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Neuroimaging Markers for Early Diagnosis of Dementia

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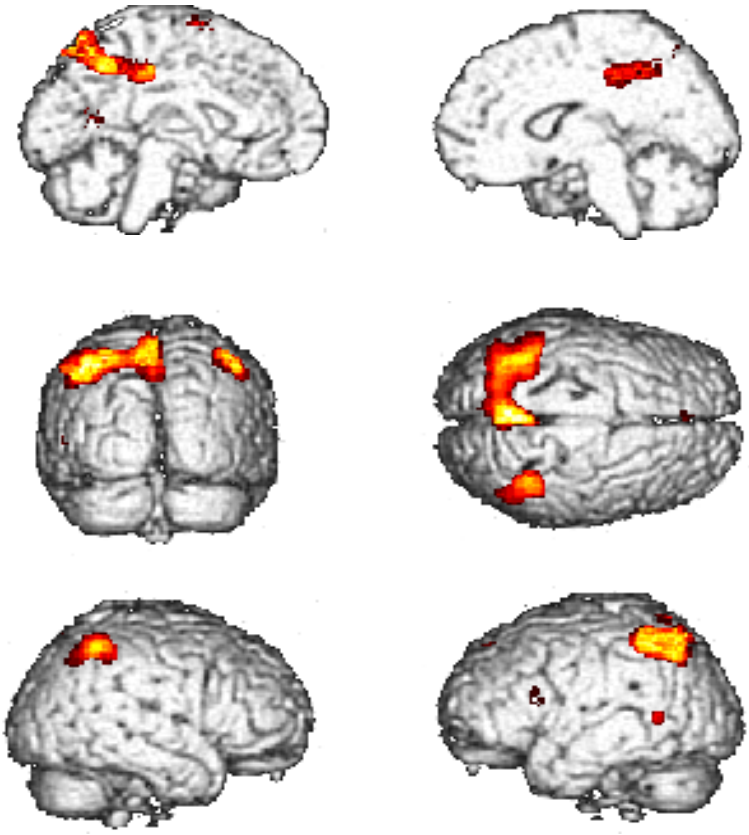

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Cover: SPM analysis of progressive mild cognitive impairment (PMCI) and stable mild cognitive impairment (SMCI) at baseline, which shows that PMCI has reduced blood flow in posterior cingulate and parietal lobe compare to SMCI at baseline.

To my family
In memory of my grandfather

CONTENTS

ABSTRACT

This thesis concerns the investigation of mild cognitive impairment (MCI) and Alzheimer's disease (AD) using single photon emission computed tomography (SPECT) and quantitative electroencephalography (qEEG).

In study I, qEEG values were cross-sectionally compared between AD, MCI and controls. AD had decreased global field power (GFP) and more anterior localization of three-dimensional dipole source in alpha and beta frequency. The results of longitudinal investigation of MCI showed a decreased alpha GFP and a more anterior localization of sources of theta, alpha and beta frequency in progressive mild cognitive impairment (PMCI), as compared to stable mild cognitive impairment (SMCI). EEG values showed a moderate diagnostic accuracy in the study of AD and MCI.

In study II & III, the baseline regional cerebral blood flow (rCBF) and neuropsychology were investigated in PMCI and SMCI. PMCI had decreased regional cerebral blood flow (rCBF) in posterior cingulate and parietal lobe as well as increased brain perfusion in prefrontal cortex compared to SMCI at baseline. The cognitive functions of PMCI were lower than SMCI with respect to episodic memory, visuospatial and general cognitive function represented by Mini-Mental State Examination (MMSE). Both SPECT and Neuropsychological test had moderate discriminant function between PMCI and SMCI at baseline and combining the two methods could improve the diagnostic accuracy.

In study IV, the longitudinal rCBF changes of PMCI and SMCI were investigated. SPECT data were analyzed with statistical parametric mapping (SPM) and BRASS program. No significant findings were detected using SPM. The results of BRASS showed a significant rCBF longitudinal reduction of PMCI in superior parietal lobe, parieto-temporal association cortex and medial temporal lobe and a significantly decreased general cognitive function represented by MMSE.

To summarize, SPECT and EEG could provide promising markers for the early diagnosis of dementia and track the disease progression. Combining imaging investigation with neuropsychological testing may increase the diagnostic accuracy of preclinical dementia.

LIST OF PUBLICATIONS

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

I. **Huang C**, Wahlund L-O, Dierks T, Julin P, Winblad B, Jelic V. Discrimination of Alzheimer's Disease and Mild Cognitive Impairment by Equivalent EEG Source: cross-sectional and longitudinal study**.** ***Clinical Neurophysiology*** 2000, 111 (11), 1961-1967.

II. **Huang C**, Wahlund L-O, Svensson L, Winblad B, Julin P. Cingular cortex hypoperfusion predicts Alzheimer's Disease in mild Cognitive Impairment. ***BMC-Neurology*** 2002, 2:9.

III. **Huang C**, Wahlund L-O, Almkvist O, Elehu D, Jonsson T, Svensson L, Winblad B, Julin P. Voxel- and VOI-based Analysis of SPECT CBF in Relation to Clinical and Psychological Heterogeneity of Mild Cognitive Impairment. ***Neuroimage*** 2003, 19 (3), 1137-1144

IV. **Huang C**, Wahlund L-O, Svensson L, Winblad B, Julin P. Longitudinal CBF changes in progressive and non-progressive Mild Cognitive Impairment. *(Manuscript)*

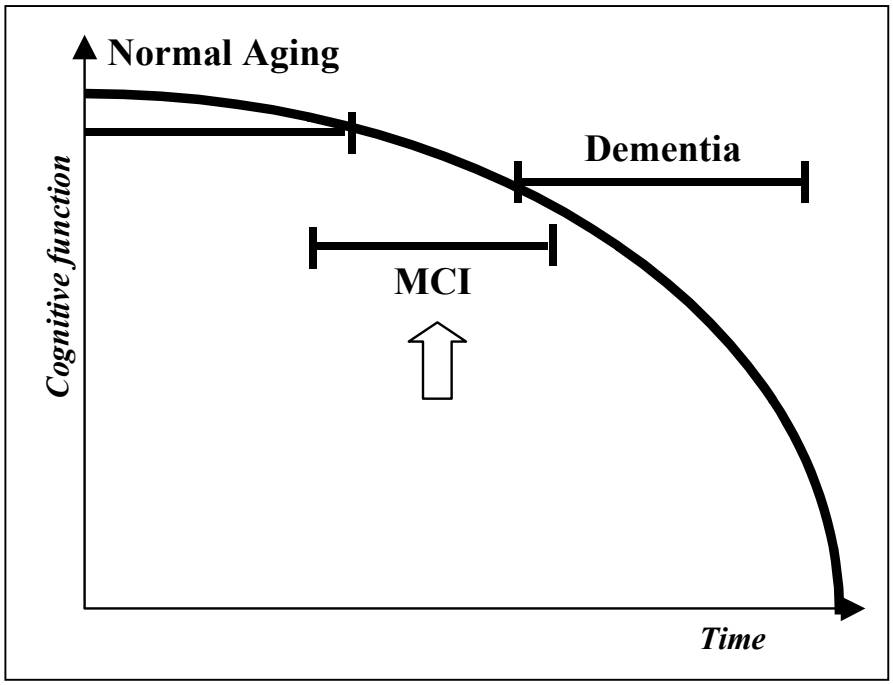
ABBREVIATIONS

AACD	Age-associated Cognitive Decline
AAMI	Age-associated Memory Impairment
AD	Alzheimer's Disease
CDR	Clinical Dementia Rating Scale
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CIND	Cognitive Impairment no Dementia
CSF	Cerebrospinal Fluid
DSM-IV	Diagnostic and Statistical Manual, 4th edition
ERP	Event-Related Potential
FFT	Fast Fourier Transformation
GDS	Global Deterioration Scale
GFP	Global Field Power
HMPAO	Hexamethylpropyleneamine Oxime
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NIA/AARP	National Institute on Aging and the American Association of Retired Persons
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
PET	Positron Emission Tomography
PMCI	Progressive Mild Cognitive Impairment
qEEG	Quantitative Electroencephalography
rCBF	Regional Cerebral Blood Flow
ROC	Receiver Operating Characteristic
SCI	Subjective Cognitive Impairment
SGRC	Stockholm Geriatric Research Center
SMCI	Stable Mild Cognitive Impairment
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
VOI	Volumes-of-Interest
WAIS-R	Wechsler Adult Intelligence Scale-Revised

INTRODUCTION

Concept of mild cognitive impairment (MCI)

Individuals who ultimately develop a degenerative dementia such as Alzheimer's disease (AD) will pass through a period of mild stage. MCI is termed to depict this transitional zone between normal aging and dementia (Almkvist et al., 1998; Jacobs et al., 1995; Morris et al., 2001; Petersen et al., 2001; Petersen et al., 1999). Elderly individuals with MCI have clinically significant memory impairment, often accompanied by the functional deficits in attention, language, visuospatial and psychomotor function, but do not fulfill the current criteria for dementia (Chen et al., 2001; Petersen et al., 2001). The field of MCI research is currently focusing on identifying the risk factors of disease progression for the purpose of early therapeutical intervention, which may in turn delay or even prevent the onset of disease process.



Concept of dementia

Dementia is essentially a disease of older people. In DSM-IV (American Psychiatric Association., 1994), dementia is characterized by multiple cognitive defects that include impairment in memory, language, learning, orientation, attention and concentration, general intelligence, problem solving, perception and judgement. A person's personality could be affected. Social or occupation functioning significantly declines as compared to the previous level of functioning. There is no impairment in consciousness. Patients with the impairment of consciousness are suspected to have delirium. The most common type of dementia is Alzheimer's disease (AD), followed by vascular dementia. Other common causes of dementia include Parkinson's disease, lewy body dementia, pick's disease and Huntington's disease etc.

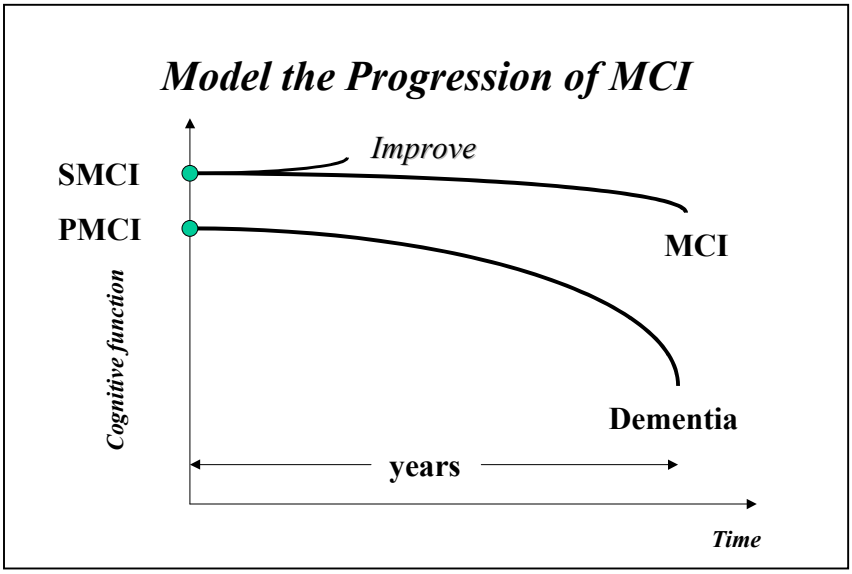
Alzheimer's disease (AD)

AD is a progressive neurodegenerative disorder, which accounts for 55% of all dementias (Dugu et al., 2003). It has an insidious onset with symptoms of mild cognitive impairment and the earliest cognitive domain affected is consistently reported in episodic memory (Almkvist and Backman, 1993). The clinical diagnosis is mainly made by National Institute of Neurological Disorders and Communicative Disorders-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984) and the Diagnostic and Statistical Manual, 4th edition (DSM-IV) criteria (American Psychiatric Association., 1994). Structural MRI studies and the functional investigations of PET and SPECT showed brain atrophy, typically medial temporal lobe atrophy as well as rCBF and glucose metabolism reduction in parieto-temporal association cortex, parietal cortex and posterior cingulate in early AD (Bobinski et al., 2000; Davis et al., 1995; Dewan and Gupta, 1992; Erkinjuntti et al., 1993; Jagust and Eberling, 1991; Minoshima et al., 1994; Postiglione et al., 1993; Scheltens et al., 1992; Waldemar, 1995; Waldemar et al., 1997). Cholinergic deficits were consistently reported, which are correlated with the dementia severity (Bierer et al., 1995; Coyle et al., 1983). Cerebrospinal fluid (CSF) level of microtubule associated tau-protein was found to elevate and β-amyloid is reduced in AD (Arai et al., 1995; Jensen et al., 1995; Jensen et al., 1999; Riemenschneider et al., 1996).

Pathologically, AD is characterized by neuron and synapse loss, senile plagues and neurofibrillary tangles, which mostly start from the transentorhinal region to limbic structures and finally spread to the associative neocortical areas (Braak and Braak, 1991). The pathological diagnostic criteria of AD is mainly made by National Institute on Aging and the American Association of Retired Persons, which is known as NIA/AARP criteria or Khachaturian criteria (Khachaturian, 1985) and Consortium to Establish a Registry for Alzheimer's disease (CERAD) criteria (Mirra et al., 1991), which are based on the use of age-related senile plaque scores to establish a neuropathological diagnosis. The recent consensus from the National Institute on Aging/Reagan Institute Working Working Group, so called NIA/Reagan Institute recommendations concerns the both the number of plaque and tangles in the neocortex, limbic and paralimbic regions (Hyman and Trojanowski, 1997).

Natural history of MCI

MCI is a heterogeneous group with variety of clinical outcomes (Petersen et al., 2001). Most of the MCI subjects will progress to dementia and are at-risk of higher rate of death (Bennett et al., 2002; Palmer et al., 2003). The most common converting type of dementia is AD and the annual converting rate is 10% to 15% in subjects with MCI, which is ten times more than in normal aging (Petersen et al., 2001). Moreover, recent studies suggest a time-dependent evolution of MCI to dementia. The persons with cognitive impairment have a higher risk of progressing to dementia over a period of up to 3 years, but the risk starts to decrease after this point (Palmer et al., 2003). However, some MCI may never progress to any significant extent (Petersen et al., 2001). This MCI sub-group includes the subjects who undergo functional memory impairment induced by psychological disorders such as depression, anxiety or somatic disorders and the cognitive function of those patients could improve after several months´ follow-up (Daly et al., 2000; Devanand et al., 1997; Hanninen et al., 1995; Helkala et al., 1997; Palmer et al., 2002; Wahlund et al., 2003; Wolf et al., 1998). It is also possible that MCI is overlapping with healthy subjects who will not progress to dementia at this point (Petersen et al., 1999).



Diagnostic criteria of MCI

There is no established formal diagnostic criteria for MCI. The diagnosis is mainly based on the neuropsychological tests, however, it varies from investigator to investigator and is modified over time.

The criteria commonly used in Mayo Clinic is Petersen's Criteria (Petersen et al., 1999). The diagnosis of MCI is made if the patients have 1) memory complaint, 2) normal activity of daily living, 3) normal general cognitive function, 4) abnormal memory for age, 5) not demented. However, other types of MCI were later proposed which are MCI with multiple domains slightly impaired and MCI with impaired single non-memory domain. Moreover, some other studies use global deterioration scale (GDS)=3 and/or clinical dementia rating scale (CDR)=0.5 as the diagnostic criteria of MCI (Hughes et al., 1982; Reisberg et al., 1982).

In our clinic, Subjects who are diagnosed as MCI performed at least 1.0/1.5 SD below average for their age on at least one neuropsychological test, but do not fulfill the diagnostic criteria for dementia according to DSM-IV criteria (American Psychiatric Association., 1994) and do not

have evidence of impairment in social or occupational functioning. For the research purpose, we define the MCI subjects who progress to dementia during the follow-up as progressive mild cognitive impairment (PMCI) and the subjects who do not progress to dementia in the observation time as non-progressive mild cognitive impairment or stable mild cognitive impairment (SMCI).

Other definitions of mild cognitive impairment

Other concepts have been used to describe the cognitive status that lies between normal aging and mild dementia, for example, age-associated memory impairment (AAMI), age associated cognitive decline (AACD), cognitive impairment no dementia (CIND), questionable dementia.

AAMI refers to healthy persons over 50 years of age who have subjective memory complaint and perform at least one standard deviation below the norms for young adults in memory test, are not demented and have no other medical or psychiatric condition that can account for this memory decline (Crook et al., 1987; Larrabee and McEntee, 1995). AAMI is generally viewed as a phenomenon of normal aging (Koivisto et al., 1995). However, some researchers questioned that it might be on a continuum with AD (Brayne and Calloway, 1988). 9% AAMI subjects were reported to develop dementia during 3.6 year follow-up (Hanninen et al., 1995). Bartres-Fas et al.´s study showed that the subjects who fulfilled both the AAMI and MCI criteria presented a neuropsychological and genetic profile closer to that previously related to AD than those who fulfilled the AAMI criteria only (Bartres-Faz et al., 2001). Frontal lobe dysfunction and hippocampal atrophy have been reported in AAMI (Golomb et al., 1994; Hanninen et al., 1997; Soininen et al., 1994). However, the structural changes of hippocampus in AAMI was not confirmed in a following study (Laakso et al., 1998).

The concept of AACD encompasses multiple domains of cognitive decline, which is based on scoring the normal elderly people (Levy, 1994). The criteria is developed by a working group of the International Psychogeriatrics Association (Wilmette, Illinois) and the World Health Organization (Geneva, Swizerland), which concerns a gradual decline in any one cognitive area

of at least six months duration and performance at least 1 SD below norms for age on relevant neuropsychological tests. The prevalence of AACD was estimated as 19.3% in the general population and the conversion rate to dementia was reported to be 28.6% during 3 year follow-up (Ritchie et al., 2001).

CIND is defined as a score one standard deviation below the age and education matched MMSE in the Kungsholmen Project in Sweden and one third of the subjects progress to dementia during the 3-year follow-up (Palmer et al., 2002). The Canadian study of CIND reported 42% of all the subjects classified as CIND at the baseline developed dementia in the following 5 years (Hogan and Ebly, 2000).

Questionable dementia is defined with a CDR score of 0.5. 19% to 41% of the subjects with questionable dementia were reported to convert to dementia during 2.5 to 3 year follow-up (Daly et al., 2000; Devanand et al., 1997).

Neuropsychological assessment of MCI

Cognitive deficits in multiple domains could be detected in MCI. Episodic memory, especially delayed recall, is found to be the most common cognitive manifestation years before the onset of dementia (Bennett et al., 2002; Celsis, 2000; Elias et al., 2000; Small et al., 2000; Tierney et al., 2000). The impairment in other cognitive domains involves verbal function, visuospatial processes, attention, executive function as well as abstract reasoning and retention (Celsis, 2000; Chen et al., 2001; Fabrigoule et al., 1998; Hanninen et al., 1997; Nielsen et al., 1998; Tierney et al., 1996; Wolf et al., 1998). Recent studies showed that considering non-memory cognitive domains could significantly improve the predictive value of the future development of AD (Masur et al., 1994). Mini-Mental State Examination (MMSE) has also been reported to be a useful test in predicting future onset of AD (Small et al., 1997; Tierney et al., 2000). It would be desirable for the clinical application if the finding could be further confirmed, since the test is easy to perform. Procedural memories, as well as sensory and motor abilities are consistently shown to be relatively well preserved in the early stage of AD (Howieson et al., 1997; Small et

al., 1997; Tierney et al., 2000). Moreover, recent research indicated that MCI subjects with a single non-memory domain deficit are more likely to go on to develop another neurodegenerative disease, such as progressive aphasia, vascular dementia or lewy body dementia (Petersen et al., 2001).

Neuropathology of MCI

Recent studies showed that neurofibrillary tangles and neuritic plague occur in the limbic structure and neocortex in MCI (Morris et al., 1991; Price et al., 1991; Price and Morris, 1999; Troncoso et al., 1996). The initial formation of tangles was reported to be separated from that of plagues (Price and Morris, 1999). Tangles are firstly formed in the limbic structures, whereas, plaques are preferentially formed in the neocortex (Price and Morris, 1999). High density of neurofibrillary tangles in MCI, as compared to the normal aging, has been found in entorhinal, transentorhinal and perirhinal cortex, hippocampus, basal magnocellular complex as well as antero-dorsal nucleus of thalamus, but with lower numbers of tangles in the neocortex (Braak and Braak, 1991; Price and Morris, 1999). Whereas, both diffuse plaques and neuritic plaques distribute widely throughout the cerebral cortex, mainly in temporal and orbital cortex in MCI, but the limbic areas have relatively fewer plaques than the neocortex (Morris et al., 1996; Price and Morris, 1999). Little or no neuronal loss is found in aging, however, there is substantial neuronal loss in entorhinal cortex, especially in layer II and in CA1 sector of hippocampus in very mild AD (Gomez-Isla et al., 1996; Price et al., 2001).

Magnetic Resonance Imaging (MRI) in MCI

Hippocampal and entorhinal cortex atrophy are consistent findings in MCI (Bottino et al., 2002; Convit et al., 1995; Convit et al., 1997; De Santi et al., 2001; Dickerson et al., 2001; Du et al., 2001; Killiany et al., 2000; Killiany et al., 2002; Visser et al., 1999; Xu et al., 2000). Equivalent discriminant values have been reported between MCI and normal controls by measuring the volume of hippocampus and entorhinal cortex (Xu et al., 2000). However, the visualization of

entorhinal cortex on MRI is more difficult as the boundaries can be obscured by anatomic ambiguity or image artifact. Hippocampal volumetry may be more preferable (Juottonen et al., 1999; Xu et al., 2000). Cingulate cortex and precuneus are interesting regions in preclinical dementia, which have been reported to be atrophic (Chetelat et al., 2002; Killiany et al., 2000). The posterior cingulate atrophy is also found in the mutation carriers at the presymptomatic stage of dementia (Fox et al., 2001; Scahill et al., 2002). Moreover, pronounced grey matter loss of parietal lobe, insular cortex, thalamus and caudate nucleus and white matter lesions as well as unexpected global atrophy were reported to be linked with the increased risk of dementia (Chetelat et al., 2002; Du et al., 2001; Fischl et al., 2002; Foundas et al., 1997; Kabani et al., 2002; Rombouts et al., 2000; van der Flier et al., 2002; Van Der Flier et al., 2002).

PET & SPECT imaging in MCI

Functional imaging studies of positron emission computed tomography (PET) and single photon emission computed tomography (SPECT) show that parieto-temporal association cortex, parietal lobe and cingulate cortex are the earliest regions affected in MCI (Grady et al., 1988; Haxby et al., 1990; Johnson et al., 1998; Kennedy et al., 1995; Kogure et al., 2000; Minoshima et al., 1997; Okamura et al., 2002). Healthy apolipoprotein E4 carriers are also found to have glucose metabolic reduction in parieto-temporal association cortex and posterior cingulate cortex (Reiman et al., 1996). Moreover, the functional alterations of posterior cingulate have been shown to precede the changes in parieto-temporal association cortex in predromal AD (Kogure et al., 2000; Minoshima et al., 1994).

Hippocampus and entorhinal cortex were also reported to be affected in preclinical dementia (De Santi et al., 2001; Johnson et al., 1998; Kogure et al., 2000; Ohnishi et al., 1995). However, despite the medial temporal lobe has the earliest structural alterations measured by MRI and pathological abnormalities in AD, it may not have the earliest functional changes examined by PET and SPECT (Kitayama et al., 2001; Kogure et al., 2000). A recent longitudinal study with serial MRI and SPECT demonstrated a considerable discordance between area of regional atrophy and areas of regional brain hypoperfusion in early AD, which showed a more

pronounced grey matter volume loss compared to cerebral blood flow (rCBF) changes in medial temporal lobe, but more extensive rCBF alterations in posterior cingulate, precuneus and associative parietal cortex than the grey matter volume reduction (Matsuda et al., 2002).

Electroencephalography (EEG) in MCI

There are not many studies concerning MCI and EEG. MCI was found to be intermediate between normal aging and dementia in EEG with considerable overlap (Grunwald et al., 2001; Jelic et al., 1996). An increased theta activity, accompanying a decrease of beta activity are found in the early stage of dementia and followed by a decrease of alpha frequency and an increase in delta activity in severe stage (Coben et al., 1985; Dierks et al., 1991).

Concerning the prediction of the future development of dementia in MCI using EEG, combined alpha, theta relative power and mean frequency were found to be predictive markers in subjects with MCI using conventional frequency analysis (Jelic et al., 2000). An event-related potential (ERP) study found the predictive value of a word repetition paradigm ERP effect for the future development of AD in subjects with MCI (Olichney et al., 2002).

Summary

MCI is an operational diagnostic term developed to describe the preclinical stage of dementia. The rate at which MCI subjects convert to AD each year is ten times more than the rate for normal subjects (Petersen et al., 1999). Identification of PMCI versus SMCI and tracing the progression of PMCI are currently of theoretical interest and practical importance. Early therapeutical interventions are more likely to be effective and the improvement of clinical outcome may significantly reduce the heavy economic and social burden. Therefore, it is of utmost importance to establish effective screening and diagnostic tests which will be simple and inexpensive to perform as well as accurate. Imaging methods have been shown to be useful for

the dementia diagnosis. It would be interesting to explore the predictive values of imaging markers for the future development of dementia in MCI subjects.

AIMS

The general aim of this study was to look for imaging markers of future development of dementia in subjects with MCI.

The specific aims were:

Study I: In the cross-sectional part of this study, we aimed to describe a profile of magnitude and localization of equivalent EEG generators in patients with AD, MCI and controls and explore the variables which have the best classification accuracy among the respective groups. In the longitudinal part of this study, we followed MCI subjects for 2 years on average in order to investigate which of the baseline EEG variables were the best predictors of the future development of AD.

Study II and III: We aimed to detect the differences of brain perfusion and compare the patterns of cognitive function among PMCI, SMCI and age matched controls in order to identify the subjects at risk for the future development of dementia. We also correlated the rCBF and the neuropsychological tests to explore the relation between the brain perfusion and cognitive function.

Study IV: We aimed to evaluate the rCBF progression and cognitive changes of PMCI and SMCI during follow-up. Both voxel-based SPM and VOI-based BRASS were applied for the SPECT quantification and the two methods were compared.

STUDY POPULATION

All patients were selected from those individuals consecutively investigated for suspected dementia at the Geriatric Clinic, Huddinge University Hospital. The control subjects were recruited through advertisements in the press, the Swedish Pensioner Society and a Driving and Aging project. Descriptive statistics for the study samples from paper I to IV are given in Table 1. The MCI subjects in study II and IV are overlapping and all the MCI subjects we have investigated were included in study III.

All subjects underwent general medical, neurological, psychiatric and neuropsychological evaluation, as well as neuroimaging diagnostic procedures SPECT, MRI and EEG.

In study I, the MCI subjects performed at least 1 SD below average for their age on neuropsychological tests representing one or more areas of cognition, but did not fulfill the diagnostic criteria for dementia according to DSM-IV criteria. Patients with AD were diagnosed according to the NINCDS-ADRDA criteria (McKhann et al., 1984).

In study II-IV, the diagnosis of MCI was made when the subject performed at least 1.5 SD below average for their age on at least one neuropsychological test, but did not fulfill the diagnostic criteria for dementia according to DSM-IV criteria (American Psychiatric Association., 1994) and did not have evidence of impairment in social or occupational functioning. Other medical conditions likely to explain the cognitive impairment were excluded during the clinical examination. In study IV, subjective cognitive impairment (SCI) was selected as reference group. The subjects have memory complaints, but performed normal in neuropsycological and medical exams.

For all studies, PMCI and SMCI are retrospective diagnostic terms based on the clinical follow-up. PMCI refers to the MCI subjects who converted to dementia according to the DSM-IV

criteria during the follow up. Whereas, SMCI was defined as the subjects who still did not fulfill the criteria for dementia according to DSM-IV during the observation time.

Table1. Descriptive statistics of the study populations.

Subjects	N	F/M	Age (years)	MMSE (baseline)	MMSE (follow-up)	Follow-up time (months)
Study I						
AD	38	21/17	62.7 (7.1)	23.2 (2.5)	-	-
MCI	31	16/15	61.2 (8.0)	26.7 (2.2)	-	25.5 (8.7)
Controls	24	15/9	63.4 (9.8)	29.0 (1.2)	-	-
Study II						
PMCI	17	9/8	63.6 (7.3)	26.2 (2.0)	-	26.6 (19.0)
SMCI	37	24/13	60.3 (8.5)	27.0 (2.3)	-	29.7 (16.6)
Study III						
PMCI	28	15/13	63.4 (7.6)	25.7 (2.1)	-	23.6 (17.1)
SMCI	54	30/24	59.6 (9.7)	26.9 (2.3)	-	27.7 (15.5)
Controls	20	13/7	61.3 (8.0)	29.4 (0.8)	-	-
Study IV						
PMCI	19	11/8	62.2 (6.8)	25.7 (2.5)	23.2 (4.1)	20.3 (10.9)
SMCI	23	14/9	58.7 (9.5)	27.2 (1.9)	26.6 (2.6)	18.5 (9.0)
SCI	12	6/6	57.3 (8.8)	29.0 (0.94)	29.0 (1.05)	19.6 (8.3)

AD: Alzheiemer's disease; MCI: mild cognitive impairment; PMCI: progressive mild cognitive impairment; SMCI: stable mild cognitive impairment; SCI: subjective cognitive impairment; m: male; f: female; values in parenthesis represent standard deviation (SD).

METHODS

EEG

Data acquisition

All EEGs were recorded referred to the linked mastoids on a computer-based system (Bio-Logic Brain Atlas) from 20 electrode locations, according to the 10/20 system. All investigations were done in a resting awake condition with the eyes closed. Vigilance control was ensured by continuous monitoring of subjects to detect and avoid changes in alertness such as drowsiness. Before AD-conversion, the EEG was filtered analogous with a band pass of 1.0-30.0 Hz. Overall amplification was 20 000 times.

Data analysis

The first fifteen successive 2-second samples were selected, a total of 30 seconds, and edited off-line by visual inspection so as to exclude artifacts. Frequency analysis was performed for 6 frequency bands: delta (1-3.5 Hz), theta (4-7.5 Hz), alpha (8-11.5 Hz), beta 1 (12-15.5 Hz), beta 2 (16-19.5 Hz).

1) Fast Fourier Transformation (FFT) approximation

The method of FFT Dipole approximation was developed to estimate the conventional three-dimensional source, which is considered as the center of gravity of the brain electrical activity. Global Field Power (GFP), which corresponds to the generalized EEG amplitude, was calculated for the 6 frequency bands mentioned above and logarithmically transformed in order to normalize data distribution. Localizations of the generators of each frequency band were calculated in the antero-posterior (Loc-X), left-right (Loc-Y), and superior-inferior (Loc-Z)

dimensions. The localizations are expressed as distance in mm from the middle point of a spherical head model (zerovalue: 10% level in the 10/20 system).

2) Conventional FFT

Frequency analysis was performed in a conventional way using a FFT algorithm with a Hanning window (Bendat et.al,1971). Absolute and relative power were calculated in the above mentioned conventional frequency bands from 8 scalp bipolar derivations: left and right fronto-central (F3-C3, F4-C4), left and right temporal (T3-T5, T4-T6), left and right centro-parietal (C3-P3, C4-P4), and left and right temporo-occipital (T5-O1, T6-O2). Prior to statistical analysis, the absolute power values were transformed using the natural logarithm transform.

SPECT

Acquisition

Each subject was injected with 1000 Mbq Tc-99m hexamethylpropyleneamine oxime (HMPAO) (Ceretec, Amersham Ltd) in a quiet surrounding with eyes closed. Acquisition started 30 minutes after injection. Data were collected in 64 projections evenly spread through 360 degrees with a single headed rotating gamma camera (Siemens Diacam) with a total acquisition time of 32 minutes. Tomographic slices were reconstructed using an iterative algorithm (Hosem, Nuclear Diagnostics AB, Sweden) with Chang attenuation correction (Attenuation coefficient: 0.12cm^{-1}). Data were formatted as a 3D dataset with 64x64x64 cubic voxels with 3.5 mm sides. The resolution in a tomographic slice was measured to be 10.2mm full width at half maximum (FWHM). The reconstructed data sets were post-filtered with a Butterworth filter, cutoff 1.0 cm^{-1}.

Registration and quantification

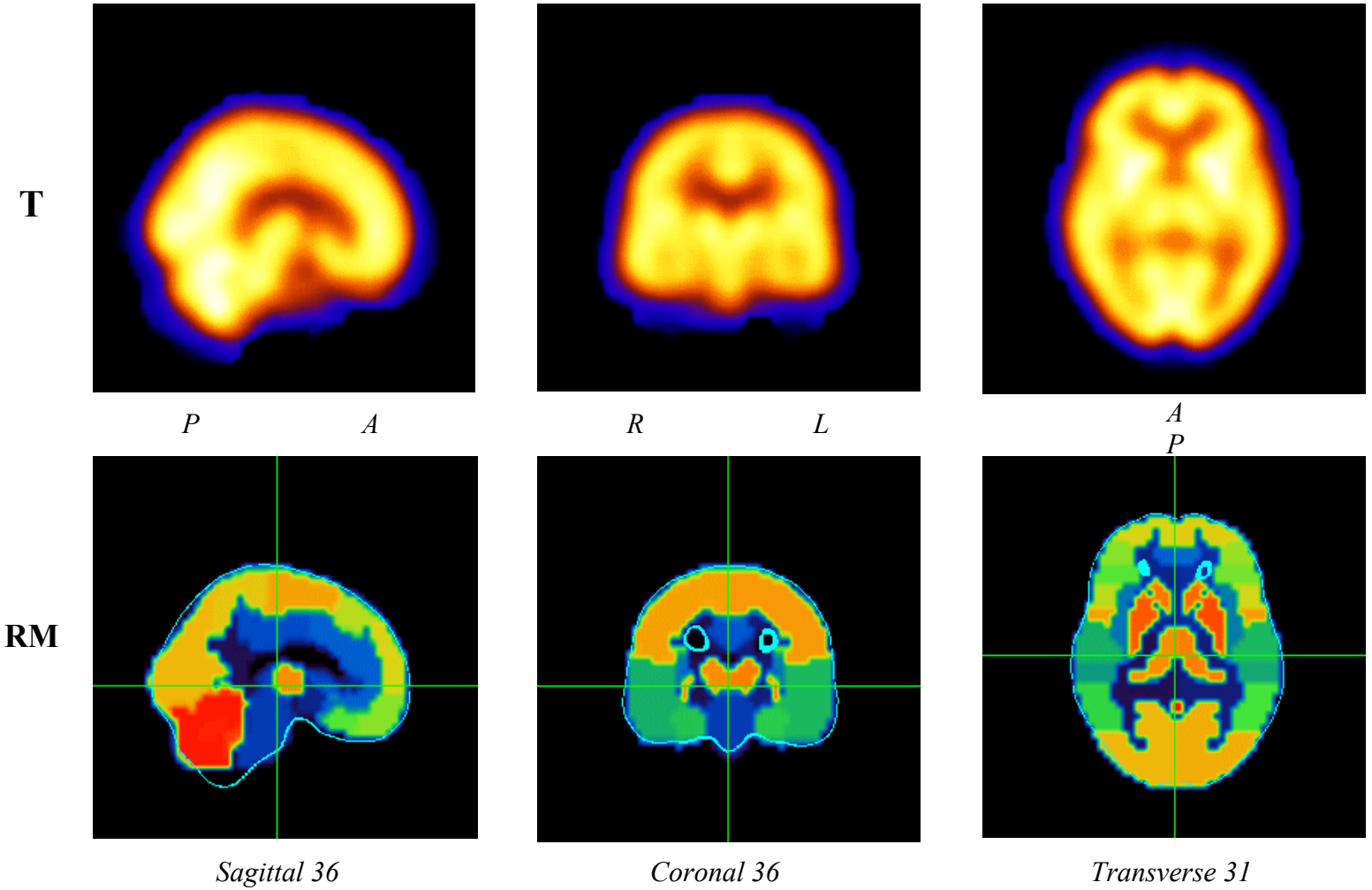
1) BRASS analysis

In study II-IV, Image registration and quantification were performed with the BRASS software developed by Nuclear Diagnostics, London, England (Radau et al., 2000; Radau et al., 2001). The patient datasets were iteratively registered using 9 parameter linear registration to a normal template using normalized mutual information as similarity function. The software uses a map of 46 volumes-of-interest (VOIs) that encompass the entire brain. The template and regionmap are shown in Figure 1. The relative rCBF in the selected regions were calculated as cerebellar ratios (Mean count per voxel of region/mean count per voxel of bilateral cerebellar cortex) or global rCBF ratio (Mean count per voxel of region/mean count per voxel of global region).

2) Statistical Parametric Mapping (SPM) analysis

In paper II and IV, SPECT registration and quantification was performed using SPM99 (Welcome Department of Cognitive Neurology, University College, London) running on Matlab 6.0 (Mathworks Inc., Sherborn, MA). Images were firstly converted from the interfile 3.3 to the Analyze format using a freeware medical image conversion program MedCon. The images with analyze format were transformed to SPM 99. Data were spatially normalized to a Talairach based template of regional rCBF using a 12 parameter affine transform, non-linear transformations and trilinear interpolation. The resultant voxel size was 2x2x2 mm. The normalized data were then smoothed using a Gaussian kernel at FWHM=10mm. Global normalization was performed using proportional scaling by setting the global value as 50ml/min/dl and grey matter threshold of 0.8. The SPM{T}maps were obtained at a height threshold of p=0.001, corrected for the multiple comparisons. Differences between groups were analyzed by 'Single subject, conditions and covariates' model. The longitudinal rCBF changes were investigated by 'paired T-test'. Correlations analyses between rCBF and neuropsychological tests were performed using 'Single subject, covariates only' model. Contrasts were defined to examine both positive and negative effects.

Figure 1. Template and regionmap in BRASS program.



T: template, RM: regionmap, A: anterior, P: posterior, L: left, R: right. The selected slice numbers sleeted to represent the template and regionmap are slice 36 for sagittal & coronal slices and slice 31 for transverse slices.

Neuropsychological tests

All subjects were examined by an experienced psychologist in five cognitive domains using nine psychological tests. The five cognitive domains evaluated were episodic memory, semantic memory, visuospatial function, attention and general cognitive function. The nine psychological tests included four subtests (Information, Similarities, Block Design and Digit Symbol) from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), Trail Making Test A and B, Recognition words test from the Stockholm Geriatric Research Center (SGRC) (Backman and Forsell, 1994) and MMSE (Folstein et al., 1975).

RESULTS

Study I: Quantitative EEG in AD and MCI

The results of cross-sectional group comparison among AD, MCI and controls showed that AD had increased delta and theta GFP and reduced alpha GFP when compared to the controls. A decrease of alpha and beta GFP was found in AD patients when compared to the MCI subjects. With respect to topography in the antero-posterior direction, sources of alpha and beta activity shifted more anteriorly in AD patients compared to both the controls and MCI subjects. No significant difference was found between SMCI and controls. Combined alpha and theta frequency were the best discriminating variables between AD vs controls and AD vs MCI subjects.

Concerning the longitudinal study of MCI, PMCI had decreased alpha GFP and a more anterior localization of sources of theta, alpha and beta frequency at baseline. A linear discriminant analysis was applied on baseline values of the two MCI subgroups. The best predictor of future development of AD was found to be antero-posterior localization of alpha frequency.

FFT dipole approximation and frequency analysis performed by conventional FFT showed comparable classification accuracy between the studied groups.

Study II and III: SPECT study of baseline MCI

The baseline rCBF and neuropsychology were compared between PMCI and SMCI. PMCI had decreased rCBF in posterior cingulate and parietal lobe as well as increased brain perfusion in prefrontal cortex compared to SMCI at baseline.

Both PMCI and SMCI had deficient functions in all the tested cognitive domains compared to controls at the initial investigation. However, the cognitive functions of PMCI were lower than SMCI with respect to episodic memory, visuospatial and general cognitive function represented by MMSE. Semantic memory and attention were negatively correlated with left prefrontal relative rCBF among the study population.

Both SPECT and neuropsychological test had moderate discriminant function between PMCI and SMCI at baseline with the area under the receiver operating characteristic (ROC) curve of 75%-77%. The combination of these two methods improved the diagnostic accuracy with the area under the ROC curve of 82%-84% (Table 2).

Study IV: Longitudinal SPECT study of MCI

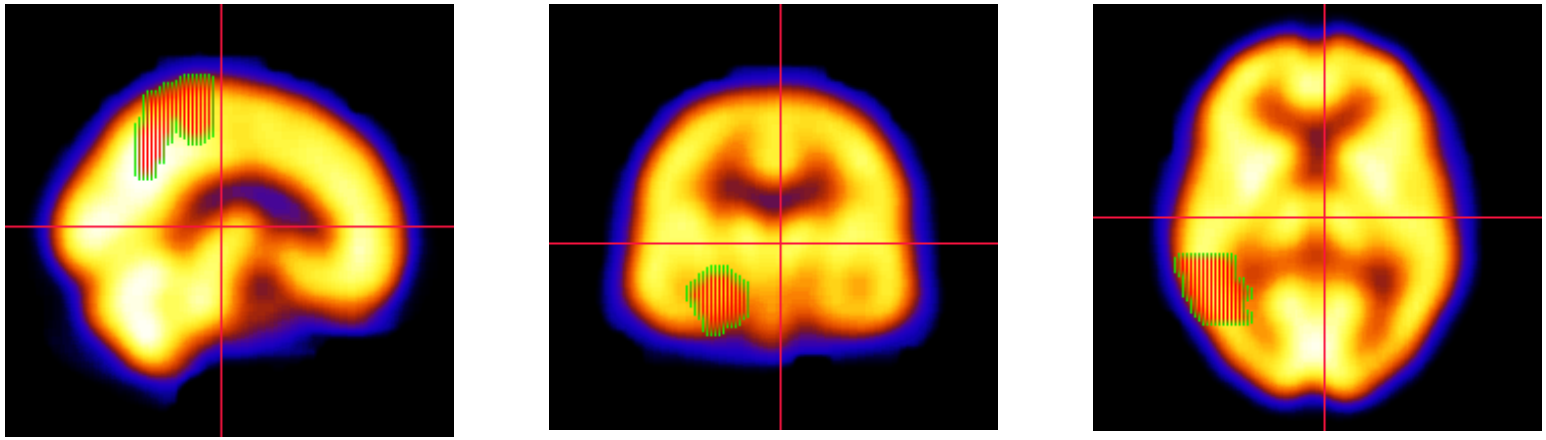
rCBF and neuropsychology status of PMCI, SMCI and SCI were investigated at both baseline and follow-up. SPECT data were analyzed with SPM and BRASS program. No significant findings were detected using SPM. The results of BRASS showed that PMCI had a significantly decreased rCBF in superior parietal lobe, parieto-temporal lobe and posterior cingulate cortex compared to SMCI at baseline. rCBF in superior parietal lobe, parieto-temporal association cortex and medial temporal lobe was significantly decreased in PMCI during follow-up (Figure 2). Concerning the neuropsychological examination, PMCI performed significantly worse on episodic memory, visual spatial function and general cognitive ability assessed by MMSE as compared to SMCI at baseline and MMSE was significantly decreased in PMCI during the follow-up.

Table 2. Estimates and Confidence Interval of Logistic Regression and ROC Analysis of rCBF and neuropsychology between PMCI and SMCI at baseline.

	Model I	Model II	Model III	Model IV	Model V
Parietal Lobe rCBF	-31.82 (-49.47, -14.18)	-	-	-33.03 (-52.75, -13.30)	-31.10 (-50.37, -11.84)
Recognition Words test	-	0.32 (0.01, 0.65)	-	0.34 (-0.02, 0.71)	-
MMSE	-	-	-0.26 (-0.50, -0.03)	-	-0.26 (-0.53, 0.01)
Block Design	-	-0.08 (-0.15, -0.01)	-0.07 (-0.14, <-0.01)	-0.08 (-0.16, 0.01)	-0.07 (-0.15, 0.01)
ROC (Sen, Spe)	75% (63%, 78%)	77% (81%, 72%)	75% (73%, 73%)	84% (81%, 76%)	82% (85%, 71%)

Table is based on Study III. ROC (Sen, Spe): represents the area under the ROC curve and the sensitivity and specificity of the selected optimal cut-off point.

Figure 2. Longitudinal rCBF defects of PMCI.



Sagittal 33 *Coronal 32* *Transverse 32*

DISCUSSIONS

Predicting dementia in MCI

This thesis aimed to predict the future development of dementia in MCI using imaging methods. The results demonstrated that the discriminative factors between PMCI and SMCI at baseline involve SPECT, EEG and cognitive function. It is important to emphasize that in the clinical diagnostic procedure at baseline, both PMCI and SMCI fulfilled MCI criteria, and could not be separated without follow-up data.

In the SPECT studies, we found selective rCBF changes in PMCI with reduced blood flow in parietal lobe, parieto-temporal association cortex and posterior cingulate as well as enhanced brain perfusion in prefontal lobe compared to SMCI two years before the onset of dementia. The reduced rCBF in medial temporal lobe was detected in the longitudinal investigation of PMCI. Concerning the EEG study, PMCI had decreased alpha GFP and a more anterior localization source of theta, alpha and beta frequency, as compared to SMCI at baseline. Reduced cognitive function was found as compared to SMCI at baseline investigation with respect to the cognitive domains of episodic memory, visuo-spatial function and general cognitive function represented by MMSE.

A moderate discriminant accuracy of PMCI and SMCI at baseline was found using SPECT, EEG and neuropsychological tests. Combined parietal rCBF and neuropsychological tests of episodic memory, visual spatial function and MMSE increased the diagnostic accuracy with the area under the ROC curve of 82-84%.

Longitudinal changes of MCI

In the longitudinal SPECT study of MCI, decreased rCBF in posterior cingulate was found in PMCI as compared to SMCI at the initial investigation, but no significant changes were detected during the follow-up. The vanishing phenomenon was also reported by Kogure et al., who explained it as a technical problem (Kogure et al., 2000). In contrast, no significant baseline rCBF reduction was detected in medial temporal lobe in PMCI as compared to SMCI, but the rCBF decreased during the two year follow-up before the onset of the disease. The incontinuous findings in posterior cingulate and medial temporal lobe could be induced by the low resolution of SPECT, which is not sensitive enough to detect the rCBF differences in limited regions and trace the slight progression of the disease. However, it is also possible that the MCI may not have exactly the same rCBF patterns throughout the disease process.

Clinical outcome of SMCI

SMCI is a subgroup of MCI, however, it is heterogeneous. A few SMCI subjects may go on to develop dementia if the follow-up time is long enough. Some subjects may never progress to any significant extent. Subjects with functional memory impairment induced by psychological disorders such as depression or might improve after several months´ follow-up. It would be desirable to have longer follow-up time and further studies on the subsets of SMCI is needed.

Neuronal network and disconnection hypothesis

The explanation of the posterior cingulate hypoperfusion in PMCI is not clear. This region shows the earliest function alteration, but not the earliest structural pathological changes in AD. Anatomical studies indicated the main components of the episodic memory that hippocampus projects to thalamus via fornix, mamillary bodies and mamillothalamic tract, thalamus connected to prefrontal cortex and indirectly linked to the parahippocampus through the association with area 29 of the posterior cingulate gyrus (Aggleton and Brown, 1999; Quirk et al., 1992; Vogt et al., 1992). This neural network system interacts at different levels, engages in memory storage

and is critical for the recall of new episodic information. The early pathological damage of medial temporal lobe and thalamus in AD may result in the disruption of this neuronal network which subsequently causes the disassociation with posterior cingulate cortex (Figure 3). Such kind of effects could either directly cause the brain hypoperfusion of posterior cingulate or induce the decreased capacity of posterior cingulate for the memory signal processing, which subsequently result in the reduction of posterior cingulate rCBF and anterograde amnesia.

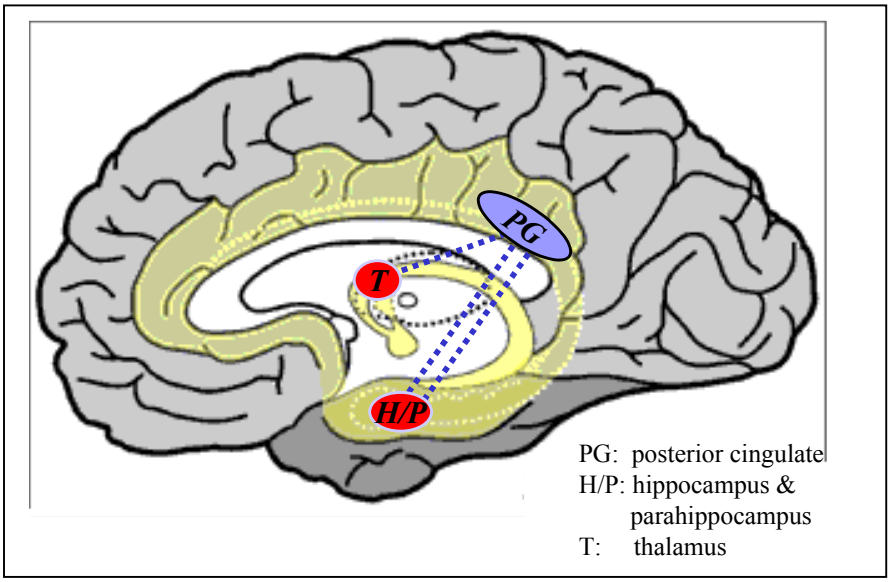


Figure 3. Disconnection hypothesis in AD

Prefrontal lobe involvement in PMCI

Baseline prefrontal rCBF was found to increase in PMCI at resting stage, as compared to SMCI, which has not been shown in previous studies. However, the finding of prefrontal lobe hyperperfusion seems robust and the relative global CBF calculation does not support the assumption that the prefrontal lobe relative rCBF was falsely elevated by global normalization. One explanation for the elevated prefrontal rCBF might be an increased rCBF at the resting state as a compensation mechanism related to decreased attention capacity as indicated by the negatively correlative findings between prefrontal rCBF and attention test. Moreover, it is

interesting to mention that the involvement of prefrontal lobe in the process of AD might be earlier than previously appreciated, which is also supported by a recent PET study showing the glucose metabolic reduction in prefrontal cortical area during the follow up of PMCI (Drzezga et al., 2003).

BRASS and SPM

Our studies included both an automated volumes-of-interest (VOI) based analysis and a voxel-based analysis of SPM. The VOI based analysis of BRASS program is designed to map significant regional changes at an individual level with predefined anatomical VOI. The voxel-based analysis of SPM give the possibility to find more anatomically discrete changes. However, the feasibility of SPM for analyzing the subjects at individual level is limited. The results of our longitudinal SPECT study of MCI indicated that VOI-based BRASS analysis might be more sensitive to detect the significant differences in preclinical dementia, since the early rCBF changes might be characterized by the slightly decreased brain perfusion in larger regions.

CONCLUSIONS

SPECT and EEG could provide promising markers for the early diagnosis and tracing the progression of dementia. Combining imaging investigation with neuropsychological testing may increase the diagnostic accuracy of preclinical dementia.

FUTURE DIRECTION

There are no established diagnostic criteria of MCI, which might cause different findings and introduce difficulties to compare the results in different studies. It is currently important to have consensus concerning the clinical diagnosis of MCI.

MRI is needed to evaluate the structural changes of MCI and correct the potential partial volume effect of SPECT measurements. The sensitivity and specificity of MRI, SPECT/PET or combined MRI/SPECT(PET) for the early diagnosis of dementia need to be investigated.

It is interesting to combine the biological and imaging markers and evaluate the diagnostic accuracy of future development of dementia in MCI subjects.

Pathological studies need to carry on and it is interesting to explore the relation between the imaging findings and pathological changes in MCI.

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REFERENCES

1. Aggleton, J. P., and Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci *22*, 425-444; discussion 444-489.

2. Almkvist, O., and Backman, L. (1993). Detection and staging of early clinical dementia. Acta Neurol Scand *88*, 10-15.

3. Almkvist, O., Basun, H., Backman, L., Herlitz, A., Lannfelt, L., Small, B., Viitanen, M., Wahlund, L. O., and Winblad, B. (1998). Mild cognitive impairment--an early stage of Alzheimer's disease? J Neural Transm Suppl *54*, 21-29.

4. Arai, H., Terajima, M., Miura, M., Higuchi, S., Muramatsu, T., Machida, N., Seiki, H., Takase, S., Clark, C. M., Lee, V. M., and et al. (1995). Tau in cerebrospinal fluid: a potential diagnostic marker in Alzheimer's disease. Ann Neurol *38*, 649-652.

5. Backman, L., and Forsell, Y. (1994). Episodic memory functioning in a community-based sample of old adults with major depression: utilization of cognitive support. J Abnorm Psychol *103*, 361-370.

6. Bartres-Faz, D., Junque, C., Lopez-Alomar, A., Valveny, N., Moral, P., Casamayor, R., Salido, A., Bel, C., and Clemente, I. C. (2001). Neuropsychological and genetic differences between age-associated memory impairment and mild cognitive impairment entities. J Am Geriatr Soc *49*, 985-990.

7. Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., Beckett, L. A., Aggarwal, N. T., Barnes, L. L., Fox, J. H., and Bach, J. (2002). Natural history of mild cognitive impairment in older persons. Neurology *59*, 198-205.

8. Bierer, L. M., Haroutunian, V., Gabriel, S., Knott, P. J., Carlin, L. S., Purohit, D. P., Perl, D. P., Schmeidler, J., Kanof, P., and Davis, K. L. (1995). Neurochemical correlates of dementia severity in Alzheimer's disease: relative importance of the cholinergic deficits. J Neurochem *64*, 749-760.

9. Bobinski, M., de Leon, M. J., Wegiel, J., Desanti, S., Convit, A., Saint Louis, L. A., Rusinek, H., and Wisniewski, H. M. (2000). The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. Neuroscience *95*, 721-725.

10. Bottino, C. M., Castro, C. C., Gomes, R. L., Buchpiguel, C. A., Marchetti, R. L., and Neto, M. R. (2002). Volumetric MRI measurements can differentiate Alzheimer's disease, mild

cognitive impairment, and normal aging. Int Psychogeriatr *14*, 59-72.

11. Braak, H., and Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol *82*, 239-259.

12. Brayne, C., and Calloway, P. (1988). Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: a continuum? Lancet *1*, 1265-1267.

13. Celsis, P. (2000). Age-related cognitive decline, mild cognitive impairment or preclinical Alzheimer's disease? Ann Med *32*, 6-14.

14. Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., and Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. Arch Gen Psychiatry *58*, 853-858.

15. Chetelat, G., Desgranges, B., De La Sayette, V., Viader, F., Eustache, F., and Baron, J. C. (2002). Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. Neuroreport *13*, 1939-1943.

16. Coben, L. A., Danziger, W., and Storandt, M. (1985). A longitudinal EEG study of mild senile dementia of Alzheimer type: changes at 1 year and at 2.5 years. Electroencephalogr Clin Neurophysiol *61*, 101-112.

17. Convit, A., de Leon, M. J., Tarshish, C., De Santi, S., Kluger, A., Rusinek, H., and George, A. E. (1995). Hippocampal volume losses in minimally impaired elderly. Lancet *345*, 266.

18. Convit, A., De Leon, M. J., Tarshish, C., De Santi, S., Tsui, W., Rusinek, H., and George, A. (1997). Specific hippocampal volume reductions in individuals at risk for Alzheimer's disease. Neurobiol Aging *18*, 131-138.

19. Coyle, J. T., Price, D. L., and DeLong, M. R. (1983). Alzheimer's disease: a disorder of cortical cholinergic innervation. Science *219*, 1184-1190.

20. Crook, T., Bahar, H., and Sudilovsky, A. (1987). Age-associated memory impairment: diagnostic criteria and treatment strategies. Int J Neurol *21-22*, 73-82.

21. Daly, E., Zaitchik, D., Copeland, M., Schmahmann, J., Gunther, J., and Albert, M. (2000). Predicting conversion to Alzheimer disease using standardized clinical information. Arch Neurol *57*, 675-680.

22. Davis, P. C., Gearing, M., Gray, L., Mirra, S. S., Morris, J. C., Edland, S. D., Lin, T., and Heyman, A. (1995). The CERAD experience, Part VIII: Neuroimaging-neuropathology correlates of temporal lobe changes in Alzheimer's disease. Neurology *45*, 178-179.

23. De Santi, S., de Leon, M. J., Rusinek, H., Convit, A., Tarshish, C. Y., Roche, A., Tsui, W. H., Kandil, E., Boppana, M., Daisley, K.*, et al.* (2001). Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol Aging *22*, 529-539.

24. Devanand, D. P., Folz, M., Gorlyn, M., Moeller, J. R., and Stern, Y. (1997). Questionable dementia: clinical course and predictors of outcome. J Am Geriatr Soc *45*, 321-328.

25. Dewan, M. J., and Gupta, S. (1992). Toward a definite diagnosis of Alzheimer's disease. Compr Psychiatry *33*, 282-290.

26. Dickerson, B. C., Goncharova, I., Sullivan, M. P., Forchetti, C., Wilson, R. S., Bennett, D. A., Beckett, L. A., and deToledo-Morrell, L. (2001). MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. Neurobiol Aging *22*, 747-754.

27. Dierks, T., Perisic, I., Frolich, L., Ihl, R., and Maurer, K. (1991). Topography of the quantitative electroencephalogram in dementia of the Alzheimer type: relation to severity of dementia. Psychiatry Res *40*, 181-194.

28. Drzezga, A., Lautenschlager, N., Siebner, H., Riemenschneider, M., Willoch, F., Minoshima, S., Schwaiger, M., and Kurz, A. (2003). Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. Eur J Nucl Med Mol Imaging *30*, 1104-1113.

29. Du, A. T., Schuff, N., Amend, D., Laakso, M. P., Hsu, Y. Y., Jagust, W. J., Yaffe, K., Kramer, J. H., Reed, B., Norman, D.*, et al.* (2001). Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. J Neurol Neurosurg Psychiatry *71*, 441-447.

30. Dugu, M., Neugroschl, J., Sewell, M., and Marin, D. (2003). Review of dementia. Mt Sinai J Med *70*, 45-53.

31. Elias, M. F., Beiser, A., Wolf, P. A., Au, R., White, R. F., and D'Agostino, R. B. (2000). The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. Arch Neurol *57*, 808-813.

32. Erkinjuntti, T., Lee, D. H., Gao, F., Steenhuis, R., Eliasziw, M., Fry, R., Merskey, H., and Hachinski, V. C. (1993). Temporal lobe atrophy on magnetic resonance imaging in the diagnosis of early Alzheimer's disease. Arch Neurol *50*, 305-310.

33. Fabrigoule, C., Rouch, I., Taberly, A., Letenneur, L., Commenges, D., Mazaux, J. M., Orgogozo, J. M., and Dartigues, J. F. (1998). Cognitive process in preclinical phase of dementia. Brain *121 (Pt 1)*, 135-141.

34. Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S.*, et al.* (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron *33*, 341-355.

35. Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res *12*, 189-198.

36. Foundas, A. L., Leonard, C. M., Mahoney, S. M., Agee, O. F., and Heilman, K. M. (1997). Atrophy of the hippocampus, parietal cortex, and insula in Alzheimer's disease: a volumetric magnetic resonance imaging study. Neuropsychiatry Neuropsychol Behav Neurol *10*, 81-89.

37. Fox, N. C., Crum, W. R., Scahill, R. I., Stevens, J. M., Janssen, J. C., and Rossor, M. N. (2001). Imaging of onset and progression of Alzheimer's disease with voxel-compression mapping of serial magnetic resonance images. Lancet *358*, 201-205.

38. Golomb, J., Kluger, A., de Leon, M. J., Ferris, S. H., Convit, A., Mittelman, M. S., Cohen, J., Rusinek, H., De Santi, S., and George, A. E. (1994). Hippocampal formation size in normal human aging: a correlate of delayed secondary memory performance. Learn Mem *1*, 45-54.

39. Gomez-Isla, T., Price, J. L., McKeel, D. W., Jr., Morris, J. C., Growdon, J. H., and Hyman, B. T. (1996). Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J Neurosci *16*, 4491-4500.

40. Grady, C. L., Haxby, J. V., Horwitz, B., Sundaram, M., Berg, G., Schapiro, M., Friedland, R. P., and Rapoport, S. I. (1988). Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer type. J Clin Exp Neuropsychol *10*, 576-596.

41. Grunwald, M., Busse, F., Hensel, A., Kruggel, F., Riedel-Heller, S., Wolf, H., Arendt, T., and Gertz, H. J. (2001). Correlation between cortical theta activity and hippocampal volumes in health, mild cognitive impairment, and mild dementia. J Clin Neurophysiol *18*, 178-184.

42. Hanninen, T., Hallikainen, M., Koivisto, K., Helkala, E. L., Reinikainen, K. J., Soininen, H., Mykkanen, L., Laakso, M., Pyorala, K., and Riekkinen, P. J., Sr. (1995). A follow-up study of age-associated memory impairment: neuropsychological predictors of dementia. J Am Geriatr Soc *43*, 1007-1015.

43. Hanninen, T., Hallikainen, M., Koivisto, K., Partanen, K., Laakso, M. P., Riekkinen, P. J., Sr., and Soininen, H. (1997). Decline of frontal lobe functions in subjects with age-associated memory impairment. Neurology *48*, 148-153.

44. Haxby, J. V., Grady, C. L., Koss, E., Horwitz, B., Heston, L., Schapiro, M., Friedland, R. P., and Rapoport, S. I. (1990). Longitudinal study of cerebral metabolic asymmetries and associated neuropsychological patterns in early dementia of the Alzheimer type. Arch Neurol *47*, 753-760.

45. Helkala, E. L., Koivisto, K., Hanninen, T., Vanhanen, M., Kuusisto, J., Mykkanen, L., Laakso, M., and Riekkinen, P., Sr. (1997). Stability of age-associated memory impairment during a longitudinal population-based study. J Am Geriatr Soc *45*, 120-122.

46. Hogan, D. B., and Ebly, E. M. (2000). Predicting who will develop dementia in a cohort of Canadian seniors. Can J Neurol Sci *27*, 18-24.

47. Howieson, D. B., Dame, A., Camicioli, R., Sexton, G., Payami, H., and Kaye, J. A. (1997). Cognitive markers preceding Alzheimer's dementia in the healthy oldest old. J Am Geriatr Soc *45*, 584-589.

48. Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., and Martin, R. L. (1982). A new clinical scale for the staging of dementia. Br J Psychiatry *140*, 566-572.

49. Hyman, B. T., and Trojanowski, J. Q. (1997). Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol *56*, 1095-1097.

50. Jacobs, D. M., Sano, M., Dooneief, G., Marder, K., Bell, K. L., and Stern, Y. (1995). Neuropsychological detection and characterization of preclinical Alzheimer's disease. Neurology *45*, 957-962.

51. Jagust, W. J., and Eberling, J. L. (1991). MRI, CT, SPECT, PET: their use in diagnosing dementia. Geriatrics *46*, 28-35.

52. Jelic, V., Johansson, S. E., Almkvist, O., Shigeta, M., Julin, P., Nordberg, A., Winblad, B., and Wahlund, L. O. (2000). Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol Aging *21*, 533-540.

53. Jelic, V., Shigeta, M., Julin, P., Almkvist, O., Winblad, B., and Wahlund, L. O. (1996). Quantitative electroencephalography power and coherence in Alzheimer's disease and mild cognitive impairment. Dementia *7*, 314-323.

54. Jensen, M., Basun, H., and Lannfelt, L. (1995). Increased cerebrospinal fluid tau in patients with Alzheimer's disease. Neurosci Lett *186*, 189-191.

55. Jensen, M., Schroder, J., Blomberg, M., Engvall, B., Pantel, J., Ida, N., Basun, H., Wahlund, L. O., Werle, E., Jauss, M.*, et al.* (1999). Cerebrospinal fluid A beta42 is increased early in sporadic Alzheimer's disease and declines with disease progression. Ann Neurol *45*, 504-511.

56. Johnson, K. A., Jones, K., Holman, B. L., Becker, J. A., Spiers, P. A., Satlin, A., and Albert, M. S. (1998). Preclinical prediction of Alzheimer's disease using SPECT. Neurology *50*, 1563-

1571.

57. Juottonen, K., Laakso, M. P., Partanen, K., and Soininen, H. (1999). Comparative MR analysis of the entorhinal cortex and hippocampus in diagnosing Alzheimer disease. AJNR Am J Neuroradiol *20*, 139-144.

58. Kabani, N. J., Sled, J. G., Shuper, A., and Chertkow, H. (2002). Regional magnetization transfer ratio changes in mild cognitive impairment. Magn Reson Med *47*, 143-148.

59. Kennedy, A. M., Frackowiak, R. S., Newman, S. K., Bloomfield, P. M., Seaward, J., Roques, P., Lewington, G., Cunningham, V. J., and Rossor, M. N. (1995). Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. Neurosci Lett *186*, 17-20.

60. Khachaturian, Z. S. (1985). Diagnosis of Alzheimer's disease. Arch Neurol *42*, 1097-1105.

61. Killiany, R. J., Gomez-Isla, T., Moss, M., Kikinis, R., Sandor, T., Jolesz, F., Tanzi, R., Jones, K., Hyman, B. T., and Albert, M. S. (2000). Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol *47*, 430-439.

62. Killiany, R. J., Hyman, B. T., Gomez-Isla, T., Moss, M. B., Kikinis, R., Jolesz, F., Tanzi, R., Jones, K., and Albert, M. S. (2002). MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology *58*, 1188-1196.

63. Kitayama, N., Matsuda, H., Ohnishi, T., Kogure, D., Asada, T., Uno, M., and Kamijima, K. (2001). Measurements of both hippocampal blood flow and hippocampal gray matter volume in the same individuals with Alzheimer's disease. Nucl Med Commun *22*, 473-477.

64. Kogure, D., Matsuda, H., Ohnishi, T., Asada, T., Uno, M., Kunihiro, T., Nakano, S., and Takasaki, M. (2000). Longitudinal evaluation of early Alzheimer's disease using brain perfusion SPECT. J Nucl Med *41*, 1155-1162.

65. Koivisto, K., Reinikainen, K. J., Hanninen, T., Vanhanen, M., Helkala, E. L., Mykkanen, L., Laakso, M., Pyorala, K., and Riekkinen, P. J., Sr. (1995). Prevalence of age-associated memory impairment in a randomly selected population from eastern Finland. Neurology *45*, 741-747.

66. Laakso, M. P., Soininen, H., Partanen, K., Lehtovirta, M., Hallikainen, M., Hanninen, T., Helkala, E. L., Vainio, P., and Riekkinen, P. J., Sr. (1998). MRI of the hippocampus in Alzheimer's disease: sensitivity, specificity, and analysis of the incorrectly classified subjects. Neurobiol Aging *19*, 23-31.

67. Larrabee, G. J., and McEntee, W. J. (1995). Age-associated memory impairment: sorting out the controversies. Neurology *45*, 611-614.

68. Levy, R. (1994). Aging-associated cognitive decline. Working Party of the International Psychogeriatric Association in collaboration with the World Health Organization. Int Psychogeriatr *6*, 63-68.

69. Masur, D. M., Sliwinski, M., Lipton, R. B., Blau, A. D., and Crystal, H. A. (1994). Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. Neurology *44*, 1427-1432.

70. Matsuda, H., Kitayama, N., Ohnishi, T., Asada, T., Nakano, S., Sakamoto, S., Imabayashi, E., and Katoh, A. (2002). Longitudinal evaluation of both morphologic and functional changes in the same individuals with Alzheimer's disease. J Nucl Med *43*, 304-311.

71. McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology *34*, 939-944.

72. Minoshima, S., Foster, N. L., and Kuhl, D. E. (1994). Posterior cingulate cortex in Alzheimer's disease. Lancet *344*, 895.

73. Minoshima, S., Giordani, B., Berent, S., Frey, K. A., Foster, N. L., and Kuhl, D. E. (1997). Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol *42*, 85-94.

74. Mirra, S. S., Heyman, A., McKeel, D., Sumi, S. M., Crain, B. J., Brownlee, L. M., Vogel, F. S., Hughes, J. P., van Belle, G., and Berg, L. (1991). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology *41*, 479-486.

75. Morris, J. C., McKeel, D. W., Jr., Storandt, M., Rubin, E. H., Price, J. L., Grant, E. A., Ball, M. J., and Berg, L. (1991). Very mild Alzheimer's disease: informant-based clinical, psychometric, and pathologic distinction from normal aging. Neurology *41*, 469-478.

76. Morris, J. C., Storandt, M., McKeel, D. W., Jr., Rubin, E. H., Price, J. L., Grant, E. A., and Berg, L. (1996). Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease. Neurology *46*, 707-719.

77. Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., and Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol *58*, 397-405.

78. Nielsen, H., Lolk, A., and Kragh-Sorensen, P. (1998). Age-associated memory impairment--pathological memory decline or normal aging? Scand J Psychol *39*, 33-37.

79. Ohnishi, T., Hoshi, H., Nagamachi, S., Jinnouchi, S., Flores, L. G., 2nd, Futami, S., and Watanabe, K. (1995). High-resolution SPECT to assess hippocampal perfusion in neuropsychiatric diseases. J Nucl Med *36*, 1163-1169.

80. Okamura, N., Arai, H., Maruyama, M., Higuchi, M., Matsui, T., Tanji, H., Seki, T., Hirai, H., Chiba, H., Itoh, M., and Sasaki, H. (2002). Combined Analysis of CSF Tau Levels and [(123)I]Iodoamphetamine SPECT in Mild Cognitive Impairment: Implications for a Novel Predictor of Alzheimer's Disease. Am J Psychiatry *159*, 474-476.

81. Olichney, J. M., Morris, S. K., Ochoa, C., Salmon, D. P., Thal, L. J., Kutas, M., and Iragui, V. J. (2002). Abnormal verbal event related potentials in mild cognitive impairment and incipient Alzheimer's disease. J Neurol Neurosurg Psychiatry *73*, 377-384.

82. Palmer, K., Fratiglioni, L., and Winblad, B. (2003). What is mild cognitive impairment? Variations in definitions and evolution of nondemented persons with cognitive impairment. Acta Neurol Scand Suppl *179*, 14-20.

83. Palmer, K., Wang, H. X., Backman, L., Winblad, B., and Fratiglioni, L. (2002). Differential evolution of cognitive impairment in nondemented older persons: results from the Kungsholmen Project. Am J Psychiatry *159*, 436-442.

84. Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., Ritchie, K., Rossor, M., Thal, L., and Winblad, B. (2001). Current concepts in mild cognitive impairment. Arch Neurol *58*, 1985-1992.

85. Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., and Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. Arch Neurol *56*, 303-308.

86. Postiglione, A., Lassen, N. A., and Holman, B. L. (1993). Cerebral blood flow in patients with dementia of Alzheimer's type. Aging (Milano) *5*, 19-26.

87. Price, J. L., Davis, P. B., Morris, J. C., and White, D. L. (1991). The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging *12*, 295-312.

88. Price, J. L., Ko, A. I., Wade, M. J., Tsou, S. K., McKeel, D. W., and Morris, J. C. (2001). Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease. Arch Neurol *58*, 1395-1402.

89. Price, J. L., and Morris, J. C. (1999). Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol *45*, 358-368.

90. Quirk, G. J., Muller, R. U., Kubie, J. L., and Ranck, J. B., Jr. (1992). The positional firing properties of medial entorhinal neurons: description and comparison with hippocampal place cells. J Neurosci *12*, 1945-1963.

91. Radau, P. E., Slomka, P. J., Julin, P., Svensson, L., and Wahlund, L.-O. (2000). Automated segmentation and registration technique for HMPAO-SPECT imaging of Alzheimer's patients. Medical imaging 2000: Image processing, Kenneth M Hansson, Ed Proceedings of SPIE *3979*, 372-384.

92. Radau, P. E., Slomka, P. J., Julin, P., Svensson, L., and Wahlund, L.-O. (2001). Evaluation of linear registration algorithms for brain SPECT and the errors due to hypoperfusion lesions. J Med Phys *28*.

93. Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K., Bandy, D., Minoshima, S., Thibodeau, S. N., and Osborne, D. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. N Engl J Med *334*, 752-758.

94. Reisberg, B., Ferris, S. H., de Leon, M. J., and Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry *139*, 1136-1139.

95. Riemenschneider, M., Buch, K., Schmolke, M., Kurz, A., and Guder, W. G. (1996). Cerebrospinal protein tau is elevated in early Alzheimer's disease. Neurosci Lett *212*, 209-211.

96. Ritchie, K., Artero, S., and Touchon, J. (2001). Classification criteria for mild cognitive impairment: a population-based validation study. Neurology *56*, 37-42.

97. Rombouts, S. A., Barkhof, F., Witter, M. P., and Scheltens, P. (2000). Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. Neurosci Lett *285*, 231-233.

98. Scahill, R. I., Schott, J. M., Stevens, J. M., Rossor, M. N., and Fox, N. C. (2002). Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc Natl Acad Sci U S A *99*, 4703-4707.

99. Scheltens, P., Leys, D., Barkhof, F., Huglo, D., Weinstein, H. C., Vermersch, P., Kuiper, M., Steinling, M., Wolters, E. C., and Valk, J. (1992). Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry *55*, 967-972.

100. Small, B. J., Viitanen, M., and Backman, L. (1997). Mini-Mental State Examination item scores as predictors of Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. J Gerontol A Biol Sci Med Sci *52*, M299-304.

101. Small, G. W., Ericoli, L. M., Silverman, D. S., Huang, S. C., Komo, S., Bookheimer, S. Y., Lavretsky, H., Miller, K., Siddarth, P., Rasgon, N. L.*, et al.* (2000). Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer´s disease. PNAS *97*, 6037-6042.

102. Soininen, H. S., Partanen, K., Pitkanen, A., Vainio, P., Hanninen, T., Hallikainen, M., Koivisto, K., and Riekkinen, P. J., Sr. (1994). Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: correlation to visual and verbal memory. Neurology *44*, 1660-1668.

103. Tierney, M. C., Szalai, J. P., Dunn, E., Geslani, D., and McDowell, I. (2000). Prediction of probable Alzheimer disease in patients with symptoms suggestive of memory impairment. Value of the Mini-Mental State Examination. Arch Fam Med *9*, 527-532.

104. Tierney, M. C., Szalai, J. P., Snow, W. G., Fisher, R. H., Nores, A., Nadon, G., Dunn, E., and St George-Hyslop, P. H. (1996). Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. Neurology *46*, 661-665.

105. Troncoso, J. C., Martin, L. J., Dal Forno, G., and Kawas, C. H. (1996). Neuropathology in controls and demented subjects from the Baltimore Longitudinal Study of Aging. Neurobiol Aging *17*, 365-371.

106. van der Flier, W. M., van den Heuvel, D. M., Weverling-Rijnsburger, A. W., Bollen, E. L., Westendorp, R. G., van Buchem, M. A., and Middelkoop, H. A. (2002). Magnetization transfer imaging in normal aging, mild cognitive impairment, and Alzheimer's disease. Ann Neurol *52*, 62-67.

107. Van Der Flier, W. M., Van Den Heuvel, D. M., Weverling-Rijnsburger, A. W., Spilt, A., Bollen, E. L., Westendorp, R. G., Middelkoop, H. A., and Van Buchem, M. A. (2002). Cognitive decline in AD and mild cognitive impairment is associated with global brain damage. Neurology *59*, 874-879.

108. Visser, P. J., Scheltens, P., Verhey, F. R., Schmand, B., Launer, L. J., Jolles, J., and Jonker, C. (1999). Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. J Neurol *246*, 477-485.

109. Vogt, B. A., Finch, D. M., and Olson, C. R. (1992). Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cereb Cortex *2*, 435-443.

110. Wahlund, L. O., Pihlstrand, E., and Jonhagen, M. E. (2003). Mild cognitive impairment: experience from a memory clinic. Acta Neurol Scand Suppl *179*, 21-24.

111. Waldemar, G. (1995). Functional brain imaging with SPECT in normal aging and dementia. Methodological, pathophysiological, and diagnostic aspects. Cerebrovasc Brain Metab Rev *7*, 89-130.

112. Waldemar, G., Hogh, P., and Paulson, O. B. (1997). Functional brain imaging with single-photon emission computed tomography in the diagnosis of Alzheimer's disease. Int Psychogeriatr *9 Suppl 1*, 223-227; discussion 247-252.

113. Wechsler, D. (1981). Wechsler Adult Intelligence Scale-Revised Manual (San Antonio, Psychological Corp).

114. Wolf, H., Grunwald, M., Ecke, G. M., Zedlick, D., Bettin, S., Dannenberg, C., Dietrich, J., Eschrich, K., Arendt, T., and Gertz, H. J. (1998). The prognosis of mild cognitive impairment in the elderly. J Neural Transm Suppl *54*, 31-50.

115. Xu, Y., Jack, C. R., Jr., O'Brien, P. C., Kokmen, E., Smith, G. E., Ivnik, R. J., Boeve, B. F., Tangalos, R. G., and Petersen, R. C. (2000). Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. Neurology *54*, 1760-1767.