

# Predictors of Alzheimer's Disease in subjects with Mild Cognitive Impairment

Focus on neuropsychology  
in relation to genetic and  
neuroimaging markers

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# CONTENTS

<b>LIST OF ORIGINAL PUBLICATIONS</b>	vi
<b>ABBREVIATIONS</b>	vii
<b>INTRODUCTION</b>	<b>1</b>
Mild cognitive Impairment (MCI)	1
Neuropsychological predictors of pre-clinical AD and MCI	9
Alzheimer Disease (AD)	20
<b>AIMS OF THE THESIS</b>	<b>24</b>
<b>METHODS</b>	
Study Samples	25
Cognition and neuropsychological assessment	28
Positron Emission Tomography (PET) method	36
Apolipoprotein 4 (APOE) genotype determination	39
Statistical analysis	39
Ethical approvals	41
<b>RESULTS</b>	<b>41</b>
<u>Chapter I:</u> Psychometric discrimination of AD and MCI	42
<u>Chapter II:</u> Neuropsychology and PET in discrimination of AD in MCI patients.	60
<u>Chapter III:</u> Cross national comparison of MCI samples.	75
<b>DISCUSSION</b>	<b>93</b>
Design Issues	93
Recruitment strategies and diagnosis accuracy	95
Tracking disease progression	98
Relation to other biological markers	98
<b>CONCLUSIONS AND FUTURE DIRECTIONS</b>	<b>100</b>
<b>ACKNOWLEDGMENTS</b>	<b>103</b>
<b>REFERENCES</b>	<b>106</b>
<b>APPENDIX</b>	<b>116</b>

# LIST OF ORIGINALS PUBLICATIONS

The thesis is based on the following studies referred to in the text by their roman numerals.

- I. **Arnaiz E**, Blomberg M, Fernaeus SE, Wahlund LO, Winblad B, Almkvist O. Psychometric discrimination of Alzheimer´s Disease and Mild Cognitive Impairment. (2000) *Alzheimer Report* 3 (2), 97-103.
- II. **Arnaiz E**, Jelic V, Almkvist O, Wahlund L-O, Winblad B, Valind S and Norberg A. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment (2001) *Neuroreport* 12 (4), 851-855.
- III. **Arnaiz E**, Almkvist O, Ivnik RJ, Tangalos EG, Wahlund LO, Winblad B, Petersen RC. Mild cognitive impairment: a cross national comparison of MCI samples (2001). Submitted to *Archives of Neurology*.

# ABBREVIATIONS

AchE	Acetylcholinesterase
AD	Alzheimer's Disease
ANOVA	Analysis of variance
APOE	Apolipoprotein E (gene)
ARCD	Age Related Cognitive Decline, (DSM-IV, 1994)
CERAD	Consortium to establish a registry for Alzheimer's Disease
CDR	Clinical Dementia Rating (scale), (Hughes et al, 1982)
CNS	Central nervous system
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CMRGlucose	Cerebral Metabolic Rate of Glucose
DSM-III-R	Diagnostic and Statistical Manual, 3 <sup>rd</sup> edition, revised (American Psychiatric Association, 1987).
DSM-IV	Diagnosis and Statistical Manual, 4 <sup>th</sup> edition (American Psychiatric Association)
EEG	Electroencephalography
FSIQ	Full Scale Intelligence Quotient (Wechsler, 1981)
GDS	Global Deterioration Scale, (Reisberg et al, 1982)
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Exam, (Folstein et al, 1975)
MRI	Magnetic Resonance Imaging
NINCDS-ADRDA	National Institute of Neurological Disorders and Communicative Disorders-Alzheimer's Disease and Related Disorders Association (McKhann et al, 1984).
PM	Primary memory
PET	Positron Emission Tomography
ROI	Regions of interest
SD	Standard deviation
SM	Secondary memory
SPECT	Single Photon Emission Computerised Tomography
WAIS-R	Wechsler adult intelligence scale revised (Wechsler, 1981)
WMS	Wechsler memory scale (Wechsler, 1945)

# INTRODUCTION

## **Mild Cognitive Impairment (MCI)**

A great deal of interest has been generated around a transitional state between the cognition of normal aging and very mild AD. Detection of prodromal and early stages of AD will be beneficial for early therapeutical interventions. MCI could be suggestive of the future development of AD (Jacobs, 1995, Petersen 1999, Morris 2001), but it is also a frequent consequence of normal aging or psychiatric diseases such as depression (Ritchie, 2000; 2001).

### *Definition of the concept*

Different diagnosis classification systems have been proposed for the characterization of mild cognitive disorders associated with aging. They all share the common concept that a single, clinically significant impairment in cognition, for example memory, is present without additional functional or cognitive impairments necessary to diagnose dementia (Redies & Caine, 1996). The best established of these classifications are Age Associated Memory Impairment (AAMI) (Crook, 1986), Age Related Cognitive Decline (ARCD) (DSM-IV, 1994), and Mild Cognitive Impairment (MCI) (Flicker, 1991; Petersen 1995). See Table 1 for a complete summary of cognitive impairment classifications and Appendix A for more complete description of definitions of MCI.

**Table 1.** Glossary of entities designating cognitive impairment in elderly people without dementia .

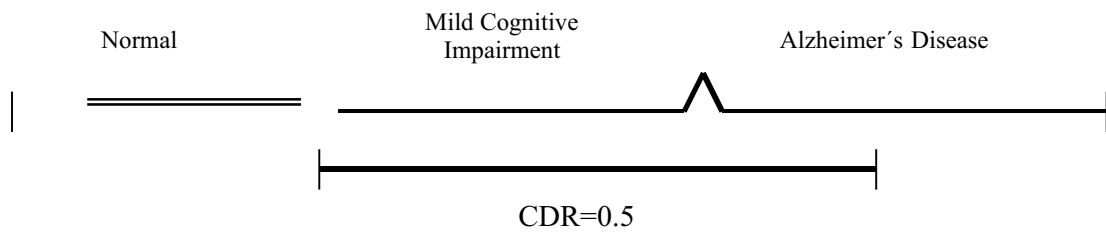
CONCEPT	AUTHOR	CRITERIA	COGNITIVE TEST SPECIFIED
Benign senescent forgetfulness	Kral et al.	Memory complaints	NO
Age-associated memory impairment	Crook et al	Memory impairment shown by decrement on formal cognitive test	NO
Late-life forgetfulness	Blackford and LaRue	Age-associated memory impairment but greater decrement on 50% of a specific test battery	YES
Ageing-associated cognitive decline	Levy et al.	Impairment on any formal cognitive test	NO
Ageing-related cognitive decline	DSM-IV	Objective decline in cognitive functioning	NO
Mild cognitive decline	ICD-10	Disorders of memory learning and concentration	NO
Mild neurocognitive decline	DSM-IV	Difficulties in memory learning and concentration, perceptual-motor linguistic, and central executive functioning.	NO
Cognitive Impairment no dementia	Graham et al.	Circumscribed memory impairment and low MMSE score	YES
Mild cognitive impairment	Petersen et al.	Complaints of defective memory, a deficit on cognitive tests, and normal general intellectual functioning	NO

**Ritchie, 2000; Lancet**

The variability in the use of the terminology to refer to patient in this transitional state leads to difficulty in interpreting the literature. However, it seems that the MCI entity is operationally better defined because it adds into the description measures from clinical rating scales such as Global Deterioration Scale (GDS) (Flicker, 1991) or Clinical Dementia Rating (CDR) (Petersen, 1995).

Interestingly, in a recent article Petersen (2000) highlighted the fact there is an overlapping of diagnosis categories, including MCI, and their relationship to the CDR scale. This overlapping is presented in Figure 1.





Currently, one of the most accepted MCI diagnosis criteria is Petersen's (1995;1999), which is fully described in Appendix A.

Evidence from SPECT and EEG support the idea that MCI is a neurological entity. TC in patients with MCI has shown atrophy of the left medial temporal lobe (Wolf, 1998), hippocampal atrophy (Jack 1999; 2000) and a smaller medial temporal lobe volume except for the right parahippocampal gyrus (Krasuki, 1998). SPECT showed low parietal-temporal perfusion and left/right parieto-temporal asymmetry in MCI (Celsis, 1997).

The observed hipoperfusion was intermediate between that found in normal people and in patients with AD.

AD patients were found to have atrophy and lower cerebral blood flow in both medial temporal and temporoparietal regions than MCI patients, whereas MCI patients showed significant reduction in cerebral blood flow without atrophy in the temporoparietal region only (Julin, 1997). Electroencephalography (EEG) showed similarities between AD and MCI which differentiated both groups from normal elderly people on temporoparietal



coherence and  $\alpha$  and U relative power (Jelic, 1996). Kordower (2001) showed a loss and atrophy of layer II entorhinal cortex neurons in elderly people with MCI.

These findings suggest that MCI and AD have similar anatomical locii, with MCI being differentiated mainly by degree of impairment, and functional, rather than structural change.

### *Conversion rates*

Several longitudinal studies have indicated that MCI individuals are at an increased risk for developing AD. However, it is important to understand that a diagnosis of MCI does not mean that an individual will develop AD in the future. Rather, individuals with MCI develop AD at ranging from 1% to 25% per year (Dawe, 1992), 24% of MCI patients progressed to AD in 2 years, (Tierney, 1996), 20% over 3 years (Wolf, 1998) whereas latest study indicated that the progression of MCI subjects was 55% in 4.5 years (Petersen, 1999). A complete revision of further studies is presented in Table 2.

**Table 2.** Progression rates to dementia in non-demented memory-impaired patients.

<b>Authors and year</b>	<b>Inclusion criteria</b>	<b>Number of patients</b>	<b>Follow-up</b>	<b>Patients who progressed to dementia</b>
Kral et al. (1978)	Benign senescent forgetfulness	20	4 years	5%
Rubin et al. (1989)	Questionable dementia, CDR=0.5	16	7 years	69%
Tuokko et al. (1991)	Memory impaired, non-demented	45	12-18 months	4%
Masur et al. (1995)	Non-demented	317	At least 4 years	20%
Hänninen et al. (1995)	Age Associated Memory Impairment (AAMI)	229	3.6 years	9.1%
Petersen et al. (1995)	Mild cognitive impairment (MCI)	66	1.5 years 3 years 4.5 years	24% 44% 55%
Linn et al. (1995)	Free of dementia	1045	7 to 13 years	13%
Cooper et al. (1996)	Minimal dementia and mild dementia	106	27 months	20%
Tierney et al. (1996)	Memory impaired, non-demented	123	2 years	23%
Devanand et al. (1997)	“questionable dementia”, CDR=0.5	16	2.5 years	41%
Bowen et al. (1997)	Individuals with isolated memory loss vs. individuals with subjective memory complaints	106	27 years	18.8%

**Table 2.** (Continued)

Fabrigoule et al. (1998)	Elderly PAQUID cohort	1159	2 years	2.1%
Johnson et al. (1998)	Questionable Alzheimer's Disease (AD)	136	2 years	40%
Ritchie et al. (2000)	Subclinical cognitive impairment	283	3 years	18%
Visser et al. (2000)	Memory impaired, non-demented	74	5 years	39%
Grober et al. (2000)	Initially non-demented	264	10 years	12%
Tierney et al. (2000)	Memory impaired, non-demented	165	2 years	17%
Ritchie et al. (2001)	Age Associated memory decline and MCI	569	6 years	12%
Morris et al. (2001)	MCI (Petersen criteria) CDR=0.5	308	3 years	19.5% if Uncertain
Bozoki et al. (2001)	Nondemented elderly with memory loss	48	2 years	More than memory problems 48% Only memory problems 6%

**Arnaiz, 2001**

The variability in the literature regarding figures of conversion from MCI to AD may arise from a) the inclusion/exclusion criteria of patients in the MCI group and b) the nature of the recruitment practices in the studies (i.e., prospective versus retrospective) c) these studies have been performed in highly selected groups which are not always representative of the community.

Additionally, the conversion rates and follow-up assessments have been discussed from different perspectives. For example, Daly et al., (2000) discussed their patients' conversion to AD in terms of a transition to a CDR rating of 1.0, but this CDR rating and clinically probable AD are not necessarily interchangeable (Petersen 2000).

Other studies (Ritchie 2000, Grober 1997) have quantified the degree of impairment based mostly on the neuropsychological performance rather than the clinical outcome. This may lead the clinician or researcher to overinterpret the degree of impairment in some individuals who may have had a lifelong memory problem and are now experiencing cognitive changes of aging. Although, there is evidence that elderly people with MCI are at risk of AD, in many studies case-selection strategies are based on screening instruments for AD, thus introducing a significant bias in the estimation of risk.

Therefore, it is likely that a combination of a good clinical interview and a complete neuropsychological battery as well as the use of other medical parameters, will provide the best tools to make the diagnosis of MCI and other transitional conditions.

### *MCI as a preclinical AD*

A more or less long pre-clinical stage of dementia has been demonstrated, corresponding certainly to a stage of the disease at which the pathology begins to have some repercussions on cognitive functioning, but when cognitive impairment are still not sufficient for the dementia criteria to be reached (Almkvist, 1993). Before people with AD become demented there is a long period in which they experience cognitive impairment. This period is called the preclinical phase of AD. It is important to identify subjects at this stage because they may benefit from early therapeutic interventions. However, these subjects should be distinguished from other subjects with cognitive impairment who do not have preclinical AD. This is difficult because there are no sensitive and specific markers of AD that can be used in subjects with MCI.

Progression of patients with MCI to “*questionable dementia*” may be confounded because the threshold for dementia diagnosis (APA, 1987) may vary considerably among clinicians and many require long observations periods, since the mildest forms of AD are marked by slow rates of cognition decline and predictable progression to more severe stages of AD occurs in MCI at a rate that depends in the severity of impairment at baseline (Morris 1993).

### *Laboratory evidence in pre-clinical AD*

Morris et al., (1991) reported that 10 autopsied “mild senile dementia cases “ with CDR= 0.5 showed sufficient neurofibrillary tangles and senile plaques in their neocortex to be diagnosis as AD. Gómez-Isla et al., (1996) further demonstrated that patients with mild AD and CDR scores of 0.5 had severe neuron loss in layers II and IV of the entorhinal cortex when compared to cognitively intact elderly patients. Structural and functional

neuroimaging methods have also demonstrated similar changes as described in AD. An asymmetry of parietal glucose metabolism, as visualized by PET, can precede cognitive deficits in early AD (Nordberg, 2001).

There are numerous reports of an association between the  $\epsilon$ 4 allele of the APOE gene on chromosome 19 and both late onset familial and late onset sporadic AD (Corder 1993, Mayeux 1993). The biological explanation of this association is that APOE genotype modulates the central nervous system (CNS) response to a variety of neurological insults (Laskowitz, 1998). Thus, the APOE-related risk could be modified by different factors. Disease progression does not seem to be related to presence of the  $\epsilon$ 4 allele (Basun, 1995). Since the APOE genotype alone does not provide sufficient sensitivity and specificity, it is not recommended as a diagnostic marker or predictive genetic test (National Institute on Aging, 1996). However, it could be utilized for early disease detection in combination with other biomarkers or diagnostic technologies (Small, 1995).

### **Neuropsychological predictors of pre-clinical AD and MCI**

In the past 20 years, several authors have attempted to find neuropsychological predictors of progression to AD. The value of neuropsychological measures in helping to identify very early cases of dementia has been documented by both cross-sectional and longitudinal studies. This approach has ensured comparability at this experimental stage of the concepts development and permit a cross-national estimates of prevalence, incidence, risk, and associated morbidity.

Neuropsychological measures are routinely used to quantify the degree of cognitive impairment in patients with dementia and are likely to be particularly helpful early in the course of a dementing illness when functional and behavioral disturbances are absent.

*Longitudinal clinical studies versus cross-sectional studies*

The majority of both longitudinal and cross-sectional studies report deficits on verbal episodic memory in their pre-clinical AD patients. That may be relatively mild and comparable to what is found in many normal elderly individuals and memory task.

However, when reviewing the literature, apparently neuropsychological measures found to be predictors of AD are not completely homogeneous across studies and some of the most important longitudinal studies found different cognitive predictors in pre-clinical AD. Masur et al., 1994, using a logistic regression model, found that verbal episodic memory measured with delayed recall, visual episodic memory measured with WAIS Digit Symbol (Wechsler, 1955) and semantic memory measured by verbal fluency were the best predictors on the Bronx cohort. Jacobs et al., (1995), in the Aging Project (North Manhattan) used a Cox regression analysis and only verbal episodic measured by Immediate recall in the Selective Reminding Test and Boston Naming test (Goodglass, 1986) and semantic memory (WAIS-R Similarities) (Wechsler, 1995) were significantly and independently associated with increased risk for subsequent AD diagnosis. In Framingham cohort, Linn et al., 1995, using stepwise regression procedures, showed that only verbal episodic memory could accurately predict the cognitive progression in pre-clinical AD. Five years later, Elias et al., (2000) increased from 55 in the study by Linn et al (1995) to 109 patients and amplified considerably the surveillance period. The pattern of tests predicting the pre-clinical AD was similar to reported by Linn et al., with one exception. Elias et al., did not find that lower Digit Span Test (Wechsler, 1981) scores were protective with regard to the development of AD. It could be due to the Linn's smaller sample of study participants and the difference in follow up in both studies.

Petersen and colleagues (Petersen, 2000) reported verbal episodic memory performance in an MCI group that was as impaired as that seen in mild AD. However, the same MCI group's performance on measures assessing other cognitive domains (naming, executive functions, etc) was equivalent to that healthy older controls. This study provides support for the hypothesis that verbal memory is the initial domain of cognition to be affected in the AD process, as 48% of Petersen et al., subjects develop probable AD within 4 years of diagnosis of MCI. Some other MCI report cognitive deficits similar to those described by Petersen and colleagues (Blesa 1996; Small, 2000).

Grober, (2000) investigated the estimation of the relative rates of dementia in initially non-demented subjects defined by baseline free recall from the FCSR test (Grober, 1997; Buschke, 1984). Their results showed that free recall powerfully predicts future dementia and supports the general view that the best approach to identifying persons at high risk for having dementia is to show the presence of cognitive impairment that is not due to other cognitive deficits by using a memory test that controls attention and cognitive processing. Other studies suggest that prediction of future dementia can be improved by combining memory indicators with an informant's perception of the patient's cognitive and functional status (Tierney, 1996). Likewise, in the European Kungsholmen project (Stockholm, Sweden), using a logistic regression analysis, it was observed that only the delayed recall item was a significant predictor of future development to AD (Small, 2000). In another European community-based study, the PAQUID cohort, Fabrigoule et al., 1998, using a multivariate approach of principal component analysis showed that pre-clinical deficits in AD are homogeneous and reflect the deterioration of a general cognitive factor which mainly includes verbal episodic memory and visual episodic memory.



Morris et al., (2001) in a prospective study of community-living elderly found that cognitive impairment in individuals with MCI was not limited to memory but involves other cognitive domains. He followed up 122 MCI patients to 9.5 years and concluded that MCI subjects progress steadily to greater stages of dementia severity at rates dependent on the level of cognitive impairment at entry. Bozoki et al., (2001) studied whether non-demented patients with impairment in memory and other domains were more likely than those with memory alone to develop AD. They concluded that, among non-demented elderly patients, memory loss alone rarely progresses to dementia but the risk of dementia is significantly increased among patients with more cognitive areas impaired beyond memory. These results are in agreement with Study III.

Several other longitudinal studies with smaller samples showed that for instance, that new learning (Grober, 1997), verbal abilities, including category and letter fluency, visuospatial and executive functioning (Small, 1997), verbal abilities (Howieson, 1997), verbal ability and visuospatial function (Devanand, 1997; Flicker, 1991 and 1993b; Bäckman, 1998) were the strongest predictors of pre-clinical AD. In addition, indices of psychomotor speed such as Digit Symbol Test (Devanand, 1997; Flicker, 1991; Tierney, 1996) were also considered valuable predictors of future cognitive decline. However, in light of objective episodic memory deficits in those individuals who develop dementia, it is interesting to note that there is conflicting evidence concerning the predictive power of subjective memory complaints for later development of dementia in otherwise healthy elderly individuals. A complete revision of the literature is presented in Table 3.

On the other hand, results from epidemiological longitudinal studies on incipient AD have also demonstrated that a variety of measures of episodic memory performance (Grober 1997; Herlitz et al., 1997; Jacobs et al., 1995; Johansson, 1997; Linn et al., 1995; Masur et al., 1994; Small et al., 1997, Petersen et al., 2000; Grober et al., 2000 et al., Marra 1999 et al., Rubin et al., 1999, Elias et al., 2000).

In any case, these results showed that consideration of cognitive domains other than memory can significantly improve the predictive value of neuropsychological testing in non-demented patients with a memory complaint. The majority of these results follow from the hypothesis that subjects with evidence of impairments extending beyond memory are more likely to have AD than those with only memory deficits (Almkvist, 1993, Bozoki, 2001, Arnaiz 2001).

**Table 3.** Neuropsychological findings in prospective longitudinal studies of pre-clinical Alzheimer's Disease and Mild Cognitive Impairment (Arnaiz, 2001)

Author	Number of subjects	Mean age	Exclusion criteria for dementia	Follow-up (Years)	Cognitive function predictors	Neuropsychological measures
Masur et al. (1989)	385	80.4	DSM-III-R <sup>(1)</sup>	1-2	Verbal episodic memory and visual episodic memory	Selective Reminding Test and Fuld Object Memory Evaluation
Tuokko et al. (1991)	45	71.5	DSM-III-R <sup>(1)</sup> NINCDS-ADRDA <sup>(2)</sup>	1-2	Verbal episodic memory	Selective Reminding Test
Flicker et al. (1991)	32	71.3	GDS <sup>(3)</sup> =3, 4	2	Verbal episodic memory and visual episodic memory	Shopping List Recall, Visual Recall Object recognition and identification
Mortimer et al. (1992)	65	63.8	DSM-III <sup>(1)</sup> NINCDS-ADRDA <sup>(2)</sup>	4	Verbal neuropsychological tests	Boston Naming test, Verbal recall (word list) and verbal fluency (animal naming).
Flicker et al. (1993)	86	69.8	GDS <sup>(3)</sup> =3, 4	2	Verbal episodic memory and executive functions	Shopping List Recall, Remote Memory questionnaire and Digit Symbol
Masur et al. (1994)	317	75-85	DSM-III-R <sup>(1)</sup> NINCDS-ADRDA <sup>(2)</sup>	4	Verbal episodic memory, visual episodic memory and semantic memory	Selective Reminding Test, Fuld Object Memory Evaluation and
Hänninen et al. (1995)	229	71.7	NIMH criteria Work group <sup>(9)</sup>	3.6	Verbal and visual memory.	Buschke Selective Reminding (Total recall), Visual reproduction (Immediate recall), verbal fluency (category), paired associated learning.
Jacobs et al. (1995)	443	73.3	NINCDS-ADRDA <sup>(2)</sup>	4	Verbal episodic memory and semantic memory	Selective Reminding Test and Boston Naming & Similarities, verbal fluency
Linn et al. (1995)	1045	65-88	DSM-III-R <sup>(1)</sup>	13	Verbal episodic memory	Logical memory-retained, Paired Associate Learning and Digit Span

**Table 3.** (Continued)

Tierney et al. (1996)	107	71.5	NINCDS-ADRDA <sup>(2)</sup>	2	Verbal episodic memory and executive functions	RAVLT and WMS-R Mental control
Devanand et al. (1997)	75	66.2	CDR <sup>(4)</sup> =3	2.5	Verbal episodic memory, verbal fluency, visuospatial memory, psychomotor speed	Delayed recall on the mMMS, long-term retrieval on the SRT, WAIS-R picture completion, WAIS-R (Digit Symbol, Block Design) and category naming in animals.
Dartigues et al. (1997)	2943	74.5	DSM-III-R <sup>(1)</sup> NINCDS-ADRDA <sup>(2)</sup>	1-3	Global cognitive performance, short-term visual memory, verbal fluency performance	MMSE, Benton's Visual Retention Test, Wechsler pair associated.
Grober et al. (1997)	537	79.3	NINCDS-ADRDA <sup>(2)</sup>	3	Learning	Free recall and cued selective reminding (FCSR) <sup>9</sup>
Bäckman et al. (1998)	24	83.7	MMSE<24 DSM-III-R <sup>(1)</sup> NINCDS-ADRDA <sup>(2)</sup>	3	Verbal episodic memory	Free and cued recall of words <sup>10</sup>
Fabrigoule et al (1998)	1159	72.9	DSM-III-R <sup>(1)</sup> NINCDS-ADRDA <sup>(2)</sup>	2	Verbal episodic memory, visual episodic memory and general cognition	MMSE, Benton Visual Retention Test, Verbal paired associates, Digit Span, Similarities, Cancellation task & Isaacs et Test
Rubin et al. 1998	82	71.6	CDR <sup>(4)</sup> =0.5	2	Verbal episodic memory	WMS: Logical memory
Marra et al. (1999)	45	66.5	NINCDS-ADRDA <sup>(2)</sup>	3	Verbal episodic memory and executive functions	RAVLT (Immediate recall) and DB Task

**Table 3.** (Continued)

Petersen et al. (1999)	76	80.9	Petersen criteria <sup>(5,6)</sup> CDR <sup>(4)</sup>	4	Verbal episodic memory, visual episodic memory and semantic memory	WMS-R: Logical memory & visual reproductions, RAVLT, Boston naming Test and controlled Oral Word Association test
Kluger et al. (1999)	213	71.2	GDS <sup>(3)</sup> =3	3.7	Verbal episodic memory	Paragraph Delay Recall
Grober et al. (2000)	68	79.4	DSM-III-R <sup>(1)</sup>	6.28	Verbal episodic memory	Free recall and cued selective reminding (FCSR) <sup>9</sup>
Small et al., (2000)	459	79.4	DSM-III-R <sup>(1)</sup> <sub>(7,8)</sub>	3-6	Verbal episodic memory	Delayed memory recall (MMSE Swedish version)
Chen et al. (2000)	120	78.2	ADRC protocol DSM-II-R CRD NINCDS-ADRDA <sup>(2)</sup>	10	Delayed recall and executive functions	Word List Delayed recall and TMT- B
Elias et al. (2000)	967	65-94	DSM-III-R <sup>(1)</sup>	22	Verbal episodic memory and abstract reasoning	WMS: Logical memory-retained and similarities
Ritchie et al. (2001)	308	<60	DSM-III-R <sup>(1)</sup>	3	Simple reaction time, reaction time on a dual attention task, semantic category fluency, delayed verbal recall, cued delayed recall, recall of name-face pairs, narrative recall, and copying of a complex design.	Examen Cognitif par Ordinateur (ECO) <sup>(11)</sup>

<sup>(1)</sup> DSM-III-R (American Psychiatric Association, 1987), <sup>(2)</sup> NINCDS-ADRDA (McKhann, 1984) <sup>(3)</sup> Global Deterioration Scale (Reisberg, 1982) <sup>(4)</sup> Clinical Dementia Rating (Hughes, 1982) <sup>(5,6)</sup> Petersen 1995;1996, <sup>(7,8)</sup> Fratiglioni 1992;1997, <sup>(9)</sup> Crook, 1998, <sup>(10)</sup> (Bäckman, 1998), <sup>(11)</sup> (Ritchie, 1993), <sup>(12)</sup> (Wechsler, 1973), <sup>(13)</sup> (Rey, 1959), <sup>(14)</sup> (Wechsler, 1973), <sup>(15)</sup> (Folstein, 1975).

As it is mentioned previously, the most salient predictor of AD appears to be different measures of episodic memory and learning. This finding is in concordance with cross-sectional studies that also found episodic memory to discriminate the best between AD, pre-clinical AD and controls as reported by Storandt,1989; Morris, 1991; Welsh, 1992; Bondi, 1994; Petersen, 1994; Smith, 1996; Grober, 1997; Almkvist, 1998; Arnáiz, 2000, (see Table 4).

**Table 4.** Cross-sectional studies in the detection of discriminative cognitive variables in MCI and early AD.

Author and year	Number of subjects	Mean age	Diagnosis	Diagnosis criteria	Cognitive function	Neuropsychological measures
Storandt et al., 1989	66	73.9	Very mild senile dementia	CDR=0.5	Memory, speeded psychomotor and language	WMS <sup>1</sup> : Logical memory
Morris et al., 1991	10	76.9	Very mild senile dementia	CDR=0.5	Verbal episodic memory	WMS <sup>1</sup> : Logical memory Associated Learning Test
Welsh et al., 1992	49	71.2	Mild Alzheimer's Disease	NINCDS-ADRDA	Verbal episodic memory	Delayed Recall (CERAD) <sup>2</sup>
Almkvist et al., 1993	30	72	Very mild dementia	DSM-III-R	Intelligence, verbal episodic and semantic memory, visuospatial function, primary memory and psychomotor speed.	WAIS-R <sup>3</sup> , WMS-R <sup>1</sup>
Petersen et al., 1994	106	80.7	Probable Alzheimer's Disease	DSM-III NINCDS-ADRDA	Learning with semantic cueing.	WAIS-R <sup>3</sup> , AVLT <sup>4</sup> , WMS-R <sup>1</sup> , WRAT <sup>5</sup> , COWAT <sup>6</sup>
Smith et al., 1996	66	79.8	MCI	Petersen et al. 1995	Delayed Recall	MOANS <sup>7</sup>
Arnaiz et al., 2000	90	64.5	MCI	Huddinge's criteria	Verbal episodic and semantic memory, visuospatial function and attention	AVLT <sup>4</sup> , WMS-R <sup>4</sup> , WAIS-R <sup>3</sup> , Trail Making <sup>8</sup>

<sup>1</sup>Weschler Memory Scale (Weschler, 1973), <sup>2</sup>The Consortium to Establish a registry for Alzheimer's Disease (Morris, 1989), <sup>3</sup>Weschle Adult Intelligence Scale-Revised Manual (Weschler, 1981), <sup>4</sup> Auditory Verbal Learning Test (Lezak, 1985), <sup>5</sup>Wide Range Achievement Test-Revised (Jastak, 1984), <sup>6</sup> Controlled-Oral Word Association Task (Benton, 1978), <sup>7</sup>Ivnik (1992), <sup>8</sup> Rey (1964).

Although episodic memory task appear to have the best predictive power to indicate early dementia development, it is still unclear which aspect of episodic memory is most vulnerable to dementia. For example, it is not known whether the deficits in memory performance of pre-clinical AD patients results from impairment in encoding, storage, or retrieval processes. Moreover, neuropsychological tests may differ in terms of their sensitivity and because of varying task difficulty rather than specific process tapped by the memory task.

*Limitation of neuropsychological predictors studies in pre-clinical AD and MCI.*

The risk to enter subjects at different stages of the disease as well as the use of different end-point criteria (functional and cognitive) represent the most confounding variables observed in this kind of study. In addition, MCI has been defined in most of the studies by the tests used to measure it, and the results of these measures have been used as validation of its definition and that is a nosological tautology (Ritchie, 2000). This is further explained in Study I (Chapter I).

The current apparent heterogeneity in some of these studies could also be explained by three methodological reasons: (i) the lag time between the evaluation of cognitive performance varies considerably between studies (ii) the specific properties of various tests commonly used are not fully understood (iii) test scores are often strongly collinear, essentially because common cognitive components are involved in different test (e.g. attention). It is expected that our approach to identifying persons at high risk for having future dementia is to show the presence of a memory impairment that is not caused by other cognitive deficits (i.e., deficits in attention, language).

Additionally, neuropsychological measures cannot fully distinguish between different types of dementia, because there is a substantial overlap in neuropsychological profiles. This problem could be partly avoided through longitudinal studies, in which the decreases in cognitive test scores that are observed can be more reliably attributed to age-related cognitive deterioration. However, longitudinal studies are more likely to yield negative results than cross-sectional studies as a consequence of the smaller age differences usually assessed and of the sampling biases inherent to the methodology. For example, it has been persistently observed that, in longitudinal studies, the healthier successfully followed up, a phenomenon referred to as selective attrition (Flicker, 1991). In addition, the validity of this kind of studies, especially comparisons of different age groups, is undermined by the presence of possible uncontrolled cohort effects -between group differences-.

Conversely, because longitudinal cognitive deterioration is a defining characteristic of AD, follow-up cognitive test results can be used to validate baseline diagnosis retrospectively and thus help to determine optimal diagnosis criteria and behavioral predictors of future cognitive loss. Hence, the combination of cross-sectional and longitudinal data might also be useful in tracing the sequential development of cognitive deficits in aging and dementia.

It is important to mention that the results of cognitive investigations of MCI and preclinical AD also have important implications for the normative studies of commonly used neuropsychological measures (Sliwinski, 1998; Petersen, 1994).

The rates of change of subjects with MCI are different from control subjects and AD patients. This could reflect that it is possible that the measuring instruments are not linear and are less sensitive to change in the more mild states (Petersen, 1999).



To sum up, current data suggest that the concurrent considerations of multiple cognitive AD risk factors are basically those involving memory deficits appearing primarily in episodic memory. In the early clinical stage of the disease, evidence points to the fact that AD is characterized by numerous impairments affecting multiple cognitive domains including episodic memory, verbal abilities and learning, visuospatial function, attention and executive functions.

### **Alzheimer's Disease (AD)**

Alzheimer's Disease is a disorder characterized by progressive dementia with typical neuropathological findings and neurochemical deficiencies in selective vulnerable regions of the brain. Dementia, a main clinical feature of AD, is a clinical syndrome characterized by significant loss in clear consciousness of intellectual abilities, such as memory, that are severe enough to interfere with social and occupational functioning.

The incidence of AD increase exponentially with age (Jorm & Jolley, 1998) and it is approximately 14 times higher among persons older than 85 years compared to those between 65 and 69 years of age (Hebert et al., 1995) and women have higher risk of developing AD than men (Fratiglioni et al., 1997).

#### *Diagnostic criteria*

Several sets of criteria have been developed, but at the time the work of this thesis was done the two widely and most frequently used were the criteria suggested by the National Institute of Neurological Disorders and Communicative Disorders Association (NINCDS-ADRDA) Work Group (Mckhann, 1984). Between 85% (Tierney, 1988) and 100% (Martin, 1987) of the cases satisfying there criteria have later been found to have the neuropathological changes characteristics of AD.

The second criteria was the Diagnosis and Statistical Manual, 3<sup>rd</sup> edition revised (DSM-III-R), (APA, 1987).

Both set of criteria are compatible and have in common two basic requirements: 1) that dementia, defines as the global and progressive loss of memory and other intellectual functions in an alert adult, has a gradual onset and progressive course; and 2) that other neurological, psychiatric, and medical disorders with the potential to impair cognition and excluded.

The NINCDS-ADRDA criteria distinguish 3 levels of diagnosis confidence: 1) probable AD where the dementia is a single disorder with typical insidious onset and progressive course; 2) possible AD where there are atypical features or variations in the clinical course, or where an other brain or systemic disorder in present, but not considered to be the cause of the dementia; 3) definite AD when the clinically diagnosed disorder is verified histopathologically .

Most recently develop are the International Classification of the Disease, 10<sup>th</sup> edition revised, ICD-10 (World Health Organization, 1992) and DSM-IV (APA, 1994) criteria. ICD-10 distinguish two subtypes of AD according to the age of onset and difference in clinical picture: with early onset below 65 years and with late onset at 65 years or more. DSM-IV criteria suggest the diagnostic term “dementia of Alzheimer type” and emphasize multiple cognitive deficits, memory impairment being obligatory. DSM-IV further subdivides AD into subtypes according to the predominant feature of the clinical presentation; namely with delirium, with delusions, with depressed mood, and uncomplicated.

These different systems of diagnostic classifications have resulted on various prevalences of dementia in a large population-based study, giving a range between 3 and 29% (Erkinjuti, 1997). These disagreements among standardized clinical criteria

emphasize that it is essential to validate them in relation to the histopathological diagnosis of the disease.

#### *Etiology and risk factors*

It is widely recognized that AD has a complex and heterogeneous etiology, which may lead to a common pathogenetic pathway. There is an increasing number of autosomal-dominant gene mutations which have been identified to cause the predispose to the disease: mutations on chromosome 21, 14, 1.

There are rare forms are associated with an early-onset, more aggressive clinical picture and early death.

So far the established risk factors for sporadic AD, which may constitute more than 90% of cases, include old age, a family history of dementia and apolipoprotein  $\epsilon 4$  (APOE) genotype, more specifically the  $\epsilon 4$  allele of the apolipoprotein  $\epsilon$  gene on chromosome 19. There are some other well-established risk factors such as female gender, head injury, a family history of Down's syndrome and vascular risk factors, i.e. hypertension, myocardial infarction and ischaemic white-matter lesions.

## AIMS OF THE THESIS

The aim of the studies described in this theses was:

### General:

- To investigate which variables predicted Alzheimer's Disease (AD) in subjects with Mild Cognitive Impairment (MCI).
- To cognitively characterize the MCI group by using longitudinal and cross-sectional studies.

### Specific:

- To optimize the best neuropsychological, neuroimaging and genetic combination in order to predict future development of AD in the MCI group.
- To investigate the reliability of MCI criteria by comparing two clinical-based MCI samples as well as survival outcome and MCI conversion rates to AD.

We used a multidisciplinary approach with cognitive, non-cognitive, and genetic and brain imaging variables. This work is predicated on the notion that the distinction between the cognitive changes of aging and very early AD is well delineated.

## **STUDY SAMPLE AND METHODS**

A comprehensive description of study samples used and methods employed, with reference to the relevant publications can be found in the chapters I-III. An overview of the demographic characteristics and global cognitive status of the study sample, as well as some additional theoretical and methodological aspects which were not addressed in the original studies is given below.

### **Study samples**

All patients and subjects were investigated for suspected dementia at the in-and out-patient Department at the Geriatric Clinic, Huddinge University Hospital, Sweden.

Sources of referral included general practitioners, neurologist, specialist of occupational medicine, or individuals seeking help directly because self-experienced memory problems. The empirical studies presented here are based on regular clinical neuropsychological examinations. Descriptive statistics for the study samples from Studies I to III are given in Table 5.

DSM-III-R criteria were used for diagnosis of dementia and NINCDS-ADRDA criteria for the diagnosis of probable AD. The patients with MCI did not fulfil diagnosis for dementia or probable AD. The objective decline of the MCI patients was 1.5 SD below the average for their age on neuropsychological tests, representing one or more areas of cognition. Further description of MCI diagnosis is in Table 13, Study III and Appendix.

**Table 5.** Descriptive statistics of the study samples.

<b>SUBJECTS</b>	<b>N</b>	<b>M/F</b>	<b>Age (years)</b>	<b>Education</b>	<b>MMSE</b>	<b>FSIQ</b>
<b><u>Study I</u></b>						
AD	94	33/61	65.7 (8.5)	9 (3)	19 (5)	71.9 (8.6)
MCI	90	45/45	64.3 (9.5)	10 (2)	26 (2)	90.6 (8.9)
C	79	41/38	64.6 (11.1)	10 (2)	28 (1)	101.1 (3.0)
<b><u>Study II</u></b>						
P MCI	9	3/6	64.9 (8.3)	11 (2.2)	26.7 (1.8)	80.1 (3.5)
S MCI	11	5/6	60.1 (8.4)	11 (2.0)	27.2 (2.9)	85.8 (2.9)
<b><u>Study III</u></b>						
MC MCI	170	70/100	78.5 (8.4)	13.2 (3.1)	26.8 (2.4)	90.2 (3.1)
KI MCI	133	74/59	69.5 (5.8)	9.3 (3.0)	25.2 (2.7)	87.4 (3.9)

**AD-** Alzheimer's Disease; **MCI-** Mild Cognitive Impairment; **C-** Controls; **P MCI-** Progressive Mild Cognitive Impairment; **S MCI-** Stable Mild Cognitive Impairment; **MC MCI-** Mayo Clinic, Mild Cognitive Impairment patient; **KI MCI-** Karolinska Institutet, Mild Cognitive Impairment patient. Values in parentheses are SD.

### *The Control Group*

In the I and III Study, a group of 90 and 75 healthy aged individuals served as controls respectively. In Study III the controls were stratified according to age- and years of

formal education-. An average scores for all the neuropsychological tests were measured for all straits.

The subjects included in the group control were selected from a pool of individuals above the age of 60, having been examined concerning their prior and present health status with the same methods as the patients.

#### *Medical examinations*

All patients were examined according to a comprehensive procedure, including a somatic examination, neurological status, psychiatric status , blood test (blood hemoglobin, sedimentation rate, complete blood cell count), serum tests (glucose, sodium, potassium, calcium, chloride, phosphate, iron, creatinine, albumin, ASAT, ALAT, cholesterol, triglyceride, thyroid hormones, vitamin B<sub>12</sub>, folic acid, HIV, Borrelia, syphilis), urinalysis (glucose, protein, pH, microscopic examination), APOE genotyping, CSF ( Tau concentrations [pg/ml]), ECG, EEG, chest radiography, SPECT, MRI and neuropsychological examination (see below).

#### *Follow-up examinations*

Subjects were reevaluated every 6 to 12 months and received the same comprehensive clinical routine and neuropsychological assessment as well as an informant interview regarding behavioral and functional status. Subjects with any evidence of clinical deterioration precipitated a repeat neurological examination. In these cases, a consensus diagnosis was again rendered from a multidisciplinary team including physicians, neurologist, geriatricians, neuropsychologist and nurses. None of the patients included

in Study I-III were under any acetylcholinesterase inhibitors treatment at initial or follow-up evaluation.

### **Cognition and Neuropsychological assessment**

The elementary concepts of most models of cognition involve the sensory motor interface, sensory memory, attention, primary memory, secondary memory, and executive functions.

*Sensorimotor and Motor functions.* The sensory organs provide information about the external world to the individual. Visual information is projected to the occipital lobe, auditory information to the superior temporal lobe, proprioceptive information to the anterior parietal lobe, and olfactory information to the olfactory cortex in the basal forebrain (see e.g. Kandell et al., 1991). The percepts resulting from transformed sensory information in one basis for cognitive functioning. Following registration of sensory stimuli, the corresponding sensory projection areas are activated, which can be confirmed by brain imaging (Ronald & Seitz, 1991). AD may not affect visual acuity *per se* and color discrimination remains intact, but visuoperceptual deficits are common (Mendez, 1990) and more generalized when eye movements are also impaired. They show up most prominently on tests requiring visual discrimination, analysis, spatial judgements, and perceptual organization. Olfactory acuity, as measured by recognition, is typically impaired early in the course of the disease (Koss, 1988, Devanand 2000).



The sensory organs connect to the cognitive system by modality-specific sensory memories (e.g. iconic memory, echoic memory), which are characterized by a very rapid access and decay (Crowder, 1971). Processes of selective attention largely determine the output from sensory memories. Sensory and motor functions are not examined in this research.

### *Attention*

The overwhelming influx of sensory and internal stimulation is reduced by a system of processes that may be called attention. Mirsky (1989) has described attention in terms of four components: (i) focus and execute, (ii) sustain, (iii) encode and (iv) shift. These four components of attention are supported by different brain regions. The focus and execute component is supported by superior temporal and inferior parietal cortices as well as by structures that comprise the corpus striatum, which may be evaluated by task drawing in psychomotor speed, such as the Digit Symbol test from WAIS-R (Wechsler, 1981) or Trail Making Test (Rey, 1959). The sustain component is supported by the reticular formation, and reticular thalamic nuclei and may be evaluated by continuous performance tests, such as Simple Reaction Time. The encode component, relies on hippocampal formation, and may be evaluated by, for example, Arithmetic test from WAIS-R. The shift component is supported by prefrontal regions and may be evaluated by the Wisconsin Card Sorting test.

Attentional deficits are part of the symptom picture of AD, although all patients may not display such problems, particularly in the early stages.

Two measures of attention were used in this thesis:

Digit Symbol test from WAIS-R (1981), which consist of four rows containing 100 small black squares, each paired with a randomly assigned number from one to nine.

Above these rows is a printed key that pairs each number with a different nonsense symbol. The task is to fill in the black spaces as quickly as possible for 90 seconds. The second test used was Trail Making Test (Rey, 1959). The subject must first draw lines to connect consecutively numbered circles on one work sheet (Part A) and then connect the same number of consecutively numbered and lettered circles on another worksheet by alternating between the two sequences (Part B).

Both tests assessed the focus and execute component of attention according to Mirsky (1989).

### *Primary Memory*

Primary memory (PM; approximately equivalent concepts are: short-term memory, working memory, immediate memory) is characterized by a rapid access of information, a limited capacity with regard to number of active information chunks and duration of unprocessed information, and specificity with regard to input modality (e.g., auditory and visual buffers). Usually, the concept of PM is equivalent to the active part of secondary memory.

When subjects are asked to repeat visually or auditory presented words, primary sensorimotor cortex as well as supplementary motor areas and insular cortex are activated bilaterally (Raichle, 1991). Lesion studies show that the temporal lobes are involved in PM, the left for auditory-verbal material and the right for visuospatial material (Milner, 1971). When subjects are performing tasks that require a mental record of recently presented words, an increased activity in prefrontal areas has also consistent with the notion that the prefrontal cortex temporarily stores or selectively activates information (Goldman-Rakic, 1990). Studies of frontal lobe lesions are also consistent with the notion that the prefrontal cortex temporarily stores or selectively

activates information (Goldman-Rakic, 1990) following a perceptual encoding in the temporal lobes adjacent to the primary projections areas involved (Kosslyn & Koenig, 1992).

The only measures of PM were used in this research are the following: Digit Span Forward and Backwards, administered according to an up-and-down technique. Both tests consist of seven pairs of random number sequences that the examiner reads aloud at the rate of one per second, and both thus involve auditory attention. In combining the two digits span tasks to obtain one score, which is the scores used in this thesis.

### *Secondary Memory*

Secondary memory (SM; or long-term memory) is characterized by a virtually unlimited capacity for storage of associatively organized information. However, the input of new information is limited in time and has been estimated to be in order of seconds (Simon, 1974). The retrieval of information has a variable access time varying from immediate through delayed to no success at all due to the specific circumstances at retrieval (e.g. type of retrieval cue, degree of elaboration of the target). The content of SM is concerned with propositional structures often termed declarative memory and actionlike structures usually called procedural knowledge (Squire, 1997). Declarative knowledge may be facts related to the person (e.g., data of birth) or generic knowledge (e.g., Paris is the capital of France), which is often referred to as *semantic memory*.

Declarative knowledge may also be time-associated single events acquired in a particular temporal-spatial context (e.g., yesterday, I ate sole for dinner), which is often referred to as *episodic memory* (Tulving, 1983).

According to studies of memory-impaired patients, PET-examinations during memory activation, and studies of memory in the monkey, the hippocampus and anatomically

related areas are associated with the formation of episodic memories (Duara, 1986; Squire 1997; Herholz, 1999). Episodic memory may rely on a set of brain structures, involving both the hippocampal formation and frontal regions. Perceptual input arrives to the parahippocampal gyrus and the perirhinal cortex, then projects to the entorhinal cortex and finally to the hippocampus (Kosslyn & Koenig, 1992). Hippocampus also receives input from the hypothalamus, which is believed to be related to motivation; moreover, hippocampus receives information from the amygdala, which is thought to be crucial for encoding of emotional information.

Activation and lesion studies suggest that the posterior association cortices may be particularly crucial to retrieval of overlearned information from semantic memory; for verbal material the left hemisphere is most involved, and for visuospatial material the right hemisphere is most involved (Lezak, 1995).

The procedural part of SM is often represented by rules of action such as “if condition X, then perform Y”, which may be organized in large sets as key-ready programs or subroutines for both mental and motor tasks (e.g., playing the piano, performing arithmetics. These programs are conceived as the counterpart of thinking, reasoning, problem solving, and all kinds of processing with both verbal and visuospatial information. The application of these programs is thought to be accomplished without conscious recollection. Thus, the *procedural memory* is involved in activation and retention of skills; certain movements and assemblies of motor coordination are stored as ready-made programs of execution. The structures responsible for learning, storage, and reinstatement of skills are only poorly understood, but some evidence points to the importance of the cerebellum in combination with certain basal ganglia structures (e.g., the striatum) (Soliveri, 1991; Thompson, 1988).

Several measures of episodic memory were used in this thesis: First, the Auditory Verbal Learning Test (AVLT) (Rey, 1959), which easily administered test measures immediate memory span and provides a learning curve, reveals learning strategies, short-term and long-term retention and allows for a comparison between retrievals efficiency and learning. It consist of five presentations with recall of a 15-word list and retention is examined after 30 minutes (delay AVLT).

Rey Figure Test (Rey, 1941) (copy delayed recall) assesses both perceptual and organization and visual memory. The test material consist in a reproduction of a complex figure. The subject is first instructed to copy the figure. The reproduction of each unit can earns as many as 36 points. After 30 minutes, the patient is asked to draw the complex figure again.

The Word list Free Recall is measured by the ratio of correct and false answers of word list recognition presented as deprime ( $d'$ ) (Bäckman, 1994) which was developed at the Stockholm Gerontological Research Center for the evaluation of secondary memory.

The last tests used to measure this cognitive function was Logical Memory I, from the WMS-R (Weschler, 1981), which included: story free recall, cued recall and delayed recall (story recall after 30 minutes, without interference). The examiner reads two stories, stopping after each reading for an immediate free recall. There is a delay recall trial after 30 minutes. If the patient showed difficulties recalling the story after 30 minutes, the neuropsychologist or psychometrician is allowed to provide standardized cues in order to facilitate the recall.

Two measures of semantic memory were used: total scores of Information and Similarities tests, both from the WAIS-R (Weschler, 1981). Information test refers to

general knowledge. The items are arranged in order of difficulty from the four simplest, to the most difficult. Similarities is a test of verbal concept formation where the subject must explain what each of pair words has in common. The word pairs range in difficulty from the simplest to most difficult.

### *Complex tasks*

When subjects solve a problem or perform a sequence of manipulation (e.g., talking, reading, writing, constructing, thinking, organizing, planning, etc) rather than produce a single answer or response, the task requires an interaction among different cognitive functions. Such tasks may be language-based or they may draw on visuospatial skills as in the performance tests of WAIS-R (Wechsler, 1981). The solution process in such tasks is driven by the *executive function*, and it is dependent on the underlying knowledge structure. The executive function may be thought of as a supervisory attentional system that determines the sequence of actions to be executed, which is particularly important when several actions are possible. The executive functions may be conceptualized as having four components: 1) volition, 2) planning, 3) purposive action, and 4) effective performance. Each involves a distinctive set of activity-related behaviors. Routine actions may be decentralized and control of these actions may be local and unconscious, whereas non-routine actions have to be planned, organized and executed step by step in order to be simultaneously evaluated. The idea of an executive system is present in many models of cognition (see e.g., Luria 1966, Lezak 1995) and, depending on the task involved, also to other regions.

In this thesis, no complex language tasks have been included, but one measure of complex visuospatial function is used: total scores from the Block Design test from the WAIS-R. This is a construction test in which the subject is presented with red and white

blocks, four or nine, depending on the item. The task is to use the blocks to construct replicas of two blocks constructions made by the examiner.

The solution of this test is determined by multiple cognitive functions, although an essential component is form comprehension, which drawn in particular on the right parietal hemisphere, as indicated by lesions as well as PET imaging studies (Nordberg, 2001).

### *Intelligence*

At the most generalized level, cognitive functioning may be described as intelligence. In the present research, two measures of general intelligence were used: the MMSE (Folstein, 1975) and the full-scale intelligence quotient (FSIQ) from the WAIS-R (Wechsler, 1981). The FISQ was estimated from the six WAIS-R (Wechsler, 1981) tests used.

All patients were tested by the same experienced neuropsychologist as part of the regular clinical examination. All patients did not complete all test due to restrictions in time for assessment, sensory deficits, motor impairment, psychiatric problems, and unwillingness to complete examination.

### **PET Method**

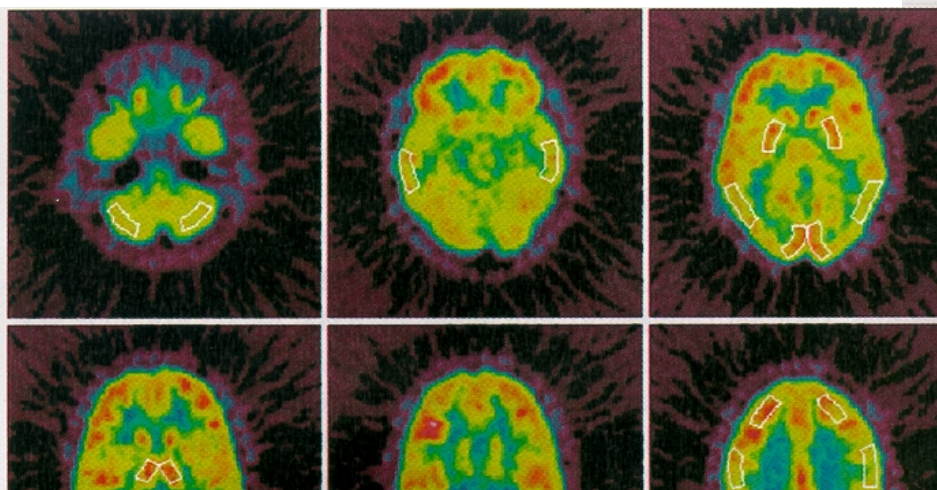
#### *Recording standards and procedure*

All PET investigations were obtained at the PET-Center, Academic Hospital, Uppsala University, with either a GEMS 2048-15 or GEMS 4096-15WB scanner (General Electric Medical System, Wisconsin, USA). Both scanners have a spatial resolution of 6 mm (full width at half maximum) covering 100 mm (15 continuous tomographic slices, each with a thickness of 6.5 mm). Multiple slices were recorded parallel to the cantho-

mental line. Venous blood was arterialized by heating of the hand and collected from the vein at the back of the hand for measurements of plasma radioactivity concentrations and of plasma glucose levels. Accumulation of the tracer 2-[18F]-fluoro-deoxyglucose in the brain was followed for 60 minutes and all together 15 samples were taken to outline the variation in plasma 2-[18F]-fluoro-deoxyglucose concentrations during the study. During the uptake of tracer, subjects were deprived of visual and acoustic sensory stimulation. The cerebral metabolic rates of glucose (CMRGlu) were expressed in micromoles per minute per 100 cm<sup>3</sup> and calculated by a graphical method (Patlak et al, 1983) using “lumped constant” equal to 0.418 for the correction of differences in utilization between 2-[18F]-fluoro-deoxyglucose and glucose.

#### *Regions of interest (ROI)*

Regions of interest were defined on transaxial slices in relation to the slices where the basal ganglia (BG) structures were best visible: temporal cortex (13 mm below the BG level), temporo-parietal association cortex (BG level and 13 mm above the BG), frontal association cortex (26 mm above BG), primary sensorimotor cortex (26mm above BG), primary visual cortex (BG level), putamen (BG level), and cerebellum cortex (slice with the best representation). ROIs are shown in Figure 2.





*Interobserver reliability*

These anatomical areas were identified by comparing the PET images to a standard anatomical atlas (Nieuwenhuys et al, 1979). Since they were delineated manually, all image analysis were performed by two individuals and interobserver reliability coefficient (Kendall's index of concordance) were calculated for all standardized regions of interest. These ranged from 0.70 (frontal association cortex) to 0.85 (putamen). Paired t-test did not reveal significant differences between two measures of each region.

Inter-observer variability expressed as a measurement error  $E = \sqrt{(\Sigma d^2/N)}$ , ranged from 4% (cerebral cortex and putamen) to 12% (temporal cortex, 13mm below BG level). Raters were blind to the clinical diagnosis and severity of disease, but they were informed that the patients were investigated for suspected dementia.

*Rationale for the choice of the reference region*

Absolute CMRGlu were normalized to the sensorimotor cortex glucose metabolic rates (regional CMRGlu divided by left and right averaged sensorimotor cortex CMRGlu), to reduce intersubject variability. We selected the sensorimotor cortex for normalization because of its reported lack of involvement in mild to moderate stages of the disease (Duara et al., 1986) as also confirmed in postmortem studies of AD brain

(Brun & Gustafson, 1976). This decision was supported by the absence of significant differences in absolute CMRGlu for this region between patients and controls.

### *Metabolic ratios*

Herlitz et al. (1990) developed the metabolic ratio as a diagnostic index for AD and demonstrated that it had a high accuracy in discriminating patients from controls.

Another studies has shown that the metabolic ratio is highly correlated with the cognitive deficits of patients with AD (Mielke et al., 1991). Therefore, we chose this parameter to supplement the standard region CMRGlu analysis, since it provides in a single number a metabolic pattern typical for the disease. The metabolic ratio was calculated as a sum of typically affected regions in nominator (frontal association cortex, temporal cortex 13 mm below the BG level, temporo-parietal association cortex at the BG and 13 mm above the BG level) divides by the sum of typically least affected regions in denominator (primary sensoriomotor cortex, primary visual cortex, putamen and cerebellum).

### **APOE genotype determination**

DNA was extracted from peripheral white blood cells using standard methods. The APOE genotype was determined using a micro-sequencing method on microtiter plates (AffiGen APOE Sangtec Medical, Bromma, Sweden).

### **Statistical analysis**

Prior to statistical analysis, the normality of distribution of the neuropsychological data and PET data was tested by Schapiro-Wilk W test. After this condition has been satisfied, parametric tests were employed: one way analysis of variance (ANOVA) with

Scheffé 's post hoc tests for comparisons among several groups (Study I) and Student's t-test for comparison between means of two groups (Study II and III, Chapters II and III respectively).

Discriminative accuracy of combination of different neuropsychology measures (Study I) was evaluated by discriminant analysis with "leaving one out" (jackknife method).

In Study II and III, linear logistic regression were constructed were in order to study which baseline PET and neuropsychological variables respectively, best predicted diagnosis group membership after the follow-up when adjusted for baseline demographics.

In Study III, a global test for proportions was used to check the assumptions of the Cox proportional hazard model, which was then used to assess risk factors for incident AD among MCI patients. Potential risk factors in the hazards analysis included age, years of formal education and APOE  $\epsilon$ 4 genotype. The statistical difference of the two curves was tested by a Long Rank test.

Missing data is a frequent problem in prospective studies of MCI (Dartigues, 1997) and often it is not randomly distributed among subjects since the distribution of missing values in moderate to severe stages is larger than in early stages.

If more than one cognitive test is used in a multivariate analysis, the number of subjects with missing data is relatively high. This problem is often solved by including only subjects with complete data, which causes considerable bias because it oversamples subjects with a relatively good cognitive performance. For this reason, we substituted the missing cognitive data in Study I in order to include all subjects in the multivariate analysis. Subjects were given the average score of the study population for that test (single imputation approach) (Small, 1997). To investigate how the substitution influenced the outcome, we performed the ordinal regression analysis with and without

the subjects with substituted data. The results from these analysis were comparable, which indicates that no major error was introduced by substituting the data. We also added a variable indicating whether a value for a test was substituted or not (Dartigues, 1997). This variable was not significant, which again indicates that no major error was introduced by substituting the data.

In Study II and III we left subjects with missing values because the number of subjects with missing data was small (5% to 7% respectively) and it is not likely that a major error was introduced.

In both Study I and II, we present the raw psychometric data. In Study II, due to comparison purposes, we standardized all the neuropsychological data.

There is some debate whether cognitive data should be corrected for age and education because these variables are also predictors of AD (Sliwinski, 1997). It is argued that the lower cognitive performance of elderly subjects or subjects with a low educational level is in part due to the fact that these subjects are in the preclinical stage of AD. The correction of the cognitive data for age and education will therefore presumably reduce the sensitivity for detecting subjects with preclinical AD. However, if data are not corrected for age and education, the specificity will decrease because there is ample evidence that even after exclusion of subjects with major neurological, psychiatric, or somatic disorders or preclinical AD, there is an affect of age, education, and sex on cognitive performance (Sliwinski, 1997). For that reason we chose to correct the cognitive data for age and education. In order to increase the sensitivity for detecting subjects with preclinical AD, we always entered age and education in the statistical multivariate models used in this thesis.

### **Ethical approvals**

The study protocols, including informed consent from all patients and subjects, were approved by the Ethical Committee, Huddinge University Hospital: No 88/95, decision date 950324 (PET investigation), No 153/95, decision date 951030 (measurements of APOE genotyping).

# **RESULTS**

## **Chapter I**

### **Psychometric discrimination of Alzheimer's Disease and Mild Cognitive Impairment**

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## **ABSTRACT**

Mild Cognitive Impairment (MCI) refers to a boundary between normal aging and dementia. People with MCI have a high risk of developing dementia, frequently Alzheimer's disease (AD). In order to develop a reduced-length psychometric battery, we performed an extended neuropsychological battery of tests on the classification of 94 individuals with AD, 90 individuals clinically diagnosed as MCI, and 79 normal elderly subjects. Using discriminant analysis techniques, it was possible to achieve a high rate of correspondence between clinical and present statistical classification of the three groups (85% ). We found that specific ability domains, particularly episodic memory, as well as semantic memory, visuospatial function and attention contributed to the two discriminant functions. The first and dominant discriminant function, which only included five tests, discriminated the three groups according to a global cognitive function. These findings demonstrate the possibility of developing reduced-length cognitive batteries so as to identify MCI in subjects at risk of developing AD.

## **INTRODUCTION**

Mild Cognitive Impairment (MCI) is an operational term which refers to a condition where there is evidence of subtle cognitive deficits in older subjects before functional impairment is evident and dementia is diagnosed (Flicker, 1991 ). Several studies have indicated that individuals with MCI are at an increased risk of developing Alzheimer's disease (AD), ranging from 1- 25% per year (Dawe, 1992), 24% of MCI patients

progressed to AD in 2 years, (Tierney, 1996), whereas the latest study indicated that the progression of MCI subjects was 55% in 4.5 years (Petersen, 1999).

Episodic memory is severely disturbed in the early clinical stage of AD with simultaneous impairments being apparent in multiple cognitive domains such as verbal and visuospatial processes, as well as attention and executive functioning. In contrast, primary and procedural memories, as well as sensory and motor abilities may be relatively well preserved (Tierney, 1996). Previous longitudinal clinical studies on AD, healthy elderly adults and non demented memory impaired subjects, that have used comprehensive neuropsychological batteries have found a number of factors relating to the future development of dementia. Among these, significant predictors include verbal abilities such as naming and category fluency. Indices of psychomotor speed such as Digit Symbol test (Almkvist and Bäckman, 1993; Almkvist, 1998) and visuospatial function (as exemplified by the Block Design Test; Devanand, 1997), have also been found to be sensitive markers for dementia development. However, the most salient predictors appear to be different measures of episodic memory function (Full., 1990; Flicker, 1991 & 1993; Toukai, 1991; Awe, 1992; Bond, 1994; Petersen, 1995; Tierney, 1996; Devanand , 1997; Almkvist and Bäckman, 1999). Using a discriminant analysis approach, Storandt and Hill (1989) found that a battery involving three tests (Logical Memory, Boston Naming, and Digit Symbol) could separate AD patients according to the Clinical Dementia Rating (Hughes , 1982) with mild dementia (CDR=1 ) and patients with mild cognitive impairment (CDR=0.5) from healthy aged individuals (CDR=0), with a high degree of correct classification. Welsh (1991) and Morris (1991) used the Consortium to Establish a Registry for Alzheimer's disease (CERAD) database



to demonstrate that episodic memory measures such as Delayed Recall, were sensitive for identifying patients with AD. Another study (Almkvist and Bäckman, 1993) suggested that three types of cognitive function namely memory, speeded psychomotor performance and language are involved in mild dementia.

Epidemiological studies on incident AD have demonstrated that a variety of measures of episodic memory performance (Fuld, 1990; Morris, 1991; Tuokko, 1991; Flicker, 1993) are reliable predictors of those individuals who will develop AD within a few years. Such distinctions may be critical in predicting future levels of functioning and may guide the design of relevant treatment protocols.

In the current study, we administered a battery of neuropsychological tests chosen to represent those cognitive domains that have previously been reported to distinguish early AD from normal aging (Welsh 1991; Almkvist and Bäckman, 1993; Tierney, 1996; Almkvist, 1998). The major purpose of the investigation was to find the most discriminative neuropsychological tests within a comprehensive cognitive test battery to detect MCI subjects. Detection was studied by contrasting individuals diagnosed as AD, MCI with healthy controls. This issue is of particular importance in the reliable detection at early stage AD, as well as for providing a shorter and more sensitive neuropsychological battery of tests.

## MATERIALS AND METHODS

### *Study Sample*

Ninety-four patients with AD, 90 patients with MCI and 79 healthy elderly subjects, were selected from the Huddinge University Hospital registry (Stockholm, Sweden). The control group comprised subjects who were recruited among relatives of dementia patients at Huddinge Hospital. They were examined as to their prior and present health status using the same protocols as for the patients (see below). None of the controls fulfilled the inclusion criteria used for MCI subjects.

Demographic data were analyzed by between group analysis of variance (ANOVA). The three groups were not significantly different with respect to either age ( $F[2,26]=0.43$ ;  $p<0.65$ ) or education ( $F[2,18]=2.11$ ;  $p<0.10$ ). The AD, MCI and control groups differed significantly in terms of their MMSE scores (Folstein, 1975), ( $F[2,260]=201.9$ ;  $p<0.0001$ ). Demographic characteristics of the three groups are shown in Table 6.

	<b>AD</b>	<b>MCI</b>	<b>Control</b>
<b><i>n</i></b>	<b>94</b>	<b>90</b>	<b>79</b>
<b>Sex (m/f)</b>	<b>33/61</b>	<b>45/45</b>	<b>41/38</b>
<b>Age (years)</b>	<b>65.7±8.5</b>	<b>64.3±9.5</b>	<b>64.5±11.1</b>
<b>Range</b>	<b>40.9-80.2</b>	<b>47.9-81.4</b>	<b>32.2-80.9</b>
<b>Education (years)</b>	<b>9±3</b>	<b>10±2</b>	<b>10±3</b>
<b>Range</b>	<b>4-18</b>	<b>6-17</b>	<b>6-19</b>
<b>MMSE</b>	<b>19±5</b>	<b>26±2</b>	<b>28±1</b>
<b>Range</b>	<b>10-28</b>	<b>20-30</b>	<b>26-30</b>

## *Diagnosis*

The diagnosis of AD was consistent with the criteria of the National Institute of Neurological Disorders and Stroke, Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKahn, 1984) and DSM-IV (American Psychiatric Association, 1994). MCI was defined in patients with cognitive impairment assessed with neuropsychological tests which fulfilled the criteria for stage 3 of the Global Deterioration Scale (GDS) (Reisberg, 1982) but lacked symptoms severe enough to fulfil the DSM-IV criteria for dementia. The objective decline was 2 S.D. below average for their age on neuropsychological tests representing one or more areas of cognition. All these subjects had normal ability to manage their daily life activities.

## *Procedure*

Controls and MCI patients lived in the community independently and in some cases an interview with a close informant was performed. All subjects were examined according to the same comprehensive procedure, which included a somatic examination of prior and present health: neurological status, psychiatric status, previous case record, blood tests (blood hemoglobin, sedimentation rate, erythrocyte indexes [MCHC, MCV], complete blood cell count), serum tests (glucose, sodium, potassium, calcium, chloride, phosphate, iron, creatinine, albumin, ASAT, ALAT, cholesterol, triglyceride).

## **Neuropsychological tests**

All subjects were tested by experienced psychologists with five subtests (Information, Digit Span, Similarities, Block Design, and Digit Symbol) from the Wechsler Adult

Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981 ); one subtest from the Wechsler Memory Scale (WMS) (Wechsler, 1973) (Logical Memory); the Forward Digit Span test (administered according to an up- and-down technique ), Trail Making Test A and B (Rey, 1959); Rey-Osterrieth Copy and Retention Test (Rey, 1941 ), Rey Auditory Verbal Learning Test (AVL T) (Rey 1959), and Free Recall and Recognition Words from the Stockholm Geriatric Research Center (SGRC) (Bäckman and Forsell, 1994 ). Five subtests from WAIS were used to assess the FSIQ (Wechsler, 1981 ).

## **RESULTS**

Mean scores on all neuropsychological tests for the AD, MCI and control groups are presented in Table 7. When significant group differences emerged, post hoc comparisons were made using Scheffe's test. It was observed that the MCI and control group differed in all cognitive tests ( $p < 0.001$  ), but not in the Digit Span Forward, SGRC False Alarm (FA), and Cued Story Recall ( $p > 0.10$ ) tests. Comparisons of the AD group with the MCI group and the control group, revealed significant differences in all neuropsychological tests. Missing values were substituted by means.

**Table 7.** Neuropsychological test scores for Alzheimer’s Disease, Mild Cognitive Impairment and healthy subjects.

Function	Test	AD	MCI	Controls	F	p
<b>Global Cognitive ability</b>	FSIQ	71.9±8.6	90.6± 8.9	101.1±3.0	156.2	****
<b>Semantic memory</b>	Similarities	8.6±4.6	17.9± 5.3	21.7± 3.2	195.5	****
	Information	11.5±5.3	19.2± 4.8	23.4±3.3	140.6	****
<b>Primary memory</b>	AVLT1 trial 1	2.7±1.8	4.1±1.6	5.7±1.8	20.8	****
	Corsi Block	4.0±1.4	5.0±1.1	5.3±0.5	11.5	****
	Digit Span Back.	3.3±1.9	5.5± 2.1	5.8±1.6	41.2	****
	Digit Span For.	4.7±2.0	6.4± 2.2	6.7±1.8	17.9	****
<b>Attention</b>	Digit Symbol	15.5±11.0	31.8±12.1	43.3±11.3	151.2	****
	TMT: A	21.5±1.2	23.7±0.6	24.0± 0.0	12.5	****
	TMT:A Time	61.9±21.8	50.1±18.3	39.3±14.0	57.8	****
	TMT: B	11.7±6.2	21.0±5.3	23.4±1.8	146.4	****
	TMT: B Time	203± 97	142±69	87±36	115.7	****
<b>Visuospatial function</b>	Block Design	6.0±6.1	22.0±9.7	28.0±7.5	180.8	****
	Rey CF copy	27.6± 3.2	31.7± 7.5	34.4±2.5	40.5	****
<b>Episodic Memory</b>	Story recall	4.7±2.3	8.2±2.6	13.8±2.9	255.1	****
	Cued recall	1.9±2.3	2.7±2.3	3.4±1.1	19.0	****
	Delayed recall	3.6±5.1	6.8±4.6	16.7±11.1	39.4	****
	Rey CF Ret.	7.7±1.4	13.9±6.2	18.8±6.1	104.5	****
	SGC d-prime	1.4±0.7	2.2± 1.0	2.2±1.0	70.7	****
	SGC Hits	8.4±2.5	9.6±2.1	10.7±1.1	25.1	****
	SGC False	4.5±2.1	2.5±1.7	2.1±0.9	54.0	****
	AVLT Total	25.0±4.5	34.7±9.5	47.1±9.9	256.4	****
	AVLT Delayed	3 .0±0.0	7.7±3.7	10.4±3.6	6.1	****

\*\*\*\* $p < 0.0001$

### *Discriminant analysis*

Because group prediction may be enhanced when consideration is given to performance on multiple measurements simultaneously, stepwise discriminant analysis (SPSS 8.0/STATISTICA 5) was used to determine the most effective combination of tests distinguishing between groups. We used a  $p$  value of 0.001 for inclusion criteria in the discriminant analysis. Thus those variables chosen were considered to have the most discriminant power. The order of variable selection in the discriminant formula was based on their partial correlation coefficients after all possible combinations had been examined. It is important to note that each predictor variable gets its predictive value from the specific combination in which it appears. At each step of the procedure, the variable accounting for the greatest proportion of unexplained variance was entered. The

remaining variables were adjusted accordingly and examined for possible entry until variables meeting the entry criteria for the model had been exhausted.

This analysis resulted in two significant discriminant functions each one including five neuropsychological tests which represented the following cognitive domains: episodic and semantic memory, visuospatial function and attention (Wilks' Lambda=0.12) and (F[2,258]=3.61; p<0.01 ). The form of the discriminant function in this analysis, in terms of the standardized coefficients: canonical variables are shown below in Table 8.

<b>Function</b>	<b>Variable</b>	<b>Root 1</b>	<b>Root 2</b>
<b>Episodic memory</b>	AVLT5	0.45	-0.13
	WMS: Story Recall	0.39	-0.80
<b>Semantic memory</b>	WAIS-R: Similarities	0.31	0.34
<b>Visuospatial function</b>	WAIS-R: Block Design	0.26	0.25
<b>Attention</b>	TMT: B	0.21	0.55
	Eigenvalues	4.38	0.27
	Proportion variance	0.94	0.05

When the five tests obtained in the discriminant analysis were combined, it was found that the battery had a specificity of 90% for AD and 86% for MCI. Using the clinical diagnosis as a criterion, it was possible to correctly classify 95% of the AD group, 90% of the MCI group and 80% of the control group (p<0.001), when substituting missing values with group mean values. In addition, a jack-knife cross-validation procedure indicated that 87% of total cases were correctly classified .

Figure 3 demonstrates the distribution of all subjects from the three different groups according to the two discriminant functions obtained. These two functions classified the

subjects according to different criteria. The first function maximally differentiated the subjects into the AD and MCI and control group based on four cognitive domains. It was the dominating factor for classifying all the subjects as covered by 94% of the total variance. The second function classified within the MCI subjects according to low episodic memory (Free Story Recall and AVLT Trial 5) and high scores in attention (TMT B) and semantic memory (Similarities). However, this function was of minor impact on classification as it only explained 6% of the total variance. To determine how each discriminant function differentiated the three groups, we calculated the canonical variable means (centroids). For function 1, the centroid values for groups 1, 2 and 3 were -2.5, 0.4 and 2.5, respectively. The corresponding function 2 centroid values were -0.2, 0.7 and -0.4. The centroid data also indicated that function 1 effectively discriminated between each of the three groups, whereas function 2 added an additional component to distinguish MCI from healthy subjects and MCI from AD.

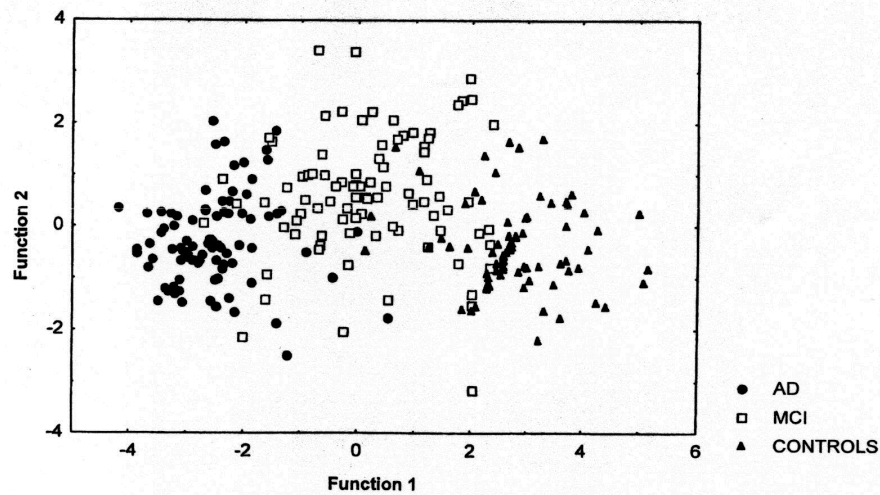
### **Misclassified subjects.**

In order to obtain a post hoc comparison of the misclassified versus the correctly classified individuals, we performed an extended analysis. The following results were obtained: the 8 AD subjects misclassified as MCI were diagnosed according to clinical criteria as a "possible Dementia Alzheimer Type" because they did not completely fulfil the AD criteria. As they were probably at an early stage of the disease, their general performance was slightly better than that of the remaining AD patients.

The 8 MCI subjects misclassified as AD were older ( $73.8 \pm 8$  years) compared to the MCI group ( $63.5 \pm 9$  years), ( $F[1,88]=9.24$ ;  $p < 0.005$ ) and had a lower education ( $F[1,90]=5.42$ ;

$p < 0.01$  ). They had lower scores in a number of tests, including MMSE ( $F[1,89]=9.81$ ;  $p < 0.01$ ), FSIQ ( $F[1,89]=9.17$ ;  $p < 0.005$ ), Similarities ( $F[1,89]=8.52$ ;  $p < 0.005$ ), Block Design ( $F[1,89]=8.21$ ;  $p < 0.005$ ) and Digit Symbol ( $F[1,89]=6.27$ ;  $p < 0.01$ ), indicating that the misclassified MCI patients constituted a subgroup with low performance in general. The 13 MCI patients misclassified as controls were more educated, ( $F[1,89]=6.08$ ;  $p < 0.01$ ) and were younger, ( $F[1,87]=3.43$ ;  $p < 0.01$ ) as compared to those correctly classified; the mean levels of education and age being  $(12.3 \pm 2.5)$ ,  $(10.0 \pm 2.3)$  and  $(58.0 \pm 5.8)$ ,  $(64.9 \pm 9.7)$  years for these two groups respectively. This indicated that the misclassified MCI had a higher level of performance compared to correctly classified MCI subjects, although the tests scores did not reach proposed statistical significance. The 9 controls misclassified as MCI were older than the correctly classified controls ( $76.0 \pm 2.3$  years,  $62.8 \pm 11.2$  years) respectively, ( $F[1,52]=9.56$ ;  $p < 0.005$ ). This suggested that these MCI subjects performed worse than the correctly classified MCI subjects did. The former subjects had lower scores in Similarities ( $F[1,77]=15.29$ ;  $p < 0.001$  ), Digit Span Backwards ( $F[1,77]=8.12$ ;  $p < 0.01$  ), Free Story Recall ( $F[1,77]=40.0$ ;  $p < 0.001$  ), Rey CF Copy ( $F[1,77]=15.9$ ;  $p < 0.001$ ) and SGRC  $d'$  ( $F[1,77]=8.0$ ;  $p < 0.005$ ).





**Figure 1** Scatterplot of Canonical Scores for the two discriminant functions. This plot determines how each discriminant function contributes to the discrimination between AD, MCI and control groups ( $F_{(2,225)}=3.62; p<0.001$ ).

## DISCUSSION

The main aim of this study was to examine cross-sectional differences in performance on psychometric tests between AD, MCI and normal elderly subjects and develop a brief battery of tests to identify cases at risk for subsequent progression to AD. Significant differences between AD and MCI individuals and healthy elderly individuals were obtained on all cognitive domains included in the analysis (global cognitive ability, episodic and semantic memory, visuospatial function, primary memory and attention ). This shows once more that the multifaceted nature of AD is not only restricted to episodic memory (Masur, 1994). However, it was possible to transform the cognitive functioning of all subjects into one dimension since the first function covered almost all variance in performance. The specific tasks that contributed mostly to the differentiation between the three groups were those which assessed episodic and semantic memory, visuospatial function and attention, as seen according to the standardized coefficients of

the discriminant analysis. The finding that episodic memory was the most efficacious measure for the differentiation of AD, MCI and healthy subjects is in agreement with data reported by several studies (Storandt and Hill, 1989; Flicker, 1991; Welsh, 1991; Almkvist and Bäckman, 1993; Masur, 1994; Petersen, 1995). Like other authors (Hughes, 1982; Morris, 1991; Bond, 1994) we used a comprehensive neuropsychological test battery that assessed a range of cognitive domain abilities. By systematically assessing diverse cognitive abilities, it was possible to delineate various cognitive skills that are affected early in the course of AD. Those measures that maximally discriminated MCI and AD appeared to tap some of the same domains that were found useful in discriminating mild dementia from normal ageing (Storandt and Hill, 1989; Masur, 1994). This is reasonable because MCI represents a group somewhere between mild AD and normal ageing.

Methodologically, the aim of the discriminant analysis was to classify individuals into three groups. Based on known classification functions it is possible to predict to which group a new case should belong. A similar multivariate stepwise discriminant analysis to reduce the number of variables to those that most effectively discriminate has earlier been used with similar results (Flicker, 1991; Almkvist and Bäckman, 1993). The discriminant function for the classification of AD and MCI yielded overall hit rates of 94% and 91% respectively, which are comparable to those reported by Welsh and colleagues (1991). A few subjects were misclassified in the three groups as explained in the results section. MCI subjects with low education were misclassified as AD due to a low general performance. Eight AD patients with a clinical diagnosis of possible AD were misclassified as MCI because of a high level of global cognitive functions. These data

underline the need for excluding confounders by a priori measures of the premorbid level of cognitive function such as general cognitive level or education. Psychiatric symptomatology such as depression which has been reported to affect the episodic memory performance should also be considered (Thomas, 1998). It is also extremely important to consider the heterogeneity of the MCI group which may lead to some differential cognitive performance overall the tests. In contrast to the AD patients, the characterization of the MCI subjects in relation to their cognitive test results is still unclear.

The graphic representation of the results from the discriminant analysis shows how the two functions discriminate between groups by plotting the individual scores for the two discriminant functions (Figure 3). The first function accounted for over 94% of the explained variance, and thus the vast proportion of discriminatory power. This important function included five tests assessing episodic and semantic memory, visuospatial function and attention. It was defined as a general neuropsychological function that better segregated subjects into the three groups according to the cognitive impairment level as shown in Figure 3. In addition, function 2 was characterized by low values in tests of episodic memory (Free Story Recall and AVL T Trial5 ) and high values in attention (TMT B). This second function showed a relatively large variation within the MCI group, as compared to the other diagnostic group, the interpretation being that MCI is more heterogeneous in terms of cognitive function than the other two groups. This led to a second function characterized by low scores in episodic memory and high scores in a variable assessing attention. In function 2, Free Story Recall was found to be the test with the lowest performance in the MCI group.

According to the model of neuropathological stages and corresponding neuropsychological deficits seen in preclinical AD (Almkvist, 1993), it is found that neuropathological changes are frequent only in the transentorhinal regions (Braak and Braak, 1991) with a parallel behavioral decline in episodic memory (Almkvist, 1996). At this stage other cognitive functions are largely unaffected. In this case, the MCI group is considered as a possible preclinical stage of AD and it obtained low scores in tests assessing episodic memory. In the clinical phase of AD it is found that neuropathological changes appear in the isocortex, in addition to extensive neuropathology in the transentorhinal regions (Braak and Braak, 1991). During this stage, an impairment of semantic memory, visuospatial function, and psychomotor speed may appear. Finally, in fully developed AD, the isocortex is severely affected neuropathologically (Braak and Braak, 1991). Cognitively, this stage is characterised by the impairment of primary memory in addition to severe deficits in episodic and semantic memory as well as visuospatial function and psychomotor speed (Almkvist, 1996).

Since the clinical MCI diagnosis is partly based on the neuropsychological data, the high sensitivity and specificity estimations reached may be overestimated. However, this methodological limitation of diagnosis circularity does not clearly interfere with the main objective of this study.

Due to the heterogeneity of the MCI group and in the absence of follow up data, it is likely that other prodromal dementias are represented in our study, as well as cases who remain stable or might improve in terms of cognitive functioning. However, it appears to be a general finding that approximately 25% of the MCI group could go on to develop AD in few years time (Dawe, 1992; Petersen, 1995; 1999).

Previous work reported that whilst an individual's subjective memory impressions of their memory function correlated best with depression, informants' assessments correlated well with objective performance (McGlone, 1990). Thus, in the future, it will be important to follow the clinical course of these patients longitudinally in order to obtain further information about the progression of their cognitive disabilities.

There is some variability in the literature with regard to diagnosis of MCI (Dawe, 1992). This is largely due to the different neuropsychological measures used and to the absence of international consensus. In order to avoid these problems, it will be important to create a standardized, short and highly accurate battery of tests as well as to decide upon common clinical criteria for the operational term of MCI. This will enable the future comparisons of clinical data from various studies and different centers using shorter and more sensitive psychometric batteries. A further advantage of our study is that the sample was well-characterized and all the subjects had been exposed to an extensive diagnosis procedure and a comprehensive neuropsychological assessment. While the reliability and validity of the dementia staging by our research group has been good, we accept the data is preliminary and its value can only be confirmed by further validation.

## **CONCLUSION**

The clinical application of our proposed model is not intended to replace a complete neuropsychological assessment. Rather, it provides a method of using neuropsychological information not only for diagnostic purposes, but also to predict future diagnosis. In summary, we showed that AD, MCI, and healthy individuals can be reliably

discriminated using measures that particularly tap episodic as well as semantic memory, visuospatial function and attention. This led to a reduced-length cognitive battery to differentiate between the AD and MCI group.

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## **Chapter 2**

### **Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in Mild Cognitive Impairment.**

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## **ABSTRACT**

The objective of this study was to assess whether reduced glucose metabolism (rCMRGlu) and cognitive functioning could predict development of Alzheimer's Disease (AD) in subjects with Mild Cognitive Impairment (MCI). Twenty MCI patients underwent baseline and follow-up investigations of rCMRGlu, as measured by Positron Emission Tomography (PET), and cognitive function measured by neuropsychological test assessments. Subjects were clinically followed up with an average interval of 36.5 months. Two groups were obtained after the second clinical assessment. Nine patients were diagnosed as AD and classified as progressive MCI (P-MCI), whereas 11 patients remained clinically stable and were classified as stable MCI (S-MCI). There were no differences in demographic variables or baseline MMSE between the two subgroups. Logistic regression indicated the two variables that most effectively predicted future development of AD as being rCMRGlu from the left temporoparietal area and performance on the Block Design. These combined measures gave an optimal 90% correct classification rate, whereas only rCMRGlu or neuropsychology alone gave 75% and 65% correct classification, respectively. Measures of temporoparietal cerebral metabolism and visuospatial function may predict evolution to AD in patients with MCI.

**Key words:** Mild Cognitive Impairment, rCMRGlu, neuropsychology, Alzheimer's Disease, predictor.



## **INTRODUCTION**

Mild Cognitive Impairment (MCI) is an operational term for cognitive deficits that are present in subjects without marked functional impairment and who do not satisfy established clinical criteria for dementia (APA, 1994) and probable Alzheimer's Disease (AD) (McKhann, 1984). Follow-up studies have indicated that MCI individuals are at increased risk for developing AD, ranking from 1% to 25% in one year (Dawe, 1992) to 55% in 4.5 years (Petersen, 1995). Given the high rate of conversion of MCI patients to full dementia syndromes, it may be the case that MCI is simply early or pre-clinical AD. However, increasing evidence suggests that the MCI group is heterogeneous with respect to the clinical presentation and evolution (Ritchie, 2000). All individuals who present clinically with very mild cognitive symptoms may not share the same fate ultimately. For instance, some subjects who present with amnesic MCI, the most common subset of MCI subjects, may have other pathologic processes involving the medial temporal lobe or may develop a dementia disorder other than AD (Dickson, 1994).

However, since a high proportion of MCI patients might represent the pre-clinical stage of AD, it is extremely important to find early markers such as functional neuroimaging and neuropsychology, which may help to characterize the early phases of AD. MCI patients may be the ideal population to target both pharmacological and psychosocial interventions.

Positron Emission Tomography (PET) offers an opportunity for more certain and specific early diagnosis of AD (Jelic, 1999; Herholz, 1990). This method has demonstrated a

typical pattern of reduced temporoparietal glucose metabolic rates in most patients with a clinical diagnosis of AD (Haxby, 1992; Duara 1986). Early metabolic deficits in the temporoparietal region have also been demonstrated in subjects at risk for developing AD, such as members of families with known gene mutations (Wahlund, 1999) or carriers of the APOE e4 allele (Small, 2000). Furthermore, there is some empirical evidence indicating that PET is a more sensitive method for detecting very early related changes than other neuroimaging methods such as SPECT and EEG (Jelic 1999; Herholz, 1990, Haxby 1990, Duara 1986).

On the other hand, more recent studies indicate that indices of psychomotor speed, such as Digit Symbol test (Devanand, 1997; Flicker 1993) and visuospatial functioning, as exemplified by the Block Design test (Larrabee, 1994), may be sensitive markers for dementia development in MCI patients.

There have been few studies on the suspected pre-clinical state of AD that have compared metabolic changes seen on PET examination with data from standard clinical examination, such as detailed neuropsychological testing. The main objective of the present study was to assess the predictive power of cerebral metabolic and psychometric measures, both isolated and when combined, in MCI subjects developing AD. Such measures could be useful as objective markers of early and presymptomatic AD.

## PATIENTS AND METHODS

### Study Sample

Twenty subjects were consecutively investigated for suspected dementia at the Geriatric Clinic, Huddinge University Hospital. The demographic and clinical data of the subjects are shown in Table 9.

**Table 9.** Demographic characteristics of patients with Mild Cognitive Impairment (MCI) (means  $\pm$  standard deviation).

	Stable MCI ( S-MCI)	Progressed MCI ( P-MCI)
N	11	9
GENDER (F/M)	5/6	3/6
AGE	60.1 $\pm$ 8.4	64.9 $\pm$ 8.3
EDUCATION	11.3 $\pm$ 2.0	11.9 $\pm$ 2.2
FOLLOW-UP Range	40.1 $\pm$ 15.3 (23-75)	33.6 $\pm$ 14.6 (18-59)
MMSE- Baseline	27.2 $\pm$ 2.9	26.7 $\pm$ 1.8

The initial, as well as follow-up examination included physical and psychiatric examinations, routine blood, serum and urine examinations, routine EEG, MRI, SPECT, PET, neuropsychological assessment and MMSE (Folstein, 1975) examination.

The diagnosis of MCI was defined as the patients having cognitive impairment, as confirmed by neuropsychological test results, fulfilling the criteria for stage 3 of the Global Deterioration Scale (GDS) (Reisberg, 1982) but lacking symptoms severe enough to fulfil the DSM-IV (APA, 1994) dementia criteria. The objective decline was 1.5 SD

below the average for their age on neuropsychological tests, representing one or more areas of cognition. The subjects lived independently in the community and in all cases an interview with a close informant was performed to gather information about the functional status of the patient. The clinical follow-ups were the same as those performed at initial examinations. The follow-up diagnosis of AD was consistent with criteria of the National Institute of Neurological Disorders and Stroke, Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKann, 1984). The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (APA, 1994). None of the patients were taking acetylcholinesterase inhibitors either at initial or follow-up evaluation.

### ***Procedure***

rCMRGlu and neuropsychological measurements were performed in the group of 20 MCI patients at baseline and were clinically followed up during an average of 36.8 (10-75) months; 9 patients (45%) were diagnosed as AD (P-MCI) and the other 11 patients remained clinically stable were classified as stable MCI (S-MCI). They were also compared in terms of global cognitive status measured by MMSE (Folstein, 1975). PET and neuropsychological investigations were performed in a time interval not exceeding 3 months. The study was approved by the Ethics Committee of Huddinge University Hospital.

## **Neuropsychological tests**

All subjects were tested by experienced psychologists with five subtests (Information, Digit Span, Similarities, Block Design, and Digit Symbol) from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981); one sub-test (Logical Memory) from the Wechsler Memory Scale (WMS) (Wechsler, 1973), Trail Making Test A and B (Rey, 1959) Rey-Osterrieth Copy and Retention Test (Rey, 1941), Rey Auditory Verbal Learning Test (AVLT) (Rey, 1959), and Free Recall and Recognition of Words from the Stockholm Geriatric Research Center (SGRC) (Bäckman, 1994). Five subtests from WAIS-R were used to assess the FSIQ.

## **PET Method**

The PET investigations were performed at the Uppsala University PET Center, using either of two scanners (GEMS 2048-15B or GEMS 4096-15WB, General Electric Medical Systems, Milwaukee, Wisc.). Both Scanners had a spatial resolution of 2 mm (full width at half maximum) covering 100 mm (15 continuous tomographic slices with a 6.5 mm slice thickness). Multiple slices were recorded parallel to the cantho-meatal line from the cerebellum to a level approximately 26 mm above the center of the basal ganglia. The accumulation of 2-[<sup>18</sup>F]-fluoro-deoxyglucose (<sup>18</sup>F-DFG) in the brain was followed for 60 minutes. The rate of glucose consumption (rCMRGlu) in the brain was expressed in mol/min x 100 cm<sup>3</sup>) and calculated by a graphical method (Patlak, 1983) which used the “lumped constant” equal to 0.418 for correction of differences in utilization between <sup>18</sup>F-Fluoro-deoxyglucose and glucose. Regions of interest (ROIs)

were defined on transaxial slices in relation to the slice where the basal ganglia (BG) structures were best visible. Based on Herholz 1999 and Jelic 1996, rCMRGlu were obtained for 3 regions of interests: the temporoparietal regions 13 mm above the level of the basal ganglia (TP<sub>above</sub>), 13 mm below (TP<sub>below</sub>), and at the level of the basal ganglia (TP<sub>BG</sub>) in the left and the right hemispheres. Estimates of the rCMRGlu were standardized to the sensorimotor area of the cortex 26 mm above the level of the basal ganglia. This region is thought to be relatively unchanged in AD patients (Duara, 1986).

### *Statistical Procedure*

Group differences in rCMRGlu and neuropsychological variables were tested by Student's t-test. These two groups were similar in terms of age, sex, and education at baseline. After testing for equal variance-covariance matrix, those variables statistically significant for neuropsychology (Block Design, Trail Making B and Digit Symbol) and for rCMRGlu (left TP<sub>above</sub>) were entered into a logistic regression analysis. Logistic regression analysis was performed using rCMRGlu and neuropsychological measures independently and combined. In addition, the same logistic regression model was applied so as to study which of the variables best predicted group membership when adjusting for baseline age, gender, follow-up time and education (Table 10).

**Table 10.**

VARIABLES	MODEL I	MODEL II	MODEL III	MODEL IV	MODEL V	MODEL VI	MODEL VII
<b>Left TP<sub>above</sub></b>	-20.6 (-46.4 to -5.5)*	----	----	----	-37.6 (-81.6 to -13.7)*	-0.12 (-0.28 to 0.01)*	-20.6 (-46.4 to -5.5)*
BLOCK DESIGN	----	-0.12 (-0.28 to 0.01)*	----	----	-0.34 (-0.79 to -0.09)*	-----	-----
DIGIT SYMBOL	----	-----	-0.1 (-0.26 to 0.00)*	-----	-----	-0.18 (-0.4 to -0.02)*	-----
<b>TMT B (time)</b>	-----	-----	-----	0.008 (-0.01 to 0.03)*	-----	-----	0.02 (-0.004 to 0.06)*
Intercept	18.6	2.6	3.68	-1.25	42.4	31.9	17.6
Classification accuracy of the model	15/20 (75%)	13/20 (65%)	15/20 (75%)	13/20 (65%)	18/20 (90%)	15/20 (75%)	17/20 (85%)

**Note.** \* =  $p < 0.05$ . Values are means and 95% confidence intervals. Left TP<sub>above</sub> = 13 mm above the level of the basal ganglia in the left hemisphere. Values in the tables are regression estimates with 95% confidence interval (CI) and predictive values for the baseline neuropsychological and PET variables.

## RESULTS

Comparison of neuropsychological and rCMRGlu values between the two groups revealed that the P-MCI subjects had significantly lower results in Block Design (df=19; t=6.25; p<0.001), Digit Symbol (df= 19; t=4.21; p<0.001) and Trail Making B time (df=19; t=3.43; p<0.01), than the S-MCI subjects. They also had significantly lower rCMRGlu values in the left TP<sub>above</sub> (df= 19; t=4.64; p<0.001). No other significant group differences were obtained.

### *Prediction*

A number of stepwise logistic regression analyses were performed using the combination of neuropsychological and PET measures as well as demographic variables. We used a

p-value of 0.01 as inclusion criteria in the logistic regression analysis and in the model we only entered those variables with significant values in the t-test comparison between P-MCI and S-MCI.

These analyses indicated that the two variables with the higher standardized regression coefficient and thus, the most effective at discriminating between both groups, were left TP<sub>above</sub> ( $\beta=0.4$ ; p<0.05) and Block Design ( $\beta=2.6$ ; p<0.05). Using these two variables, the total classification accuracy of the model V was 90% (as is shown in Figure 4, model V). One patient with P-MCI was classified as S-MCI, and one patient with S-MCI was classified as P-MCI.

When we used model I, (left TP<sub>above</sub> measure isolated), the model reached a 75% classification accuracy (p<0.05). Three patients with P-MCI were classified as S-MCI and two S-MCI were classified as P-MCI. Using only Block Design as a predictor



(Figure 1, model II), the classification accuracy was 65% ( $p < 0.05$ ). Five patients with P-MCI were classified as S-MCI and two S-MCI were classified as P-MCI (Figure 4, model II).

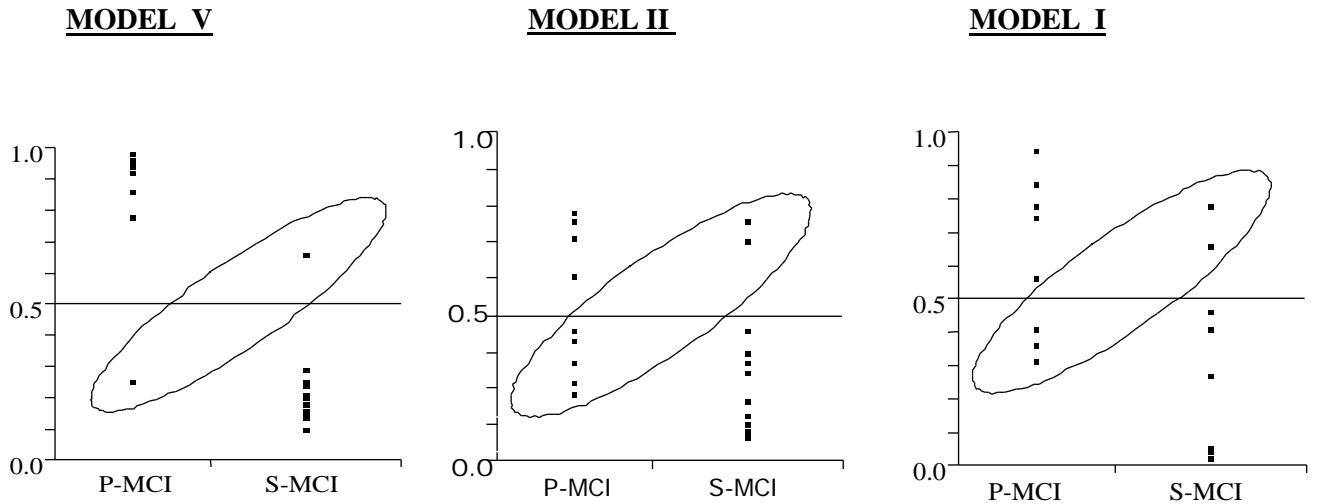
**Table 11.** Values in the tables are regression estimates with 95% confidence interval (CI) and predictive values for the baseline neuropsychological and PET variables adjusted for the demographic variables (age, gender, education) and follow-up.

VARIABLES	MODEL viii	MODEL ix	model x	MODEL xi
<b>Left TP<sub>above</sub> (rCMRGlu)</b>	-38.1 (-95.1 to -12.4)*	-46.1(-132.8 to -14.8)*	-37.5(-84.4 to -13.0)*	-37.5(-84.8 to -12.5)*
BLOCK DESIGN	-0.34 (-0.98 to -0.1)*	-0.4 (-1.2 to -0.1)*	-0.3(0.8 to -0.1)*	-0.3 (-0.8 to -0.1)*
AGE	-0.01(-0.4 to 0.3)	---	---	---
GENDER	---	0.7 (-1.2 to 3.9)	---	---
FOLLOW-UP	---	---	-0.02 (-0.1 to 0.1)	---
EDUCATION	---	---	---	0.003 (-0.9 to 1.0)
Intercept	43.5	52.2	43.0	42.4
<b>Classification accuracy of the model</b>	18/20 (90%)	18/20 (90%)	19/20 (95%)	18/20 (90%)

Note. \* =  $p < 0.05$  Values are means and 95% confidence intervals.

When the Digit Symbol and TMT B time test were used independently, the total accuracy of the model was 75% and 65%, respectively (Figure 4, model III and IV), and when combined with left TP<sub>above</sub>, 75% and 85%, respectively (Figure 4, model VI and VII).

**Figure 4.** Plots of predictive probabilities obtained from the logistic regression models using baseline rCMRGl<sub>u</sub> of 2 Left TP<sub>above</sub> and Block Design as a predictors ( Model V), Block Design variable (Model II) and baseline rCMRGl<sub>u</sub> of 2 Left TP<sub>above</sub> (Model I). Misclassified subjects are marked by ellipses.



To control the effect of demographic variables (age, gender, education) in the model V (left TP<sub>above</sub> and Block Design combined) as well as the time of follow-up, when adjusted them by entering each demographic variable separately in the logistic regression. We found that the total accuracy increased with adjustment for the follow-up time (see Table 11, model X). On the other hand, Models VIII, IV and XI, which included age, gender and education as a covariates, respectively, did not modify the classification accuracy of model V.

## DISCUSSION

This study shows that combination of one rCMRGlu measure and one neuropsychological measure has higher predictive power of the future development of AD than when these tests are used separately. The finding that glucose metabolism in the temporoparietal region is affected early is in accordance with other studies (Jelic, 1999; Helhorz, 1990). An interesting finding of our study is that the Block Design, test which represents visuospatial function appears as the second best predictor in terms of total accuracy. The existing literature (Hill, 1995) suggests that visuospatial abilities make an independent contribution to the discrimination and staging of dementia. It also seems that patients with left, particularly parietal, lesions tended to show confusion, simplification and concrete handling of the design (Lezak, 1995), which is a typical feature of early AD. Furthermore, it is known that early AD can be also characterized by bilateral TP hypometabolism or predominantly right or left TP metabolism in conjunction with corresponding cognitive deficits (Grady, 1988). Therefore, it seems plausible that the model which shows the optimal classification accuracy combines indices of left and right hemisphere function, i.e. left temporoparietal rCMRGlu and a test of visuospatial functioning respectively.

This study also suggest that the two variables with the higher predictive power in the model I (Block Design and left TP<sub>above</sub>) made an independent contribution to the discrimination of subjects between the two groups. This could mean that the two variables are not completely interrelated but are to some degree unrelated as the results have shown. Although, the model III and IV (Digit Symbol and TMT B time respectively), and the model VI and VII (Digit Symbol or TMT B combined with left TP<sub>above</sub>) were significant, the best overall classification accuracy was the combination of left left TP<sub>above</sub> and Block Design, as shown in Table 10. This finding is further

supported by the fact that there was an overlap between patients correctly classified by either model I or II.

Contrary to our predictions, those tests assessing episodic memory were found not to be significant predictors of MCI progression. Episodic memory is consistently reported as being able to discriminate between very early AD and normal aging (Duara, 1986; Tierney, 1996, Almkvist, 1993;1998; Small 2000, Ritchie, 2000). Our results could be explained either by the more advanced deterioration in memory of MCI patients than that reported in other studies. It is most likely that P-MCI and S-MCI had the same impairment in memory and the differences found may not be due to a differential decline. Furthermore, as mentioned previously, the existence of heterogeneous neuropsychological MCI profiles has been recently recognized (Arnaiz, 2000).

Two methodological limitations could interfere with the present findings. Firstly, the sample of MCI subjects was limited due to strict exclusion criteria, and the prospective design of the study. However, the conversion rate to AD seen in the current study reflects the real proportion of incident cases reported in some other population-based studies (Petersen 1999, Bozoki, 2001, Morris 2001).

If we consider that the conversion rate increases considerably over the years, our follow-up time was relatively short. The inclusion of follow-up period as a covariate increased the accuracy of the model. On the other hand, the patients used in the present study were on average younger and more cognitively affected than those used in other similar studies. It is plausible that our study group represent a cognitive subtype within the spectrum of MCI patients.

Future studies should determine the optimal predictive variables from these domains which when combined can form an efficient diagnostic algorithm. The clinical heterogeneity of the MCI population, as well as its natural history suggest the necessity of using various biological markers in the early diagnostic assessment of AD. The results of the present study may contribute to the understanding of clinical progression and the cognitive predictors of MCI patients who could develop AD in the future.

In conclusion, the main finding of the present study was that the best predictive power of MCI subjects developing AD was the combination of cerebral glucose metabolism and psychometric measures rather than single measures. This finding has a practical relevance for an easy identification of subjects at risk for developing dementia.

#### **ACKNOWLEDGEMENTS**

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### **CHAPTER 3**

**Mild Cognitive Impairment diagnosis:  
A cross national comparison of MCI samples.**

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**ABSTRACT**

**Context-** The MCI is a relatively new term. It is important to assess the reliability of this diagnosis criteria. **Objective-** The main aim of this collaborative study was to assess the reliability of the Mild Cognitive Impairment (MCI) criteria by comparing the

cognitive performance of MCI patients in samples from the Mayo Clinic (MC) (Rochester, MN, USA) and from the Karolinska Institutet (KI) (Stockholm, Sweden).

**Participants-** The MCI groups consisted of 170 subjects from the MC and 133 from the KI. After standardized the neuropsychological MCI scores comparing to an age- and education- matched control, we compared the two samples in relation to the number of cognitive functions below 1.5 SD. Consecutively, a global test for proportions was used to check the assumptions of the Cox proportional hazard model in both institutions independently and combined, which was then used to assess the risk factors for incident AD among MCI patients. **Results-** When the two institutions were considered together in the Cox proportional hazard model, the number of affected cognitive areas below 1.5 SD was a significant predictor of time to AD diagnosis with age (n.s.), education (n.s.) and APOE 4 genotype entered into the same model as a covariates and it remained a significant predictor when the institutions were considered separately. The logistic regression modeling of AD outcome showed that only tests assessing learning and retention were predictors of developing AD. **Conclusions-** Population differences as well as differences in methodology, for case ascertainment as well as other aspects of the study, may account for much of the observed MCI samples variability. The number of impaired cognitive factors at baseline can predict the progression from MCI to AD. Furthermore, tests assessing learning and retention are the best predictors for progression to AD.

## **INTRODUCTION**

An area of particular research interest in Alzheimer's Disease (AD) is the detection and characterisation of prodromal cases where irreversible brain damage is not widespread

and a treatment to slow the progression of the disease would be more likely to be beneficial.

Flicker et al. (1991) first introduced the label of MCI to describe the patients who have cognitive impairment in one area but do not meet the Diagnostic and Statistical Manual of Mental disorders third edition (DSM-III; American Psychiatric Association, 1987). Later, Petersen et al., (1995) suggested the MCI term to refer to complaints of defective memory and demonstration of abnormal memory functioning for age, with a normal general cognitive functioning and conserved ability to carry out activities of daily living. This later definition referred to memory impairment beyond that expected for both age and educational achievement (Petersen, 1999).

Prodromal cases of AD may be identified within samples of mild cognitive impairment (MCI). MCI is a widely cited concept in clinical research on ageing-related cognitive disorders. Several studies have suggested a significantly increased risk of AD in MCI patients, with estimates of 10% to 15% of MCI patients developing AD per year over 4 years (Petersen, 1999), 24% over 2 years (Tierney, 1996), 25% over a year (Dawe, 1992), 40% over 2 years (Johnson, 1998), 20% over 3 years (Wolf, 1998), 53% over 3 years (McKelvey, 1999) and 100% over 4-5 years (Krasuki, 1998). The performance of patients with MCI on global measures of cognitive function also declines at a more rapid rate than that of healthy controls (Rubin, 1998).

The MCI concept has the advantage of providing a diagnostic entity for those individuals who will ultimately convert to dementia but do not yet meet dementia diagnostic criteria. It applies mainly to elderly individuals complaining about cognitive



changes irrespective of the aetiology or potential evolution of these changes. This group represents a large proportion of patients consulting memory disorders clinics.

Despite the importance of this new clinical term, there is an absence of general agreement on standardised diagnostic criteria. Due to this lack of criteria, there is a danger of including either cases that already are incident AD cases and/or cases with normal ageing memory problems. Entering subjects at different stages of the disease and the use of different end-point criteria (functional and cognitive) will confound MCI studies and limit comparability across studies

To our knowledge, there have not been any cross-national studies of the diagnostic reliability of MCI criteria. In this study, we compared the cognitive characteristics associated with two clinical-based MCI samples as well as the survival outcome. One sample was from the Mayo Clinic, Rochester, Minnesota, USA (MC). The other was from the Karolinska Institute, Stockholm Sweden (KI). To place our findings in a broader context, conversion rates to AD for both MCI groups were also examined.

## **MATERIAL AND METHODS**

### **Study Sample**

The MCI groups consisted of 170 subjects from Mayo Clinic (MC) and 133 from Karolinska Institutet (KI). At the initial evaluation patients with MCI from MC had a mean age of 78.5 and a mean of education of 13.2 years. For KI group, the mean age was 69.5 and the mean education was 9.3 years. Demographic variables as well as the APOE 4 genotype are shown in the table 12.

**Table 12.** Demographic variables of the two groups (mean±standard deviation).

	MAYO CLINIC	KAROLINSKA INSTITUTET	p value
n	170	133	
AGE	78.5±8.4 (50-98)	69.5±5.8 (59-81)	p<0.0001
EDUCATION	13.2±3.1 (4-20)	9.3±3.0 (5-18)	p<0.0001
SEX (m/f)	70/100	74/59	p<0.06
MMSE	26.0±2.4 (18-30)	25.2±2.7 (17-30)	p<0.05
FOLLOW-UP (months)	37.50±17.72 (9-128)	27.55±17.72 (8-84)	p<0.005
<b>APOE ε4 genotype</b>			} ns
ε4/4	12 (7.1%)	9 (6.8%)	
ε4/3	50 (29.4%)	35 (26.3%)	
ε2/4	7 (4.1%)	4 (3%)	
ε3/3	60 (35.4%)	41 (30.8%)	
ε2/3	11 (6.5%)	11 (8.3%)	
Missings	30 (17.5%)	33 (24.8%)	

### Mayo Clinic

The Mayo subjects were recruited through the Mayo Alzheimer's Disease Center/Alzheimer's Disease Patient Registry (ADC/ADPR) using a standardised clinical protocol (Petersen 1994; 1995). A more detailed description of the recruitment procedure has been reported elsewhere (Petersen, 1999). The recruitment scheme involved screening patients who were examined by the primary care physicians for periodic general medical evaluations. On referral, patients were seen by a behavioural neurologist who obtained a medical history from the patients and corroborating sources, performed the Short test of Mental Status (Kokmen 1987; 1991), Hachinski Ischemic

Scale (Rosen, 1980) and a neurological examination. All MCI patients received a CT, MRI, cerebrospinal fluid analysis, and APOE 4 genotype. EEG and SPECT were utilized if clinically indicated. A consensus committee meeting was held involving behavioural neurologists, a geriatrician, neuropsychologists, nurses, and other study personnel. At each evaluation, the neuropsychological tests were administered by experienced psychometrists who were supervised by two clinical neuropsychologists. Patients were seen for follow-up on an approximately annual basis.

### **Karolinska Institutet**

The 133 MCI patients were recruited from the community and ongoing projects and they were consecutively investigated for suspected dementia at the Geriatric Clinic, Huddinge University Hospital. The objective decline of the MCI patients was 1.5 SD below the average for their age on neuropsychological tests, representing one or more areas of cognition. The MCI diagnosis is further described in table 13. All subjects were examined according to the same comprehensive procedure, which included a physical examination, evaluation of neurological status, psychiatric status, review of previous case record, blood test, urine analysis, cerebrospinal fluid analysis, routine ECG, routine EEG, MRI, SPECT, and MMSE (Folstein, 1975). Neuropsychological examination was performed by an experienced neuropsychologist who evaluated all the patients. The subjects lived independently in the community and in all cases an interview with a close informant was performed to gather information about the functional status of the patient.

### **Diagnostic Procedures**

MCI diagnosis for both institutions is described in table 4. Follow-up diagnoses of dementia and AD were made according to the DSM-III-R, (American Psychiatric Association, 1987) and the NINCDS-ADRDA (McKhann, 1984) for both institutions.

**Table 13.** MCI diagnosis criteria for MC and KI.

<b>MAYO CLINIC</b>	<b>KAROLINSKA INSTITUTET</b>
<ol style="list-style-type: none"> <li>1. Memory complaint.</li> <li>2. Normal activities in daily living.</li> <li>3. Normal general cognitive function.</li> <li>4. Abnormal memory for age.</li> <li>5. Non-demented</li> </ol>	<ol style="list-style-type: none"> <li>1. Memory complaint.</li> <li>2. Cognitive dysfunction in one or two domains as verified with neuropsychological assessment.</li> <li>3. No social interaction with daily life as reported.</li> <li>4. Non-demented.</li> </ol>

### **Follow-up procedures**

For MC follow-up examinations were made in annual basis. Subjects were reevaluated every 12 to 18 months and received an abbreviated neuropsychological battery at that visit as described previously (Petersen 1999). Subjects with any evidence of clinical deterioration precipitated a repeat neurological examination. The initial and the follow-up examinations included the same psychometric routine as well as an informant interview regarding behavioural and functional status. In these cases, a consensus diagnosis was again rendered as described above. KI MCI patients were reevaluated every 6 months. This included the same clinical comprehensive procedure applied at baseline as well as neuropsychological assessment.

None of the patients from the two institutions were under acetylcholinesterase inhibitors treatment at initial evaluation.

### **Neuropsychological assessment**

Neuropsychological assessment at both centres contained a common set of measures which facilitated this cross comparison. This set included the Wechsler Adult Intelligence Scale-Revised (WAIS-R), (Wechsler, 1981) (Information, Digit Span, Similarities, Block Design and Digit Symbol and Digit Span subtests), immediate and delayed recall of the story from the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1973) and Auditory Verbal Learning Test (AVLT) (Rey, 1964). We excluded those tests that were not similar for both institutions.

### **Standardisation of the samples**

#### **Mayo Clinic**

Mayo's Older Americans Normative Studies (MOANS) standard scores were calculated for MC patients. MOANS scores provide norms for a number of cognitive tests (core battery) that are commonly used to evaluate individuals from age 55 to 97 (Ivnik, 1992; 1997). Smith, et al 1992, 1993 have previously demonstrated that a five cognitive factors underlies the MOANS core battery in both normative sample and a clinical sample. Those factors, labeled the five Mayo Cognitive Factor Scores (MCFS) included verbal comprehension, perceptual organisation, attention/concentration, learning and retention, as described elsewhere (Smith, 1994).

#### **Karolinska Institutet**

The KI MCI neuropsychological scores were standardised by using age- and education-reference control group. The control subjects were a) patients relatives b) members of the Swedish Pensioner Society in Huddinge and c) non-mutations carriers from AD families.

For comparisons of the MC and KI groups, we organised the neuropsychological measures according to MCFS. We assumed that scores below 1.5 Standard Deviation (SD) according to age and years of education were a sign of cognitive abnormality. We were thus able to calculate the number of impaired cognitive domains, with scores ranging from zero to five. For purpose of comparison, we restricted our analysis to those patients who had 1, 2 or 3 cognitive areas affected. These patients represented the major proportion overall the cognitive spectrum.

### **Statistical procedure**

Group differences on demographic and standardised z-scores neuropsychological variables were tested by Student's t-test. APOE 4 genotype distributions were compared with chi-square (see table 14). Next, a Kaplan-Meier survival function, with dementia diagnosis used as "an event," was calculated. A global test for proportions was used to check the assumptions of the Cox proportional hazard model, which was then used to assess risk factors for incident AD among MCI patients. Potential risk factors in the hazards analysis included age, years of formal education and APOE 4 genotype. The choice of these covariates was based on their associations the outcome of AD in the literature (c.f. Petersen 1995; Tierney 1996). We also examined the AD diagnosis as a discrete binary outcome. Logistic regression analysis were conducted with the same covariates after restricting the group with MCI to patients who had completed 50 months follow-up or developed AD before that time.

## **RESULTS**

### **Baseline clinical features**

KI and MCI groups were different in terms of age, education and MMSE as shown in table 12.

The APOE 4 genotype was evaluated in a total of 240 patients from MC and KI (see table 12). The distribution of the APOE 4 genotype frequencies for the two institutions was not different ( $\chi^2=1.66$ ;  $df=3$ ;  $p>0.05$ ). On the other hand, there was no association of the 4 allele and the outcome of AD.

**Table 14.** Neuropsychological standardised z-scores of MCI group for Mayo Clinic and Karolinska Institutet, (mean±standard deviation).

COGNITIVE FUNCTION	TESTS	MAYO CLINIC (N=170)	KAROLINSKA INSTITUTET (N=133)
<b>Verbal comprehension</b>	WAIS-R: Information	-1.11±0.99	-1.45±1.04*
	WAIS-R: Similarities	-2.2±1.22	-2.15±0.98
<b>Attention</b>	WAIS-R: Digit Symbol	-0.12±1.01	-1.13±0.96*
	WAIS-R: Digit Span	-2.96±0.98	-4.01±1.98**
<b>Perceptual organisation</b>	WAIS-R: Block Design	-0.40±1.09	-0.24±0.90*
<b>Learning and memory</b>	WMS-R: Logical Memory (Immediate story recall)	-5.12±0.75	-6.45±1.25**
	AVLT Learning over trials	-0.29±1.14	-1.25±1.35*
<b>Retention</b>	WMS-R: Logical Memory (Delayed story recall)	-1.29±1.31	-2.3±1.7**
	AVLT Delayed recall	-1.1±1.9	-2.3±1.9**

\* $p<0.05$ , \*\*  $p<0.01$

### Prediction of AD

Figure 5.A shows the survival function when all the patients from the two institutions are considered together, without taking into account the number of impaired cognitive functions at baseline. The two curves differed significantly (Long Rank =11.8;  $df=1$ ;  $p<0.0001$ ). Since the major proportion of patients had 2 impaired cognitive domains, we performed a Kaplan-Meier survival curve for MC and KI MCI which is presented in Figure 5.B. The comparison of the two Kaplan-Meier curves was significant (Long Rank =3.61;  $df=2$ ;  $p<0.05$ ). When the two institutions were considered together in a

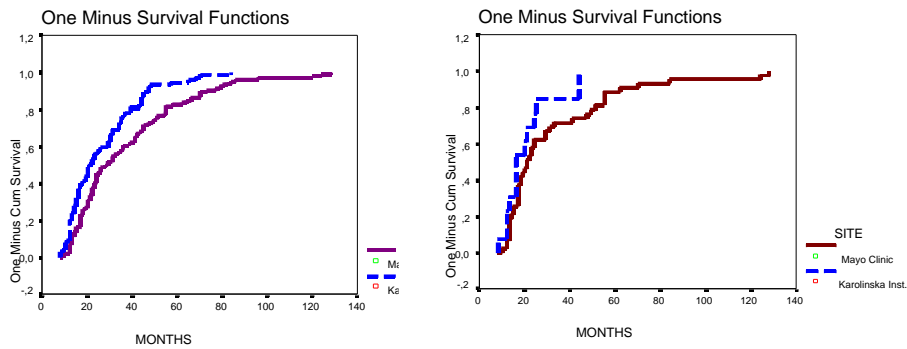
Cox proportional hazard model, the number of affected cognitive factors was a significant predictor of time to AD diagnosis with age (n.s.), number years of formal education (n.s.), and APOE 4 genotype (n.s.) entered into the same model as a covariates. The only significant covariate in the model was “institution belonging” (MC vs KI). Additional Cox analysis were conducted in the two institutions separately; the number of impaired cognitive domains remained a significant predictor when the model was adjusted for each institution independently for age, years of formal education and APOE 4 genotype. However, APOE 4 genotype was a significant when KI was investigated isolated.

**Figure 5.A.** Kaplan-Meier survival curve of probability of developing Alzheimer’s Disease (AD) over 140 months (Mayo Clinic and Karolinska Institutet MCI patients combined ). **Figure 5.B.** Kaplan-Meier survival curves of probability of developing AD over 50 months (Karolinska Institute) and over 140 months (Mayo Clinic) in subjects with mild cognitive impairment with 2 cognitive functions below 1.5 S.D.s at baseline.

**A.**

**B.**





For these two groups followed up at 2 years, baseline number of impaired cognitive factors (scores 1.5 SD) led to (80%) sensitivity and (75%) specificity for the diagnosis of AD, including a progressive increase in sensitivity and a decrease in specificity with two or three cognitive factors below 1.5 SD.

Neuropsychological measures were also entered into logistic modelling of AD outcome. Logistic regression using all neuropsychological tests as predictors revealed that WMS: Free Story recall ( $\beta = -0.20$ ;  $p < 0.01$ ) and was the only significant predictor of AD when

the two samples were added together. When KI MCI sample was considered in isolation, the predictive values were AVLT Delayed recall ( =0.14, p<0.05), WMS: Story delay recall ( =-0.23, p<0.05), WAIS-R: Information ( =-1.12, p<0.05), WAIS-R Digit Span ( =0.12, p<0.05). Similarly, when the MC sample were analysed independently, the best two predictors were WMS: Delayed story recall ( =-1.7; p<0.01) and WMS: Immediate Story Recall ( =-0.2; p<0.005) (see Table 15). Neither age, education or APOE 4 genotype were significant in any of the three models.

**Table 15.** Values in the tables are regression estimates and predictive values for the baseline neuropsychological variables for the two institutions.

MAYO CLINIC			KAROLINSKA INSTITUTET			MAYO CLINIC and KAROLINSKA INSTITUTET		
Tests	p		Test	p		Tests	p	
WMS: Story delayed recall	-0.17	<0.01	AVLT Delay recall	0.14	<0.05	WMS: Story delayed recall	-0.20	<0.01
WMS: Immediate story recall	-0.22	<0.005	WMS: Story delayed recall	-0.23	<0.05			
			WAIS-R: Information	-1.12	<0.05			
			WAIS-R: Digit Span	0.12	<0.05			
Constant	4.77	p=0.05	Constant	2.23	p=0.03	Constant	3.55	p=0.05

## DISCUSSION

The main aim of this collaborative study was to assess the reliability of the MCI term by comparing the cognitive performance of MCI patients in two well-establish institutions, as well as defining the survival outcome of the MCI group for the two institutions. The results showed that the number of impaired cognitive factors at baseline in the MCI samples from the Mayo Clinic and Karolinska Institutet, predicted the diagnosis of AD at follow-up. According to the present results, KI MCI patients were impaired not only in memory function and MC MCI only showed scores below normality in those tests assessing memory. This data suggests that there was a large cognitive heterogeneity

when comparing the two samples from the two institutions. This cognitive variability within the MCI group has been previously highlighted by other studies (Petersen 1999, Almkvist 1998).

These results may be explained by the differential MCI recruitment approaches when comparing the two samples. Mayo Clinic recruited the MCI patients mainly from community patients on the primary care. This afforded them the opportunity to detect patients before they present dementia or memory disorders. Contrary, KI MCI patients were recruited from ongoing projects at the Geriatric Department, meaning that this group could have already been contaminated with moderate to advanced cognitive impaired subjects. In relation to that, in this study we observed that a) KI MCI patients were possibly early AD cases to a large extent, and that could explain the low performance of the MCI KI sample in several tests, as shown in table 14, b) MC MCI patients were closer to be healthy individuals compared to KI MCI cases.

It is interesting to note that there was also a clinical heterogeneity observed when the two institutions were considered separately, and this bring us to a second point. Some controversy exists as to precise manner in which to characterise these subjects. Evidence suggest that detailed neuropsychological testing can accurately identify individuals experiencing mild or even unrecognised cognitive impairment and who are at a greater risk of developing AD (Rubin 1989, Jacobs 1995, Elias 2000) but excessive reliance on neuropsychological data may lead to overinterpret the degree of impairment since MCI is a clinical diagnosis not a neuropsychological one as our data suggested. Regarding to this issue, Ritchie et al (2001) recently reported that the MCI entity could not accurately predict early AD cases. The authors of that study, set the memory

criterion at 1 SD and required other cognitive domains to be absolutely normal. Petersen et al. in 1999 showed that memory was the most prominent cognitive deficit when defining MCI, but the subjects were statistically impaired on several other domains, but not of sufficient magnitude to be clinically significant. Therefore, Ritchie's MCI group was defined strictly neuropsychologically. In addition to that, they used a retrospective criteria, which enabled them to capture any type of outcome depending on how they operationalize the criteria. This does not negate the exercise, but puts limitations on its interpretation.

There were also few more methodological differences between the two institutions. For example, the use of the five MCFS scores allowed the MC to assess quantitatively the MCI cognitive profile, whereas the KI neuropsychological assessment made probably more arbitrary cutoffs for specific neuropsychological tests and therefore cognitive function. On the other hand, the restricted number of neuropsychological tests included in the comparison, caused that each cognitive function had to be merely assessed by two or three tests, which possibly limited the statistical power of the so-called "cognitive function". In addition, further definition of "cognitive function" should be clearly established in order to improve the operationality of the MCI diagnosis.

The regression model found that tests assessing retention and learning were the best predictors for progression to AD when the two samples were considered together. This finding has been extensively reported by other studies (Petersen 1994; Almkvist 1998; Arnaiz 2000; Grober, 2000).

As the Kaplan-Meier curves showed, the number of impaired cognitive functions at baseline were able to predict the progression from MCI to AD in both groups. The two

survival curves for the two institutions were slightly different meaning that the conversion from MCI to AD varied depending on the institution belonging, even though the number of cognitive areas impaired were supposedly similar for the two institutions at baseline, which support what we previously mentioned.

The fact that APOE 4 genotype was a significant predictor in KI and not in MC may reflect the influence of the allele 4 in the early stages of the disease since KI MCI patients were relatively young. Initial work has shown that 4 allele is not able to increase the risk of AD at early age, but it may modify the expression of the AD phenotype determining by other genetic and/or environmental factors underlying the familial aggregation of AD (van Duijn, 1994).

One potential limitation of the present study is that we could not examine the relationship of cognitive measures to dementia other than AD because a relatively small number of incident non-AD dementia was identified in these two community samples. The conversion rates to AD reported in this study were 27% for KI MCI over an average of 27.5 months and 23% for MC MCI over an average of 37.5 months. These results are in agreement with previous clinical observations, which reported similar conversion to AD (Petersen 1995, Morris 2001).

MCI concept appears to raise progressively clinical interest since they are at an increased risk of developing AD as reported previously in several studies (Flicker, 1993; Petersen 1999). Identification of subjects at potential risk of dementia open a door for an early therapeutically intervention. Hence, the present operational use of the MCI entity in several on-going clinical trials, makes of extremely importance to homogenise this group for both theoretical and practical purposes. Furthermore, it seems plausible

that diagnosis tests such as clinical, cognitive and neuroimaging information need to supplement each other in order to increase the accuracy of the MCI clinical diagnosis.

Hence, in order to further understanding the progression and clinical features of the MCI subjects, it is needed to describe the clinical course of these patients and reduce the potential MCI diagnostic instability, such as, recruitment strategies, diagnostic variability and cultural-effects which may not be considered in the present study. MCI diagnosis appears reasonably reliable across these settings but additional cognitive assessment standardisation could enhance the reliability of using the MCI concept. Our study further expands previous research by analysing characteristics of the cognitive phenotype of two different MCI samples.

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## **DISCUSSION**

In this chapter the main issues raised in the aims of this thesis will be discussed and results critically evaluated in the light of some methodological limitations such as MCI diagnosis and recruitment conflicting as well as supporting evidence from the literature. The data presented in this thesis may give some clues towards better understanding of the natural history of Mild Cognitive Impairment and prodromal Alzheimer's Disease, and provide some ideas for further research in this field.

In order to evaluate the empirical results of the present thesis, a number of issues have to be considered. First, with regard to design issues, the studies involved the general problems in cross-sectional and longitudinal research. Second, the recruitment of

patients and controls subjects may have affected the results. Third, the accuracy in diagnosis, as well as the issue of what defines normal aging have to be considered. Finally, the specific tests used in these studies set limits on what can be observed concerning functions.

## **Design Issues**

### *Cross-sectional studies*

The use of cross-sectional design in Study I involves a number of possible problems related to *external validity* (e.g., the extent to which the patient group and the control group are representative of their respective populations; the extent to which the tests used are representative of the underlying cognition function and brain structure involved) as well as *internal validity* (e.g., the extent to which the true causative factors have been identified; see Kausler, 1991 for a detailed discussion).

### *Longitudinal studies*

The quality of a longitudinal study depends on a number of factors including: (i) the stability of the original samples of subjects, (ii) the absence of sequential dependency from one assessment to the other, and (iii) the absence of confounding from time to assessment. One of the advantages of longitudinal work is that it should eventually permit researchers to distinguish between stages and subtypes of AD (Yesavage, 1991). In Study II and III, one potential limitation is that we could not examine the relationship of cognitive measures to dementia other than AD because a relatively small number of incident non-AD dementia was identified. However, the conversion rates to AD reported in these two studies are in agreement with previous clinical observations, which reported similar conversion to AD (Petersen 1995, Morris 2001).



Studies that investigate pre-clinical AD in subjects with MCI should have follow-up period of at least 5 years, but preferably 10 years (Almkvist, 1998). If 5 years is too long to wait for the results for the new diagnostic markers, secondary endpoints can be used (Visser, 2000). In relation to that, Study II and III had a relatively short follow-up comparing to similar studies which may have affected the results as well as conversion rates. Furthermore, it will be worthwhile considering improvement as an separate outcome because subjects with improvements are less likely to become demented than subjects with persisting MCI.

### **Recruitment strategies and diagnosis accuracy**

The extend of the progression of the MCI patients over time, is difficult to assess because case-identification criteria differ, as shown in Study III, and non-study samples are non-representative. There is also evidence that elderly people with MCI are at high risk of AD, although in many studies selection and recruitment strategies are based on different instruments and settings respectively, thus introducing a significant bias in the estimation of the risk as we mentioned previously. In Study III, Karolinska Institutet used a retrospective criteria, which enabled to capture any type of outcome depending on how the criteria was operationalized. This does not negate the exercise, but puts limitations on its interpretation. Thus, in order to detect patients in early stages of the disease, community medical practices should be our main recruitment center and not neurological/geriatric departments or memory clinics where the population is highly “contaminated” with essentially very impaired patients who are in a high proportion pre-clinical cases. The clinical and cognitive intervention may be so late by then.

Apart from the general absence of standardized criteria, there are two central conceptual issues relating to MCI that remain unresolved. Firstly, whether or not MCI should be confined exclusively to isolated memory impairment, Secondly, is MCI a prodrome of AD, or it is a clinically heterogeneous group at increased risk of dementia due to any cause? Thirdly, a general support for the notion that MCI is a neurological disorder has to come from brain imaging and EEG studies (Ritchie, 2000).

If MCI is a future viable clinical classification, increasing rigor must be introduced into its definition, case-finding criteria, and cognitive assessment.

#### *Control group: normality*

The control group was selected taking into account what is known about normal cognitive performance in elderly people. The control group used in this research (Study I and II) was not a random sample of aged individuals. On the contrary, it was selected to represent “successfully aged individuals”. It is, therefore, expected that this group is healthier than an unbiased sample of elderly people. It is also expected that this group should operate at a relatively high level of cognitive functioning. Comparing the results for the controls with norms for the neuropsychological test proper, Almkvist (1993) observed that it is clear that the controls performed above average for his cohort in all neuropsychological tests. Thus, the control group is probably not always representative of the population nondemented older adults.

#### *Neuropsychological tests, cognition, and Brain*

The selection and use of neuropsychological tests is associated with a number of problems. Ideally, the neuropsychological test should be selected to map all regions of the brain, but there is no brain-behavior theory that informs how tests may be used to

map different parts of the brain. In the future, findings from cognitive neuropsychology are likely to be gradually more utilized in combination with modern neuroimaging techniques to explore brain-behavior relationships in detail, by registering ongoing cognitive processes and brain activity simultaneously.

In current clinical practice, the traditional neuropsychological tests are associated with several problems. First, many tests consist of tasks that are not solved instantaneously but rather in terms of process. Yet, the measurement is related to the end product of the solution process, which probably is adequate when the solution is immediate, but not when the solution is extended over time. Second, the solution of a task often requires a sequence of information-processing steps and activation of several different cognitive functions. The task of reading may exemplify the case.

Letters and words have to be perceived (visual perception), semantic memory is accessed in order to understand the meaning and the syntax, phonological rules are accessed (procedural memory activation) and the utterances are produced (motor activation). The same type of analysis is possible for most tasks used in neuropsychological research. Again, the problem is that the task is evaluated as a whole, and the components of the task are not evaluated at all. Third, a task may be solved by using different cognitive strategies, which are not similar with respect to cognitive demands, but typically no notice is made of the strategy used. Conceivably, the problem of strategy differences is more pronounced in complex tasks.

Thus, the assessment of cognitive functions is hampered by lacking knowledge regarding brain-behavior relation, the lack of tasks that map certain brain structures or a certain functional system in the brain, the variation in solution strategies for a given task, the scanty data on solution processes of complex tasks, and the domination of omnibus tests over more specific tasks in relation to brain structures of interest.

Nevertheless, evaluation by using standard psychometric methods may be worthwhile and valuable in the clinical setting. But the future research purposes, the development and use of specific cognitive tasks for mapping specific brain regions is desirable. The present selection of neuropsychological tests followed other rules, for example, that the tests should (a) cover an appropriate range of cognitive decline (e.g., to avoid floor and ceiling effects), and (b) be standardized, reliable, valid for different types and levels of dementia, internationally well-known, etc. Consequently, the tests used in this thesis are not ideal in view of the points raised above.

### **Tracking disease progression**

A longitudinal study design is certainly the best way to validate cross-sectional findings and to determine their prognostic significance. In Study II, subjects with mild cognitive impairment who after the follow-up developed AD, had significantly decreased scores in Block Design and reduced glucose metabolism in temporo-parietal areas when compared to baseline. Thus, these parameters are sensitive state markers, i.e. variables that change over time with disease progression and which are suitable for the functional staging of the disease. Furthermore, the combination of one temporoparietal rCMRGlu measure and one neuropsychological test assessing visuospatial function has higher predictive power of the future development of AD than when the variables are used separately. Sensitivity to the progression of cognitive and functional decline is important as objective selection criteria of patients for clinical trials. However, it is important to mention that the patients used in this study were on average younger and more cognitively affected than those used in similar studies.

### **Relation to other biological markers**

An important research activity in this field should be the comparison of the merits and shortcomings of available biological markers, as well as the advantages of integrated information coming from different diagnostic sources.

#### *APOE*

Although the APOE 4 allele is an established risk factor for AD, it is still an open issue as to whether it influences the progression of disease. We were able to demonstrate in Study III, that APOE heterogeneity did affect any in Karolinska Institutet since the MCI sample was relatively younger to similar studies. The fact that APOE 4 genotype was a significant predictor in Karolinska Institute and not in Mayo Clinic may reflect the influence of the allele 4 in the early stages of the disease. Initial work has shown that 4 allele is not able to increase the risk of AD at early age, but it may modify the expression of the AD phenotype determining by other genetic and/or environmental factors underlying the familial aggregation of AD (van Duijn, 1994).

## CONCLUSIONS AND FUTURE DIRECTIONS

The results of this work have raised additional questions and opened possibilities for new projects. We now conclude with recommendation for future research in MCI and preclinical AD, the clinical relevance of the findings and general conclusion. They can be summarized in the following points:

- Neuropsychology variables could be considered as contributory diagnostic evidence, which when combined with clinical impression and other biological and neuroimaging markers may increase diagnosis accuracy of MCI and AD. This means that it has a potential for diagnosis screening in the case-finding approach of initial assessment.
- It is possible to develop a reduced-length cognitive battery which includes tests assessing specific domains such as episodic and semantic memory, visuospatial function and attention which highly discriminate among MCI, AD and controls. It is possible to transform the cognitive functioning into one dimension as described by the first function.
- The combination of one temporoparietal rCMRGlu measure and one neuropsychological test assessing visuospatial function has higher predictive power of the future development of AD than when the variables are used separately.

- There is a large MCI cognitive heterogeneity. Various diagnostic criteria and/or different institutional practice (i.e. different recruitment approach) as well as cultural differences may increase the cognitive discrepancy between the two institutions.
- Number of impaired cognitive functions at baseline can predict the progression from MCI to AD and tests assessing retention and learning were the best predictors for progression of AD in MCI patients.
- The APOE polymorphism is a significant predictor development of AD in young MCI patients. This may reflect the influence of the allele  $\epsilon_4$  in the early stages of the disease.

#### *Future directions*

- To establish the value of neuropsychology separately and combined with other techniques as a confirmatory test in prodromal cases, the discriminant functions based on variables defined in these studies should be prospectively evaluated on a large cohort of MCI subjects followed for a longer time. Longer period of observation may be necessary to determine the rate of progression to more severe stages of AD in very minimally impaired individuals.
- The specificity of the combination of different methods should be revised and a larger sample of healthy subjects followed to ascertain whether changes in these variables reflect either normal or pathological aging.
- The multivariate approach to increasing diagnosis certainty in early phases of the disease should be applied by combining currently existing biological, cognitive markers and neuroimaging methods. Novel approaches for this purposes, such as the computation of algorithms by using expert systems (i.e. neural networks, genetic algorithms, etc) (Hamilton, 1997) should be applied to further understand the role of

predictors and optimize the accuracy of the diagnosis in prodromal cases as well as test new parameters that could provide additional sensitivity and specificity.

- The hypothesis that neuroimaging methods of various modalities provide information on different aspects of normal and pathological brain function could be tested by analyzing the characteristics of misclassified and correctly classified patients and healthy controls.
- Future clinical trials designs for antidementia agents that incorporate a placebo treatment arm will need to consider the ethical and practical implications of withholding active treatment from individuals with very mild AD.
- Further studies are needed to determine whether this group that does not develop dementia represents a completely different disease process from that affecting the group with more than memory affected and which aspect of episodic memory is affected in MCI and early stages of AD.



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## **APPENDIX:**

### **Definitions of mild cognitive impairment**

In this appendix we describe various concepts of mild cognitive impairment. These concepts have in common that they apply to subjects without dementia. After each definition we provide the reference of the study that gives the original description (first reference) and references of a selection of cross-sectional and longitudinal studies.

#### *Age-Associated memory impairment (AAMI)*

- complaint of memory impairment
- memory functioning 1SD below the mean performance of young adults
- age>50
- adequate intellectual functioning (scaled score of 9 on the Vocabulary subtest of the WAIS)
- absence of dementia (MMSE>24)
- absence of memory-affecting disease: delirium, confusion, disturbances consciousness; neurological disorders that could procedure cognitive deterioration; infectious or inflamatory brain disease; significant cerebral vascular pathology HIS >4; repeated minor head injury of head trauma with period of unconsciousness for one hour or more; current psychiatric diagnosis of depression, mania, or any major psychiatric disorders; current diagnosis of history of alcoholism or drug dependence; HDRS>13; any medical disorder that could produce cognitive deterioration (including renal, respiratory, cardiac or hepatic disease, uncontrolled diabetes mellitus, malignancy not in remission for more than 2 years, endocrine, metabolic or hematological disturbances); use of any psychotropic drug or any drug that may significantly affect cognitive function during the month prior to psychometric testing.

*Reference:* Crook et al., 1986; Coria et al., 1995; Dawe et al., 1992; Hänninen et al., 1995; Helkala et al., 1997; Parnetti et al., 1996; Richards et al., 1999; Schröder et al., 1998, Youngjohn et al., 1993).

*Age-Associated Memory Impairment (AAMI); Modification Blackford and LaRue*

- inclusion and exclusion criteria as AAMI criteria except:
- Verbal and performance IQ between 90 and 130.
- Exclusion: hypertension, forward span less than 5.
- Including: Skin cancers, cancer in remission for 12 months, adequately treated hypertension and diabetes mellitus.

*Reference:* Blackford et al., 1989; Schröder et al., 1998, Smith et al., 1991.

*Age-consistent memory impairment*

- 75% or more of the memory testing within  $\pm 1SD$  below the age corrected average.
- other inclusion and exclusion criteria as AAMI criteria modified by Blackford and La Rue.

*Reference:*

Blackford et al., 1989, Schröder et al., 1998, Smith et al., 1991

*Age related cognitive decline*

- “An objectively decline in cognitive functioning consequent to the aging process, that is within normal limit giving the person age”.

*References:* DSM-IV 780.9 Z41.8; APA, 1994; Celsis et al., 1997.



### *Aging-associated cognitive decline*

- Report by individual or reliable informant that cognitive function has declined
- Gradual decline in any one cognitive area that goes perfect for the least 6 months.
- Difficulties in any one of the following areas: memory and learning, attention and concentration, thinking, language, visuospatial functioning.
- Performance on neuropsychological test of mental state examinations and least 1 SD below age and education corrected population mean.
- Exclusion criteria: cerebral disease or physical disorder known to cause cerebral dysfunction; depression, anxiety or other significant psychiatric disorders that may contribute to the observer difficulties; delirium; postencephalitic syndrome, postcontusional syndrome; persisting cognitive impairment due to psychoactive substance use of the effect of any centrally active drug.

Reference: Lewy et al., 1994 (working party of International Psychogeriatric Society/WHO); Häninnen et al., 1996; McKelvey et al., 1999; Richards et al., 1999, Schröder et al., 1998).

### *Amnesic syndrome*

- History of memory lost of a definite onset lasting more than 6 months
- Evidence for memory lost on neuropsychological testing
- No dementia (DSM-III-R).
- No specific disease or drug intake capable of memory impairment

Reference: DSM-III-R, APA, 1987.

*Borderline dementia*

-Score of 8 or 9 on the Information/Orientation subscale from the Clifton Assessment procedures for the elderly (CAPE).

*Reference:* Clarke et al., 1996

*Late Life forgetfulness*

-50% or more of the memory tests between 1 and 2 SD below the age-corrected average.

-Other inclusion and exclusion criteria as age-associated memory impairment criteria modified by Blackford and La Rue.

*References:* Blackford et al., 1989; Schröder et al., 1998, Smith et al., 1991.

*Mild cognitive decline (Global Deterioration Scale stage 3, GDS =3)*

At least two of the following:

-Getting lost when travelling to unfamiliar location

-decline in work performance apparent to co-workers

-work- and name-finding deficit apparent to intimates

-relatively little retention to material read in passage or book

-decreased facility remembering the names of newly introduced people

-losing or misplacing an object of value

-a concentration deficit apparent upon clinical testing

*References:* Reisberg et al., 1982; de Leon et al., 1993; Flicker et al., 1991

### *Mild Cognitive disorder*

-A: objective evidence and/or a history of cerebral dysfunction or systemic physical disorder known to cause cerebral dysfunction.

-B: a report of cognitive dysfunction by self or a reliable informant

-C: abnormality on psychological tests

-D: Exclusion criteria (probable) dementia (ICD-10), delirium, amnesic syndrome, alcohol misuse.

*References:* ICD-10, WHO, 1999, 1993; Christensen et al., 1997; Ebly et al., 1995)

### *Mild Cognitive Impairment (Mayo Clinic)*

-memory complaint by patient, family, or physician

-normal activities of daily living

-normal global cognitive functioning

-objective memory impairment in one other area of cognitive function as evidenced by scores  $>1.5$  SD below age appropriated norms.

-CDR scores 0.5

-not demented

-age between 60 and 89 years

*References:* Smith et al., 1996; Jack et al., 1999; Petersen et al., 1995; Petersen et al., 1999; Petersen et al., 1994

### *Mild Cognitive Impairment (DSM)*

-short-and long-term memory impairment with or without impairment in abstract thinking, impairment judgement, disturbance of higher function (aphasia, apraxia, agnosia), or personality change.

*Reference:* DSM-III-R, APA, 1987; Ebly et al., 1995

*Mild Impairment*

-mild impairment on at least three out of five cognitive tests (including MMSE)

-no dementia

*References:* Johansson et al., 1992; Johansson et al., 1997

*Minimal Dementia*

-“A limited and variable impairment of recall, minor and variable error in orientation, a blunted capacity to follow arguments and solve problems and occasional errors in everyday tasks”

*References:* CAMDEX, Roth et al., 1986; Cooper et al., 1996; O’Connor et al., 1990; O’Connor et al., 1991; Paykel et al., 1994.

Moderate cognitive impairment

-Two neuropsychological test (out of 16) below cutoff scores

-CDR score 0.5

-no functional impairment

*References:* Stern et al., 1992; Devanand et al., 1996

*Questionable dementia* (Clinical Dementia Rating Scale 0.5)

-consistent slight forgetfulness; partial recollection of event “benign” forgetfulness.

Three of the following other combination also possible see (Morris, 1993):

-fully orientated or slight difficulties with time relationship

-slight impairment in solving problems, similarities and differences

-slight impairment in “community affairs”

-life at home, hobbies and intellectual interests are well maintained or only slightly impaired.

-fully capable of self-care

*References:* Berg et al., 1982 (update Morris, 1993); Devanand et al., 1997; Hughes et al., 1982; Morris et al., 1988, 1991, 1996, 1997.

*Subclinical cognitive decline*

-score on the “Détérioration Cognitive Observé” questionnaire (DECO) below 38.

*References:* Ritchie et al., 1997, 2001

*Very mild cognitive decline* (Global Deterioration Scale stage 2, GDS 2)

-report of decline in cognitive capacities in comparison to their abilities 5 or 10 years previously

-no memory impairment evident at clinical interview

*References:* Reisberg et al., 1982; Flicker et al., 1993.