT – Hidden Goal Task

MCI – Mild Cognitive Impairment

a-MCI – amnestic MCI

a-MCI-sd – amnestic MCI single domain

a-MCI-md – amnestic MCI multiple domain

Ha-MCI – hippocampal amnestic MCI

md-MCI – multiple domain MCI

na-MCI – non amnestic MCI

na-MCI-sd – non amnestic MCI single domain

na-MCI-md – non amnestic MCI multiple domain

NHa-MCI – non-hippocampal amnestic MCI

MIS – Memory Impairment Scale

MMSE – Mini Mental State Examination

MRI – Magnetic Resonance Imaging

fMRI – functional MRI

MRM – Money Road Map

MTL – Medial Temporal Lobe

MWM – Morris Water Maze

NFTs – Neurofibrillary Tangles

NINCDS-ADRDA – National Institute of Neurological, Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association

NMDA – N-Methyl-D-Aspartate

NPI – Neuropsychiatric Inventory

PD – Parkinson's disease

PDD – Parkinson's Disease Dementia

PET – Positron Emission Tomography

FDG-PET – fluorodeoxyglucose PET

PIB – Pittsburgh Compound B

PNFA – Progressive non-fluent aphasia

PS-1 – Presenilin-1

PS-2 – Presenilin-2

P-tau – Phospho tau protein

RCFT – Rey Complex Figure Task

SD – Standard Deviation

SeD – Semantic dementia

SMC – Subjective Memory Complaints

SPECT – Single Photon Emission Computerized Tomography

SPs – Senile Plaques

TMT – Trail Making Test

T-tau – Total tau protein

VD – Vascular Dementia

WAB – Western Aphasia Battery

WCST – Wisconsin Card Sorting Test

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1. INTRODUCTION

1.1. Ageing of population

Ageing of population is a summary term for shifts in the age distribution of a population toward older ages. The population ageing is progressing rapidly mainly in industrialized countries and it is expected to continue over the next few decades, eventually affecting the entire world. The percentage of the world population aged 65 and over was 6.9% in 2000, in Europe the proportion was 14.7% in 2000. For the world as a whole, the elderly will grow from 6.9% of the population in 2000 to a projected 19.3% in 2050. Among the countries classified as more developed, the median age of the population rose from 29.0 in 1950 to 37.3 in 2000, and is forecast to rise to 45.5 by 2050. Population ageing has many important socio-economic and health consequences, including the increase in the elderly dependency ratio (EDR) – the ratio of the elderly dependent population to the economically active (working) population. This ratio had increased from 1:14 in 1950 to 1:4 in 2000 and it is expected to increase in more developed countries to 1:3 in 2030. It is expected that in twenty years the most people in Europe will be over 65 and the average age will be approaching 50.

It is well known that the higher age may be associated with the higher likelihood of memory complaints and the higher prevalence of chronic diseases. The ageing of the world's population means that the number of people with age-related conditions such as memory complaints and dementia, especially Alzheimer's disease (AD), will dramatically increase. The forecast indicate a considerable increase in the number of demented elderly from 25 million in the year 2000 to 63 million in 2030 and to 114 million in 2050.

1.2. Memory complaints

In the last decades a variety of terms has been used to describe memory complaints, which are more common and frequent among seniors, and transitional stages between normal ageing and early dementia. One of the first terms was 'benign senescence forgetfulness' (BSF) (Kral, 1962). BSF was a term, which was proposed in 1962 by a Canadian clinician of

the Czech descent, Vincent Kral, to distinguish memory problems in residents of a nursing home that were benign from those that were malignant (fulfilling dementia criteria) and associated with poor prognosis. The BSF was characterised by an awareness of problems, inability to recall incidental details from the recent past rather than whole events and the 'tip of the tongue phenomenon', with recall some time later. Importantly there had to be no objective evidence of memory dysfunction. BSF was believed to be a variant of normal ageing, but more recent data have cast some doubt on that (Ritchie et Touchon, 2000) and have defined this entity more towards abnormal conditions.

In 1986, a National Institute of Mental Health work group proposed the term, 'age-associated memory impairment' (AAMI). This concept was meant to characterize memory changes in ageing which were felt to be a manifestation of normal cognition (Crook et al., 1986). It refers to persons aged 50 years and older who are experiencing a decline in memory function reflected in everyday life and who perform at least one standard deviation below the mean of younger people on standardized tests of recent memory. The person must be otherwise healthy, with adequate intellectual function and without delirium, depression or dementia, determined by a Mini Mental State Examination (MMSE) score over 23. These criteria compared memory function in older individuals to the performance of younger adults and this was found to be problematical for a wider application of this term (Smith et al, 1991). High numbers of elderly people meet these criteria and only a minority will progress to dementia, so this can not be clasified as a pre-dementia syndrome. Using these criteria the annual incidence of dementia was 1%, which is the same incidence as in the general age-matched population. For that reason the term AAMI should not be probably used as a clinical diagnosis.

The International Psychogeriatric Association and World Health Organization Working Party proposed in 1994 the term, 'age-associated cognitive decline' (AACD) (Levy, 1994) to refer to multiple cognitive domains presumed to decline in normal ageing. Although it sounds similar to AAMI it is distinct in many important aspects. Subjective complaints or informant report of cognitive decline are important and impairment may affect any of the following cognitive domains: memory, attention/concentration, abstraction, language, visuo-spatial, and executive functions. Performance on cognitive testing must be one standard deviation below the mean for an age and education-matched population. Evidence of systemic, psychiatric or neurological disorder is an exclusion criterion and decline is to have been evident for at least 6 months. As with AAMI, the onset must be gradual and dementia is not present. Using these criteria one can identify individuals who are doing badly in relation

to their peers on cognitive tests, but this designation does not imply any defined pathological process. Individuals with sudden onset of problems or those with no insight and no reliable informant would not meet the criterion.

The Canadian Study of Health and Aging has used the term, ‘cognitive impairment no dementia’ (CIND), to characterize cases in which an objectively defined cognitive impairment is proved, but of insufficient severity to constitute dementia (Graham et al., 1997). According to this koncept the memory impairment does not represent an obligatory komponent. Often when it is applied, reference is made to the age and education matched norms. As CIND makes no presumptions about aetiology or progression, it includes a heterogeneous group of patients and therefore it is not very helpful in a clinical context. On the other hand, the lack of restrictive criteria can be useful in epidemiological studies, because the term can be applied to subjects doing poorly on cognitive tests but not clearly fitting into any other category. A disadvantage may be that there are more variations in the application of the term between studies. This concept has been rather heterogeneous with regard to its inclusion of a variety of types of cognitive dysfunction, but more recently it has been refined to correspond more closely to the mild cognitive impairment (Fisk et al., 2003).

1.3. Mild cognitive impairment

1.3.1. The concept of mild cognitive impairment

In recent years an increasing attention has been paid to the mild end of the cognitive spectrum encompassing a transient zone between the normal ageing and dementia, the most frequently represented by AD. This transitional zone has been described using a variety of terms such as dementia prodrome, incipient dementia, prodromal AD, preclinical AD, isolated memory impairment, but the most influential is the term ‘Mild Cognitive Impairment’ (MCI) introduced by Flicker and colleagues (Flicker et al., 1991) and the Mayo Clinic group (Smith et al., 1996; Petersen et al., 1999). The MCI concept has two different aspects. Firstly it presumes that individuals are functioning normally as they age. In a group of persons, particularly in those who are destined to develop AD, there is a decline in cognitive functions, which can be very subtle at first. The aim of this concept is to identify these individuals at the earlier point in the cognitive decline. Secondly it presents MCI as a continuum of cognitive

changes between normal ageing and very early dementia with the overlap in the boundary at the both ends of MCI. It means that the distinction between normal ageing and MCI can be quite subtle as well as between MCI and very early dementia.

The concept of MCI refers to a group of individuals who have some cognitive impairment but of insufficient severity to constitute dementia. These individuals do not meet criteria for dementia due to a very slight degree of functional impairment. Originally the most typical MCI patient had memory impairment beyond what is felt to be normal for age but was relatively intact in other cognitive domains. The Original Mayo criteria (Petersen et al., 1999) were used for making the diagnosis. They were focused on memory impairment with relative preservation of other cognitive domains. These criteria were as follows: 1. memory complaint, preferably corroborated by an informant, 2. objective memory impairment for age, 3. relatively preserved general cognition for age, 4. essentially intact activities of daily living, and 5. not demented. Using these criteria approximately 12% of MCI patients progress to dementia per year (Petersen et Morris, 2003) (incidence rates of normal population are less than 1% per year). In six years 80% of MCI patients convert to dementia and form the at risk population.

Now we will describe each of the criteria. The first criterion refers to the subjective memory complaint. The aim of this criterion is to detect the notion of a change in memory performance. It could be mentioned by a patient, and ideally corroborated by an informant. This criterion is helpful in excluding individuals with lifelong static cognitive deficits (Levy, 1994).

The second criterion refers to objective memory impairment for the age. To fulfil this criterion it is necessary to provide neuropsychological tests. The problem is that there is no specified cut-off score for any test. The cut-off score of 1.5 SD below age norms has been used in the most studies, but some later definitions have allowed for 1.0 SD. Originally in the MCI cohort followed at the Mayo Clinic the MCI group‘s mean performance was 1.5 SD below the peers, it means that nearly half of the group had memory performance score lower than 1.5 SD below the mean, but it was not a cut-off score. Commonly the decision on actual memory impairment remains to the clinical judgment that should be made in the clinical context and in conjunction with the first criterion, which represents a change in a patient’s function. So these two criteria, which are bound together, can not be used separately and this is also valid for the combination of precise medical history from a patient (or an informant) and neuropsychological testing.

The third criterion refers to the essentially preserved general cognitive function for the age. General intellectual function refers to the other non-memory cognitive domains, e.g. language, executive function, visuo-spatial skills, praxis, attention etc. To fulfil this criterion it is very useful to provide neuropsychological tests, but no specific instruments or cut-off scores are predetermined and the final decision is based mainly on the clinical judgement.

The fourth criterion refers to the largely intact functional activities. For the conclusion that the activities of daily living are essentially normal it is necessary to get information about the functional capacity from the subject and preferably from the informant as well. For this purpose we can use several activities of daily living scales, but the degree of impairment is based on the clinical judgement (Grundman et al., 2004). The functional impairment of the daily activities is insufficiently severe to constitute a major disability and it must be solely caused by cognitive impairment, and not by medical comorbidities and physical limitations.

The final criterion refers to the ‚not demented'one. This criterion is also based on the clinical judgement and results from the combination of the previous criteria. To fulfil this criterion there has to be clinically significant cognitive impairment and only slight functional impairment. But in spite of this, it is sometimes difficult to differentiate between the normal ageing (with slight functional impairment caused by medical comorbidities and slight cognitive impairment) and MCI, because the threshold between them is very subtle.

1.3.2. The subtypes of mild cognitive impairment

In the course of time it has become apparent that several clinical subtypes of MCI exist besides amnestic MCI (a-MCI) (Petersen et al., 2001; Grundman et al, 2004). So, the criteria of MCI have been expanded and refined and they include other types of cognitive impairment beyond memory. A second subtype of MCI is called multiple domain MCI (md-MCI). In this subtype there is impairment in multiple cognitive domains such as language, executive function, praxis, attention and visuo-spatial skills with or without memory impairment. Those with a memory impairment (amnesia) are labelled md-MCI + amnestic and those without are labelled md-MCI – amnestic. It is very important to distinguish between these two subtypes, because they have different outcomes. The third, and least common subtype of MCI, is the single non-memory domain MCI. In this type there is an impairment in a single non-memory cognitive domain such as the language, executive function or visuo-spatial skills. Each clinical subtype could be also caused by various aetiologies (degenerative, vascular etc.). The a-MCI subtype the most commonly represents a prodromal form of AD, as

well as the md-MCI + amnestic subtype. The other subtypes with impairments in non-memory domains such as executive function and visuo-spatial skills have a higher probability of progressing to a non-AD dementia such as dementia with Lewy bodies (DLB), frontotemporal dementia (FTD) or vascular dementia (VD). So, the combination of clinical subtypes and presumed aetiologies can be useful in predicting the type of dementia to which these persons will convert.

1.3.3. General criteria for mild cognitive impairment and proposed diagnostic scheme

The next milestone in the concept of MCI was reached in September 2003 in Stockholm, where the First Key Symposium was held. A multidisciplinary and a worldwide group of experts proposed a revision of Petersen's criteria and recommended to set the new General criteria for MCI, where impairment in various cognitive domains (not only memory) was taken into account. The General criteria for MCI were as follows: 1. not normal, not demented (does not meet criteria (DSM IV, ICD 10) for a dementia syndrome), 2. cognitive decline: a) self and/or informant report and impairment on objective cognitive tasks and/or b) evidence of decline over time on objective cognitive tasks, 3. preserved basic activities of daily living, minimally impaired or intact complex instrumental functions.

The setting of the general MCI criteria was followed by proposing the classification process of MCI. So, how to make a diagnosis of MCI in a new patient? The patient or patient's informant expresses concern about patient's cognitive functioning. Based on the history and the mental status examination, the doctor would judge whether the person has normal cognition or suspected dementia. For example, if a patient has a clear impairment in functional activities and scores low on the MMSE, it is likely, that this patient has dementia. On the other hand, if a patient scores high on the MMSE and has no impairments in complex activities of daily living, this person may be normal, despite the subjective complaints. In this case the clinician must exclude depression as a cause of the complaints. Once the clinician has determined that the patient is neither normal nor demented, the next step is to asses a decline in the cognitive functioning. This could be done through a structured history from the patient and the patient's informant. If there is an evidence for decline in cognition, the clinician must then determine whether this change causes a significant impairment in functional activities such that the person would be considered as having a very mild dementia. If the functional impairment is not significant, the clinician may consider the diagnosis of MCI. The next step is to identify the clinical subtype and for this purpose is necessary comprehensive cognitive

testing, using neuropsychological tests (Petersen, 2004). Unfortunately up to now there are no generally accepted instruments for determination of MCI subtypes. However the activities like establishing of Unified Data Set at US memory clinics is a step forward in this way (Morris et al., 2006). First of all it is necessary to assess carefully specific domains of episodic memory with a word list learning procedure or paragraph recall. If the subject's memory is significantly lower than would be expected for their age, the patient is classified as having a-MCI with memory impairment. However, if no memory impairment is present then the patient has non amnestic MCI (na-MCI). The next step is to determine if the patient has an isolated cognitive impairment or not. For that reason the clinician needs to assess other cognitive domains such as language, executive function or visuo-spatial skills to determine if the impairment in a-MCI patient is just memory or whether it involves other domains as well and so is a-MCI-multiple domain (a-MCI-md). If there is assessed only memory impairment with preservation of other cognitive domains, the patient is labelled as a-MCI-single domain (a-MCI-sd). If other domains are impaired besides memory, the patient is labelled as a-MCI-md. Similarly, if memory is not impaired the patient is classified as na-MCI and as a next step the clinician determines if there is either a cognitive impairment in a single non-memory domain (for example an isolated deficit in visuo-spatial skill) and the patient is labelled as na-MCI-single domain (na-MCI-sd) or there is an impairment in multiple non-memory domains and the patient is labelled as na-MCI-multiple domain (na-MCI-md). After the clinical sub-classification is done, the clinician should determine the cause or aetiology of the clinical syndrome. This procedure is the same as the clinicians determine the aetiology of dementia. For example, if there is a suspicion that a patient with amnestic MCI has a degenerative disorder, then this would likely be prodromal AD. Lately the term pre-MCI was introduced to characterise the intraindividual decline of cognition.

1.3.4. The concept of prodromal Alzheimer's disease

This concept was proposed by Dubois (Dubois, 2000) as an alternative to the MCI concept. He claims that as used today, MCI is a syndrome, which is caused by various aetiologies, and to have full clinical usefulness, the underlying aetiology must be determined. The aetiological heterogeneity limits the value of MCI, because the heterogeneity prevents the definition of specific diagnostic criteria for MCI, which must remain sufficiently broad to include disorders of different causes. Further, heterogeneity prevents the development of specific therapeutic approaches because of the large range of possible underlying conditions.

Finally, the heterogeneity makes it difficult to predict clinical progression for any patient with MCI. This concept suggests that it is possible and necessary to identify the underlying pathological disorders before the affected patients meet the criteria of dementia. Particularly the patients with AD, the most important subgroup of patients with MCI, can already be identified before the appearance of the fully developed clinical dementia syndrome. So, the most difficult problem for a clinician should not be to diagnose MCI but rather to detect incipient AD. This is important because there is a high prevalence of memory complaints in the elderly, while only a few of them are at risk of developing dementia and because the treatment for AD might be more efficient in the early stages, before the patients become demented. Therefore AD has no more be restricted to dementia as it can be diagnosed prior to the functional capacity is lost. In the coming future it can be expected that the diagnosis of AD may be established by means of biomarkers in individuals with no change in cognition – i.e. current approach is to diagnose AD without dementia, but the future approach is to diagnose AD without cognitive changes.

So, how to detect the presence of AD in its earliest, predementia stages? For this purpose specific memory tests are used, which are aimed at distinguishing the characteristic pattern of memory disorders associated with the disease. It is well known that impairment in memory recall is crucial for fulfilling the diagnostic criteria for a-MCI, but deficits of free recall are not specific for AD and prodromal AD, because they are common in many disorders causing memory impairment. There are three different underlying mechanisms that cause recall deficits: 1. impaired registration – deficit in the activation of encoding processes, as in disorders of attention due to depression, confusion or drugs; 2. impaired consolidation and storage – genuine memory deficit, where information, although registered, cannot be processed into stable memory traces, as in diseases associated with lesions of the hippocampus, related structures and hippocampo-mamillo-thalamic circuit, such as AD; and 3. impaired retrieval of stored information – deficit in the activation of retrieval processes, as in executive dysfunction due to frontal lobe-related or subcortico-frontal circuit-related dysfunction. If a clinician wants to diagnose a true amnestic syndrome (putative AD), one needs to establish that information has been registered and cannot be retrieved, even with the use of facilitation techniques (cueing or recognition). If the free recall is impaired and associated with a limited effect of cueing on recall (low total recall), many intrusions and false positives on recognition tasks, than this picture is highly suggestive of AD (if effective encoding of information has been previously controlled). This neuropsychological profile of memory deficit is called “amnestic syndrome of the hippocampal type” and it has been shown

in early stages of disease in patients with AD (Tounsi et al., 1999). This profile is in contrast with that seen in depression, where encoding deficits are predominant, and with that seen in FTD, VD, or even normal ageing, where impaired free recall is greatly improved or normalised with cueing or recognition (Fossati et al., 2002; Lavenu et al., 1998; Petersen et al., 1992).

Dubois and colleagues claim that the MCI term is useful because it represents a stage of severity for specific disorders that have not yet reached the dementia threshold, but it must be associated with identification of the important MCI subgroup that leads to AD. They propose that this type should be qualified as “MCI of the Alzheimer type” and they propose clinical diagnostic criteria that have a high specificity for “MCI of the Alzheimer type” or “prodromal AD” or “Hippocampal amnestic MCI” (Dubois et Albert, 2004). The proposed diagnostic criteria for “prodromal AD” or “MCI of Alzheimer-type” or “ Hippocampal amnestic MCI (Ha-MCI)” are as follows: 1. memory complaints by the patient or by the family, 2. progressive onset, 3. normal or mildly impaired complex activities of daily living, 4. amnestic syndrome of the “hippocampal type” defined by: a) very poor free recall despite adequate (and controlled) encoding, b) decreased total recall because of insufficient effect of cueing or impaired recognition, c) numerous intrusions, 5. persistence of memory changes at a subsequent assessment, 6. absence of the fully developed syndrome of dementia, 7. exclusion of other disorders that may cause MCI, with adequate tests, including neuroimaging and other structural, functional and metabolic biomarkers. At this place two terms should also be clarified, intrusions and confabulations. The former is seen in AD and the latter is usually described in Korsakoff syndrome.

1.4. Alzheimer’s disease

1.4.1. Epidemiology

It is estimated that 25 million people in the world have dementia. About 8 – 10 million people in Europe suffer from dementia with an incidence rate 1.5 million new patients every year, which is more than the incidence of stroke, diabetes or breast cancer. The overall prevalence of dementia is equal to 0.3 to 1.0% in individuals aged 60 to 64 years, and increases to 42.3 to 68.3% in individuals aged 95 years and older. The incidence varies from

0.08 to 0.4% in people aged 60 to 64 years, and increases to 4.98 to 13.57% when the population was older than 95 years (Hendrie, 1998). In people under the age of 60 years, dementia is seen relatively rarely, with a prevalence of about 0.008%. Prevalence and incidence rates rise exponentially with age and double every 5 years over the age of 60 (Rocca et al., 1991). More than 85% of dementia cases occur in those aged over 70 years. It is estimated that approximately 50 to 70% of individuals with dementia have AD (Morris, 1994).

1.4.2. Risk factors

1.4.2.1. Age

Age is the number one risk factor for AD. The prevalence and incidence rise exponentially as a function of the age between 65- to 85-year-old range and AD doubles approximately every 5 years in the persons between the ages of 65 and 95 years of age.

1.4.2.2. Family history

One of the most predominant risk factors for AD is a family history of AD. The relative risk is 3.5 if a first-degree relative has AD (van Duijn et al, 1997). The relative risk is higher in those with relatively early onset (at 60 to 69 years of age) (relative risk 5.3), but it is still significant in those with late onset (at greater than 70 years of age). The relative risk increases to 7.5 in persons who have two or more first degree relatives with AD.

1.4.2.3. Chromosomal abnormalities

It has been known for years that patients with trisomy 21 (Down's syndrome) develop AD-like neuropathologic changes after the age of 40. In a very small proportion of AD patients, the condition shows autosomal dominant transmission, with identified mutations in the amyloid precursor protein (APP) gene on chromosome 21, in the presenilin-1 (PS-1) gene on chromosome 14 and in the presenilin-2 (PS-2) gene on chromosome 1. Over 70 mutations capable of producing the clinical and pathological features of AD have so far been identified on these three genes, 60 of them on the PS-1 gene.

1.4.2.4. Apolipoprotein E

An association has been found between AD and the locus of the gene coding apolipoprotein E (ApoE), located on chromosome 19. A particular allele of the gene, the APOE ε4, responsible for the synthesis of the ApoE4 phenotype, is genetically associated not only with familiar (Corder et al., 1993) but also with sporadic forms of the disease (Saunders et al., 1993a). It has been shown that as the number of APOE ε4 alleles (which code for the ApoE4 protein) increases (from 0 to 2), so does the risk of developing the disease. It means that individuals who carry the APOE ε4 allele are three (heterozygotes) to eight (homozygotes) times more likely to develop AD than individuals who do not have the ε4 allele. After age, APOE ε4 allele is the most significant up to date identified genetic risk factor for AD. One of the effects of the ε4 allele is to decrease the age of onset of AD (Corder et al., 1993). It is not yet clear to what extent these genetic associations are reflected in the course, severity, and other clinical aspects of the disease (Bird, 1995). They might increase beta amyloid deposition even in intellectually normal subjects (Berr et al., 1994). The presence of APOE ε4 allele has not a predictive, but a confirmation value in at risk subjects.

1.4.2.5. Gender

The prevalence rates for AD in several studies are significantly higher in women than in men of the same age (Fratiglioni et Rocca, 2001). AD occurs in about twice more women than men. The factors that are responsible for this are unknown. One of the explanations could be an abrupt decline in estrogen production in postmenopausal women or differential longevity of demented women. On the other hand survival to AD is shorter for male patients than for females. It must be considered that women live longer.

1.4.2.6. Head injury

There appears to be a strong link between serious head injury (especially repeated concussions) and future risk of AD.

1.4.2.7. Cardiovascular risk factors

These factors such as high blood pressure, diabetes, hypertension, heart disease, and stroke are believed to be associated with higher increase of AD.

1.4.2.8. Education

The lack of education is generally believed to be a risk factor for AD (Kawas et Katzman, 1999). When uneducated persons are compared with those who have more than 6 years of education, the relative risk is about 2. It is hypothesized that education actually increases the density of neocortical synapses, allowing the accumulation of “reserves” and therefore delaying the appearance of dementia (Katzman, 1993), but not protecting. Paradoxically, there is an increased risk of mortality in AD patients with more advanced educational and occupational attainment. (Stern et al., 1995). It is suggested that this is because lower education is accompanied by an earlier expression and therefore longer survival.

1.4.3. Neuropatology

The degenerative process probably starts 20–30 years before the clinical onset of AD (Wilcock et Esiri, 1982). The typical neuropathological features of AD are extracellular neuritic (senile) plaques (SPs) containing beta amyloid and intraneuronal neurofibrillary tangles (NFTs), formed by paired helical filaments of hyperphosphorylated tau protein, together with synaptic reductions, and neuronal loss. SPs and NFTs do not have the same distribution. SPs involve all the isocortical areas, spare the hippocampus and subcortex except for the amygdala and their density increases with the severity of the disease. They are detectable early in the temporal and frontal lobe. NFTs involve an increasing number of areas in a stereotyped order: entorhinal area, hippocampus-subiculum, multimodal and unimodal association cortices with sparing primary cortices (Braak et Braak, 1991). Confirmation of the diagnosis relies on quantitative (e.g. plaque count) rather than qualitative features. Both plaque and tangle count correlate with the dementia severity, although the best correlation is with the degree of synaptic loss. Significant synaptic loss was found in certain regions of hippocampus mainly in the dentate gyrus (Scheff et al., 1996) and in frontal and temporal cortices (in layers 2, 3, and 5) (DeKosky et Scheff, 1990; Scheff et Price, 1993). Also the

cholinergic nucleus basalis of Meynert (Vogels et al., 1990), noradrenergic locus ceruleus, and serotonergic dorsal raphe nuclei (Aletrino et al., 1993), which have widespread neocortical projections, show significant synaptic loss and loss of neurons that is supposed to cause a loss of synapses throughout its projection zone. Synaptic loss and loss of neurons cause gross atrophy of the brain (Gomes-Isla et al., 1997) that is connected with thinning of cortical ribbon. These findings are the hallmark of AD. Other histopathological features of AD include dystrophic neurons, granulovacuolar degeneration, congophilic angiopathy and Hirano bodies.

Much recent interest has centred on the role of beta amyloid in AD as it was accepted as a main pathological hallmark of the disease (Selkoe, 2002). This is the main constituent of the core of the neuritic plaque and is formed from beta amyloid generated by proteolytic cleavage of its precursor, the APP. Mutations within the APP gene are responsible for some cases of early onset, dominantly inherited AD. Transgenic mouse models with this mutation develop Alzheimer's plaque (but not tangle) histology (Games et al., 1995), which can be prevented by immunisation with beta amyloid 42. The APP gene is over-expressed in Down's syndrome (where AD changes necessarily develop). Beta amyloid deposition also occurs after head injury and may be increased in the presence of APOE ε4. Beta amyloid is metabolized along two pathways. In the nonamyloidogenic pathway, APP is cleaved within the beta amyloid domain by a protease called alfa secretase which results in the release of alfa-secretase-cleaved soluble APP (α-sAPP). APP cleavage within the beta amyloid domain precludes generation of free beta amyloid. In the next step, the 83 amino acid C-terminal fragment (CTF) of APP (C83) is cleaved by the gama secretase complex releasing a shorter peptide called p3. In the amyloidogenic pathway, APP is first cleaved by beta secretase, resulting in the release of beta-secretase-cleaved soluble APP (β-sAPP). In the second step, the 99 amino acid CTF of APP is cleaved by the gama secretase complex releasing free 40- and 42-amino acid beta amyloid peptides. The amyloid deposited in neuritic plagues is predominantly the 42-amino acid form, which has a greater potential to aggregate than the more common 40-amino acid peptide. In AD, intraneuronal accumulation of 42-amino acid beta amyloid is thought to increase phosphorylation of tau, leading to the formation of neurofibrillary tangles, which severely disrupt the microtubule dependent transport system and lead to cell death. Extracellular accumulation of 42-amino acid beta amyloid leads to microglial activation and an inflammatory response that causes neuronal dysfunction and cell death and further impairs brain function. It has to be pointed out that certain amount of non-demented individuals also has amyloid deposits in the brain.

1.4.4. Clinical features

Dementia involves acquired cognitive impairment and behavioural alterations of multiple domains. AD is the typical cortical dementia syndrome. The earliest symptom is usually the insidious onset of declarative memory deficit that is caused by neuropathological changes in medial temporal regions, areas critical for long-term episodic memory (Squire, 1992). Already in the early stages the patients have difficulties with learning of new information due to impairment on the each level of memory processing (encoding, consolidation, storage, and retrieval), but with predominant alteration of memory course. For the early stages of the disease is typical an amnestic syndrome of the hippocampal type, it means, that the information that has been registered cannot be retrieved, even with the use of facilitation techniques (cueing or recognition). The impairment in free recall associated with a limited effect of cueing on recall (i.e. low total recall), many intrusions and false positives on recognition tasks is highly suggestive for AD. Early in the course of the disease the memory impairment is followed by executive dysfunction, which means impairment of problem solving skills, abstract reasoning, and judgement. With executive dysfunction is also connected immediate and working memory impairment, and mild word-finding difficulties. Other presenting cognitive deficits may include impairment of language (comprehension and expression), reading and writing, praxis, visuo-perceptual and visuo-constructive skills and attention. As the disease advances the cognition progressively declines, remote memory is affected as also older memories from the childhood could be lost. Characteristically patients are less aware and concerned about their problems and this loss of insight often means they are not greatly distressed by their condition.

The dementia syndrome in AD is characterised not only by gradual cognitive impairment but also by behavioural and psychological symptoms occurrence. The most common neuropsychiatric feature in AD is apathy (72%), followed by aggression/agitation (60%), anxiety (48%) and depression (48%) (Cummings, 2004). Transient delusions of theft or intruders, often rather vaguely expressed, are also present in demented patients. For these patients is further typical aberant motor behaviour such as pacing and rummaging. In the course of disease sleep disturbances may occur and are often associated with daytime drowsiness. A major component of the dementia syndrome is the decline in every day functional abilities caused by proceeding cognitive impairment. At the beginning the patients have problems with instrumental activities of daily living such as use of devices, shopping, but later they develop problems with basic activities as eating and dressing followed by

hygienic disturbances or failures. With increasing loss of social skills and deterioration in personal habits, the patient becomes totally dependent. Symptoms progressively worsen, usually over 5 to 10 years, but there is great variability in rate of decline and some patients, especially the very old, seem to remain stable for years. The disease probable begins early in adulthood and may last in average 7 to 10 years from the onset of clinical symptoms. Not rarely are described more rapid (5 years) or longer survivals (15 years).

1.4.5. Diagnosis and management

The diagnosis of definite AD can only be made by neuropathological confirmation of persons who had clinical syndrome of dementia. The accuracy of the clinical–pathological correlation has been quite good when standard published criteria for the clinical diagnosis of AD are met (Galasko et al., 1994), but the diagnosis can only be made in terms of probability. If we consider the diagnosis of dementia or AD in a clinic, we can evaluate a typical set of criteria such as those in Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR (APA, 2000). The essential features of these criteria include memory impairment, and one or more of the following: aphasia, apraxia, agnosia, and/or executive dysfunction. In addition, these deficits must include a significant impairment in social or occupational functioning and constitute a change from a previous level of performance. They also need to exclude other psychiatric disorders or neurological explanations for the decline in function. For setting the diagnosis of probable AD are mostly used the National Institute of Neurological, Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984), which do not require evidence of interference with social or occupational functioning but they include the specification that the onset of AD is insidious and that there is a lack of other systemic or brain diseases that may account for the progressive memory and other cognitive deficits. The DSM-IV-TR and NINCDS–ADRDA criteria have been validated against neuropathological gold standards with diagnostic accuracy ranging from 65–96% (Petrovitch et al., 2001). However, the specificity of these diagnostic criteria against other dementias is only 23–88% (Varma et al., 1999). The new proposed revision of the NINCDS-ADRDA criteria (Dubois et al., 2007) is more focused on the prodromal stages of AD and put emphasis on using biomarkers in the diagnostic process. To meet these revised criteria for probable AD, an affected individual must fulfil the core clinical criterion and at least one or more of the supportive biomarker criteria. The core criterion requires presence of early and significant

episodic memory impairment. Supportive biomarker criteria are as follows: Presence of medial temporal lobe (MTL) atrophy, abnormal findings of cerebrospinal fluid biomarkers, specific pattern on functional neuroimaging with PET, and/or proven AD autosomal dominant mutation within the immediate family. These criteria represent a shift toward more biologically focused approaches in the AD diagnostic process.

1.4.5.1. Neuropsychology

The assessment of cognitive functions forms the core of diagnostic evaluation, because the diagnosis of dementia mainly relies on the evidence of cognitive deficits. At first it is necessary to evaluate global cognitive functions. For this purpose are mostly used screening instruments as the MMSE (Folstein et al., 1975) time-sparing test with low sensitivity or the 7-minute test (Solomon et al. 1998). As a second step, specific cognitive domains like memory, executive functions, attention, language and visuo-spatial skills are assessed. Among these domains the memory function should be assessed at first, because episodic memory impairment is required to fulfil the diagnostic criteria for dementia. Patients with AD can be distinguished from non-demented people using word recall, for example in the Auditory Verbal Learning Test (AVLT) (Incalzi et al., 1995) or in the California Verbal Learning Test (CVLT) (Delis et al., 1989). In these tests the AD patients exhibit poor recall, mainly delayed, and a poor learning curve. However, these tests have high sensitivity, but lower specificity in diagnosis of the AD, because subcortical or frontal lobes impairment and emotional states as anxiety or depression have influence on free recall performance. For assuring higher specificity the tests with controlled encoding connected with semantic cueing or recognition are used. The recommended tests, which help in separating retrieval from storage deficits, are the Memory Impairment Scale (MIS) (Buschke et al., 1999) and the ‘5 word’ test (Dubois et al., 2002). Nonverbal memory is assessed by having the patient copy an image and then redraw it from memory as in the Rey Complex Figure Task (RCFT) (Osterrieth, 1944) or in the Benton Visual Retention Test (BVRT). Next, executive functions involving strategy organization, cognitive flexibility and set shifting should be assessed. Measures of executive functions include the following tests: the Wisconsin Card Sorting Test (WCST), the Trail Making Test (TMT), the Tapping test, the Go, no-go task and the Stroop test. Attention is tested by the A test and by the Digit span testing also immediate memory. Further cognitive domain that should be assessed is language comprising fluency, comprehension, repetition, naming, reading, and writing. One of the most complex language tests is the Western Aphasia

Battery (WAB) test, but the tests focused on separate components of language as the Boston Naming Test (BNT) testing confrontation naming, the Category Fluency Task (CFT) and letter fluency tasks (FAS test for example) testing spontaneous speech, but also executive functions, can be used. Visuo-spatial skills are assessed by copying figures such as the intersecting pentagons, copies of three-dimensional figures, such as a cube, and more complex two-dimensional figures. For this purpose are used: the BVRT, the RCFT and the Clock Drawing Test (CDT), which together with the RCFT reflects also executive functions.

1.4.5.2. Activities of daily living (ADL)

We can use different scales for objective measuring of ADL. These scales are based mainly on the interview with the patient and his/her caregiver, and measure basic, or general (such as dressing, eating, etc) and instrumental activities (such as the shopping, using of devices). Frequently used scales include the Alzheimer Disease Cooperative Study (ADCS) ADL Scale (Galasko et al., 1997), Functional Activities Questionnaire (FAQ) (Pfeffer et al., 1982), the Disability Assessment for Dementia (DAD) (Gelinas et al., 1999), and the Clinical Dementia Rating (CDR) (Morris, 1993).

1.4.5.3. Behavioural and psychological symptoms of dementia (BPSD)

The accurate identification of BPSD is essential for management of AD. The presence of these symptoms varies in the course of disease: e.g. apathy, depression and anxiety tend to occur early in the course of AD with delusions, hallucinations and agitation appearing in the moderate to late stages. Several rating instruments have been designed for this purpose, evaluating not only the presence or absence of different symptoms but also their frequency, severity and impact upon the caregiver. They usually rely upon the patient's informant or patient report. Scales that are mostly used include the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), the Geriatric Depression Scale (GDS) (Yesevage et al., 1983), and the Beck Depression Inventory (BDR) (Beck, 1978).

1.4.6. Diagnostic tools

1.4.6.1. Medical history

Is obtained preferably from an independent informant and forms a corner stone of medical practice.

1.4.6.2. Neurological and physical examination

It should be performed on all patients with dementia (Good Practice Point).

1.4.6.3. Neuropsychological examination

The neuropsychological battery should investigate global cognitive functions, memory functions, executive functions and other cognitive domains as mentioned above.

1.4.6.4. Blood tests

Blood tests can exclude the other causes of the cognitive impairment.

1.4.6.5. CT

This technique can exclude the other causes of cognitive impairment (haematoma and hydrocephalus, vascular infractions) and may confirm general brain atrophy.

1.4.6.6. MRI

It is used for the same reason as CT, but it has higher sensitivity and specificity in diagnosis of AD. MRI can detect specific volume reductions of various specific brain regions, but the most emphasis is placed on the MTL and especially on the hippocampus, whose atrophy is an early and specific marker of AD (Killiany et al., 1993; Jack et al., 1992). The overall sensitivity and specificity of MRI volumetry for detection of mild to moderate AD comparing to controls were 85% and 88% (Scheltens et al., 2002).

1.4.6.7. SPECT and PET

These functional imaging techniques can increase the sensitivity in diagnosis of AD. The most often applied functional imaging studies include regional blood flow measurements

performed with SPECT (99mTc-HMPAO or 133Xe) and measurement of glucose metabolism performed with 18F-FDG-PET. A reduction in blood flow or glucose metabolism in parieto-temporal areas is the most commonly described diagnostic criterion for AD (Kogure et al., 2000). The most specific in vitro imaging provides still expensive and not easy accessible Pittsburgh Compound B (PIB) PET imaging.

1.4.6.8. Cerebro spinal fluid (CSF) analysis

Specific biomarkers in CSF, i.e. 42 amino acid form of β-amyloid (Aβ42), total tau (T-tau) and phospho tau (P-tau) proteins, can improve the diagnostic accuracy in patients with suspicion of AD. The sensitivity and specificity of these biomarkers in AD patients comparing to controls is more than 90% (Blennow et Hampel, 2003; Verbeek et al., 2003) and their combination is useful in distinguishing AD from other dementias (Blennow et Hampel, 2003).

1.4.6.9. Genetic testing

Identification of mutations in APP, PS-1 and PS-2 may be useful in determining the autosomal dominant form of AD where cognitive impairment occurs in younger patients and where a family history of AD is positive. A variety of risk genes have been identified and the most carefully studied has been the APOE polymorphism, especially on the APOE ε4 allele.

1.4.6.10. EEG

Generalised slowing of background rhythm is a feature of AD and there is an overall relationship between the severity of dementia and abnormalities on the EEG in AD, but these findings are not specific. Transient epileptic amnesia due to focal temporal lobe seizure activity can imitate AD (Hogh et al., 2002) and the EEG may be diagnostic in this situation. However EEG is generally considered as inefficient and abundant tool.

1.4.7. Treatment

1.4.7.1. Cholinesterase inhibitors

Current treatment options include cholinesterase inhibitors (ChEI), which represent the first class of drugs approved for the specific symptomatic treatment of AD. There are currently available three ChEI - donepezil, galantamin and rivastigmin. Many clinical trials with these substances have established efficacy on cognitive functions and ADL in patients with mild to moderate AD (Tariot et al., 2000). The ChEIs are generally well tolerated, although some gastrointestinal adverse effects may occur and lead to discontinuation of treatment in some patients. The available cholinesterase inhibitors have similar treatment potential, but may differ in the rate of the side effect and individual patient's response. This variability rises from their different pharmacological profile.

1.4.7.2. Memantine

Memantine is a non-competitive N-Methyl-D-Aspartate (NMDA) receptor antagonist, which represents the second class of drugs approved for the specific symptomatic treatment of moderate to severe AD. The compound blocks the chronic hyper-activation of NMDA receptors that is thought to contribute to the symptomatology and pathogenesis of AD. The memantine at six months caused a clinically noticeable reduction in deterioration in patients with moderate to severe AD measured by less functional and cognitive deterioration (Reisberg et al., 2003). Memantine is generally well tolerated and patients taking memantine appeared to be less likely to develop agitation. There is a mayor rationale for combination of ChEI with memantine in moderate dementia as the mechanism of action is different in both groups. There is the evidence suggesting that this combination is well tolerated and can add more value than separate treatment exploring only one mechanism of action (Tariot et al., 2004).

1.4.7.3. Other drugs and interventions

Nowadays, there is insufficient evidence to consider the use of gingko biloba, anti-inflammatory drugs, nootropics, selegiline, oestrogens, vitamin E or statins in the treatment or prevention of AD. Since ChEI and memantine are only symptomatic medicaments, there is a significant effort to develop disease modifying medication. These strategies should interfere with the underlying pathological processes represented mainly by amyloidogenesis and are expected to reduce the progression of AD. Currently available medications only temporarily reduce the rate of decline.

Pharmacotherapy of AD also includes management of neuropsychiatric symptoms. In this field, selective serotonin reuptake inhibitors antidepressants are preferred and atypical neuroleptics are used to cope with agitation, aggression, delusions, or hallucinations. Also non-pharmacological management, including cognitive training, is an undivided part of the treatment approach.

1.4.8. Other dementias

It is apparent that there are also other types of dementia besides the most common one – the AD. As they were not a part of our studies a brief survey will follow.

1.4.8.1. Dementia with Lewy Bodies and Parkinson's Disease Dementia (PDD)

The DLB is the second most common cause of dementia after AD and represents more than 20% of all cases of dementia. Approximately 80% out of Parkinson's disease (PD) patients have cognitive impairment of various intensities, but only some of them develop PDD.

PD and DLB are both neurodegenerative diseases classified as "synucleinopathies" because of the aggregation of α-synuclein protein forming Lewy bodies. A prevailing hypothesis that PDD and DLB represent a continuum of one disease and differ each other mainly by beginning and location of the Lewy bodies deposition was originally proposed by A. Korczyn.

Typical features of DLB include dementia with fluctuating cognition, recurrent visual hallucinations, and spontaneous features of parkinsonism (muscle stiffness, hypokinesia, tremor and postural instability). Disproportionate early visual impairment and visuo-constructive dysfunction are characteristic for this disease. Other features which may occur include REM sleep behaviour disorder, severe neuroleptic sensitivity, repeated falls and syncopes, transient and unexplained loss of consciousness, hallucinations in other modalities, and delusions.

In PD the cognitive impairment is very frequent and typically is represented by executive deficits due to dysfunction of the frontal lobe connections. In the case of development of PDD the clinical picture is similar to DLB as the patients may exhibit fluctuating cognition, visual hallucinations, and spontaneous features of parkinsonism. The difference is that dementia in DLB occurs before the onset of parkinsonian symptoms and

PDD is diagnosed when dementia develops in fully established PD, but at least 12 months after the onset of parkinsonian features.

1.4.8.2. Vascular dementia

Approximately 5-10 % out of all dementia affecting patients over the age 65 has the vascular origin. The pure VD is considered to be relatively rare in comparison to AD. There is, however, an increasing evidence that many patients may in fact suffer from mixed dementia, e.g. coexistent AD and VD or vascular involvement in AD.

The term "vascular dementia" is quite heterogeneous and may refer to following conditions:

1) Involvement of an important ("strategic") brain area, with subsequent cognitive impairment.

2) Multiple lesions (corresponding to the term "multi-infarct dementia") with a sudden onset after a stroke with a fluctuating or stepwise course. The cognitive impairment corresponds to the subcortical profile, and may be accompanied by focal neurologic signs, such as gait disturbance, extrapyramidal features, or incontinence.

3) Binswanger's disease is a histological description of subcortical VD and refers to the development of large and confluent lesions in the white matter in the subcortical regions of the brain. It is manifested by general slowing, forgetfulness and attention or executive functions difficulties.

Besides these "pure" forms of VD, a coincidence of vascular involvement and other primary neurodegenerative dementia (AD in most cases) may be seen, corresponding to the term mixed dementia.

1.4.8.3. Frontotemporal dementia

FTD also referred to as frontotemporal lobar degeneration (FTLD) is the third most common dementia of degenerative origin and accounts for 5-20% of all patients with dementia. The disease onset is usually before 65 years of age.

FTLD is a neurodegenerative disease where atrophy of the frontal and anterior temporal lobes is seen. Based on neuropathological findings and immunohistochemical analysis we can talk about "tauopathies" with intracellular inclusions that contain insoluble τ protein and are therefore τ-positive (Pick's disease) or "ubiquitinopathies" with protein

aggregates that contain ubiquitin and are therefore τ-negative but ubiquitin-positive and which account for approximately 60% of all FTLD cases. If no pathological protein aggregates are found, the term dementia lacking distinctive histopathologic features has been used.

FTLD spectrum in addition to the described entities also includes the progressive supranuclear palsy or corticobasal degeneration.

The dominant features of FTLD are early alteration in personality and social conduct, dysexecutive syndrome, and speech problems. Three main clinical syndromes can be the manifestation of FTLD: 1) behavioural-dysexecutive (frontal) variant (fvFTLD), 2) progressive non-fluent aphasia (PNFA), and 3) semantic dementia (SeD).

1. The fvFTD is the most frequent variant and features by a profound alteration in personality, social conduct, social disinhibition with impulsive and inappropriate behaviour, loss of volition, distractibility, emotional blunting, and loss of empathy and insight. The typical "dysexecutive syndrome" refers to impaired attention, abstraction, planning and problem solving.

2. In the PNFA the non-fluent spontaneous speech is a dominant feature. It is particularly characterized by phonological and grammatical errors (sound-based errors; e.g. "cap" for "cat") and word retrieval problems. Writing and reading difficulties develop as well. In contrast, the word and sentence comprehension is relatively well preserved. In addition to the "telegraphic" speech, drawing may also be very simplistic and organic.

3. In the SeD a severe naming and word comprehension impairment develops, while the speech is fluent and grammatically correct. Also copying, writing, reading, and repetition are relatively spared. An inability to recognize the meaning of visually presented items is characteristic and refers to associative agnosia. Progressive, fluent, empty spontaneous speech, loss of word meaning with impaired naming and comprehension together with semantic paraphasias (semantically related words replace correct nominal terms; e.g. "animal" for "elephant") are typical for this variant.

1.5. Biomarkers of Alzheimer's disease

There is a long asymptomatic period between the first neuropathological and neurophysiological changes in AD and the first appearance of the clinical symptoms. There is the assumption that it is possible to detect the presence of the neurodegenerative process of

AD very early in the course of the disease using specific biomarkers. Biomarker is a characteristic which is objectively measured and evaluated as an indicator to reflect normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention. In other words, a biomarker is an indicator of a particular disease state or a particular state of an organism. The ideal biomarker should detect the main neuropathological changes in AD with high diagnostic sensitivity (more than 80%) and specificity (more than 80%) confirmed by an autopsy. It should be accurate, reliable, reproducible, non-invasive, simple, and cheap and confirmed by at least two independent studies published in journals with impact factor (Thal, 2006). The importance of biomarkers underlines the fact that they are an integral part in the new proposed revision of the NINCDS–ADRDA criteria (Dubois et al., 2007).

1.5.1. Neuroimaging markers

Neuropathological studies show that brain degeneration occurs very early in the course of the disease, even before the first clinical signs, and predominates in certain areas, especially the MTL. Thus, neuroimaging, which comprises structural and also functional neuroimaging, may enable us to visualize these early brain changes in the living subject. If we focus on structural brain imaging, the highest sensitivity and specificity we can reach with MRI. There are several methods how to assess atrophy of the brain and specific brain structures. The first one is a visual inspection using a 4 point scale (0 = no atrophy; 1 = questionable; 2 = mild; 3 = moderate to severe). This method is quick, but is eminently subjective and has poor reliability (Frisoni, 2001). The second more precise method comprises linear measurements for the thickness, height, length, or width between well-identified landmarks, or surface measurements of a region of interest (ROI) drawn on a single predetermined section. A well-known example is “the interuncal distance” (Laakso et al., 1995a) and “the minimum width of the MTL” (Jobst et al., 1992). It is quick, fairly easy, objective, and usually well reproducible, but an estimation of the actual volume of the structure is indirect. Especially, choosing a section “a priori” implies that changes may not be detected in other planes. The last method comprises volume measurements, which are based on delineating the contours of the structure of interest on every section where it is present. With this direct measurement, the volume of the structure can be computed, which seems to be the best way how to assess atrophy. However, it is a particularly time-consuming method, which requires adequate image resolution. It is well known that MTL structures are impaired in early stages of AD and it points to the importance of this brain area in the study of at-risk

subjects. Nevertheless considerable interest has recently also emerged in the study of the neocortex and other nonhippocampal areas in MCI.

1.5.1.1. MRI volumetry in AD

Several studies have repeatedly found significant atrophy of the hippocampal and parahippocampal formation in AD, ranging from 20 to 52% (Mega et al., 2000), and already present at the first stages of AD (Celsis, 2000). Based on these studies it is shown that hippocampal atrophy is a quite good discriminator in separating mild AD from normal ageing, with an overall accuracy ranging from 67 to 100%. Concerning the amygdala, the overall accuracy for amygdala atrophy ranged from 58 to 95%, which would suggest that, amygdala volume is less efficient than hippocampal volume to discriminate mild AD from normal ageing (Laakso et al., 1995b). However, a combination of the amygdala and hippocampal volumes was shown to enhance accuracy, consistent with results suggesting that the volume of the amygdalo- hippocampal complex may be particularly efficient to differentiate mild AD from normal ageing (Pantel et al., 1997). Concerning the entorhinal cortex the results of studies were rather inconsistent. In some studies the entorhinal cortex was the most atrophic structure (Chan et al., 2001; Juottonen et al., 1999) and the entorhinal volume was more efficient for classifying subjects (with 87% accuracy) than the hippocampus, temporo-polar cortex, or perirhinal cortex. On the other hand some (Frisoni et al., 1999) reported a lesser atrophy and lower accuracy for the entorhinal cortex than for the hippocampus (67% vs. 85% accuracy). According to these studies, the measurement of the entire parahippocampal gyrus lacks accuracy, and so its components should be assessed separately. In the same way, isolated measurements of the frontal and lateral temporal cortex have systematically little accuracy, but when add to them volume measurements of the entorhinal cortex, measurements of the temporal neocortex may allow a better classification of mild AD patients and normal ageing, resulting in 100% accuracy (Killiany et al., 2000).

1.5.1.2. MRI volumetry in MCI

Studies on patients with MCI report a significantly lower hippocampal volume in these patients as compared to normal ageing, ranging from 11 to 23% (Convit et al., 1997; Xu et al., 2000; Du et al., 2001). This is in contrast with findings that no significant difference was found for lateral temporal neocortex volumes between patients with cognitive impairments

and normal ageing. Rather inconsistent results were reported for the parahippocampal gyrus, and only a limited number of studies was focused on the entorhinal cortex (Xu et al., 2000; Du et al., 2001). Consistent with histological studies, volume of entorinal cortex was significantly lower in MCI than in normal ageing, similarly (Du et al., 2001) or almost doubly to hippocampus (Xu et al., 2000). Nevertheless, the volume of the hippocampus was found to be more efficient than that of the entorhinal cortex in separating both groups (Du et al. 2001). The hippocampus was also more efficient than other temporal lobe structures to separate MCI subjects from normal ageing (Convit et al., 1997) (overall accuracy of 73%).

1.5.1.3. MRI volumetry in longitudinal studies

Longitudinal studies on at-risk subjects reported significant reduction of parahippocampal gyrus (12%) (Visser et al., 1999), hippocampus (11%) and fusiform gyrus (14%) initial volumes (Convit et al., 2000) in converters to AD compared to nonconverters, while other temporal lobe structures were not significantly atrophied. In MCI patients was found (Jack et al., 1999) that the hippocampal volume was statistically significantly predictive of conversion, the patient group with the most marked hippocampal atrophy had the highest rate of conversion (46% vs. 15% for the group with no atrophy). And later was reported that the annual rate of hippocampal volume loss was higher in converters than in nonconverters (Jack et al., 2000). But some studies (Yamada et al. 1996; Kaye et al., 1997) reported a similar annual rate of hippocampal atrophy for converters and nonconverters, as opposed to temporal lobe atrophy rate, which was higher in converters than in nonconverters.

1.5.1.4. Functional imaging

If we focus on functional imaging, the most used methods are single photon emission computerized tomography (SPECT), positron emission tomography (PET) and functional MRI (fMRI). Studies with SPECT demonstrate hypoperfusion in several brain regions, mainly temporoparietal areas, of patients with AD (Jagust et al., 2001). Reduced cerebral perfusion was also shown in temporoparietal regions, cingulate gyrus, and hippocampus of patients with MCI (Dobert, et al. 2005). Studies with PET demonstrate glucose hypometabolism in several brain areas of patients with AD (Herholz, et al. 2002) and in temporoparietal regions, cingulate gyrus, and also in hippocampus of patients with MCI (Mosconi et al., 2005), where was associated with progressive cognitive decline (Chetelat et

al., 2003). New milestone in functional imaging was reached discovering a specific ligand – PIB that binds to β-amyloid plaques in the brains of living AD subjects (Klunk et al., 2004), mainly in frontal, temporal and parietal regions, which corresponds with postmortem studies. PIB retention was also detected in a group of cognitively intact elderly, who can represent presymptomatic AD (Mintun et al., 2006), and in MCI patients, but where the findings are rather heterogeneous (Price et al., 2005). Studies with fMRI demonstrate decreased activation in the MTL of AD patients during encoding tasks (Rombouts et al., 2000), but on the other hand studies on MCI patients show increased activation of the right parahippocampal gyrus (Dickerson et al., 2004). In some studies was found decreased activation in anterior frontal, prefrontal, precuneus, and posterior cingulate gyri of MCI patients (Rombouts et al., 2005).

1.5.2. CSF biomarkers

The CSF is in direct contact with the extracellular space of the brain, and so biochemical changes in the brain are reflected in the CSF. Because AD pathology is restricted to the brain, CSF is an obvious source of biomarkers for AD. Candidate biomarkers for AD should be a protein, or molecule, reflecting the central pathogenic processes in the brain, i.e. the neuronal degeneration, the aggregation of β-amyloid (Aβ) with subsequent deposition in plaques, and the hyperphosphorylation of tau with subsequent formation of tangles. Up to date three CSF biomarkers, T-tau, Aβ-isoforms, in particular the Aβ42, and different P-tau epitopes, have been found to have the highest diagnostic potential.

1.5.2.1. CSF total tau

An increase in CSF T-tau in AD has been consistently found in numerous studies, with a mean of 3.2 times higher levels in AD than in controls (Blennow et al., 2001). At a specificity level of 90%, the mean sensitivity to discriminate AD from nondemented aged individuals is above 80% (Blennow et al., 2003). In an acute stroke, there is a marked transient increase in CSF T-tau that correlates with infarct size (Hesse et al., 2000). Further, the level of increase in CSF T-tau is highest in disorders with the most intensive neuronal degeneration, such as Creutzfeldt-Jakob disease (CJD) (Otto et al., 1997), while a moderate level of increase is found in AD, with less intense degeneration (Andreasen et al., 1999). Thus, the CSF level of T-tau probably reflects the intensity of the neuronal damage and axonal degeneration. Normal levels of CSF T-tau are found in patients with depression

(Blennow et al., 1995), alcoholic dementia, and in chronic neurological disorders such as PD and progressive supranuclear palsy (Sjögren et al., 2000), so the CSF T-tau assessment could help in the differentiation between these diagnoses and AD. A mild-to-moderate increase in CSF T-tau has been found in FTD in some studies (Green et al., 1999), but not in all. In the studies focused on MCI, high CSF T-tau was found to discriminate MCI patients that later progressed to AD from those that did not progress with 90% sensitivity and 100% specificity (Arai et al., 1997).

1.5.2.2. CSF phospho-tau

There have been found several different phosphorylated epitopes of tau, including threonine 181 + 231, threonine 181, threonine 231 + serine 235, serine 199, threonine 231, and serine 396 + 404. An increased level of P-tau in CSF in AD has been found detecting all these different epitopes. At a specificity of 92%, the mean sensitivity of CSF P-tau to discriminate between AD and nondemented aged individuals is around 80% (Blennow et al., 2003). Interestingly, the specificity of CSF P-tau to differentiate AD from other dementias seems to be higher than for T-tau and Aβ42; increased P-tau has only been found in AD, while normal P-tau levels is not only found in psychiatric disorders such as depression, in chronic neurological disorders such as amyotrophic lateral sclerosis and PD, and in an acute stroke (Hesse et al., 2001), but also in other dementia disorders such as VD, FTD, and DLB (Buerger et al., 2002a; Parnetti et al., 2001). Further, CSF P-tau levels are normal in CJD, despite a very marked increase in T-tau (Riemenschneider et al., 2003), which is together with the high ratio of T-tau/P-tau (mostly more than 10), typical for this disease. Thus, addition of P-tau will increase the specificity of CSF biomarkers in the discrimination between AD and other dementias. These indirect evidences suggest that CSF P-tau is not simply a marker for neuronal damage, like CSF T-tau, but that it specifically reflects the phosphorylation state of tau. CSF P-tau assessment was found useful in patients with preclinical AD, because a marked increase was found in MCI cases that at follow-up had progressed to AD compared with stable MCI cases (Buerger et al., 2002b).

1.5.2.3. CSF total Aβ

Some studies found a slight decrease in the CSF level of total Aβ in AD (van Nostrand et al., 1992), but there was a large overlap between AD patients and controls, and other

researchers found no change in CSF total Aβ in AD (van Gool et al., 1995).

1.5.2.4. CSF Aβ 42 and Aβ 40

Later was discovered that there are several C-terminal forms of Aβ. Focus was set on the longer form ending at Ala-42 (Aβ42), which was found to aggregate more rapidly than Aβ40 (Jarrett et al., 1993), and to be the initial form of Aβ deposited in diffuse plaques, and also the predominating form of Aβ in senile plaques (Iwatsubo et al., 1999). A decrease in CSF-Aβ42 to about 40–50% of control levels has been found in AD in several papers (Blennow et al., 2001). At a specificity level of 90%, the mean sensitivity of CSF-Aβ42 to discriminate between AD and normal ageing is above 85% (Blennow et al., 2003). Normal CSF-Aβ42 is found in psychiatric disorders like depression, and in chronic neurological disorders such as PD, and progressive supranuclear palsy (Sjögren et al., 2000). So, CSF-Aβ42 helps in the clinical differentiation between AD and these diagnoses. It was initially hypothesized that reduced CSF level of Aβ42 in AD is caused by the deposition of Aβ42 in plaques, with lower levels diffusing to CSF, but subsequent studies found a marked reduction in CSF-Aβ42 also in disorders without Aβ plaques, such as CJD, amyotrophic lateral sclerosis, multiple system atrophy, and a mild-to-moderate decrease in CSF-Aβ42 is found in a percentage of patients with FTD and VD (Sjögren et al., 2000). On the contrary, autopsy studies found strong correlations between low Aβ42 in ventricular CSF and high number of plaques in the neocortex and hippocampus (Strozyk et al., 2003), so the reduction in CSF-Aβ42 in AD may at least partly be due to a deposition of Aβ in plaques. Moderately low levels are also found in DLB (Kanemaru et al., 2000), in a disorder which is also characterized by the presence of senile plaques. In studies focused on MCI was found low CSF-Aβ42 together with high CSF T-tau in 90% of MCI cases that later progressed to AD with dementia when compared with 10% of stable MCI cases (Riemenschneider et al., 2002). Moreover a recent population-based study also found that reduced CSF-Aβ42 is present in asymptomatic elderly that during a 3-year follow-up period developed dementia (Skoog et al., 2003). Assessing specific Aβ-isoforms is important, because in contrast to the marked reduction of CSF-Aβ42 in AD, there is no change in CSF-Aβ40 (Kanai et al., 1998). As a consequence, a marked decrease in the ratio of Aβ42/Aβ40 in CSF has been found in AD in several papers (Shoji et al., 1998). The reduction in the CSF-Aβ42/Aβ40 ratio was more marked than the reduction in CSF-Aβ42 (Kanai et al., 1998; Shoji et al., 1998). Preliminary data suggest that the CSF-Aβ42/Aβ40 ratio may be of special use in early AD and MCI cases.

1.5.3. Genetic biomarkers

The genetic research is based on the idea that asymptomatic carriers of AD mutations may be studied in order to improve diagnostic criteria for MCI. The four genes for which the relation to AD is established are the APP, PS-1 and PS-2 genes which are involved in rare autosomal dominant forms of AD, and the APOE, which is a common genetic risk factor for AD. There have been a number of studies of asymptomatic carriers of APP mutations which have been studied in order to characterize MCI and improve its diagnosis (Almkvist et al., 2003), but these studies have been limited by small numbers of carriers and by the fact that mutations in APP are rare. Also PS-1 mutations, the most common cause of autosomal dominant forms of AD are relatively rare occurring in about 0.065% of all patients with AD and this finding makes it difficult to study these mutations with sufficient statistical power, even in multi centre studies (Tol et al., 1999; Almkvist et al., 2003). Another problem is that each of these dominant mutations is usually involved in early onset forms of disease, which makes it difficult to translate the findings to the general population, and that's why screening for each of these mutations will have no value in diagnosing AD and MCI in the general population.

1.5.3.1. Apolipoprotein E

Among the candidate genes most studies have been focused on the APOE ε4 polymorphism. This interest has been grounded in neuropathological studies, which showed that APOE ε4 is related to the earlier presence and greater density of amyloid plaques in patients meeting criteria for AD, and in identification of isoform-specific differences in the binding of ApoE to the microtubule-associated protein T, which forms the paired helical filament and neurofibrillary tangles, and to amyloid β peptide, a major component of the neuritic plaque. Clinical studies have proved the association of APOE ε4 with late-onset AD (Strittmatter et al., 1993). This finding was confirmed in a study with autopsy verified sporadic AD patients, where was found that although the Caucasian control population allele frequency of APOE ε4 was 0.16, that of the AD patients was 0.40 (Saunders et al., 1993b). Some studies have demonstrated a dose effect of the inheritance of APOE ε4 on the distribution of age of onset in familial AD (Corder et al., 1993). Each inherited APOE ε4 increases risk and lowers the distribution of the age of onset and the risk for AD increases from 20 to 90% with increasing numbers of APOE ε4 alleles. It has been shown that the

inheritance of an APOE ε2 allele decreases the risk and increases the mean age of onset. These findings lead to the conclusion that inheritance of the APOE ε4 remains the most clear risk gene for AD (Saunders et al., 1996). The APOE ε4 has been found to be associated with the development of AD among the persons with MCI, it is also associated with amnestic MCI (Petersen et al., 1995), and the increased frequency of the APOE ε4 allele is the strongest predictor of clinical progression from MCI to AD (Petersen et al., 1995). In AD the APOE ε4 carriers show more pronounced atrophy in the MTL structures (Geroldi et al., 1999) compared to non-carriers. Presence of APOE ε4 allele has been associated with smaller hippocampal volume in AD and VD within just 1 year of disease onset (Bigler et al., 2000). PET studies have proved that in MCI patients who are carriers of the APOE ε4 allele is present more extended relative cerebral metabolic rate for glucose reductions than the noncarriers, with a metabolic pattern suggestive of AD, which may reflect the known APOE ε4-related increased vulnerability to dementia. In addition, there is evidence that the APOE ε4 allele leads to greater longitudinal metabolic decline in healthy elderly persons converting to MCI (de Leon et al., 2001). At follow-up and among those subjects who declined to MCI, the APOE ε4 carriers showed marked temporal metabolic reductions.

The problem with genetic testing is that although the APOE ε4 allele is consistently associated with late-onset AD, risks are only moderately increased for APOE ε4 carriers. For this reason, the APOE has been shown to be unsuitable for diagnosis of AD. As MCI is more heterogeneous than AD, APOE or genes with a comparable effect are predicted to be not suitable for MCI diagnosis. Although APOE ε4 status is one of the strongest predictors of progression from MCI to AD, the presence or absence of an APOE ε4 allele itself lacks both sensitivity and specificity for the diagnosis of either AD or MCI. So the information of an individual's APOE genotype of those already symptomatic for dementia may not improve knowledge about the patient's prognosis, but the information about the APOE status of patients with MCI might have the potential to offer insight into the likelihood of conversion to clinical dementia.

1.6. Spatial representation and spatial navigation

The relationship between living organisms and their environment is crucial to assure organism's survival. The ability to move from one place to another allows both animals and

humans to satisfy their needs. Tasks such as foraging or hunting for food, locating shelter, avoiding predators, and remembering dangerous locations all require a reliable system where important elements of the external world, and their relations to each other and to the organism, are represented. This internal model of the environment has been termed a spatial representation, and the behaviour of negotiating a route through the world based on this model is spatial navigation (Healy, 1998). Another description of spatial navigation came from Gallistel (Gallistel, 1990a) where according to his definition the navigation is the process of determining and maintaining a course or trajectory from one place to another. To understand how transitions between places are executed, one must investigate how knowledge of the environment enables organisms to form and execute movement plans. In the first half of the last century most spatial navigation theories were focused on the formation of associations. They claimed that navigation mostly consists of a chain of associations between stimuli, such as features of environment or landmarks, and responses to these stimuli (Hull 1934a; Hull 1934b). In opposition to this view Edward Tolman (Tolman, 1948) demonstrated that rats can acquire internal representations of space. In the Annual Faculty Research Lecture, delivered at the University of California, Berkeley, on March 17, 1947, he outlined a series of experiments the results of which he argued could not be convincingly explained by stimulus–response learning but only by what was termed field theory, the formation of cognitive maps. The next milestone was reached in 1978 when O'Keefe and Nadel published a landmark book: The Hippocampus as a Cognitive Map, where they claimed that not only many species do possess cognitive maps, but that in vertebrates this map may be located in the hippocampus (O'Keefe et Nadel, 1978). Their idea was built mainly on the observation of single neurons in the hippocampus of rats showing spatially selective firing. These neurons, so-called 'place cells', become active only when the animal happens to be in a specific region of the environment called 'firing-field'.

O'Keefe and Nadel proposed that learning to navigate to a place in the environment is based on the two strategies that are dependent on different neural structures (O'Keefe et Nadel, 1978). These two strategies are the taxon navigation and the locale navigation. The taxon navigation involves moving to or from distant landmarks. It includes two processes: the orientation is navigation to individual landmarks while the guidance is a behavioural response to a landmark. The taxon navigation can be then thought of as a sequence of orientations and guidances. In the locale navigation, called also cognitive mapping, the landmarks are used as an ensemble to define a space through which an animal can calculate a path from its current position to a goal position. The positions are not marked by any single landmark but defined

by this ensemble. This ensemble is termed cognitive map as a system encoding information about geometric relationship of landmarks and goals.

Another type of classification was proposed by Mittelstaedt and Mittelstaedt (Mittelstaedt et Mittelstaedt, 1973), who emphasized the importance of the subject's movement and divide navigation strategies into idiothetic orientation and allothetic orientation. In the idiothetic orientation spatial information can be only acquired by means of the subject's active or passive movement and this information originate only from inside of the body. By exclusion, the allothetic orientation refers to any external information yielded by cues whose orientation can change independently of the animal's movement, like the sun or the visual flow caused by air or water or any other stable cue. In the similar way Gallistel (Gallistel, 1990b) defined two processes estimating position and orientation – dead reckoning and piloting. The dead reckoning is a continuous process of determining the change in subject's position by integrating one's movement with respect to time. The piloting is an episodic process of determining one's path to or from unobserved goals by reference to visible landmarks and to a map containing geometric relationship between the goals and landmarks.

The current terminology of the spatial navigation is varied and somewhat confusing, but generally the spatial navigation can be divided into three main categories:

1) Egocentric navigation, with equivalent terms 'response-learning' (Packard et Knowlton, 2002), 'trail-following' (Maguire et al., 1998), 'taxon navigation' (O'Keefe et Nadel, 1978), 'route knowledge' (Siegel et White, 1975), 'procedural representation' (Thorndyke et Hayes-Roth, 1982) and 'non-mapping strategies' (Brandeis et al., 1989)
2) Allocentric navigation, with equivalent terms 'way-finding' (Maguire et Cipolotti, 1998; Hartley et al., 2003), 'locale navigation' (O'Keefe et Nadel, 1978), 'configural knowledge' (Siegel et White, 1975), 'survey representation' (Thorndyke et Hayes-Roth, 1982) and 'mapping strategy' (Brandeis et al., 1989)
3) Path integration, with equivalent terms 'dead reckoning' (Gallistel 1990a) and 'idiothetic' navigation (Mittelstaedt et Mittelstaedt, 1973)

1.6.1. Egocentric navigation

Egocentric navigation uses a coordinate system relative to the body midline, vertical visual meridian, or relative self-movement of the animal's body (body-centred navigation).

This type of navigation requires the presence of some kind of discrete external stimuli (visual, auditory, olfactory or tactile) or concentration gradients.

The simplest form of this navigation type is the taxis, which is a movement towards or away from a stimulus, and which is probably present in all organisms. One type of the taxis is cue guidance, the simple strategy of identifying features or landmarks in the environment and moving toward them. When vision is involved, the landmarks used in such guidance tend to have dominant forms, distinguished by their structure or meaning (Appleyard, 1970). In a simple form, cue guidance may involve pattern or object perception and recognition.

The more developed form of egocentric navigation is taxon navigation (O'Keefe et Nadel, 1978). Taxon navigation describes the information that encodes a sequential record of steps that lead from a starting point, through or nearby landmarks, and finally to a destination. This representation is essentially linear, in that each landmark is coupled to a given instruction (i.e. go right at the big oak), that leads to another landmark and another instruction, repeated until the goal is reached. Indeed, the learning of landmark-instruction paths has been likened to the learning of stimulus-response pairs (Thorndyke, 1981) for example, going from one landmark to another, without knowing the relationship of landmarks. In remembering a route, the overall path may be stored in a series of visual snapshots or scene memories (Gaffan, 1994; King et al., 2004). Such a process may be invoked as a strategy in the absence of spatial mapping (Bohbot, et al., 2004). While more information can be stored along with a learned route-for example, distances, the angles of turns and features along the route (Thorndyke and Hayes-Roth, 1982) – there is an evidence that subjects often encode only the minimal necessary representation (Byrne, 1982). A crucial aspect of this type of navigation is its presumed inflexibility. Because a route encodes only a series of linear instructions the representation is fragile, in that changes in crucial landmarks or detours render the learned path useless.

In the most developed form of egocentric navigation the spatial information is specifically encoded in the form of distances and directions. Through application of a viewpoint-dependent reference system, the egocentric spatial memory involves incorporating body orientation into the spatial representation. Therefore, the egocentric memory provides a vector that can orient a location in the environment with respect to a person’s body. Experimentally it is possible to isolate the egocentric memory from scene memory by requiring participants to remember locations from specific directions while background cues are rotated or removed (Feigenbaum et Morris 2004; King et al., 2004; Parslow et al., 2004).

There is evidence that egocentric information is processed outside of the hippocampal system (O'Keefe et Nadel, 1978), probably involving the parietal cortex and the caudate nucleus. Association of the egocentric processing with the parietal cortex was proved in several studies with rats (McDaniel et al., 1995) and monkeys (Pohl, 1973; Andersen et al., 1993). Furthermore studies of the parietal cortex in monkeys have revealed cells with firing properties that represent the position of stimuli in both retinotopic and head centred co-ordinate spaces simultaneously (i.e. planar gain fields, Andersen et at., 1993). Moreover there is an evidence that neurons in the posterior parietal cortex are involved in the translation among different egocentric representations and between allocentric and egocentric frames of reference (Anderson et al., 1985). In rats there is a strong evidence, that the caudate nucleus (as well as putamen) supports the response learning used in taxon navigation (Packard et Knowlton 2002; White et McDonald 2002).

Activation of the parietal cortex and the caudate nucleus in egocentric navigation was proved in several studies with human subjects using virtual reality tasks. The right inferior parietal cortex was active in the both trail-following and way-finding tasks during navigation in a familiar virtual reality town without any significant difference in activation between them (Maguire et al., 1998). The authors concluded that both tasks had similar egocentric requirements, where the right inferior parietal cortex used egocentric information to compute the correct body turns to enable movement toward the goal and computed the actual heading direction. Moreover the right inferior parietal activation, along with bilateral activation of medial parietal areas was found in comparison between movement tasks and the static scenes task. Authors therefore assumed that medial parietal areas are also involved in the egocentric aspects of movement, mainly in processing the optic flow generated by the movement. In this study activity of the right caudate nucleus correlated with speed of navigation. Another study using virtual reality town setting showed activation of the head of the caudate nucleus while following a fixed familiar route, indicating involvement of caudate nucleus in egocentric navigation (Hartley et al. 2003). The activity of the caudate nucleus was also increased in subjects using non-spatial strategy in a virtual reality analogue of eight-arm radial maze (Iaria et al., 2003). In the case report studies bilateral or unilateral lesions of the right posterior parietal cortex, commonly involving the superior parietal lobule, caused egocentric disorientation, where the patients had severe deficits in representing the relative location of objects with respect to the self (Kase et al., 1977; Stark et al., 1996; Holmes and Horax, 1919; Levine et al., 1985).

1.6.2. Allocentric navigation

Allocentric navigation involves identifying location of the unmarked goal relative to perceptible landmarks and provides a system to determine location of the subject moving around the environment. This type of navigation includes forming of cognitive maps. The term cognitive mapping, derived from Tolman (Tolman, 1948), refers to representing the vectors between different locations or landmarks. Cognitive mapping provides spatial information that allows the distances and directions between locations in the environment to be computed. A cognitive map has image-like properties that allow an individual to plan effective short-cuts and detours and to quickly estimate distances and bearings from any location within the map to any other such location (Peruch et al., 2000). Cognitive maps consist of points, lines, areas surfaces and direction which are learned, experienced and recorded in quantitative and qualitative forms (Garling et Golledge, 2000). The prominent feature of cognitive maps is their flexibility – they include information of routes that have never been traversed (Maguire et al., 1996). But building up the cognitive map requires extensive exploration of the environment (O'Keefe et Nadel, 1978), stability of landmarks and sufficient time to learn. Setting up the cognitive map is relatively slower compared to learning a route, but once the map is established, it can be used in a very flexible manner.

Hypothesis about existence of cognitive map in the rat brain was supported by finding neurons in the rat hippocampal formation with location-specific activity. So called 'place-cells' were firing particularly when the rat was in a relatively small circumscribed part of the experimental arena called 'firing-field' (O'Keefe et Dostrovsky, 1971; O'Keefe et Nadel, 1978). A hypothesis that the hippocampus in rats is involved in cognitive mapping and is a key structure for allocentric navigation was further supported by experiments performed in various mazes, especially in the Morris Water Maze (MWM) (Morris et al., 1981). It has been demonstrated that rats with lesion of hippocampus are not able to find a hidden goal in the water maze when released from different points at the periphery of the pool (Morris et al., 1982). It was further proved that the severity of navigation impairment strongly depends on the location of the hippocampal lesion. Lesions of the dorsal parts of the hippocampus proper disrupt navigation more severely than lesions of the ventral parts (Moser et al., 1993). Several studies support the hypothesis that the hippocampus plays crucial role in spatial navigation and perception in subhuman primates. For example single-unit recordings in the hippocampus in primates has been shown to have location specific neurons that fire when the monkey moves to a certain location in the environment or looks at a specific part of it (Ono et al.,

1993; Matsumura et al., 1999; Rolls, 1999). Allocentric memory may be reliant not just on the hippocampus but also on surrounding or interconnected neuronal structures. For example, lesions of the perforant pathway in rodents cause similar learning deficits on the MWM task to those of hippocampal lesions (Skelton et McNamara, 1992). In addition, lesions to related mnemonic structures, including the lateral septum, medial septum, and fornix in rodents, all lead to deficits in allocentric spatial memory (Kelsey et Landry, 1988; Noonan et al., 1996).

In humans, damage to the hippocampus has also been linked to specific problems in using allocentric information about space (Burgess et al., 1999). Maguire and colleagues (Maguire et al., 1998) investigating navigation in a familiar virtual reality town found the bilateral activation of the hippocampus in successful navigation trials compared to arrows task. Moreover the accuracy of navigation covaried significantly with activation of the right hippocampus. Another study with healthy volunteers was performed in a virtual reality town by Hartley and colleagues (Hartley et al., 2003). In this study accurate navigation in allocentric task activated the right posterior hippocampus and the accurate navigators activated more the anterior hippocampus in the allocentric task than the unsuccessful ones. The most valuable studies are in patients with selective hippocampal lesions. Astur and colleagues (Astur et al, 2002) examined patients with unilateral hippocampal lesion in a virtual MWM task. These patients were found to have severe impairment in spatial navigation task, which was dependent on the use of spatial cues. This effect was evident regardless of side of surgery. On the other hand allocentric navigation was impaired only in patients with right temporal lobectomy including hippocampus in an analogy of the MWM, which was displayed in an over-head view (Feigenbaum and Morris 2004). This finding was supported by Spiers and colleagues (Spiers et al., 2001), who found more serious impairment in right temporal lobectomy patients during navigation in a virtual town. Impairment in allocentric memory was also shown in patients with right hippocampal sclerosis (Abrahams et al., 1999), where the extent of focal hippocampal damage correlated with allocentric spatial memory loss. In concordance with animal studies also in humans allocentric memory may be dependent on the neural structures connected with hippocampus. As in study performed by Aguirre and colleagues (Aguirre et al., 1996), where was demonstrated parahippocampal activity during exploration of a virtual-reality maze. Delayed allocentric memory was impaired in patients after right parahippocampal lesions in a human analogue of MWM (Bohbot et al., 1998). Specifically, the parahippocampus appears to be activated by tasks that involve processing visual scenes or more simple tasks involving attention to landmarks (Aguirre et al., 1996), whereas those that require more complex integration of location

between several areas within a spatial domain tend to activate the hippocampus (Burgess et al., 2001; Maguire et al., 1998). One of the strongest pieces of evidence of the hippocampal and parahippocampal involvement in spatial navigation was reached using in vivo single-cell recording in humans. In this study Ekstrom and colleagues (Ekstrom et al., 2003) recorded place-sensitive neurons from the human hippocampus and parahippocampal cortex in vivo using intracranial electrodes while participants navigated in a virtual town. It is interesting that the place fields were found primarily in the hippocampus whereas cells in the parahippocampal cortex responded more to views of target landmarks. In summary, when memory for spatial relationships is used to build a cognitive map of the environment (O'Keefe et Nadel, 1978), it was found that the hippocampal contribution is necessary.

1.6.3. Path integration

Path integration is a process of recording, storing and integrating the information generated during active or passive locomotion and using it for continuous computation of the homing vector that allows the subject to return from any point on its path to the starting point and also repeat the same path once more (Mittelstaedt et Mittelstaedt, 1973). In other words the term the path integration refers to the updating of position on the basis of velocity, temporal and acceleration information. It involves recognizing an origin and (usually) a destination and identifying route segments, turn angles, and the sequence of segments and angles that make up the desired path. This type of navigation is based on vestibular inputs (from vestibular semicircular canals and vestibular otolithic receptors), inputs from truncal graviceptors and proprioception but it can be updated by involving an azimuthal reference (e.g., the dawn or setting sun, or a mountain range), optic flow and local features of the environment (Tversky, 2000). Using only interoceptive information for computation of the homing vector causes random and systemic errors in path integration, which are accumulating during self-motion mainly after rotations. These errors can usually be corrected by using external landmarks or azimuthal reference during spatial updating (Gallistel, 1990a). Spatial updating is served by a mnemonic component that tracks the outward route and/or the distance and direction of the initial reference point, relative to the individual's current position (Worsley et al., 2001).

There is a wide support for the idea that the hippocampus (McNaughton et al., 1996) is involved in path integration, which has been proved in the studies conducted with animals. These studies have shown that in the hippocampus are located place cells which code position

in space and form a kind of a ‘cognitive map’ of the environment. It was later demonstrated that fimbria-fornix-lesioned rats are impaired in a homing task, which involved returning to the point of departure in darkness (Whishaw et Maaswinkel, 1998). Also the posterior parietal cortex of the rat appears to generate a robust and redundant internal representation of body motion through space (McNaughton et al., 1994). Such a representation could be useful in constructing ‘cognitive maps’ of the environment. The latest studies proved that in the medial entorhinal cortex are located grid cells, which might perform some of the essential underlying computations involved in path integration (McNaughton et al., 2006). The other type of neurons which are involved in path integration besides the place cells and grid cells are the ‘head-direction’ cells (O'Keefe, 1976 Taube et al., 1990a; Taube et al., 1990b). These ‘head-direction’ cells signal head orientation without any reference to location and were found in various structures, including the posterior parietal cortex, retrosplenial cortex, dorsal presubiculum, postsubiculum and anterior thalamus (Muller et al., 1996). McNaughton and colleagues (McNaughton et al., 1996) proposed the concept of neural basis of path integration in the following way: “Hippocampal place cells and the head-direction cells of the dorsal presubiculum, postsubiculum and related neocortical and thalamic areas appear to be part of a preconfigured network that generates an abstract internal representation of two-dimensional space whose metric is self-motion. It appears that viewpoint-specific visual information (e.g. landmarks) becomes secondarily bound to this structure by associative learning. These associations between landmarks and the preconfigured path integrator serve to set the origin for path integration and to correct for cumulative error. In the absence of familiar landmarks, or in darkness without a prior spatial reference, the system appears to adopt an initial reference for path integration independently of external cues.”

A number of researchers (Loomis et al., 1993; Rieser, 1989) have focused on the ability of sighted individuals to navigate without the use of vision in order to investigate path integration in humans. Some of them (Thomson, 1983) showed that humans with eyes closed can reach a previously seen target on the floor several meters away. Other researchers (Rieser, 1989; Loomis et al., 1993) have investigated the ability of persons, with and without vision, to imagine standing at a known location and to indicate by pointing or walking toward, the direction of obscured locations. Accuracy was seen to vary considerably depending on the participant’s familiarity with the test area. Some studies were performed with congenitally blind individuals who were tested against adventitiously blind subjects and blindfolded sighted subjects. However results of these studies were inconsistent, where in some of them

congenitally blind individuals performed worse and in some of them they performed similarly to the other groups. (Rieser et al., 1986; Passini et al., 1990).

Although there is wide support from animal research for the idea that the hippocampus is involved in path integration, there is a paucity of studies examining the process of path integration in humans. In one single paper Worsley and colleagues (Worsley et al., 2001) focused on the role of the left and right temporal lobes (including the hippocampal region) in human path integration in a lobectomy study. In this study the right temporal lesioned group was impaired in the computation of a homing vector and in a route reproduction, where the impairment was only related to errors in estimating the directions but not distances and this impairment did not correlate with the homing vector error. The lesioned group was also not impaired in two additional simple tests that required reproducing a simple turn or simple distance. So the authors concluded that path integration involved a number of key processes, such as establishing an initial reference point, monitoring relevant self-motion inputs, processing self-motion inputs to derive information about distance and direction travelled, and integrating of distance and directional information to derive a homing vector. They suggested that path integration is a discontinuous process in which the homing vector is derived at discrete points in time as the point of return to the start, which is different to continuous process, where the homing vector is derived at every point of the subject's trajectory. One single study had also proved vestibular-hippocampal interactions in humans (Lobel et al., 1996), where after a caloric stimulation of the vestibular apparatus there was shown bilateral activation of the hippocampus.

1.6.4. Spatial navigation impairment in Alzheimer's disease

Patients with AD frequently have difficulties with spatial orientation in everyday activities and may fail to find their way in unfamiliar environments when facing entirely new spatial settings during travelling or shopping. In advanced stages of the disease, they may be disoriented in familiar surroundings within their neighbourhood or even inside their own flat. Spatial disorientation and episodes of getting lost were well documented in outpatients (McShane et al., 1998) and in community-residing patients (Pai et al., 2004) with AD. Different studies explained the disorientation in AD by optic flow discrimination deficit (Tetewsky et Duffy, 1999; O'Brien et al., 2001), poor route navigation (Cherrier et al., 2001), inability to link scenes with locations in the environment (Monacelli et al., 2003) or by impaired allocentric mode of navigation (Kalova et al., 2005; Burgess et al., 2006).

Most studies on spatial disorientation in AD focus on its connection with optic flow discrimination deficit, which possibly reflects posterior parietal cortical dysfunction in integrating multi-sensory cues on self-movement. This theory was documented by a significant correlation of optic flow discrimination thresholds with several measures of spatial navigation. In a test of navigation in a hospital lobby (Tetewsky et Duffy, 1999), poor performance was associated with an elevated optic flow threshold. In contrast, there was no significant correlation between the MMSE score and spatial navigation score. Another study found significant correlation of the optic flow thresholds also with a score in the table-top left-right orientation Money Road Map (MRM) test and the ability to respect lane boundaries during sustained driving in On-the-Road Driving test (O'Brien et al., 2001). In the next study (Kavcic et al., 2006) elderly and AD subjects went through a battery of tests of navigation in a hospital lobby. The AD subjects were impaired in all tests of navigation, with best results in route and location knowledge and with worst results in identifying photo and video location along the route. The total score of navigation in AD subjects correlated significantly with optic flow discrimination thresholds, visual motion evoked potentials and contrast sensitivity, but with none of the memory tests. The authors concluded that navigational impairment in AD is linked to deficit of visual cortical motion processing reflected in specific perceptual and neurophysiological measures.

Also further studies using route learning tests in a hospital lobby are consistent with a theory of perceptual deficit influence on spatial disorientation in AD. In one of these studies (Cherrier et al., 2001) all AD patients got lost during recall of the travelled route on a Route Learning Test. They performed best on recognition of landmarks compared with recognition and recall of spatial layout or recognition of incidental items in the environment. The authors concluded that visuo-spatial attention deficit and poor incidental learning of non-landmark items are important factors for disorientation in AD. Analogous real-world navigational task in the hospital lobby was used in the next study (Monacelli et al., 2003), in which almost all patients with AD had the tendency to become lost. This impairment was not related to memory impairment, but instead, it reflected an inability to link recognized scenes with locations in the environment and to use spatial architectural information. The authors concluded that this may reflect topographic imperception, consistent with visual processing deficits in AD and the topographagnosia commonly attributed to parietal or parietotemporal lesions. Another study (Liu et al., 1991) compared perceptual and higher cognitive spatial skills in AD patients and healthy control subjects with the functional spatial skills in the subjects' own house and in an unknown building. The AD group was impaired in navigation

inside an unknown building but not in their house. This group was also impaired in all cognitive spatial orientation tests and perceptual spatial orientation tests requiring mental representation of shapes, but not in the basic orientation skills. It seems that visuo-spatial deficits seen in early AD, such as getting lost or misplacing objects, are probably due to the impairment of mental shape representation or other higher order processes, rather than to basic visual-perceptual skills.

Only a paucity of studies has shown impairment of allocentric spatial memory, which contributed to successful navigation, in AD patients. Kalova and colleagues (Kalova et al., 2005) examined a group of AD patients in a human analogue of the MWM and on its computer version. They found specific allocentric navigation deficits in AD group in both real space and computer versions of the test together with non-verbal episodic memory impairment. The authors hypothesized that the allocentric navigation impairment is present in the early stages of AD. A single case study (Burgess et al., 2006) reported a patient in the very early stages of AD, who presented with topographical disorientation. This patient had intact recognition memory for unknown buildings, landmarks and outdoor scenes, although she showed impairment in face processing. On the other hand her navigational ability within a virtual reality town was significantly impaired. Moreover there was dissociation between her memory for object locations when tested from a shifted viewpoint compared to when tested from the same viewpoint as at presentation. The authors concluded that the deficit in allocentric spatial memory for the locations of places underlines patient's poor navigation.

1.6.5. Spatial navigation impairment in mild cognitive impairment

Only a few studies have focused on spatial disorientation in MCI and all of them deal with visuoperceptual deficit and its influence on spatial navigation in this group. Visual attention deficits were documented in MCI patients in two studies (Tales et al., 2005b; Tales et al., 2005a). The authors investigated visual search and attention disengagement in amnestic MCI patients and they found deficits in both of them. MCI patients showed significantly increased search time after surrounding the visual search target by distracters and also increased reaction time to invalidly relative to validly cued target. Both the optic flow perception and the visual attention deficits may have negative impact on spatial navigation.

The next study (Mapstone et al., 2003) was focused on the optic flow perception in MCI subjects. In this study, approximately half of the MCI patients were impaired in radial motion perception, suggesting a visuospatial subtype of MCI based on spatial perception. The

motion perception thresholds correlated significantly with the results of the MRM test, requiring subjects to follow a path through a city on a map and indicate left and right turns, but not with figural and verbal memory. However the MCI subjects were not impaired on the MRM test, therefore the study does not document any spatial navigation deficit.

1.6.6. Neural substrate of spatial navigation impairment in MCI and AD

Whereas several studies have described spatial disorientation in patients with AD and MCI, only one of them has been focused on the mechanisms underlying navigation impairment in AD and MCI. The authors of this study (deIpolyi et al., 2007) assessed navigation behaviour in MCI and mild AD patients using a Route-learning Task and correlated selective navigation impairments of these patients to specific patterns of neural atrophy involving the hippocampus and parietal cortex, specific regions playing critical roles in human spatial navigation and being also among the earliest regions damaged by AD. They found that approximately 50% of AD and approximately 25% of MCI patients got lost on the route in the forward direction, compared with less than 10% of controls. Approximately 50% of MCI patients and approximately 75% of mild AD patients got lost on the road in the reverse direction, compared with none of controls. Furthermore, MCI patients performed as poorly as mild AD patients in drawing the route on a map, and both patient groups performed worse than controls. Moreover, AD and MCI patients could not find locations of landmarks on maps or recall the order in which they were encountered, although they were able to recognize landmarks as effectively as controls. Regardless of diagnosis, patients who got lost had lower right posterior hippocampal volume and bilateral inferior parietal volumes, predominantly on the right, than patients and controls who did not get lost. The ability to identify locations of landmarks on a map correlated with right posterior hippocampal volume and bilateral inferior parietal volumes, predominantly on the right, whereas order memory scores correlated with bilateral inferior frontal volumes, particularly on the left, and with left superior frontal volumes. The authors concluded that the navigation disability in AD and MCI involves a selective impairment of spatial cognition and is associated with atrophy of the right lateralized navigation network.

1.7. Morris Water Maze

(Technically, it is not a ‘maze’, since a maze must, by definition, include a network of passages. Nonetheless, the term ‘water task’ and ‘water maze’ are often used interchangeably in the literature and this liberty will also be taken here.)

The MWM was originally developed by Morris (Morris, 1981) as a tool for testing navigation abilities in rats. It consisted of a circular pool filled with opaque water and a small circular platform placed in the centre of one of four quadrants of the pool. In this task the rats were released from different points at the pool periphery and were trained to escape from the pool via platform, which they have to find and climb upon. The platform could stuck out of water and was visible for the rats (cued version of the task), or the platform could be hidden under the water surface and was invisible for them (place version of the task). Further, the position of the platform could be either stable in the coordinate frame of the room or it could be changed quasi-randomly from trial to trial. It was demonstrated that two groups of rats heading toward the visible platform (either in a constant or in a changing location) learn to orient toward it and reach it very quickly. The third group of rats searching for the hidden platform performed with nearly the same efficiency as previous two groups with the visible platform after several days of training, in case the platform location was constant (even if the rats are released from different points at the pool periphery). Furthermore even though the rats were released only from a single start point during all learning trials, they could still orient themselves correctly toward the platform, when they were released from a different point. The fourth group of rats searching for the hidden platform randomly changing its position in the pool could localize it only by random search and their performance was clearly worse than in rats from previous groups. These experiments provided strong evidence that rats could remember spatial relationships between the landmarks outside the pool and the hidden platform. It was also shown that if this relation is broken (in case of invisible platform changing its position) the escape latencies are substantially increased. This test was shown to be strongly dependent on the hippocampal function (Morris et al., 1982), and based on these results the general hippocampal function has been explained. The essential role of the hippocampus in the MWM s task supports the cognitive map theory proposed by O’Keefe and Nadel (O'Keefe et Nadel 1978).

Several researchers tried to use a human analogue of the MWM in order to study the role of hippocampus and adjacent parahippocampus in spatial memory in humans. They used either virtual reality or real space experiments. The virtual analogue of the MWM was used

by Astur and colleagues (Astur et al., 2002) to examine the effect of unilateral hippocampal lesion on navigation in humans. It was a computerized 3-dimensional water pool, where the participants with unilateral hippocampal removals (either left-sided or right-sided) were told to escape from the water as quickly as possible using a joystick to move to a platform which was hidden under the surface of the water. Procedurally, participants started from four different locations as is standardized in animal experiments. As a result they found severe impairment in spatial navigation in both hippocampal groups relative to age-matched controls that was evident regardless of the side of surgery. As the subjects were required to use distal spatial cues to locate the goal, this result suggests the principal role of the hippocampal formation in allocentric memory in humans.

Later Astur and colleagues (Astur et al., 2004) used the same apparatus as in their previous mentioned study to examine the sex differences in humans. In this experiment males swam to the hidden platform significantly more quickly than females, and they spent significantly more of their distance in the training quadrant than did females during the performance on the probe trial. Moreover males tended to use a direct strategy (they swim directly to the platform location), while females preferred strategies that were non-spatial or unclassifiable during the probe trial. Similar male superiority in performance was also shown in rodents (Jacobs et al., 1990).

The side effect of hippocampal lesions on spatial memory was investigated by Feigenbaum and Morris (Feigenbaum et Morris, 2004) on a computerized human analogue of the MWM. The participants were instructed to find a hidden platform by moving their finger around the water pool. Their movements were recorded by a horizontal touch-sensitive screen. In this task egocentric and allocentric memory were tested separately. In the allocentric condition, the participants were instructed to move to different locations around the horizontal monitor between trials, which disrupted the egocentric memory. Only the right unilateral temporal lobectomy subjects were impaired in the allocentric condition, but they had no impairment in the egocentric condition. This result supports the notion that the right hippocampus is involved in long-term storage of map-like representations.

A real space analogue of the MWM was introduced by Bohbot and colleagues (Bohbot et al., 1998), who explored the functioning of patients with focal unilateral right or left hippocampal or parahippocampal thermocoagulation lesions. In this task the participants had to search for an invisible sensor hidden under the carpet of the testing rectangular room using room landmarks. On the first trial the subjects entered from one door and 30 seconds after finding the sensor, they had to enter from another door and find the sensor again. After a 30-

minute delay, they entered the room again to search for the sensor, but this time from the first used door. Impairment was seen in this delayed condition in 3 participants with right parahippocampal lesions, all involving perirhinal damage, with 2 patients having additional damage to the anterior hippocampus. Bohbot and colleagues found that the right parahippocampal cortex was involved in delayed spatial memory without the necessary involvement of the hippocampus. On the other hand patients with lesions of the right hippocampus sparing the parahippocampal cortex could have identified the target location in relation to the view of a single scene.

2. AIMS OF THE THESIS

Our current research has been focused on the spatial navigation impairment in the early stages of AD and other neurodegenerative disorders, mainly in patients with MCI. We tested the hypothesis that the spatial navigation is impaired early in the course of AD and therefore our tests can bring new pieces of knowledge useful for its early diagnosis.

1. The aim of the first study was to characterize spatial navigation deficits in MCI and early AD and to assess how spatial navigation impairment could distinguish the MCI subjects from healthy subjects.

2. The aim of the second study was to explore whether spatial navigation ability could discriminate amnestic MCI patients with encoding and consolidation deficit (hippocampal impairment, potential preclinical AD) from those with isolated retrieval deficit (i.e., non-hippocampal impairment) as suggested in the executive dysfunction hypothesis (Dubois et Albert, 2004).

   Our next goal was to investigate a specific pattern of spatial navigation impairment in patients with hippocampal versus non-hippocampal (frontal lobe) impairment and compare it with spatial navigation impairment of the AD group.

The spatial cognition laboratory currently located in Motol University Hospital was funded by a McDonnell Pew Foundation grant. This grant enabled to create a human analogue of the Morris Water Maze – circular Blue Velvet Arena with computer-controlled orientation cues and a computerized tracking system and for analysis of human navigation behaviour in real life conditions. Also similar computer tests, which could be used by a wider group of physicians, were created.

The previous research was aimed at development of a battery for human spatial navigation testing and assessment of spatial function impairment in patients with temporal epilepsy and AD (Stepankova et al., 2003; Kalova et al., 2005).

3. METHODS

3.1. Subjects in the first study

All subjects were recruited at the Memory Disorders Clinic of the Department of Neurology at the Charles University, 2nd Medical School and Motol University Hospital in Prague and signed standard informed consent. All patients were examined according to a standard protocol and were examined by magnetic resonance imaging, neurological, medical and laboratory evaluation, a semi-structured interview and neuropsychological tests: CDR, ADL, Hachinski Ischemic Scale, GDS, MMSE, CDT, AVLT, 16 words Grober and Buschke's Test (GB's test), BVRT, digit span forward and reversed, Category Fluency and FAS tests, TMT A and B, and ROCF.

Patients were classified into groups (Table 1) based on the results of the psychological tests mentioned above, subjectively reported memory problems, and information provided by the patients' informants:

Table 1. *Demographic characteristics of the groups*

	Control	SMC	na-MCI	a-MCI-sd	a-MCI-md	AD
Men/women	8/18	5/3	5/2	4/7	13/5	5/16
Age	69.4 (1.3)	65.6 (4.0)	70.6 (3.0)	71.7 (2.0)	72.9 (2.4)	75.8 (1.2)
Years of education	15.5 (0.6)	16.4 (0.6)	14.3 (1.1)	15.5 (0.7)	13.9 (0.8)	12.4 (0.7)

Values are mean (SD). SMC, Subjective memory complaints; na-MCI, non-amnestic MCI; a-MCI-sd, amnestic MCI single domain; a-MCI-md, amnestic MCI multiple domain; AD, Alzheimer's disease.

1) Mild to moderate probable AD group (n = 21). Subjects were included when meeting the DSM IV criteria for dementia and NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984). Patients with dementia had an impairment of memory and other cognitive domain. They had their ADL impaired and their CDR was ≥ 1.0.

Table 2. *Neuropsychological characteristics of the groups*

	Control	SMC	na-MCI	a-MCI-sd	a-MCI-md	AD
MMSE score	29.3 (0.9)	29.8 (0.4)	29.0 (1.0)	28.6 (1.5)	27.1 (2.3)	23.1 (4.0)
AVLT1	60.4 (14.5)	61.8 (8.9)	53.4 (9.4)	38.8 (10.9)	32.3 (9.7)	22.7 (5.4)
AVLT30	10.7 (4.1)	12.0 (3.1)	8.4 (2.8)	3.9 (3.6)	1.9 (2.4)	0.4 (0.7)
TMT A	18.4 (4.4)	17.8 (7.0)	21.1 (7.7)	27.5 (31.3)	33.8 (15.0)	42.7 (26.8)
TMT B	76.1 (23.2)	85.8 (25.1)	179.3 (42.8)	100.2 (31.1)	212.4 (106.1)	369.0 (260.3)
FAS	43.2 (10.4)	51.4 (12.9)	41.3 (9.1)	42.0 (12.0)	26.6 (6.3)	26.1 (12.8)
BVRT A errors	3.9 (2.8)	4.0 (1.4)	7.0 (3.2)	6.9 (3.2)	10.8 (4.2)	15.1 (3.1)
BVRT C errors	0.5 (1.2)	0.0 (0.0)	1.2 (1.5)	0.7 (1.1)	2.1 (2.7)	2.8 (2.6)
Digit span	6.4 (1.1)	6.2 (1.3)	5.6 (1.1)	6.4 (1.5)	6.4 (3.5)	5.6 (1.3)
Reversed digit span	4.7 (1.1)	5.2 (1.3)	4.0 (0.8)	5.2 (0.9)	4.1 (1.1)	3.6 (1.4)
Buschke spont.	10.7 (2.4)	9.8 (1.6)	9.0 (2.2)	6.7 (3.0)	4.9 (3.4)	2.2 (1.5)
Buschke total	16.0 (0.0)	16.0 (0.0)	13.3 (6.5)	14.6 (2.3)	13.4 (3.2)	8.7 (3.4)

Values are mean (SD). SD is used here to allow direct comparison of the groups based on the diagnostic criteria. An impairment of at least 1.5 SD from the control group defined the subtypes of MCI. MMSE, Mini-Mental State Examination; ALVT1-6, average of AVLT 1 to 6 words presentation; AVLT30, word recall after 30 minutes; TMT A and B, Trail Making Tests A and B; FAS, Initial Letter Fluency Test; BVRT A and C errors, errors in Benton's Visual Retention Test; Buschke spont., spontaneous (non-cued) recall; Buschke total, total recall after cueing. Further abbreviations are explained in the Table 1.

2) Patients with MCI met the Petersen's criteria (Petersen, 2004) by impairment in at least one cognitive domain (Table 2). They were further classified in the following groups: patients with na-MCI (n = 7) or a-MCI, which included pure a-MCI-sd (n = 11) and a-MCI-md (n = 18). All amnestic MCI patients had memory complaints and scored >1.5 of SD lower than the control group in memory tests, either verbal or non-verbal (verified by AVLT, GB's test or, BVRT). Of the 29 broadly defined amnestic MCI cases, only 11 had pure amnesia (all of the other tests were within the normal range), whereas the rest, labelled as a-MCI-md, further suffered from other subtle semantic and/or attention-executive function deficits (>1.5 SD). Patients with na-MCI had impairment only in the non-memory cognitive domains, manifesting as attentional-executive deficits, language, praxis, or visuo-spatial deficits. These

domains were assessed by other cognitive tests (TMT, digit span, CDT, BNT, FAS, Category fluency, or ROCF). All MCI groups had a normal ADL and a CDR of maximum 0.5 (Morris, 1993).

3) The subjects with Subjective Memory Complaints (SMC) (n = 8) complained about everyday memory problems (any memory, not only spatial) but did not display any objective memory impairment or lower than 1.5 SD, as defined by deviation from results in the control group. These subjects received an overall CDR of 0.5 and had the following characteristics: memory complaints, normal ADL, normal general cognitive function, and no dementia.

4) Subjects in the control group (n = 26) denied having any memory problems, which was confirmed by neuropsychological testing and their CDR was 0.0. These individuals were recruited from relatives of staff and patients. These subjects were selected to have a similar age, education, and sex ratio as the other groups.

The CDR score, central to the categorization of the subjects, was derived from the semi-structured interview administered to each subject and the subject's collateral source (Morris, 1993). All subjects completed the GDS and were excluded if they scored >5 points. The Hachinski scale was up to 4 points. Unlike MCI and SMC, all patients with AD were treated by cholinesterase inhibitors.

3.2. Subjects in the second study

All subjects were recruited at the Memory Disorders Clinic of the Department of Neurology at the Charles University, 2nd Medical School and Motol University Hospital in Prague and signed an informed consent approved by the local ethics committee. They underwent standard protocol and were examined by magnetic resonance imaging, neurological, medical and laboratory evaluation, and the following clinical assessment: CDR (Morris, 1993), ADL (Galasko et al., 2005) where scores had to be in normal range (range 95-100/100) in MCI patients and participants from the control group, Hachinski Ischemic Score where participants scoring more than 4 points were excluded, and 15-item GDS (Yesavage, 1988) where participants scoring more than 5 points were excluded.

We used the same neuropsychological battery as in the first study and we put emphasis on the new verbal memory test – 16–item version Grober and Buschke's test with enhanced cued recall procedure (Grober et Buschke, 1987). GB's test was administered to distinguish

encoding/consolidation impairment from isolated retrieval deficit. This test is described in detail below in the text.

Patients were classified based on the results of the tests mentioned above, subjectively reported memory complaints, and information provided by the patients' informants into the following three categories:

1. *The mild probable AD group*: Met the Diagnostic and Statistical Manual of Mental Disorders IV criteria for dementia and the NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984). Patients with dementia had an impairment of memory and another cognitive domain, impaired functional activities, and their CDR was 1.0 or higher. All AD patients were treated by cholinesterase inhibitors. This group included 21 participants, 4 men and 17 women. The age ranged from 66 to 87 years and the mean age was 76 years. The years of education ranged from 8 to 19 years and the mean was 12 years. The MMSE ranged from 19 to 26 and the mean was 23.

2. *The MCI group*: Met the revised Petersen's criteria for MCI (Petersen, 2004). The participants had cognitive complaints, were impaired on objective cognitive tasks, were not normal for age, not demented, and they had intact functional activities with a maximum CDR of 0.5 (Morris, 1993). This group included 52 participants, 30 men and 22 women. The age ranged from 50 to 87 years and the mean age was 74.5 years. The years of education ranged from 9 to 22 years and the mean was 14 years. The MMSE ranged from 21 to 30 and the mean was 27.5.

The MCI patients were further classified into the following groups: patients with na-MCI (n=10) or a-MCI (n=42). All a-MCI patients had memory complaints and scored more than 1.5 of standard deviation (S.D.) lower than the control group in memory tests, either verbal or non-verbal (verified by AVLT, GB's test or BVRT). Patients with na-MCI had impairment only in the non-memory cognitive domains, manifesting as attentional-executive deficit, language or visuo-spatial deficits as assessed by the neuropsychological tests mentioned above. The na-MCI group included 10 participants, 6 men and 4 women. The age ranged from 54 to 85 years and the mean age was 72 years. The years of education ranged from 11 to 18 years and the mean was 15 years. The MMSE ranged from 27 to 30 and the mean was 28.

All a-MCI patients were subsequently classified according to Dubois's criteria (Dubois et Albert, 2004) using GB's test into the hippocampal a-MCI group (Ha-MCI; n=10) and the non-hippocampal a-MCI group (NHa-MCI; n=32). The Ha-MCI group had very poor free recall despite adequate (and controlled) encoding and decreased total recall because of

insufficient effect of cueing (less than 10 of 16 words, or 10 to 14 of 16 words with more than 30% recalled spontaneously) in the GB's test. This group included 10 participants, 6 men and 4 women. The age ranged from 51 to 87 years and the mean age was 77 years. The years of education ranged from 9 to 18 years and the mean was 13.5 years. The MMSE ranged from 21 to 30 and the mean was 26. The NHa-MCI group had impaired free recall in AVLT and the GB's test with great improvement (10 to 14 of 16 words with 30% or less recalled spontaneously) or normalization (15 to 16 of 16 words) with cueing in the GB's test. This group included 32 participants, 18 men and 14 women. The age ranged from 50 to 86 years and the mean age was 72.5 years. The years of education ranged from 9 to 22 years and the mean was 14 years. The MMSE ranged from 25 to 30 and the mean was 27.5.

3. *The control group:* Reported no cognitive problems, which was subsequently confirmed by neuropsychological testing and a CDR score of 0.0. They were recruited from staff and patient's relatives and were selected to be as similar as possible to the other groups in age, education and gender. This group included 28 participants, 8 men and 20 women. The age ranged from 52 to 82 years and the mean age was 69 years. The years of education ranged from 10 to 22 years and the mean was 15.5 years. The MMSE ranged from 27 to 30 and the mean was 29.

Table 3. *Basic characteristics of the groups (mean ± S.D.)*

	Controls	na-MCI	NHa-MCI	Ha-MCI	AD	P-Value[a]	P-Value MCI[b]
Characteristics	(N=28)	(N=10)	(N=32)	(N=10)	(N=21)		
Gender (male/female)	8/20	6/4	18/14	6/4	4/17	0.02	N.S.
Age (years)	68.9 ± 7.2	72.0 ± 7.9	72.7 ± 9.2	77.3 ± 10.8	75.9 ± 5.6	0.02	N.S.
Education (years)	15.5 ± 3.0	14.7 ± 2.8	14.3 ± 3.3	13.6 ± 3.5	12.3 ± 3.3	0.02	N.S.
MMSE score	29.3 ± 0.9	27.9 ± 2.3	27.6 ± 1.5	26.2 ± 3.0	23.1 ± 3.7	<0.001	N.S.

[a] *P-Value indicates the level of significance in the differences among all groups.*

[b] *P-Value MCI indicates the level of significance in the differences only among the MCI groups.*

The basic characteristics of the groups are summarized in Table 3. The groups differed in age ($F[4,95] = 3.147$, $p=0.018$), years of education ($F[4,95] = 3.076$, $p=0.020$), gender (Chi-square [4] =11.531, $p=0.021$) and MMSE ($F[4,95] = 17.583$, $p<0.001$). The MCI groups did

not differ in age, years of education, gender or MMSE (F[2,49] <2.200, p>0.120 in all analyses). The detailed neuropsychological characteristics of the groups are presented in Table 4.

Table 4. *Neuropsychological characteristics of the groups (mean ± S.D.)*

Tests	Controls (N=28)	na-MCI (N=10)	NHa-MCI (N=32)	Ha-MCI (N=10)	AD (N=21)
GDS	1.3 ± 2.1	3.6 ± 2.9	4.4 ± 3.5	3.1 ± 3.1	3.1 ± 3.0
AVLT	61.2 ± 14.3	53.4 ± 9.0	37.0 ± 10.2	29.9 ± 8.8	24.6 ± 7.3
TMT A	18.0 ± 4.5	21.1 ± 7.4	28.19 ± 13.2	27.1 ± 12.8	43.6 ± 26.4
TMT B	74.8 ± 22.8	179.3 ± 41.1	162.0 ± 75.5	223.0 ± 118.1	369.9 ± 252.7
FAS	43.2 ± 9.9	41.3 ± 8.8	31.9 ± 8.5	32.0 ± 12.5	25.9 ± 11.8
BVRT A errors	3.8 ± 2.7	7.0 ± 3.0	9.6 ± 4.2	10.8 ± 4.3	14.9 ± 3.7
BVRT C errors	0.5 ± 1.2	1.7 ±1.4	1.8 ± 2.6	1.6 ± 0.8	2.9 ±2.7
Forward DS	6.5 ± 1.1	5.6 ± 1.1	6.4 ± 2.8	6.3 ± 1.1	5.6 ± 1.3
Reversed DS	4.7 ± 1.1	4.0 ± 0.8	4.5 ± 1.0	4.1 ± 0.9	3.6 ± 1.3
GB's free	10.8 ± 2.3	9.0 ± 2.1	6.1 ± 2.9	2.8 ±2.3	2.7 ± 2.7
GB's total	16.0 ± 0.0	16.0 ± 0.0	15.4 ± 1.2	9.7 ± 2.3	8.9 ± 3.8

GDS, Geriatric Depression Scale; AVLT, Auditory Verbal Learning Test; TMT A and B, Trail Making Tests A and B; FAS, Initial Letter Fluency Test; BVRT A and B, Benton Visual Retention Tests A and B; DS, Digit Span; GB's free, *Grober and Buschke's Test with 16 verbal items - spontaneous (non-cued) recall;* GB's *tot., total recall after cueing.*

3.2.1. 16–item version Grober and Buschke's Test

This test is a part of the 7 minute neurocognitive screening battery [52] and consists of 16 items presented on four individual cards (four items per card). While displaying the first card, a semantic cue is given by the examiner and the subject is asked to identify the picture on the card that best fits with the cue. (e.g., question: "There is a bird on this page, what is it?" answer: "An eagle."). When the patient successfully identifies all four items, the examiner removes the card from view and immediately tests the subject's recall by again providing the cue and asking the patient to recall the item (eg, "There was a bird on this page, what was

it?"). After all four cards are presented the subject is distracted and is then asked to recall as many of the items as possible without providing any cues. When the patient cannot recall any additional items, appropriate cues for the remaining items are provided (e.g., "There was a bird on this page, what was it?"). The scores for this test are the free–items remembered in uncued recall and total recall–total number of items remembered in both the uncued and cued recall, with a maximum score of 16. This test takes advantage of the finding that subjects with frontal lobe impairment benefit from mnemonic strategies that facilitate the retrieval of information (e.g., reminder cues), whereas patients with Ha-MCI show significantly less benefit from these strategies (Dubois, 2004).

3.3. Hidden Goal Task

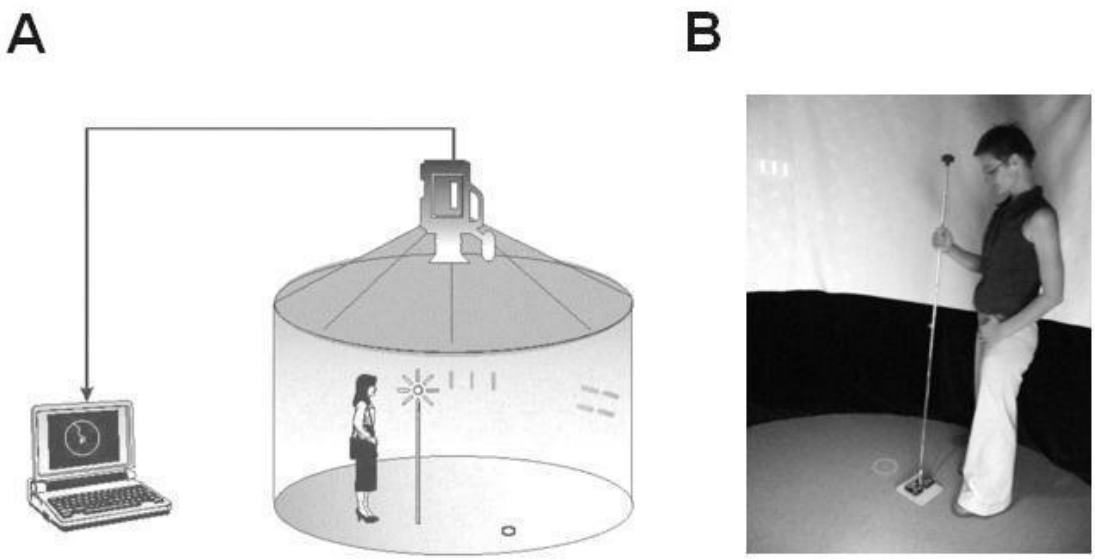
The Hidden Goal Task (HGT) is a human analogue of the MWM (Kalova et al., 2005). It is designed to separate two different modes of navigation, allocentric and egocentric, using a real space navigation setting called the Blue Velvet Arena (BVA) (Figure 1A and 1B) (Stepankova et al., 2003; Kalova, et al., 2005), as well as a computer-based imitation of the BVA (Figure 2A) (Kalova et al., 2005).

The task of the subjects was to locate an invisible goal in four different subtests using start position and/or two orientation cues (Figure 2B). Each subtest consisted of eight virtual trials on the computer screen followed by eight real-space trials, with the exception of the delayed subtest, which consisted of only two virtual and two real-space trials. The location of the goal was revealed after each trial and feedback was provided after each trial in all subtests but the delayed subtests. There was no time limit to locate the goal. The relative position of the goal, start position and orientation cues was stable across all trials of all subtests, and in the individual trials of each subtest the whole configuration only assumed eight equally spaced rotations around the arena in a fixed order.

The first 'allo-ego' subtest (allocentric + egocentric) involved locating the goal using its spatial relationship with both start position and the two orientation cues. The second 'ego' subtest (egocentric) involved using only the start position to locate the goal with no orientation cues displayed. The third 'allo' subtest (allocentric) involved using two orientation cues at the arena walls for navigation with the start position unrelated to the goal position. Only the cues-goal configuration remained the same during all trials, so the subject could not

use the starting position for navigation. The shifting of the two cues and of the goal to the new positions in the each trial with the same cue-goal configuration remained the same as in the first subtest. The starting position shifted randomly and independently of this configuration. The fourth 'delayed' subtest involved the same design as the allo subtest but was administered thirty minutes after the end of the allo subtest. During this delay, other tests from our spatial navigation battery were administered in standardized order. In this delayed subtest, the correct goal position was not shown so as to prevent the subjects from learning.

Figure 1. *Blue Velvet Arena*

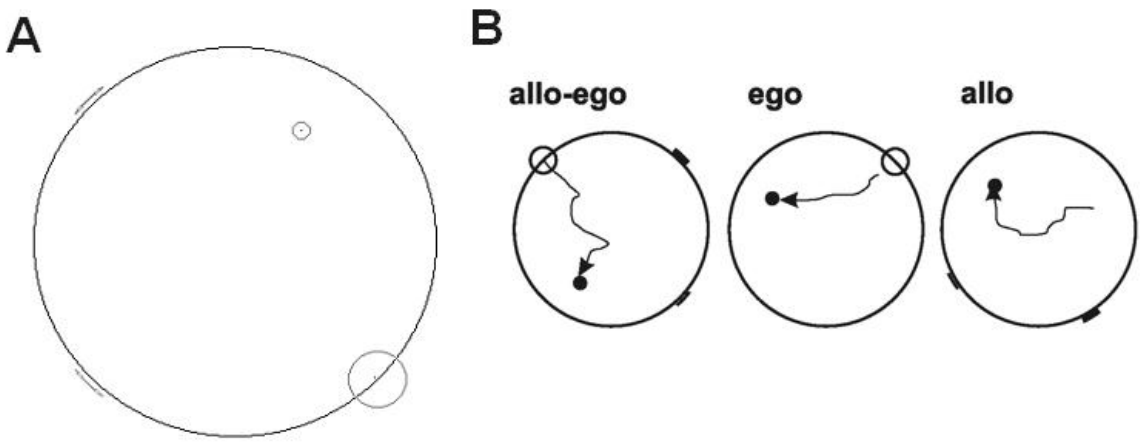


The Blue Velvet Arena. (A) In-scale diagram of the real space testing environment. (B) Subject examination in the Blue Velvet Arena.

The real space navigation setting called the Blue Velvet Arena (BVA) (Figure 1A and 1B), which was funded by a McDonnell Pew Foundation grant, is an apparatus designed for testing of human navigation behaviour in real life conditions (Kalova et al., 2005; Stepankova et al., 2003). It consisted of a fully enclosed cylindrical arena 2.9 meters in diameter surrounded by a 2.8 meter high dark blue velvet curtain. A television (TV) camera above the center of the arena was connected to a computerized tracking system and it enabled recording of the position of an infrared light-emitting diode (LED) on the top of a standing pole (1.6 meters high). This pole was used by the subject to indicate a position of the goal on the floor. Eight large digital numerical displays with light patterns of two horizontal or three vertical

short lines were used as the orientation cues. Depending on the subtest two or none of them were turned on, the rest of them was invisible to the subject. These displays were placed at 45° intervals on the arena wall 1.5 meters above the floor. The red decimal point sign on the numerical display indicated the start location. The horizontal and vertical bars together with the single decimal point sign were controlled by the computer. The goal was a twelve-centimeter circle of laser light on the arena floor, which was created by turning on the appropriate one of eight laser pointers placed at 45° intervals mounted on the ceiling of the arena.

Figure 2. *Hidden Goal Task*



The Hidden Goal Task. (A) The view of the centre of the computer screen before the first trial of the test allo-ego, showing the goal position (the smallest circle with the dot inside), the start position (the middle-size circle) and the cues (red and green on the computer screen). The largest circle represents the arena. (B) The scheme of the individual subtests. The task was to navigate to a goal (small circle) inside of a circular arena. The invisible goal could be identified either by its position relative to the start (larger circle) as in the ego subtest, relative to two landmarks (short lines on the border of the arena) as in the allo subtest, or relative to both start and landmarks as in the first subtest allo-ego.

The computer version of the test was performed on a 17” LCD monitor (640x480 pixel screen) where a large circle (280 pixels in diameter) represented an overhead map-like view of the arena (Figure 2A). The starting point was indicated by a red circular mark on the arena contour, the orientation cues by a red and green mark on the arena contour, and the goal by a

small red circle inside the arena. The spatial relationship between the start, two cues and the goal was demonstrated to the subjects at the beginning of the test and the subjects were instructed to remember the location of the goal (Figure 2A). Then, the goal disappeared and the subjects had to indicate it moving a mouse pointer from the start to its supposed position. After that the correct position was shown and the subject was again encouraged to notice the position of the goal relative to the start and cues. Then a new trial was started while the positions of the goal, two cues and start shifted turning around the arena center by a multiple of 45° in a pseudo-random order. There were eight trials in each subtest. The position of the goal changed from trial to trial, but the start-cues-goal configuration remained the same during all trials. There was no time limit to locate the goal. The virtual subtest was completed after eight trials and was followed by the real space version in the BVA.

In the real space version, the starting position was marked by a small red decimal point sign on the arena wall and two orientation cues were shown as two and three short lines on the arena wall, 1.5 meters above the floor, as described above. The subjects were instructed that the relative positions of the hidden goal, starting position and the two cues were the same as in the preceding computer version. The subjects were asked to take the long standing pole and go to the starting position. Then the cues were turned on and the subject should go to the goal and place the long pole at the presumed goal location on the arena floor. After the subject placed the pole, the correct location was shown as a small red circle on the arena floor. Than the subject was instructed to place the pole at this location and was encouraged to notice the position of the goal relative to the start and cues. The goal was subsequently turned off, the start and the cues were shifted to the new positions and the subject was instructed to go to the new start position and proceed with the test. There were eight trials in each subtest with the same start-cue-goal configuration, but in eight different positions. The change of the physical location of the start, two cues and the goal from trial to trial guaranteed that the subject could only use the start location or the positions of orientation cues to locate the goal. The experimental room was quiet and the subject listened to instructions through wireless headphones. There was no time limit to locate the goal. After the eighth trial of the first real subtest was completed, the examination continued with the computer and real versions of the second subtest followed similarly by the third and fourth subtests.

3.4. Data analysis in the first study

Original software created in MS-DOS Quick-Basic was used to track the LED-diode position during the test and to control the cues and starting point signs position in the arena. For analysis, the diameters of the real and computer circular arena were divided into 280 pixel units to enable direct comparison of errors made by the subjects.

Several measures of the subject performance were used. The distance errors, in pixels, between the subject's choice and the correct goal location were used in most of the analysis (marked as 'distance error'). The navigational strategies were analyzed using two other measures. The first one (marked 'correct side') estimated whether the subject knew at least the approximate location of the goal. The arena was divided into two equal parts by a line going through the start position in the ego subtest or by a line going in the middle between the two cues in the allo and delayed subtest. The measure was then computed as the number of positions given by the subject that were lying in the same half of the arena as the goal. The second measure (marked 'side error') was used to estimate how much confusion of the side of the arena contributed to the error in estimating the goal position. The sides of the arena were determined as in the previous measure. The measure was then computed as the distance between the position given by the subject and the goal position, but regardless of the side. The first allo-ego subtest was excluded from this analysis, because the side of the arena that should be taken as reference was ambiguous.

Analysis of covariance (ANCOVA) was used to evaluate the group differences, controlling for the effect of covariates sex, years of education and age. Simple contrasts with control and AD as reference groups were used to compare individual groups. The group differences in the correct side measure were evaluated by the Mann-Whitney U test. The significance level used throughout the analysis was 0.05. All statistical analysis was run using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL).

3.5. Data analysis in the second study

The distance between the subject's choice and the correct goal location measured in pixels was used in the analysis as the measure of the navigational accuracy, averaged across all eight trials of each of the subtests. One-way analysis of variance (ANOVA) was used to

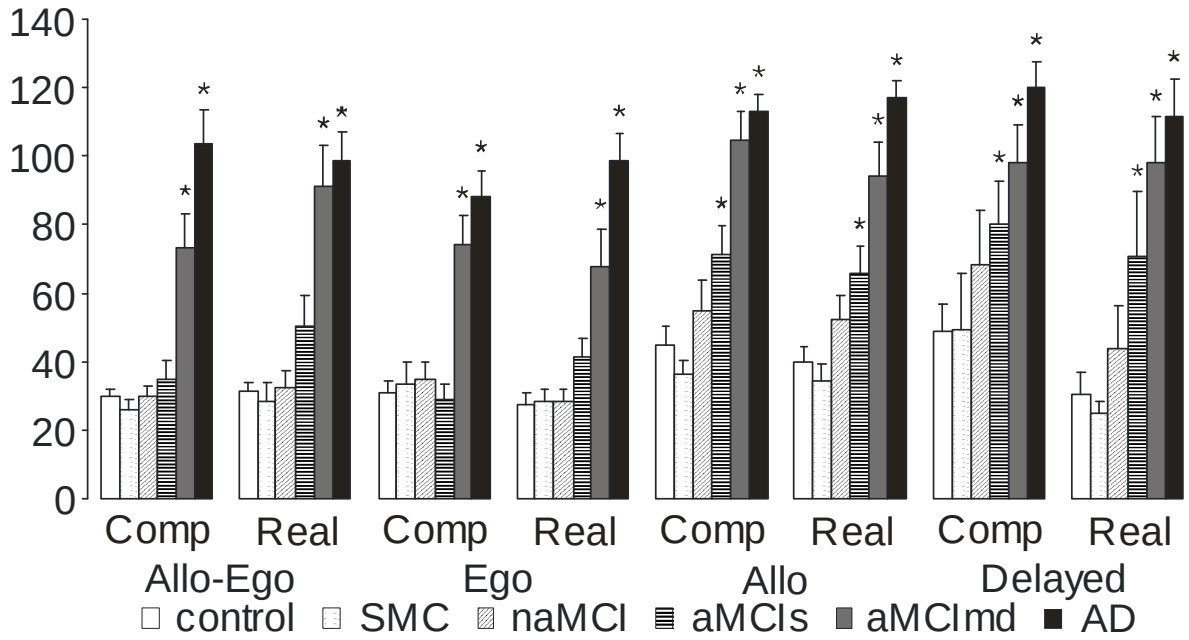
evaluate the between-group differences in age, years of education and MMSE. The Chi-square test was used to evaluate differences across groups. Because the groups differed in the basic characteristics, the analysis of covariance (ANCOVA) was used to evaluate between-group differences, controlling for gender, education and age. Post hoc repeated contrast analysis and post hoc contrast analyses with AD and control as reference groups were used to compare individual groups. In the subsequent ANCOVA, we added to the previously used covariates the free recall procedure (AVLT) to control for the potential effect of memory on the spatial navigation tests. All follow-up contrasts were done on the adjusted means in the context of the ANCOVA. The significance level set at two-tailed 0.05. All analyses were run using SPSS 13.0 for Windows.

4. RESULTS

4.1. Results in the first study

The spatial navigation impairment of the AD group was evident in all subtests (Figure 3). The differences between the MCI subtypes, however, were obvious predominantly in the third allocentric subtest: although the results of the na-MCI group were similar to the control group, on the figure, of all hits in the allocentric subtest, the hits of both amnestic MCI groups (a-MCI-sd and a-MCI-md) were less clustered around the goal and more distributed over the arena (Figure 4).

Figure 3. *The distance errors*

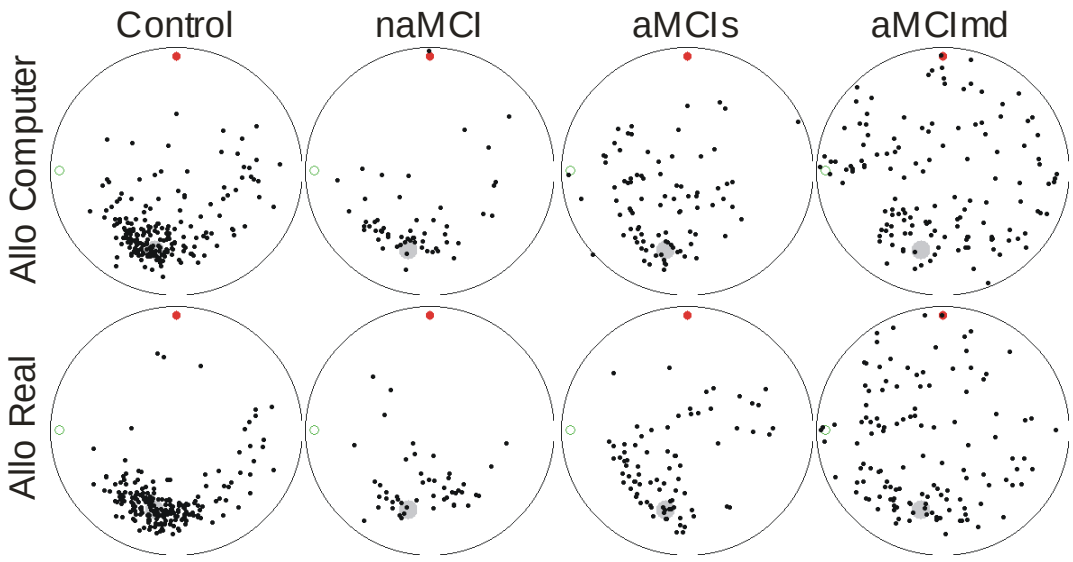


The Distance errors. The errors averaged across subtests are depicted (mean ± SEM). The asterisks represent significant differences ($p < 0.05$) from the control group. Please note the significant impairment of the a-MCI-sd in both the allo and delayed subtests and the impairment of the a-MCI-md group in all subtests.

4.1.1. Average distance errors

Significant differences across these groups were found in average distance errors in all subtests (ANCOVA, all $F > 5.201$, $p < 0.001$). The contrast analysis relative to controls showed impaired performance of AD and a-MCI-md groups in all subtests (ANCOVA, all $p < 0.001$) (Figure 3). No differences were found in the performance of the SMC (all $p > 0.382$) and na-MCI groups (all $p > 0.127$). Only the a-MCI-sd group showed differential impairment depending on the subtest: in the first and second subtests (allo-ego and ego) in which navigation by starting position could be used, it did not significantly differ from the control group (all $p > 0.157$). In the third and fourth subtests (allo and delayed), where only two orientation cues on the wall could be used for navigation, the a-MCI-sd group showed at least 1.5-fold worse estimates of the goal position than the control group and was significantly impaired (allo computer, $p = 0.015$; allo real, $p = 0.016$; delayed computer, $p = 0.047$; delayed real, $p = 0.021$).

Figure 4. *Example of the hits pattern in the subtest allo computer and subtest allo real*



Example of the hits pattern in the subtest allo computer and subtest allo real, demonstrating the differences between the control and MCI subjects. In this subtest, only two cues on the wall of the arena, here represented by the small circle and disk, could be used as orientation cues. The position of the goal (larger grey disc) was not constant relative to the starting position (which therefore is not shown). Hits are represented by small black dots.

The spatial navigation impairment of the a-MCI-sd and a-MCI-md groups showed significant differences. The chart in Figure 3 suggests the a-MCI-md group is closer to the AD group than the a-MCI-sd group. We tested this hypothesis with the AD group as a reference. The a-MCI-sd group performed similar to the AD group in the delayed computer subtest ($p = 0.051$) and was slightly better than the AD group in the delayed real subtest ($p = 0.042$). In all other (not-delayed) subtests, the a-MCI-sd group scored considerably better than AD (all $p < 0.003$). In contrast, the a-MCI-md group performed better than the AD group only in the first computer subtest (allo-ego computer, $p = 0.028$) and in two real space subtests (ego real, $p = 0.018$; allo real, $p = 0.045$). This group was similar to the AD group in the first real space subtest allo-ego real, as well as in the two following computer subtests, ego computer and allo computer, along with both 30-min delayed subtests delayed computer and real (all $p > 0.509$).

4.1.2. Individual trials

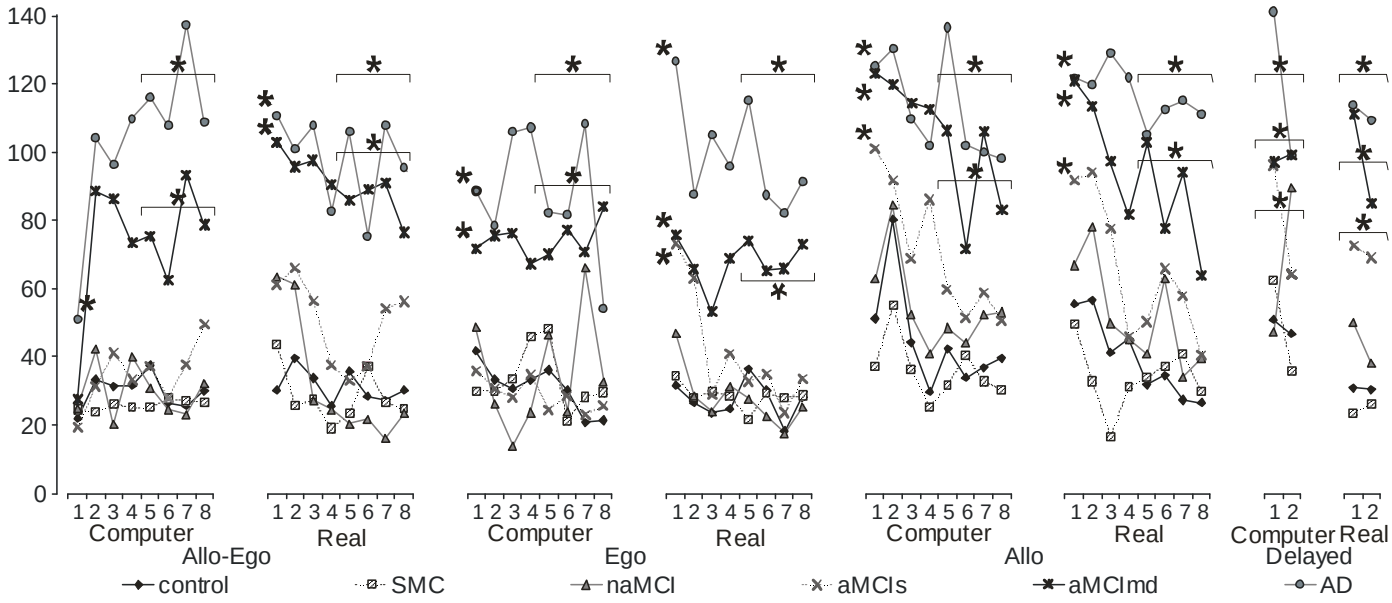
The correct position of the goal was shown to the subjects after each single trial. Consequently, learning was expected to occur during the trials of each subtest. Because the position of the goal was constant relative to the starting position and/or cues throughout the test, the first trial in each subtest assesses the subject's ability to use the information from the previous subtests. We were therefore interested in comparing the results from these first trials with the averages of the whole subtests and evaluating learning during each subtest by examining group differences in the averages of the second half of each subtest (trials 5–8).

From the chart showing all trials of the test (Figure 5), it is obvious, that the AD group was largely impaired throughout the test and exhibited no apparent learning. This observation was confirmed by significant differences across the groups in all subtests (all $F > 2.984$, $p < 0.017$), and the AD group's impairment in both the first trial and the average of trials 5–8 within each subtest (all $p < 0.004$). Similar general impairment was found in the a-MCI-md group with the exception being the allo-ego computer subtest. The a-MCI-md group was similar to controls in the first trial of this subtest ($p = 0.722$), possibly reflecting this trial requires only recalling the correct goal position on the computer screen without any delay or rotation, testing simple short-term visual memory. This view was supported by the impairment of this group in the average of trials 5–8 (ANCOVA, $p < 0.001$). The impairment of the a-MCI-md group was highly significant in all other subtests ($p < 0.007$), except for borderline differences in the first trial of ego computer ($p < 0.031$). Similarly to the allo-ego

computer subtest, this subtest assesses simple visual memory but after a delay. The a-MCI-md group was impaired in the second half of this subtest ($p < 0.001$).

The a-MCI-sd group was impaired relative to controls in the first trial of the two allocentric subtests (allo computer, $p < 0.008$; allo real, $p < 0.042$). The curve of the individual trials in Figure 5, however, suggests that this group could reach the level of controls in these subtests. This observation was supported by comparing the groups in the second half of the two subtests, where a-MCI-sd performed similarly to controls (allo computer, $p = 0.165$; allo real, $p = 0.054$). Although these differences in learning were distinct in the computer version, they were only slight in the real version. The a-MCI-sd group also was impaired in the first trial of the ego real subtest ($p < 0.038$) but performed similarly to controls in the second half of this subtest ($p = 0.760$). This contrasted with the lack of impairment of a-MCI-sd group in the ego computer subtest, both in its first trial ($p = 0.751$) and its second half ($p = 0.760$). No impairment was found in the first trial of the allo-ego subtest in both the computer ($p = 0.669$) and real versions ($p = 0.150$).

Figure 5. *The average distance errors in all trials of each subtest of the HGT*



The average distance errors in all trials of each subtest of the Hidden Goal Task. The standard errors are not included because of clarity. The asterisks represent significant differences ($p < 0.05$) from the control group. These significant differences were analyzed in the first trial of each subtest and in the average of trials 5–8 during each subtest. The horizontal line above several trials means that the significance applies for the average of

trials 5–8. Please note the learning curves of the a-MCI-sd and a-MCI-md (and other) groups, which are most distinct in the allo subtest.

4.1.3. Test components

To evaluate the structure of the subtests, we analyzed the common factors explaining the variability in our results using principal component analysis with varimax rotation. Both the averages of the individual subtests and the first trials of each subtest were included in the analysis. The eigenvalue > 1 revealed a two-factor solution. Together, these two factors explained 65% of the variance. Factor 1 explained 57% of the variance, correlating most with the delayed real (0.834) and allo real (0.804) subtests. Correlation with other variables was only slightly lower but the six highest correlation coefficients (range 0.648–0.834) belonged to the six variables from the allocentric subtests (allo and delayed, both computer and real). Factor 2 explained 8% of the variance, correlating most with the ego computer (0.775) and allo-ego computer (0.757) subtests. Similarly to factor 1, correlation coefficients of other variables were only slightly lower but among the nine variables with highest correlation (range 0.439–0.775), eight of them were from the egocentric subtests (allo-ego and ego, both computer and real). This suggests that at least that allocentric and egocentric components are dissociable in HGT.

4.1.4. Navigational strategies

We further analyzed several types of errors made by the subjects during the task to investigate, which of them contributed to their impairment. From Figure 4, which pictures all hits of the groups in individual subtests, we can guess that many a-MCI-sd subjects confused the two cues in the allo real subtest because the hits form two symmetrical clusters. Similarly, we can assume that the subjects from the a-MCI-md group generally remembered the correct side of the arena because their hits are more clustered near the goal than on the opposite side of the arena. Thus, in addition to the previously analyzed distances between position given by the subject and the correct goal position, two other variables reflecting this observation were analyzed. The correct side variable estimated whether the subject recognized the side of the arena with the goal and the side error variable was used to estimate how much confusion of the arena side contributed to the error in estimating goal position.

There was no difference in the correct side between the a-MCI-sd group, and controls in any subtest (Mann-Whitney test, all $p > 0.081$) and the a-MCI-sd group was better in determining the side than the AD group in all subtests (all $p < 0.028$) except for the delayed subtests (both computer $p = 0.389$ and real $p = 0.475$). The impairment of the a-MCI-sd group in the side error was different in the computer and real subtests: the group was impaired relative to controls in the allo computer (ANCOVA, $p < 0.004$) and delayed computer subtests ($p < 0.007$), but similar to controls in the allo real ($p = 0.084$) and delayed real subtests ($p = 0.108$). The group also performed similar to controls in ego computer ($p = 0.824$) and ego real ($p = 0.166$) subtests. These results confirm our observation that the a-MCI-sd group confused the sides of the arena in the allo real and allo delayed subtests.

The a-MCI-md group was impaired in correct side in all subtests (Mann-Whitney test, all $p < 0.017$) but remembered the side better than the AD group in the ego real ($p < 0.010$) and allo real ($p < 0.021$) subtests. The group was also impaired relative to controls in all subtests in side error (ANCOVA, all $p < 0.001$) and performed similarly to the AD group in all subtests (all $p > 0.196$) except for the ego real subtest ($p < 0.018$).

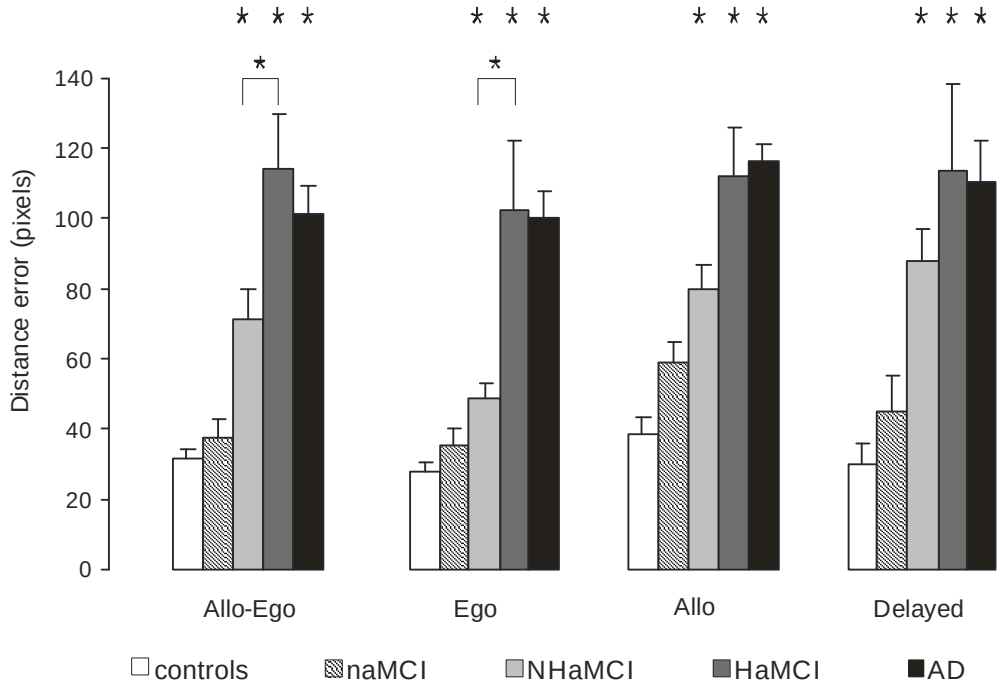
4.2. Results in the second study

4.2.1. Differences in spatial navigation

The main hypothesis was that the Ha-MCI group would be impaired in navigation skills compared with the results of the NHa-MCI group.

We used the multivariate ANCOVA which revealed significant differences among the groups in average errors of all subtests of HGT ($F[4,92]>8.874$, $p<0.001$ in all analyses). We subsequently performed the post hoc repeated contrast which showed substantial differences in spatial navigation between the Ha-MCI and NHa-MCI groups such that the Ha-MCI group performed worse than the NHa-MCI group in the allo-ego and ego subtests (allo-ego: $p=0.004$; ego: $p<0.001$) (Figs. 6 and 7). The difference between these two groups in the allo subtest approached statistical significance (allo: $p=0.069$) and the groups were similar in the delayed subtest (delayed: $p=0.286$).

Figure 6. *The between-group differences*

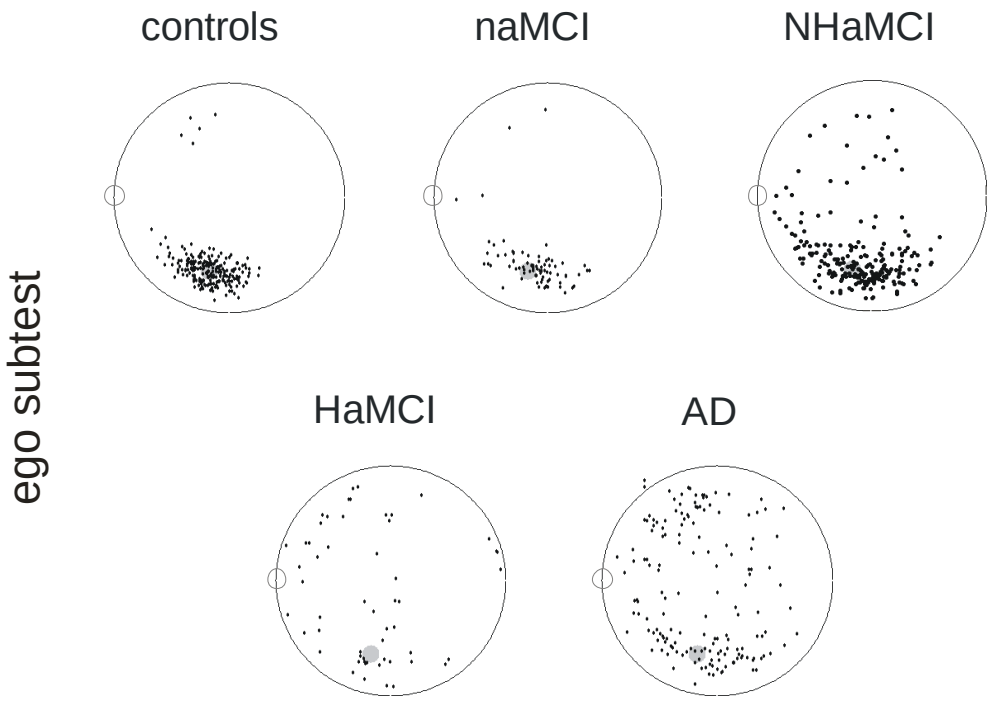


The between-group differences. The distance errors averaged across subtests are depicted (mean ± S.D.). The asterisks represent significant differences ($p<0.05$) from the control group. The horizontal lines with the asterisks above represent significant differences ($p<0.05$) between the Ha-MCI and NHa-MCI groups.

4.2.2. Differences in individual trials

To further examine whether the differences between the Ha-MCI and NHa-MCI groups in spatial navigation skills were more obvious in the second halves of the subtest due to the supposed differences in spatial learning, we evaluated the results from the first trials, calculated averages for the second half of each subtest (trials 5-8), and examined between-group differences. The multivariate ANCOVA showed significant differences across the groups in both the first trials and the second halves of each subtest ($F[4,92]>3.228$, $p<0.016$ in all analyses). Subsequently, we used the post hoc repeated contrast analysis which showed substantial differences in spatial navigation between the Ha-MCI and NHa-MCI groups such that the Ha-MCI group performed worse than the NHa-MCI group in the averages of trials 5–8 within each subtests (allo-ego: $p=0.018$; ego: $p=0.007$; allo: $p=0.044$), and in the first trial of the ego subtest ($p=0.004$) (see Fig. 8).

Figure 7. *Pattern of hits in the ego subtest*



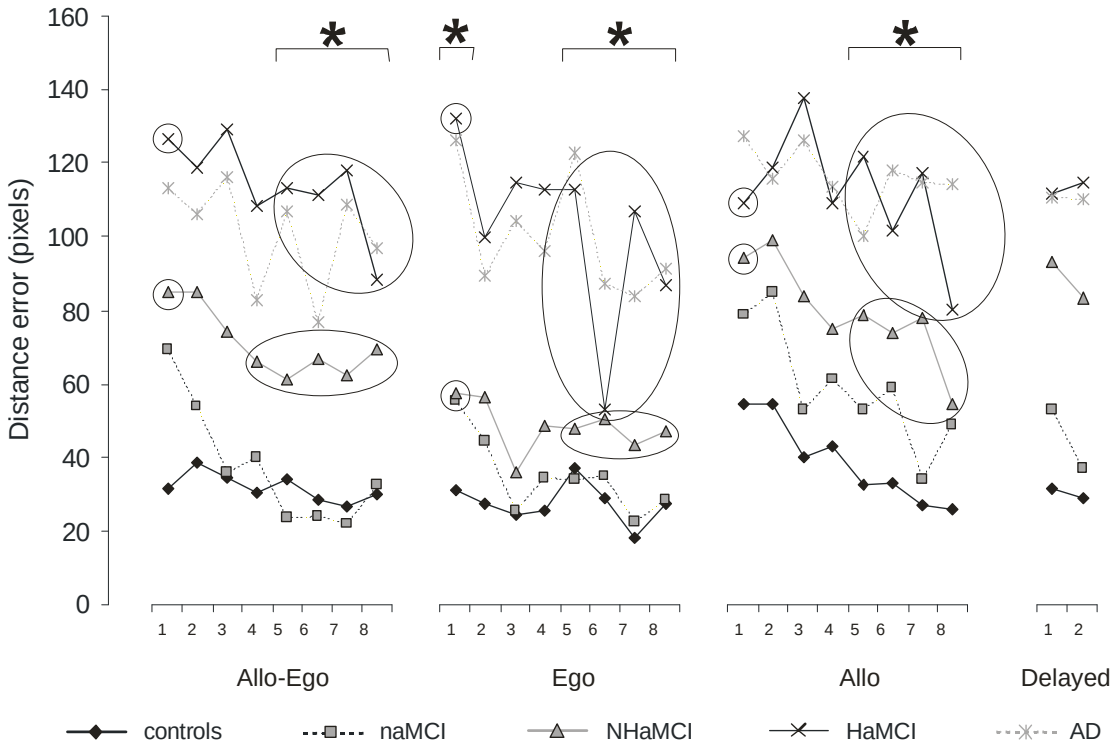
The pattern of hits (small black dots) in the ego subtest demonstrating the differences among the groups. Only the position of the start (larger grey disc) could be used for orientation.

4.2.3. Differences in memory tests

To explore whether differences in spatial navigation performance between the Ha-MCI and NHa-MCI groups had not been caused only by memory impairment, we used multivariate ANCOVA and the post hoc repeated contrast on standard neuropsychological tests. The multivariate ANCOVA revealed differences among all groups in verbal (AVLT, $F[4,92]>19.935$, $p<0.001$; GB's test free recall, $F[4,92]>14.881$, $p<0.001$; GB's test total recall $F[4,92]>20.544$, $p<0.001$), and non-verbal (BVRT A, $F[4,92])>13.887$, $p<0.001$) memory tests. On the other hand, the post hoc repeated contrast showed that the Ha- MCI and NHa-MCI groups did not differ in any verbal [AVLT ($p=0.144$), GB's test free recall ($p=0.190$)] or non-verbal [BVRT A ($p=0.857$)] memory tests except total recall in GB's test ($p<0.001$), which was a criterion in classification of MCI subjects into Ha-MCI and NHa-MCI groups.

Although the two a-MCI groups did not differ in any memory tests, we could not exclude the possibility that the differences in spatial navigation tests between these groups were caused mainly by the different memory performance. So we repeated the multivariate ANCOVA to evaluate between-group differences and we added to the previous covariates (gender, education, and age) results of the free recall procedure - AVLT. Even with this new covariate, the multivariate ANCOVA indicated that the NHa-MCI group performed better than the Ha-MCI group with respect to average errors of allo-ego, ego and allo subtests of HGT [allo-ego: $F(4,92)>3.006$, $p=0.025$; ego: $F(4,92)>4.746$, $p=0.002$; allo: $F(4,92)>2.743$, $p=0.037$]. The difference in the delayed subtest was in the same direction but it only approached statistical significance [$F(4,92)>3.474$, $p=0.067$]. The significant differences between Ha-MCI and NHa-MCI groups in the ego subtest were retained in the post hoc contrast test ($p=0.003$).

Figure 8. *The learning curves*



The learning curves. The distance errors in all trials of each subtest of the Hidden Goal Task are depicted in this chart. The asterisks represent significant differences ($p<0.05$) between the Ha-MCI and NHa-MCI groups. These significant differences were analyzed in the first trials of each subtest and in the averages of trials 5–8 within each subtest. The

horizontal line above several trials means that the significance applies for the average of trials 5–8. Please note the learning curves of the NHa-MCI group, which are the most apparent in the allo subtest.

4.2.4. Characteristics of spatial navigation performance

We used the post hoc contrast analysis with controls as a reference group after the multivariate ANCOVA to reveal characteristics of spatial navigation performance. This analysis showed that Ha-MCI group was impaired in all spatial navigation subtests (all p's<0.001), which mirrored the result when contrasting the control group with the AD group (all p's<0.001) (Fig. 6). The NHa-MCI group was also impaired in spatial navigation subtests, but the impairment was not as profound as in the previous groups ($p<0.05$). There were no differences between the na-MCI and control groups ($p>0.105$ in all subtests).

We then compared the spatial navigation performance of the a-MCI groups with the AD group using the post hoc contrast analysis. This analysis showed that Ha-MCI group did not differ from AD in any subtests (all p's>0.383). On the other hand, the NHa-MCI group outperformed the AD group in all subtests ($p<0.003$) except the delayed one ($p=0.225$).

4.2.5. Characteristics of performance in individual trials

In additional analyses, we tested whether the subjects were able to improve their performance within the subtests by presenting a learning effect. We used the controls as the reference group. We hypothesized that the Ha-MCI group, as well as the AD group, would not exhibit any apparent learning when compared to the control group. We evaluated the results from the first trials and calculated averages for the second half of each subtest (trials 5-8) and examined between-group differences.

In agreement with our hypothesis, results from the multivariate ANCOVA and the subsequent post hoc contrast indicated that the Ha-MCI group exhibited no apparent capacity to learn in any of the subtests compared to the control group (see Fig. 8) ($F[4,92]>3.228$, $p<0.016$ in all analyses), which mirrored the result when contrasting the control group with the AD group (all p's<0.001).

5. DISCUSSION

5.1. The first study

Our goal in the first study was to characterize spatial navigation deficits in MCI and early AD patients and to assess how spatial navigation impairment could distinguish MCI patients from healthy subjects. We investigated allocentric and egocentric navigation in a human analogue of the MWM in mild to moderate AD patients, na-MCI, a-MCI-sd, a-MCI-md patients, and patients with SMC and we compared their spatial navigation performance with age, education and sex matched healthy control subjects.

According to our assumption we found the extensive spatial navigation impairment in the patients with early AD. These patients were impaired in all spatial navigation (in the real-space as well as in the virtual) subtests and they could not even recognize the correct side of the arena, where the goal was located. Regions affected earliest in AD like medial temporal lobes, ventral occipitotemporal, posterior parietal, and restrosplenial cortices are those thought to play critical roles in human navigation (Aguirre et al., 1998), potentially explaining why so many AD patients have navigation impairments. Our findings provide further support that spatial disorientation and spatial memory deficits are an early diagnostic signs of AD (Cherrier et al., 2001; Monacelli et al., 2003; Kalova et al., 2005; Burgess et al., 2006).

Our results indicate strong differences in spatial navigation impairment among the subtypes of MCI. The na-MCI patients were not impaired in any spatial navigation subtest and performed similarly to controls, as we previously reported (Laczo et al., 2006). Further, pronounced differences appeared also between the two amnestic types of MCI, a-MCI-sd and a-MCI-md. The a-MCI-md subjects were impaired in all subtests and the impairment was present in the first trial as well as in the second half of all subtests, indicating the a-MCI-md subjects could not learn how to find the goal in the course of repeated testing. They were impaired not only in the distance error during all subtests, but even in the recall of the correct side of the arena, suggesting serious impairment in spatial orientation. The only trial where they performed similar to controls was the first trial of the first virtual subtest, possibly reflecting this trial requires only recalling the correct goal position on the computer screen without any delay or rotation, testing simple visual memory.

In contrast, the a-MCI-sd subjects were impaired only in several specific parts of the test, namely in the first trial of the ego real-space subtest, the first trials of both the allo virtual and real-space subtests, and the averages of both the delayed computer and delayed real subtests. This pattern of the impairment suggests that the allocentric navigation by two cues independent of the starting position contributed to impairment of this group. This also corresponds with the results of the principal component analysis, where most variance-explaining factors correlated with the allocentric subtests. The impairment of the a-MCI-sd group was not found in the second half of the subtests, which indicates preserved capacity to learn.

Although memory deficit is a defining and important diagnostic feature of AD, its impact on spatial disorientation in AD and MCI is not clear yet. The selective impairment in a-MCI-sd in all allocentric subtests suggests a hippocampal deficit. Disrupted allocentric navigation after medial temporal lobe damage was described in analogues of the MWM (Feigenbaum et Morris, 2004; Holdstock et al., 2000), an invisible sensor task in a hospital room after a 30-min delay (Bohbot et al., 1998), and in a virtual reality shifted-viewpoint spatial memory test (King et al., 2002). Temporal lobe damage also disrupted topographical orientation in a real environment (Maguire et al., 1996). On the contrary, optic flow perception activates right posterior parietal cortex (Morone et al., 2000). Therefore, impairment in both allocentric mode of navigation and memory for configurations in the real space are consistent with the medial temporal lobe damage found in MCI (Grundman et al., 2004; Pennanen et al., 2004), but not with a parietal dysfunction connected with optic flow discrimination deficit.

We can hypothesize about the nature of the impairment in the a-MCI-sd patients because of its selectivity. However we are not able to specify the cognitive domains influencing bad results in our AD and a-MCI-md patients because they were impaired in all subtests. Presumably, both parietal dysfunction and memory deficit had a significant impact. The more global defect in the a-MCI-md and AD groups could be explained by the disease spreading beyond the hippocampus (Braak et Braak, 2001; Brun et Gustafson, 1976) with affection of other non-memory domains. The early episodic memory deficit in AD (Nagy et al., 1999) is followed by the early impairment of executive functions with later involvement in constructional praxis, language, and sustained attention (Baudic et al., 2006). Our findings are consistent with other papers suggesting that multidomain MCI is similar to AD in many domains of cognition as well as in behavioural and psychological symptoms (Cummings, 2005).

The similarity of spatial navigation impairment in the a-MCI-md and AD groups demonstrated by our results is prominent and consistent with the contemporary view of a-MCI-md as a prodromal stage of AD. a-MCI-md has a less favourable prognosis with a higher proportion of conversion to AD and may represent a more advanced prodromal stage of dementia than a-MCI-sd (Alexopoulos et al., 2006). Bozoki and colleagues (Bozoki et al., 2001) showed that patients exhibiting impairment in other cognitive areas beyond memory loss have a higher risk of developing dementia than those with memory loss alone. Our results might suggest that the a-MCI-sd represents an earlier stage of AD than a-MCI-md. At the same time, memory impairment is a presymptomatic stage of AD because the early non-memory domain deficit precedes other non-AD dementias (Petersen, 2004). Yaffe and colleagues (Yaffe et al., 2006) proved that the subtype of MCI influences the rates of progression toward dementia and death and has a major influence on future diagnosis of dementia type. Among patients who progressed to AD, 76% had prior amnestic MCI; of the patients who progressed to VD, 50% had prior amnestic MCI; and all patients who progressed to a frontal dementia syndrome had single non-amnestic MCI (Yaffe et al., 2006).

SMC subjects were similar to the control group. Intact spatial memory in this group is consistent with other studies evaluating other kinds of declarative memory (Jonker et al., 2000). This group was placed in our study because SMC individuals form a large proportion of clients in memory clinics and should be monitored because some of these patients may convert into a MCI group.

Our study shows that spatial navigation impairment is not limited to AD, but is, instead, detectable earlier in MCI and therefore can be expressed in a more complex or novel environment. According to our results, the spatial disorientation in MCI detected in our subjects tested by an analogue of the MWM is due to impaired spatial memory.

If spatial navigation begins to decline early in the disease process, presymptomatic measures of spatial navigation should predict the onset of clinical symptoms. The occurrence of spatial navigation impairment in the amnestic MCI, and the similarity of deficits in multiple domain MCI with those of early AD, suggests that these manifestations may assist in identifying patients in the earlier stages of AD distinguishing them from the patients with MCI of other origin. This fact makes it a potential biomarker of AD. Similar computer tests can serve as an inexpensive, but reliable, proof to the degree of impairment of critical brain structures in AD.

5.2. The second study

The purpose of the second study was to examine whether spatial navigation ability could discriminate two groups of amnestic MCI patients – with hippocampal memory impairment versus non-hippocampal (frontal) memory impairment as suggested in the executive dysfunction hypothesis (Dubois et Albert, 2004). Given that encoding/consolidation deficit, typical of hippocampal deficit, is present in AD patients (Deweer et al., 2004) and in the prodromal stage of AD (Dubois et Albert, 2004), this investigation may have important implications for understanding the underlying mechanisms important in the identification of preclinical AD. In addition, the findings could help refine commonly accepted Petersen's criteria for MCI (Petersen, 2004), which are based on the identification of memory recall impairment without stratification into encoding/consolidation and retrieval impairment.

In agreement with our hypothesis, we found substantial differences between the Ha-MCI and NHa-MCI groups in spatial navigation performance. The Ha-MCI group performed worse in the combined egocentric + allocentric subtest, in the egocentric subtest and in the allocentric subtest (although this difference was not statistically significant) than the NHa-MCI group. The differences between these two groups became more obvious in the second halves of the subtests, suggesting particularly pronounced differences in learning ability. In the second halves of the subtests, not only that the NHa-MCI group consistently outperformed the Ha-MCI group, but the Ha-MCI group remained almost identical to the AD group. The Ha-MCI and NHa-MCI groups did not differ on the standard memory tests based on free recall. Still, to exclude the possibility that the main difference between them was caused by the different performance in memory recall, we corrected the spatial navigation results for results on the qualifying memory test (AVLT). Even after this correction, the differences in spatial navigation between these two a-MCI groups remained. We propose that the differences in spatial navigation performance between Ha-MCI and NHa-MCI groups were due to the different underlying pathology and structural deficits in the hippocampal and frontal areas rather than due to the severity of the disease or the severity of memory impairment. Future research should test this hypothesis using structural imaging techniques.

We found out that spatial navigation was generally impaired in the Ha-MCI group within all subtests in the HGT. This group also did not exhibit any apparent learning effect within HGT tasks. The same pattern of spatial navigation impairment was found in the mild AD group. The different pattern was observed in the NHa-MCI group, where the spatial

navigation impairment was mainly present in the allocentric subtest and was less pronounced than in the Ha-MCI group. Further the NHa-MCI group was able to improve their performance and the learning effect was present.

Our findings suggested that the Ha-MCI group (which might represent preclinical AD) exhibited relatively severe spatial navigation impairment, mainly in the allocentric tasks. This was in agreement with studies showing that the hippocampus is essential brain structure for learning (Squire et Zola-Morgan, 1991) and for allocentric spatial navigation processing as was well documented in many animal and human studies (Astur et al., 2002; Morris et al., 1982; O'Keefe et Dostrovsky, 1971; O'Keefe et Nadel, 1978). The Ha-MCI group was also impaired in the egocentric task which indicated extra-hippocampal impairment. It is known that egocentric navigation is connected with parietal lobes (Aguirre et D'Esposito, 1999; Burgess et al., 1999; Astur et al., 2002; Feigenbaum et Morris, 2004; Maguire et al., 1998). Parietal and temporal lobe abnormalities are thought to be a hallmark of AD (Ibanez et al., 1998; Kemper, 1994; Rossor et al., 1996) and are affected also in MCI patients (Mapstone et al., 2003). In addition, pathological studies indicated that parietal disease burden corresponds to visuo-spatial disorientation in AD (Galton et al., 2000; Rascovsky et al., 2002). Several studies also indicated that navigational defects in AD and MCI patients are connected with parietal lobes and/or the junction of the parietal-occipital-temporal cortex (Mapstone et al., 2003; Monacelli et al., 2003). Further it is well known that optic flow visual motion stimuli contribute to guidance of self-movement. Neurons that process optic flow motion stimuli can be found in the medial superior temporal areas (Duffy et Wurtz, 1991). All of this work, as well as other work, points strongly to dysfunction in dorsal stream of visual processing regions of the brain as the cause for much of the navigational and visuo-spatial dysfunction found in AD and MCI. It is probable that these regions play some role also in spatial navigation impairment in the Ha-MCI patients. Future studies can highlight the underlying pathology and the roles of the temporoparietal regions in spatial navigation impairment in these Ha-MCI patients.

Our finding suggested that the NHa-MCI group with the frontal lobe impairment exhibited the partial spatial navigation impairment which was more apparent in the allocentric task. Many studies showed that the frontal cortex is necessary for complex problem solving, planning, keeping in mind a goal over time (Koechlin et al. 1999), and for maintaining the intention to reach the destination and switching between tasks (Burgess et al., 2000). All the above mentioned findings, and particularly the last one, could contribute to spatial navigation impairment in NHa-MCI group as this group had the largest difficulties in switching from

egocentric to allocentric navigational strategy. The ability to improve the performance within the tasks testified against the hippocampal impairment.

We further found that subjects in the mild AD group were severely impaired in all spatial navigation subtests with no learning improvement. This finding provides further support that spatial disorientation and spatial memory deficits are an early diagnostic sign in these patients as discussed before (Cherrier et al., 2001; Kalova et al., 2005; Kessels et al., 2005; Monacelli et al., 2003).

Finally, our study showed that the na-MCI group was not impaired in any spatial navigation subtest and performed similarly to controls, which was consistent with our previously reported findings (Hort et al., 2007a).

Among the diagnostic tests of the early AD and MCI, the spatial navigation may represent a new promising avenue as it may be among the first cognitive domains to show impairment demonstrative of underlying neuropathology. In this study, we tested the value of spatial navigation in the HGT, a human analogue of MWM, a test commonly used in the assessment of interventions to improve cognitive functioning. We were particularly interested to test whether the spatial navigation performance could discriminate the amnestic MCI patients with hippocampal impairment from those with non-hippocampal impairment. We built on our earlier studies (Hort et al., 2007a; Laczo et al., 2006) where we had reported spatial navigation impairment in patients with AD and MCI but were unable to distinguish between hippocampal and non-hippocampal amnestic syndromes.

We found that the amnestic MCI patients demonstrated spatial navigation problems. Among the a-MCI patients, spatial navigation was significantly poorer in those with (versus without) hippocampal deficits. The patients with Ha-MCI also were more similar to the AD patients than to the other MCI subgroups. This is consistent with the view that a-MCI is a prodromal stage of AD (Lopez et al., 2006), especially in those with the hippocampal amnestic syndrome (Dubois et Albert, 2004). We did not classify patients according multiple- and single-domain scheme (Petersen et al., 2001) due to a low number of patients with single-domain Ha-MCI, a relatively rare category (Alladi et al., 2006).

In addition to its use as a research tool, the HGT has a potential practical utility in several areas, in particular as a diagnostic test to identify presymptomatic or early AD patients, a biomarker of disease progression, and a translational tool in the development of new drugs for cognitive enhancement. At present, attempts to extend clinical assessment to prodromal stages of the disease have not been satisfactory. The similarity of deficits in hippocampal a-MCI with those of early AD suggests that the HGT may help distinguish

preclinical patients from those with MCI of other aetiologies. In addition, early diagnosis of AD by means of HGT was found to provide comparable efficiency as other biomarkers used in a memory clinic setting as cerebrospinal fluid biomarkers or structural brain imaging (Horinek et al., 2007; Hort et al., 2007b). HGT may serve as an inexpensive, reliable biomarker of the degree of impairment of critical brain structures in the progression of AD.

In conclusion, we found deficits in the spatial navigation in the amnestic MCI that were more substantial in the hippocampal than in the non-hippocampal subtype. These results were consistent with the previously posited differentiation of susceptibility to conversion to AD based on hippocampus-related deficits in MCI (Dubois et Albert, 2004). In addition, from the clinical point of view, our results provide new evidence that the spatial navigation may need to be considered separately from the non-verbal memory in the context of identifying preclinical signs of AD.

The Ha-MCI patients were found to have a severe impairment of the allocentric navigation and an inability to learn, which was consistent with the probable hippocampal impairment in this patient group. The poor egocentric navigation in this group suggested an additional extra-hippocampal impairment most likely in the parietal and temporal cortices. Our finding of allocentric navigation impairment in NHa-MCI patients with retrieval deficit and very likely the frontal lobe impairment might illustrate the importance of frontal lobes for spatial navigation. The global spatial navigation impairment in AD patients provided further support for previous findings on topographical disorientation and spatial memory deficits in these individuals. Although we are aware of limitations of this study not having performed structural brain imaging, these findings may add further insights into the nature of the spatial navigation deficit in MCI and AD patients by exploring an up to now partially neglected modality and may have relevance in explaining why most AD and some MCI patients lost often their way. Further studies are required, especially imaging ones, to highlight the structural and functional deficit in AD and MCI patients underlying spatial navigation impairment.

6. CONCLUSIONS

Our studies of spatial navigation in MCI and AD patients in the human analogue of the Morris water maze revealed that

- the spatial navigation is impaired in the early stage of AD

- the spatial navigation impairment is present in patients with amnestic MCI, especially with multiple domain impairment

- the impairment of spatial navigation is detectable even in amnestic MCI patients with isolated memory impairment (single domain)

- the amnestic MCI patients with hippocampal memory impairment (potential preclinical AD) have severe spatial navigation impairment similar to that seen in AD patients

- the patients with non amnestic MCI and subjective memory complaints have intact spatial navigation

In conclusion, the spatial navigation testing may help in identifying patients in the earlier stages of AD distinguishing them from patients with MCI of other aetiologies. This fact makes it a potential biomarker of AD. The spatial navigation testing may serve as an inexpensive, reliable biomarker of the degree of impairment of critical brain structures in the progression of AD. It may serve as a biomarker – a) of AD, b) translational from the animal to the human research – because of MWM analogue.

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8. APPENDIX

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